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FACULTY OF ENGINEERING
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Thesis Title:

“Molecular Modelling of the early stages of Metal-
Organic Framework self-assembly”

by

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Declaration

I, Loukas Kollias, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

London, May 2020

Dedicated to my parents Lina and Akis.

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London, May 2020

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- L. Kollias, D. C. Cantu, R. Rousseau, V.-A. Glezakou, M. Salvalaglio, “On the role of Entropic and Enthalpic contributions on the conformational landscape of MIL-101(Cr) structural building units”, DOI: 10.26434/chemrxiv.9947228.v3
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- L. Kollias, D.C. Cantu, R. Rousseau, V.-A. Glezakou, M. Salvalaglio, “On the conformational complexity in the early stages of metal-organic framework self- assembly”. UK MOF 2018, University of Southampton, UK (9-10 April 2018). Oral presentation.
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- L. Kollias, D.C. Cantu, R. Rousseau, V.-A. Glezakou, M. Salvalaglio, “Assessing the role of ions on the formation of crystal-like building units of a metal-organic framework”, Materials and Molecular Modelling Hub Conference and User Meeting, University College London, UK (5-7 Sept 2018). Poster presentation.
- L. Kollias, D.C. Cantu, R. Rousseau, V.-A. Glezakou, M. Salvalaglio, “Understanding the free energy landscape in the early stages of MOF nucleation”, American Chemical Society National Meeting and Exposition, (31 March - 4 April 2019) Orlando, FL, USA. Oral presentation.
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Awards

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Abstract

Metal-Organic Frameworks (MOFs) constitute a class of novel hierarchical materials. MOFs are strong candidates in several applications including catalysis, carbon capture and storage and drug delivery. Past and current research on MOFs has utilised several experimental techniques. Nevertheless, a thorough investigation of MOF synthesis requires molecular simulations in order to provide information at length scales unreachable scale for experimental techniques and thus understand the mechanisms of assembly. The purpose of this research project is to study the formation of the MIL-101(Cr) structural building units (SBU) using Molecular Dynamics. A bottom-up approach of assembly is followed starting from the evaluation of half-SBU conformational flexibility in solution. SBU association-dissociation and rearrangement are then assessed leading to a connection between synthesis conditions and the configuration of small scale adducts at an early stage of assembly. In particular the effect of ions (Na^+ , F^-) and solvent (water, DMF) on promoting crystal-like configurations of SBUs is investigated. The enthalpic and entropic contributions are also calculated under various conditions leading to a better understanding on the thermostructural behaviour of the conformers. Finally, the collective behaviour of SBUs during assembly is analysed through simulations in which numerous half-SBUs interact and form clusters. In summary, this work provides a molecular-level understanding to the experimental finding that ions favour crystallinity in MOFs. Ultimately, the conformational complexity in early stages of MOF self-assembly leads to the conclusion that guest molecules that affect the entropic landscape of MOF precursors are key in order to regulate the extent of defects in a MOF cluster.

Motivation and Impact

Metal-Organic Frameworks are novel hierarchical materials studied mainly in the last couple of decades. There is an increased interest in MOFs as these are strong candidates for numerous applications due to their large porosity and surface area that make them excellent for separation and storage processes. Current front-runners in numerous industrial, biomedical and green chemistry applications, MOFs, have the potential to be a prominent multifunctional material of the current and future industry. Nevertheless, robustness and durability are typical issues, when these are exposed to industrial conditions of high temperature and pressure. The purpose of this project is to investigate the self-assembly of these materials at the molecular-level and consequently improve our current understanding of the mechanisms of this process. In this way, certain characteristics (e.g. rigidity, crystallinity) of the final product can be fine-tuned, while the high modification freedom of MOFs should facilitate the choice of pathway and parameters during production. In this research, self-assembly of a representative MOF, MIL-101(Cr), from its constituents is investigated. The selected candidate shows interest in applications and data on kinetics are available for validation of results with the current literature. At last, this work makes important leap in manufacturing MOFs that are robust for industrial applications through understanding the origins of defects and consequently regulate their occurrence through the introduction of guest species.

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Chapter 1

Introduction

This chapter aims to introduce the reader to the world of hierarchical materials (section 1.1) also providing relevant examples (section 1.1.2). Metal-Organic Frameworks (section 1.2) are hierarchical materials studied in more detail as they are the focus of this work. The structure (section 1.2.2), development (section 1.2.3), applications (section 1.2.4) and characteristics (section 1.2.5) of Metal-Organic Frameworks are discussed in further detail. Furthermore, a particular Metal-Organic Framework, MIL-101(Cr), is presented in more detail as it is the system of particular interest in this work. At first, general information about MIL-101(Cr) is available in section 1.3.1. The various synthesis procedures are discussed in section 1.3.2. Its structure and connection with the equilibrium product of synthesis are explained in sections 1.3.3 and 1.3.4. Section 1.3.5 includes applications where MIL-101(Cr) is currently used. Furthermore, current commercial applications where Metal-Organic Frameworks are used overall are discussed in section 1.4. The remaining part of the introduction is focused on recent efforts to study the early stages of Metal-Organic Framework self-assembly as this is the main scope of this work. In this context, an overview of experimental works on the early stages of Metal-Organic Framework self-assembly is provided in section 1.5. At last, this introductory chapter closes with a review of computational studies targeted on modelling the self-assembly of Metal-Organic Frameworks along with emerging opportunities for further research that are relevant to this work (section 1.6).

1.1 Hierarchical Materials

1.1.1 General Information

Numerous hierarchical biomaterials exist in the human body. In the very small scale, the cell membrane is hierarchically structured [1]. At a bigger scale, tendon, intestine, intervertebral disc, articular cartilage and soft tissues such as skin and liver follow the same assembly process [1], [2]. Also, nacre, wood and shark skin share the same characteristics [1], [2]. At last, plants follow hierarchy in assembly from cellulose to their tissues [3].

There is an increased interest in hierarchical (or hierarchically structured) materials as they exhibit the same structure across multiple size scales [4]. Self-assembly has a specific form in each scale; hence scale-up follows a highly organised structure [5].

These novel compounds have raised special interest as their purpose is to enhance current and future processes. In this broad category, compounds with structural hierarchy are investigated for their applicability and effectiveness in various fields. These might be natural or made in the laboratory [4]. Current and potential applications include gas and energy storage, catalysis, separations, biomedicine and development of materials that can be used as chemical sensors or magnets [6]–[8].

1.1.2 Examples of Hierarchical Materials

Prominent examples in this category are Zeolites-based compounds and Metal-Organic Frameworks (MOFs). Zeolites can be found in nature as well. Another name that is less frequently used for MOFs is also Porous Coordination Polymers (PCPs) [9]. The ability to tune the level of porosity is one of the main reasons that highlighted the importance of hierarchical in a range of processes [7]. Zeolites are extensively used today due to their porosity and robustness in industrial processes [10]–[12]. Nevertheless, their potential successors and competitors, MOFs, offer larger surface area and porosity for a range of processes [10]–[13]. MOFs will be discussed in the following section as they are the focus of this work.

1.2 Metal-Organic Frameworks

1.2.1 General Information

In this research work, Metal-Organic Frameworks are investigated. Highly coordinated flexible compounds, MOFs, have increased interest due to their unique characteristics. These consist of metal clusters linked by organic ligands in a polymeric form. Research on how to manipulate those is very important as it will increase their applicability. The reason for this level of control is their versatile hybrid nature. The combination of inorganic and organic chemistry on a single crystal renders them highly tuneable and ubiquitous. The available combinations of inorganic ions or clusters and organic ligands are plentiful [14]. Numerous different interactions are possible; hence there is a plethora of MOFs. Each one has its own specific

attributes that result in different capabilities and application focus. This results in freedom of choice in order to specify a MOF with the desired characteristics for a process of interest.

Although it is still debatable to find one and only definition of a MOF, it can be conceptually thought of as a framework consisting of “nodes” linked by “rods” as in Ref. [15]. The “nodes” are the metal clusters and the “rods” are the organic ligands that connect the structure and produce a repeatable form of an organic-inorganic hybrid polymer.

Generally MOFs exhibit a higher modification freedom than zeolites as they show easier structure manipulation [16], [17]. These compounds have been attracting interest in the last couple of decades [18]–[20]. The combinations of inorganic ions or clusters and organic ligands available are plentiful [14]. MOFs collectively exhibit very high surface area and controllable porosity [21].

1.2.2 Structure and Synthesis

MOFs mainly consist of centres of transition metals forming bonds with organic ligands coordinated by either oxygen or nitrogen atoms [22], [23]. Transition metals can potentially provide a MOF with redox, magnetic and catalytic capabilities [23]. The choice of a transition metal and its oxidation state can result in different coordination number between the metal cluster and the ligands that are connected on that [24]. This gives the possibility of having different geometries. These can be linear, square planar or pyramidal, tetrahedral, T or Y shaped, trigonal, pentagonal etc. [24]. Most of the transition metals are cations. Therefore, anionic acids should be used in order for the overall charge of the MOF to be neutral [24]. A well-known example of an anionic acid is 1,4 benzene dicarboxylic acid (BDC) [25]. This acid offers rigidity, plethora of coordination geometries and the creation of large pores in the MOF [25]. Nevertheless, a recent study by Aguirre-Diaz et al. [26] has shown that other metals such as Indium and Gallium can be used in order to form MOFs.

Pore size determination is possible through combining specific selections for the metal cluster, the ligand and the medium [9]. The “building block approach” is a common strategy in order to make these choices. Metal clusters are interconnected by organic linkers that are responsible for the formation of the network [9], [27]. It should be noted that there exist complex frameworks with more than six building blocks in coordination [28]–[31].

Widely used methods to synthesize MOFs in the laboratory include impregnation, solid grinding, infiltration, co-precipitation, encapsulation [32]. Synthesis takes place either at room or higher temperature that can be achieved through heating with microwaves, electricity. Electrochemistry, mechanochemistry and sonochemistry (ultrasound) have also been introduced to the range of available techniques for MOF synthesis [33], [34]. The reaction conditions can be distinguished in solvothermal / hydrothermal and non-solvothermal [33]–[35]. Solvothermal conditions refer to reactions occurring inside an autoclave above boiling point of the solvent and under autogenous pressure (generated inside the vessel) [34]. Hydrothermal are solvothermal conditions when the solvent used is water. Non-solvothermal conditions refer to reactions below the boiling point of the solvent [34]. Solvothermal conditions are more frequently used in MOFs [36], [37]. However, this can affect stability and coordination of the organic linkers [37]. The most common solvents used include amides such as dimethylformamide (DMF) and diethyl formamide (DEF), alcohols such as methanol (MeOH) and ethanol (EtOH) and finally water (H₂O). In a lot of cases a fraction of those is mixed with terephthalic acid (H₂BDC) as in the synthesis of MIL-101(Cr) [38].

1.2.3 Timeline of Development

The term Metal-Organic Framework or MOF became popular following the work of Yaghi et al. [39]. Two of the very first prominent MOFs were synthesized in 1999 by Li et al. [40] and Chui et al. [41]. These MOFs are the MOF-5 and HKUST-1 (Hong Kong University of Science and Technology). A blossom of new MOFs was apparent in 2000s with the invention of UiO-66 [42], ZIF-8 [43], MOF-74 [44], MIL-100 (Cr), MIL-101(Cr) [38], MIL-53 [45] among others. Due to interest in applications as well as modification and combination possibilities there are numerous MOFs nowadays. A recent publication by Moghadam et al. [46] estimates that there are 70,000 structures in the Crystal Structural Database (CSD) [47]. Based on that, the computation ready experimental (CoRE) MOF database has been created in order to provide the research community with properties and atomic coordinates of 4,700 structures [48].

1.2.4 Applications

The range of materials manufacturing and processes where MOFs have a significant role follows a constant expansion due to current developments in the field. These applications include heterogeneous catalysis [49]–[55] and photocatalysis [56], [57]. Furthermore, they can be used for separations of benzene derivatives, such as xylenes [58]. Another interesting aspect is gas and liquid storage and adsorption; especially H_2 [59], [60], CH_4 [61], [62], CO_2 [63], MeOH, H_2S [64] and H_2O [65]. Removal of H_2S and CO_2 impurities in natural gas streams can be achieved using MOFs [64]. Furthermore, MOFs can be used in other energy-related applications such as in electrochemical devices [66], [67], as semi-conductors [68] and for magnetic coating [49], [66]. Also, MOFs are used as chemical and biological sensors [14]. Filtration and sequestration of gaseous compounds leading to air purification can be achieved with MOFs [69], [70] as well as water desalination [71]. At last, MOFs are very prominent for biomedical applications [17].

1.2.5 Characteristics

At this point, it should be noted that stability of MOFs under different temperature and pressure conditions is essential in order to increase robustness when used in industrial processes [55], [65]. Increased stability ensures difficulty in degradation [72]. More precisely, stability under different chemical, thermal, hydrothermal and mechanical conditions need to be tested before selecting a MOF for a specific process. It is still difficult to find a compound that embodies all these characteristics [72]. Moreover, interactions with solvents and co-solvents should be assessed in order to determine if there is strong binding between the metal clusters and solvent molecules [73]. This can be achieved through gas adsorption calorimetry as suggested in the work of Wu and Navrotsky [73]. Structural transformations leading to loss of order can be induced by adsorption of solvents [74]. Furthermore, solvents or co-solvents affect various properties of a MOF, such as elasticity, photochemical and electrical properties [74]. A prominent example of solvent interaction is DMF (N,N-dimethylformamide) with ZIF-8 (Zeolitic Imidazolate Framework) that results in increased stiffness for the MOF [75].

Mechanical stability is important in many industrial processes [72]. Crystal structure and porosity should be maintained under mechanical stress. Industrial conditions mean that the material should withstand pressure in the order of Mbar

without collapsing [75]. Attributes of MOFs are directly affected by pressure, for instance, a pressure increase by a few Mbar can yield the same results as increasing temperature for several hundred K [76]. Consequently, crystal structure and high level of order are converted to an amorphous structure under these conditions. High porosity means low density that is caused by longer carbon chain in the organic linkers of these molecules [77]. This is the reason for the fragility of MOFs under industrial pressure values. Therefore, increasing mechanical stability has a cost in porosity [78]. Zeolites are more stable in all the aforementioned areas when compared to MOFs, but MOFs exhibit larger pores that is a significant advantage for separations and storage [79]. The most stable MOFs according to Stock and Biswas [34] are: MIL-101(Cr), MIL-100 (Cr) [38], MIL-125 [80], CAU-1 [81], CPO-27 (Ni) [82], UiO-66 [42], [83], ZIF-8 [43].

1.3 MIL-101(Cr)

1.3.1 General Information

In this study, the early stages of MIL-101(Cr) synthesis are investigated at the molecular level. MIL-101(Cr) provides a stable structure under thermochemical stress in numerous solvents along with a large surface area [84]. Also, it is considered as a very stable MOF in general [85]. The structure remains intact even in boiling water [51][86]. At atmospheric air it remains unchanged for months [38]. Thermogravimetric analysis in air reveals that MIL-101(Cr) is stable up to 275 °C [38], [53].

1.3.2 Synthesis

MIL-101(Cr) has been synthesized by Férey et al. [38] and belongs to the class of MIL (Materials Institute Lavoisier) MOFs [87]. The characteristics that have given MIL-101 the ability to enhance many processes. More precisely, its pore sizes range from 29 to 34 Å and its surface area is 5900 m²/g [38]. In the laboratory it is synthesized through a hydrothermal reaction between terephthalic acid-H₂BDC, where BDC stands for benzene dicarboxylate [53], chromium (III) nitrate nonahydrate-Cr(NO₃)₃·9H₂O, hydrofluoric acid-HF and H₂O at 220 °C for 8 hours. The product of this reaction is Cr₃F(H₂O)₂O[(O₂C)-C₆H₄-(CO₂)₃·nH₂O where the value of n is approximately 25. It should be noted that F can be replaced by OH in the previous formula when an HF-free synthesis route is selected. A more succinct way to write

the chemical formula of MIL-101 is $[\text{Cr}_3\text{O}(\text{H}_2\text{O})_2(\text{bdc})_3\text{X}]\cdot n\text{H}_2\text{O}$, where X is either F^- or NO_3^- or OH^- [88], [89]. In more detail, the positively charged $[\text{Cr}_3\text{O}(\text{bdc})_3]^+$ is balanced by the previously mentioned anions which coordinate to form the final MOF [88].

In a later study, Bromberg et al. [90] performed synthesis without adding hydrofluoric acid. They suggest two different methods for synthesis. The first one uses an oven for heating, while the second uses microwaves [90]. This method requires a significantly larger amount of water (a 300% increase compared with conventional synthesis as in reference [38]) and longer synthesis time (approximately 20 hours) to allow for crystal growth [84].

Leng et al. [84] carried out MIL-101 synthesis without the addition of solvent or hydrofluoric using a solid-phase reaction scheme. More elaborately, linkers and metal clusters are mixed and ground for 30 minutes before the mixture was placed in an autoclave at 220 °C for 4 hours. The final MOF crystal size was appreciably smaller (40-200 nm) than the one obtained by the method of Bromberg et al. [90] (300-500 nm). Nevertheless, MIL-101 formed using this method presented better catalytic activity (they tested MIL-101 formed through different synthesis routes for the oxidation of cyclohexene) than the hydrofluoric acid (HF) [38] and solvent [90] routes as more chromium sites were acting as catalyst sites due to the smaller crystal size.

Rallapalli et al. [91] also synthesized MIL-101 without adding HF and they used deionised water instead. They explain that MIL-101 can be successfully synthesized using acetic ($\text{C}_2\text{H}_4\text{O}_2$) or perfluorobenzoic acid (PBFA, $\text{C}_7\text{HF}_5\text{O}_2$) instead of HF. These resulted in products with similar properties as the one obtained via the HF route.

Another synthesis route includes the use of microwave radiation as described by Jhung et al. [92]. This leads to significantly smaller duration of synthesis (about 1 hour) at a slightly smaller temperature (483 K) and microwave radiation of 600 W in presence of HF [92]. The resulting crystals are smaller in size than the ones obtained using the hydrothermal synthesis route (as in reference [38]), but their size can be controlled through adjusting the overall duration of the crystallization process [92]. The final product has similar physical and chemical properties as the one obtained through the hydrothermal route. Additionally, an HF-free route is available as the latter is replaced by aqueous sodium hydroxide [93].

Dry-gel conversion is another synthesis route that can be followed in order to form MIL-101. This method has certain advantages as it produces less waste, the reaction volume is relatively small and the product yield is relatively high as explained

by Bhattacharjee et al. [93]. Kim et al. [94] used this route in order to synthesize MIL-101. They mixed metal-containing precursors with terephthalate linkers and then ground this mixture. This was put in an autoclave along with HF and water for 10 hours at 493 K. Afterwards, the product was washed with distilled water and then put in an oven to dry. This process led to a highly porous material with no recrystallized terephthalate linkers and a relatively high surface area [93], [94].

Liu et al. [95] used zeolite seeds in order to accelerate the crystallization of certain MOFs, including MIL-101. These seeds need to be added only in very small amounts and the resulting MIL-101 has similar pore volume and slightly smaller average pore size compared to MIL-101 synthesized using the conventional hydrothermal method [95].

At last, there exist synthesis procedures that use various modulators in order to avoid the use of HF. More elaborately, Ren et al. [96] used formic acid as a modulator in MIL-101 synthesis and they obtained high product yields in a reproducible manner. Additionally, Zhao et al. [97] tested various modulators and their effect on the MIL-101 synthesis process. They concluded that nitric acid (HNO_3) results in higher product yields than HF while the surface area is slightly smaller than the one in the MIL-101 obtained using HF. Also, the use of acetic acid ($\text{C}_2\text{H}_4\text{O}_2$) instead of HF allows for smaller synthesis temperatures, but this results in smaller product yield and surface area [97].

1.3.3 Structure

MIL-101 is a chromium terephthalate MOF with a cubic structure [92]. Its mesopores feature an augmented zeotype (or zeolite-like as explained in reference [98]) architecture with Mobil Thirty-Nine (MTN) topology (the name is due to the origin of this topology that is zeolite ZSM-39 [99]–[101]) as stated in references [38], [92]. Moreover, it is a hybrid polymer that consists of Cr_3O clusters with triangular shape. These are interconnected by linear terephthalate linkers [102].

In its physical form, MIL-101 is a green powder with a crystal structure [38]. This solid material contains several impurities both within and outside its pores. These are terephthalate linkers which have not been incorporated in the crystal; hence they remain after synthesis [93]. Therefore, post-synthesis treatment should be followed to remove these impurities [93]. This includes filtration, further washing water with organic solvents (ethanol, DMF) and aqueous solution of ammonium fluoride [93]. The crystal size of MIL-101 ranges from 70-150 nm [32]. The cell volume is

approximately 702,000 Å³ [38], [53]. The void space is enclosed in pentagonal and hexagonal windows [92]. Its structure is stable as it remains unaffected in air, organic solvents and even in boiling water [51], [103].

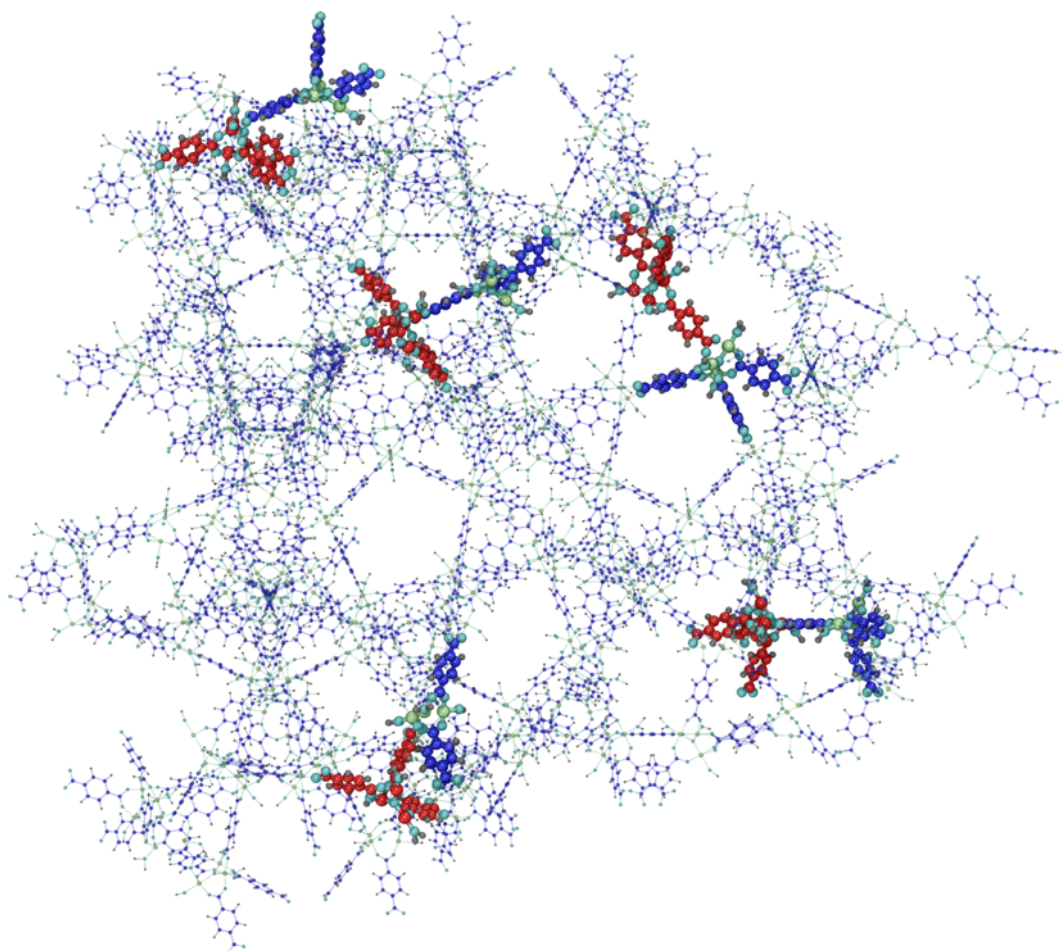


Figure 1-1. A cluster of MIL-101(Cr) consisting of half-Secondary Building Units. Colour code – Cr: lime, O: cyan, H: grey, C: blue and red. Two colours are used for carbon atoms as a means to distinguish between different half-SBUs interacting in the crystal lattice.

The building block is geometrically modelled as a super tetrahedron (ST) in order to agree with the ratio of metal centres against terephthalate linkers found experimentally. This consists of chromium (III) oxide octahedral clusters and 1,4 BDC terephthalate linkers [104], [105]. More precisely, the three octahedrally coordinated chromium atoms are bound to a central oxygen atom. These are Cr₃O trimers [106]. Terephthalate linkers contain eight carbon, four oxygen and four hydrogen atoms [107]. Six of the carbon atoms are in an aromatic ring formation. These terephthalates are benzene dicarboxylate linkers and they are the edges of the super tetrahedra [98],

[107]. It should be mentioned that the super tetrahedra share their corners in the MIL-101 lattice [106].

There exist two types of pores in the MIL-101 structure. The small pores are formed of 20 super tetrahedra and this leads to a pore diameter of approximately 29 Å. The large pores consist of 28 super tetrahedra; hence their diameter is about 34 Å [89], [98]. These are accessible through separate windows which have a microporous structure [89]. The windows of the smaller pores are pentagonal with diameter of 12 Å [89], [92], [97]. The windows of the larger pores are pentagonal and hexagonal with diameters of 16 Å and 14.5 Å respectively [97]. The Langmuir surface area of MIL-101 is equal to 5,900 m²/g with an uncertainty interval of 300 m²/g; hence this MOF is an excellent candidate for adsorption applications [92], [98]. The surface area calculated using the Brunauer-Emmett-Teller (BET) method is 4,100 m²/g with an uncertainty of 200 m²/g around this value [100]. Ultimately, a graphical representation of a MIL-101(Cr) cluster is given in Figure 1-1.

1.3.4 Connection with MIL-53

MIL-101 is the kinetically favoured product of synthesis. For longer synthesis times, the thermodynamically favoured product, MIL-53 [108], is formed [109]. In further detail, MIL-101 structure is degraded after staying for longer times under synthesis conditions. Its constituents are decomposed at first and then they reorganise into forming a new MOF that is MIL-53 [110]. Millange et al. [108] report that the MIL-53 synthesis is carried out in an autoclave at 493 K for 72 hours that is a considerably longer period compared with MIL-101.

MIL-53 has an orthorhombic structure with considerably smaller pore size and volume than MIL-101 [110]. As stated by Khan and Jung [110], the pore volumes and sizes are 0.6 mL/g and 8.5 Å for MIL-53, while for MIL-101 the respective values are 1.9 mL/g and 29-34 Å [110], [111]. The chemical formula of MIL-53 is Cr(OH)[C₆H₄(CO₂)₂] $\cdot$ nH₂O. MIL-53 has one-dimensional (1D) pores, while MIL-101 has three-dimensional (3D) pores [112]. MIL-101 is structured from triangular metal-containing clusters, while MIL-53 is formed out of infinite chains of metal-containing octahedra, which share their corners, and terephthalate linkers [113], [114].

Another interesting feature of MIL-53 is that it presents breathing effects that lead to expansion and contraction of pores when external stimuli are applied (e.g. a change in conditions such as temperature and pressure or interactions with guest molecules) [115], [116]. Therefore, MIL-53 can interconvert between narrow and large

pore structures in a reversible manner [116], [117]. This is mainly due to a change of the hydrogen-bonding network upon interaction with water molecules [45], [118]. In contrast, MIL-101 has a rigid framework that does not present breathing effects mainly due to its pentagonal window structure [115].

Ultimately, the duration of synthesis is very important as it determines which one of these two MOFs (MIL-101 and MIL-53) will eventually form. This is an example of how thermodynamic and kinetic factors can promote different structures with an appreciable effect on the properties of the final MOF. This observation highlights the intrinsic complexity of MOF synthesis as a number of different structures emerges from the same setup; hence a thorough understanding of the synthesis mechanism is needed to understand the origins of the conformational complexity associated with MOF synthesis.

1.3.5 Applications

MIL-101(Cr) has a significant role in hydrogen storage [119], water purification [86], [120], gas (CH_4 , CO_2) adsorption [106], [121] to name a few. In the last case, compounds that contain nitrogen can be readily adsorbed due to its interaction with chromium cations. This makes it a very good adsorbent in the purification of diesel fuel that has very low sulphur content [102].

Catalysis is one of the most common applications of MIL-101(Cr) due to its large pores [90]. Properly treated MIL-101(Cr), either with Pd or Au or Phosphotungstic acid (PTA) can be used as a catalyst. MIL-101(Cr) treated with PTA is highly durable as it can be reused several times without significant losses in performance and effectiveness according to Blomberg et al. [90]. Also it can be easily regenerated using acetone [102]. Modification freedom in the development of MOFs enables them to be adjusted properly in order to serve as solid catalysts in various applications [52]. Also, MIL-101(Cr) is used in the hydrogenation of olefins especially when it is combined with Pd (Pd@MIL-101(Cr)). This is effective, durable and the amount of metal loss per cycle is extremely low. Alkenes, alkynes, aromatics, ketones and compounds that contain nitrogen can be hydrogenated even with a conversion rate that is almost 100 % [122]. Also, polyoxometalate anions (POM) can fill the large pores of MIL-101(Cr) following the addition of phosphotungstic acid during synthesis. The product can be used as an oxidation catalyst [123]. Moreover, it can be used as a stationary phase in the separation of xylene isomers and ethylbenzene using novel

techniques such as gas chromatography (GC). These compounds are important for the industry, the environment and the analysis of air quality and blood [124].

Finally, drug storage and transport are very important fields where MIL-101(Cr) is a strong candidate. There it challenges conventional chemicals and other MOFs [17], [125]. Apart from the toxicity of chromium that renders it non-biocompatible [125], this MOF has large mesoporous windows with a diameter between 25 and 34 Å that can be easily accessed through micropores with a diameter ranging from 5 to 16 Å [17]. Also, its pore volumes of 2 cm³/g and the large BET surface area of 2100-4400 m²/g ensure increased amounts of drugs can be loaded on a single molecule. Ibuprofen is a prominent example drug molecule that can be encapsulated in MIL-101(Cr). Furthermore, there are several unsaturated chromium sites (up to 3 mmol/g) that can serve as Lewis acid sites for catalytic reactions [126]. Its overall performance for separation from solution outperforms conventional chemical separators as well as numerous MOFs [17], [125]. At last, structural stability in an aqueous solvent is important when selecting materials suitable for biomedical applications [17].

1.4 Commercial applications of MOFs

The industrial applications of MOFs as of today are rather limited due to their lack of robustness as previously mentioned [10]–[12]. Also, the limited number of commercially available MOFs as well as production costs do not allow for the extensive use of MOFs for large scale applications [127]. Furthermore, the use of toxic chemicals (such as hydrofluoric acid) increases safety concerns in MOF manufacturing [127]. Consequently, environmental-friendly or “green” synthesis routes are investigated [91], [128], [129]. Furthermore, production of MOFs at a large scale is cost-intensive as sealed vessels, heating for several days, the use of metals, organic solvents and linkers as well as post-synthesis purification stages are factors that increase the manufacturing cost of these materials [130], [131]. Also, downstream processes, such as separation of small MOF particles at low concentration from a highly dilute solution with similar particle and solvent density, are difficult at a large scale [132].

Nevertheless, MOFs have already found commercial uses; hence they have progressed past the laboratory experimentation stage. In 2017, Rubio-Martinez et al. [132] conducted a review on targeting production of MOFs for industrial applications. According to this review, the first products based on MOFs were made commercially

available by MOF Technologies and NuMat Technologies in 2016 [132]. In more detail, MOF technologies, established in 2012, uses a patented solvent-free process, invented in Queen's University Belfast, in order to manufacture MOFs using mechanochemistry [133]. Their first product was a MOF based micro-adsorbent that decelerated fruit ripening; hence extending storage life. This product was made available by Decco Worldwide Post-Harvest Holdings, a fruit and vegetable supplier [130], [132], [134]. Nevertheless, it should be noted that the first patent concerning MOFs for industrial applications was filed about two decades before the first application (in 1995). This was assigned to O. M. Yaghi and NALCO chemical company and it was concerned with purification of fluid materials [135].

NuMat Technologies, founded in 2013 from researchers at Northwestern University [136], invented a MOF based product that can store toxic gases (e.g. arsine) for the electronic industry [132]. MOFapps, also founded in 2013, is another company that uses MOFs for gas storage, industrial cooling systems and healthcare [134]. They have tested MOFs for adsorbing natural gas from vehicles [132]. Another company that uses MOFs for gas storage, healthcare applications is Atomis that was founded by researchers in Kyoto University [134]. They use MOFs to deliver gases such as nitric oxide to various organs in order to enhance medical treatment of various diseases [134].

Sigma-Aldrich is a well-established company that is also active within the MOF community. In more detail, the company distributes MOFs manufactured at BASF to several research groups at universities and laboratories for research purposes [132]. ACSYNAM is a company founded from researchers at McGill University that manufactures MOFs used in fuel components targeted for spacecraft propulsion [134]. MOFGen, founded in 2013 from researchers at the University of St Andrews, work on the development of MOFs for the healthcare industry including MOFs to be used in medical devices [132]. In more detail, they use MOFs to release nitric oxide that has antimicrobial properties [137]. Furthermore, Inmondo Tech, founded by researchers at Georgia Tech, is another company dedicated to scale up production of MOFs at an affordable cost [138].

At last, a Horizon 2020 project, ProDIA, was granted by the European Commission [132], [134]. The scope of this project is to develop methods for production of nanoporous materials that can be used for adsorption applications at an industrial scale [134].

1.5 Experimental works on the early stages of MOF self-assembly

Recently, numerous experimental studies examined the early stages of MOF synthesis. Lee et al. [139] and Taddei [140] focused on regulating the presence of defects in the final MOF by carefully engineering the early stages of synthesis as these defects are linked with the mechanical stability of MOFs. Considerable efforts on this aspect can be seen lately [72], [140]–[143]

In situ spectroscopy as well as nuclear magnetic resonance (NMR) methods were employed to study the early stages of synthesis. Férey et al. [144] used in situ NMR methods to monitor the evolution of MOF synthesis. They identified neutral unstable and soluble prenucleation building units (PNBUs). These are structurally similar with subsequently formed SBUs. PNBUs are critical complexes because nucleation proceeds immediately after these precursors are formed and reach a critical concentration corresponding to supersaturation. At that point, they start to aggregate in order to form the MOF structure [144]. They suggest a synthesis mechanism for MIL MOFs (specifically MIL-96, MIL-100 and MIL-110) that starts from the formation of SBU precursors, then proceeds with their nucleation followed by crystal growth and concludes with a thermodynamic equilibrium of dissolution and recrystallisation processes [144]. It should be noted that the half-SBUs in the current work are PNBUs as they are precursors of SBUs in agreement with reference [144]. At last, SBUs result from unstable precursors (half-SBUs) that are present in the solution before aggregation [144], [145]. This work leads to the conclusion that interactions between half-SBUs are key to determine the structure of subsequent SBUs incorporated in the final MOF.

Haouas et al. [146] employed in situ NMR, ex situ X-ray diffraction (XRD) and scanning electron microscopy (SEM) in order to examine the formation of MIL MOFs (MIL-96, MIL-100, MIL-110). They conclude that the nature of the soluble MOF precursors highly affects the final MOF structure; hence understanding the behaviour of building units during the early stages leads to prediction of the final MOF properties. In a subsequent review by Haouas [145], PNBUs are found experimentally and they have a similar structure to the SBUs. Solvent effects have a considerable impact on the final MOF, while temperature affects the stability and reactivity of building units.

In another study, Xu et al. [147] used in situ pair distribution function analysis to investigate the synthesis of UiO-66. They experimentally observed SBUs and they

suggest a mechanism where SBUs are the building blocks of clusters that combine upon heating and aggregate to a lattice that further rearranges to form the final MOF. Nevertheless, the question of how SBUs and their clusters are formed remains open. Therefore, understanding the interactions that lead to SBUs and their clusters should provide significant insight into MOF synthesis.

Furthermore, Wu et al. [148] used in situ XRD to observe the time evolution of MOF-5 crystallisation. They also identify metastable intermediate phases involving MOF precursors that is structurally different from the final MOF; hence understanding the origins of this complexity during the early stages is important in order to model MOF synthesis.

Embrechts et al. [149] used in situ Raman and Fourier-transform infrared (FTIR) spectroscopy to monitor the synthesis of MIL-53 over time. It should be noted that MIL-53 is the thermodynamic product of the synthesis where MIL-101 is the kinetic product [109], [150]. They obtained kinetic profiles through which they identified the rearrangement of PNBUs to be the rate-limiting step of synthesis. Also, they observed nucleation before the emergence of the final MOF structure. Consequently, assessing the behaviour of MOF precursors is important as their rearrangement in solution, a result of their flexibility, is a process relevant to the kinetics of MOF synthesis [149]. Also, Goesten et al. [151] conducted in situ NMR measurements and they found that DMF promotes the formation of NH₂-MIL-101(AI) over NH₂-MIL-53. In more detail, MIL-101 is the entropically, thermodynamically and kinetically favoured structure in DMF. Therefore, this solvent should be further investigated in order to provide a thorough understanding of the nature of interactions during the formation of MIL-101.

Wagia et al. [152] used in situ techniques to experimentally investigate the crystal growth of another MOF (CdIF-4). They also identified MOF precursors as critical species that once formed, nucleation is initiated. Lee et al. [139] studied the crystallisation of UiO-66 and In-MIL-68 using several experimental methods (XRD, FTIR, SEM amongst others). They imply that stereo-selectivity involving linker interactions with the metal-centre directs the formation of SBUs. They also found that crystallinity is linked with the number of linkers attached to the metal centre of the SBU when aggregation occurs. Hassan et al. suggest that investigating the behaviour and formation of building units is key to the rational design of MOFs with favourable characteristics for potential applications [153].

At last, the recent comprehensive review by Van Vleet et al. [154] is focused on collectively discussing both experimental and computational efforts on understanding and modelling MOF synthesis. The studies discussed above support the hypothesis of classical MOF nucleation involving SBUs as intermediate species [154]. Nevertheless, there are works supporting the hypothesis of nonclassical MOF nucleation proceeding through formation of amorphous clusters [154]. Therefore, a mechanistic understanding of the early stages should conclude on the mechanism of nucleation under various conditions.

Furthermore, they suggest that nucleation and early stages of crystal growth are very important steps towards MOF synthesis. Nevertheless, there is a lack of understanding those processes at the molecular level. In more detail, there is limited knowledge of the structures that dominate during these early stages of synthesis [154]. Also, they suggest that systematic studies that can be generalised for a large number of MOFs should be conducted in order to understand how synthesis conditions and composition affect the final MOF [154]. Therefore, a mechanistic understanding of interactions between MOF building blocks under various conditions and compositions should provide appreciable insight into the intrinsically complex nature of MOF synthesis.

1.6 Computational works on MOF self-assembly

In recent years, MOF computational studies are used in two separate fields. The first involves the modelling of processes in MOFs, such as adsorption [63], [155]–[158]. In this field, the research community has departed from the simulation of just one adsorption isotherm to investigating the effect of guest molecules and the mechanical behaviour of MOFs amongst others [159]. Furthermore, novel applications can be discovered through molecular modelling and current processes can be investigated further in areas difficult to study using conventional laboratory techniques. Examples include MOF-assisted protein folding [160], biofuel purification [67], hydrogen filtration [161], liquid separations [103]. Also, recent studies by Colón and Snurr [162], and Pulido et al. [163] have shown that structure and properties prediction is possible for evaluating the suitability of current and future compounds for different applications.

The other relevant field is modelling the synthesis of MOFs. This area is currently under development as there is limited computational research yet [107], [164]. The reason is the difficulty in modelling the behaviour of MOFs due to the

increased chemical complexity of metal-organic interactions. Along with novel experimental methods, such as in situ measurements, computational studies allow for a thorough understanding of the behaviour of complex materials at the molecular level [159]. For example, simulations can provide a mechanistic understanding of the role of ions that are commonly used in MOF synthesis [38], [99], [165], [166]. Furthermore, the effect of various conditions on the mechanical stability of a MOF can be assessed through simulation; hence guide experimentalists on the synthesis setup (e.g. temperature and pressure conditions, mixture composition, molecular identity of species present in solution) that favours crystallinity [167]. Following this approach, the extent of defects can be regulated and this is important as defects affect the mechanical stability [72], [143] of a MOF as stated previously.

Recently, a number of computational research studies on the assembly of complex materials, such as MOFs, have been established. These include studies on the assembly of metal nanoparticles [168], [169]. These works rely on implicit solvents and the use of Langevin dynamics to allow for a relatively large time step. They conclude that kinetic effects are pronounced during the assembly of large metal-ligand complexes; hence they lead to difficulties in studying the self-assembly of large complexes.

Also, the assembly of covalent organic frameworks were studied by Nguyen and Grünwald [170]. These are investigated following similar approaches as MOFs, but they are “metal-free”; hence the versatile physicochemical behaviour of metals is not present in these systems. Maula et al. [171] used Monte Carlo methods to study the assembly of COFs, while representing building blocks with a coarse-grained model. They conclude that the ability of certain ligands to bind to specific sites by incorporating appropriate functional groups in the building unit hinders the occurrence of polymorphism and that is key to form a specific framework.

In the work of Yoneya et al. [164], the self-assembly of a MOF is demonstrated through simulation incorporating dummy atoms and implicit solvent models in absence of an in-depth assessment of the validity of these approximations. The reason was that their work was devoted in the optimisation of simulation parameters. Also, the thermodynamics and kinetics of the self-assembly process were not evaluated.

Moreover, the self-assembly of MOF-2 [172] and MOF-2-like materials was investigated by Biswal and Kusalik [173]. The authors support the hypothesis for multiple metastable states arising during the self-assembly process. Nevertheless,

they rely on the trajectory of potential energy while the free energy landscape is not computed. Therefore, thermodynamics and kinetics of the process are not quantitatively assessed. In contrast, the current work provides estimates of the equilibrium probability as well as SBU dissociation constants considering relevant metastable states during the early stages of self-assembly. Furthermore, mechanistic insights on how to promote or hinder certain metastable states that can potentially evolve to defect formation on the final MOF are provided in the work described in this text.

Interestingly, Wells et al. [174] studied the early stages of MOF formation using Monte Carlo methods. Also, a new algorithm was developed in order to separate between the probability of forming clusters based on local geometry, and the Metropolis criterion used to accept Monte Carlo moves. This work involved unbiased molecular simulations that can capture the different phase of cobalt succinate MOFs [174]. The effect of composition with respect to the number of ligands present in solution is assessed in this study as it probes different phases of the MOF. Nevertheless, the effect of an alternate composition of the solution mixture involving different solvents as well as the role of ionic species at varying concentrations were not investigated in this work. Also, this implementation is not able to capture kinetically favoured intermediates involved in the formation of the final MOF that could potentially lead to an explanation of how defects form during synthesis.

Furthermore, the self-assembly of MOF-5 [40] has been studied by Colón et al. [175]. The system of dispersed building blocks in [175] is biased towards a specific transition pathway in order to simulate the formation of the final MOF. The approach followed in [175] suggests that there exist pathways to the formation of a MOF that are not investigated as this model results in a free energy profile that implies spontaneous transition from dispersed monomers to the final MOF; hence it did not capture metastable states visited during assembly from intermediate states [175]. Therefore, this model is not able to characterise the possible intermediate states that arise during the self-assembly of a MOF. This is in contrast with the work described in this text where the system is free to visit all relevant metastable states during the self-assembly process; hence a thermodynamic study involving both crystal-like and a plethora of possible noncrystal-like states is possible. At last, the effect of different solvents and various ions was not assessed. This does not explain why ions are typically used during MOF synthesis [38], [99], [165], [166].

At last, Cantu et al. [107] studied the formation mechanism of MIL-101(Cr) half-SBUs through simulations at the DFT level. Reactions that lead to the formation

of the metal centre and subsequent interactions with terephthalate linkers were modelled. Consequently, SBU formation rates were calculated and possible pathways for the formation of a half-SBU were identified. As a result, three half-SBU isomers emerge and these are studied in the current work. Ultimately, half-SBUs combine for MOF nucleation. Therefore, understanding interactions between them are key to regulate defects in the final MOF.

Following the aforementioned studies that focused on the early stages of the MOF self-assembly, the objectives of this work are introduced in this paragraph that brings the introduction section to a conclusion. Succinctly, the scope of this study is to understand how different factors affect the crystallinity during the early stages of MOF self-assembly. This is relevant as nucleation is considered the rate-limiting stage in the synthesis of numerous MOFs [107]. Consequently, understanding the nature of interactions during this stage should provide a mechanistic pathway on how to regulate the extent of defects in the final MOF. In this context, several factors should be evaluated. These include the presence of ions at varying concentrations, different solvents, tuning the composition of SBU isomers as well as synthesis conditions (temperature and pressure). This analysis should provide experimentalists with possible synthesis routes that regulate the extent of defects by promoting or obstructing the emergence of crystal-like conformers. Ultimately, the scope of this study is to evaluate the propensity of building units to form defects under different setups through understanding the free energy landscape along with entropic and enthalpic drivers relevant to the early stages of MOF self-assembly.

Chapter 2

Methods

This chapter is focused on the computational methods employed in order to model the early stages of synthesis of MIL-101(Cr). A brief introduction to why molecular modelling is chosen in this project (section 2.1) is presented first.

Molecular dynamics, the method employed in the project, is presented in detail, including equations of motion (section 2.2.1), calculation of forces (section 2.2.2), periodic boundary conditions (section 2.2.3), and the setup of a production simulation (section 2.2.4). Enhanced sampling methods follow (section 2.3) with a focus on metadynamics and the process of reweighing the bias constructed during the simulation. Also, the collective variables used in this work are discussed in section 2.3.3. The breakdown of the free energy profiles obtained with metadynamics into enthalpic and entropic contributions (section 2.4) follows.

Departing from the analysis of independent free energy profiles, the calculation of the equilibrium distribution of species from a set of simulations is explained in section 2.5. Convergence and error analysis associated with the molecular simulations conducted is discussed in section 2.6.

At last, the calculation of molecular properties is provided in section 2.7. This includes radial distribution functions, principal axes and corresponding moments of inertia and root-mean square deviations of atomic positions.

2.1 Molecular Modelling

The main focus of this work is the characterisation of MIL-101(Cr) self-assembly in solution. This process is investigated through molecular modelling techniques in order to study events that cannot be observed, described and therefore understood with conventional experimental techniques.

Computer simulation accompanies conventional experiments in a way to investigate events which are difficult to study in the laboratory. These experiments are either extremely time consuming or humans are not capable to see with laboratory equipment as they happen faster than the apparatus can read. Also, computer simulation enables the prediction of properties of materials under conditions in which experiments are difficult to perform, such as high temperatures and pressures.

Simulation methods based on molecular dynamics are chosen in this work in order to provide a mechanistic understanding of MIL-101(Cr) self-assembly at the molecular level. In this section, the principles of these methods is explained in further detail.

2.2 Molecular Dynamics

In this project, Molecular Dynamics (MD) is used extensively. In MD, the motion of particles representing atomic nuclei obeys the laws of classical mechanics [176]. That is an important assumption that decreases the cost of computations significantly and it is valid for a wide range of problems. MD is selected instead of other molecular modelling techniques such as Monte Carlo methods. Both MD and MC methods are discussed extensively in references [176], [177]. In MD, a system is simulated over time; hence calculations regarding kinetics can be performed in a straightforward manner. In MC, equilibrium properties [178] are calculated based on change in the internal structure of the system (such as rotation, translation of random molecules) [179] without inherently considering the time scales for transitions. Therefore, MC simulations are typically used for the calculation of the thermodynamic properties of the system [179].

The reason for selecting MD over MC is based on the particular MOF that is chosen for this study, MIL-101(Cr) [38]. It should be noted that MIL-101 [38] is the kinetically favoured product, while the thermodynamically favoured MIL-53 [108] is formed through MIL-101 when the synthesis proceeds for longer times [109], [150].

Therefore, MC simulations would be preferred to study the synthesis of MIL-53 (equilibrium product) [108]. MD simulations are better suited to investigate the synthesis of the kinetically favoured MIL-101 [38]. This would be very difficult with MC simulations, as MIL-53 [108] would be favoured by the synthesis conditions instead of MIL-101 [38]. In other words, assembly of building units would result to MIL-53 instead of MIL-101 [38].

2.2.1 Equations of Motion

The Hamiltonian is equal to the total energy and it is also sum of the kinetic and potential energy. The equations of motion can be derived by the partial derivatives of the Hamiltonian (H) with respect to positions and momenta [177], [180]:

$$\dot{q}_i = \frac{\partial}{\partial p_i} H, \quad \dot{p}_i = -\frac{\partial}{\partial q_i} H \quad (2.1a)$$

$$\dot{q}_i = \frac{p_i}{m_i}, \quad \dot{p}_i = -\nabla_{q_i} V = f_i \quad (2.1b)$$

where the total energy is conserved; hence $\dot{H} = 0$ [181]. Each atom, i , of the system possesses a mass m_i , a position represented by a vector in Cartesian coordinates, q_i and momentum, p_i . The potential energy is labelled V and the force on each atom, f_i . The dot represents a time derivative and ∇_{q_i} is the gradient with respect to q_i .

In MD, the equations of motion are solved iteratively, and then average properties are calculated until they converge.

The equations of motion are solved using the leapfrog integrator (LF) that is considered to be fast and sufficiently accurate for typical MD. It is a symplectic integrator; hence the volume of the phase space is conserved [182], [183] and that offers good energy conservation [184]. Furthermore, LF offers time-reversibility. This means that changing the sign of momenta will cause the system to follow the trajectory backwards as when the continuous equations of motion are used [177]. The LF algorithm calculates forces and positions at each time step and velocities at half time steps. Following this approach, the energy can be calculated at the full step and velocities are handled more efficiently than other schemes that do not use half-time steps (e.g. Verlet) [177]. The equations used by the leapfrog integrator to calculate positions and velocities over time are provided below,

$$\mathbf{v}\left(t + \frac{1}{2}\delta t\right) = \mathbf{v}\left(t - \frac{1}{2}\delta t\right) + \mathbf{a}(t)\delta t \quad (2.2a)$$

$$\mathbf{r}(t + \delta t) = \mathbf{r}(t) + \mathbf{v}\left(t + \frac{1}{2}\delta t\right)\delta t \quad (2.2b)$$

$$\mathbf{v}(t) = \frac{1}{2} \cdot \left(\mathbf{v}\left(t + \frac{1}{2}\delta t\right) + \mathbf{v}\left(t - \frac{1}{2}\delta t\right) \right) \quad (2.2c)$$

Where, t is the time and δt is the time step. Furthermore, $\mathbf{v}$ is the velocity, $\mathbf{a}$ the acceleration and $\mathbf{r}$ the position vector.

A velocity calculation at the full step is needed in order to evaluate the Hamiltonian of the system each step. The acceleration of every atom is evaluated through Newton's second law as the ratio between the force acting on it and its mass. Acceleration is then used to calculate velocities after a half step. These velocities can be used to evaluate positions at the full step. Forces are calculated again for the new positions and the whole process is iterated over a specified time step.

2.2.2 Calculation of Forces

The force acting on each atom is evaluated in order to calculate the acceleration at each time step as in equation 2.2a and thus propagate dynamics. The force on each atom is calculated as the gradient of the potential (equation 2.1b) that is a sum of intramolecular and intermolecular interactions involving the atom. The collection of these interactions between the atoms is called a force field [176], [177], [185]. The force field provides the relationship between the atomic coordinates and the potential energy of the system [186]. Databases for each force field are constructed and the appropriate choice should be made for the system under study [177]. Recent advances on the development of force fields suitable for MOF simulations are summarised in the work of Heinen and Dubbeldam [187].

The selected force field in the work of this thesis is the Optimised Potential for Liquid Simulations treating all atoms explicitly (OPLS-AA) that shows very good agreement for organic molecules in conventional organic liquid solvents (e.g. DMF). Therefore, the terephthalate linkers are modelled with this force field. The metal centre consists of chromium atoms which are not included in OPLS-AA. The modifications on the OPLS-AA force field have been implemented by the collaborators of the project and they discussed in detail in reference [188]. The force field is

validated through comparing classical and ab initio MD trajectories as described in the appendix (section A.1).

Potential energy ($V(\mathbf{R})$, $\mathbf{R}$: is the position vector) is calculated as the sum of bonded and non-bonded terms [185] as:

$$V(\mathbf{R}) = V_{bonded} + V_{non-bonded} + V_{other} \quad (2.3)$$

where,

$$V_{bonded} = \sum_i k_i \cdot (r_i - r_0)^2 + \sum_j k_j \cdot (\theta_j - \theta_0)^2 + \sum_{\phi} \sum_{n=1}^3 \frac{V_n^{\phi}}{2} \cdot (1 + \cos(n\phi + f_{\phi}n)) \quad (2.4)$$

where, subscripts i, j and ϕ are used for numbering purposes of bonds, angles and dihedral angles respectively. The k parameters are force constants. The r_0 and θ_0 terms are the equilibrium bond distance and angle respectively. The value of the dihedral angle is ϕ , V_n^{ϕ} are coefficients and $f_{\phi}n$ are phase angles [139, 140, 143–145].

$$V_{non-bonded} = \sum_i \sum_j f_{ij} \left(4\epsilon_{ij} \cdot \left(\frac{\sigma_{ij}^{12}}{r_{ij}^{12}} - \frac{\sigma_{ij}^6}{r_{ij}^6} \right) + \frac{q_i q_j e^2}{r_{ij}} \right) \quad (2.5a)$$

$$\sigma_{ij} = \sqrt{\sigma_{ii}\sigma_{jj}} \quad \epsilon_{ij} = \sqrt{\epsilon_{ii}\epsilon_{jj}} \quad (2.5b)$$

where i, j are non-bonded atoms. The first is a Lennard-Jones term, that describes attractive and repulsive Van der Waals interactions, and the second is a Coulombic term that is used for the electrostatic interactions. Parameters σ_{ij} are the Lennard-Jones radii and ϵ_{ij} are the well depths of the Lennard-Jones Potential. The partial charges of atoms i, j are q_i, q_j , their distance is r_{ij} and e is the elementary charge ($\sim 10^{-19} C$). The factor f_{ij} is 1 except from interactions that are separated by three bonds, where it is equal to 0.5.

2.2.3 Periodic Boundary Conditions

The simulation box where atoms are placed in a Molecular Dynamics (MD) setup has finite size. In a finite box, molecules on the surface will experience different forces than those in the centre of the box; hence the bulk solution is not properly simulated [177]. Therefore, periodic boundary conditions are applied in order to lift this size limitation and sample in the bulk of a solution by replicating the system of atoms in the box in three dimensions. When an atom leaves the box, then an image

of that atom enters the box from the opposite way. Interactions involving an atom i are calculated with the nearest image of another atom j . This can be obtained through the following expression (pseudo-code) for the x dimension (y and z dimensions are calculated in a similar fashion) [176], [177] ,

$$rx_{ij} = rx_{ij} - l \cdot \text{anint}\left(\frac{rx_{ij}}{l}\right) \quad (2.6)$$

Where rx_{ij} is the x component of the distance between i and j , l is the length of the box and anint is a function that returns the nearest integer. At last, an appropriately large simulation box to avoid artefacts is needed, so that interactions between the neighbouring systems are not smaller, in terms of distance, than the non-bonded interactions of the unit cell [185]. In all MD simulations, periodic boundary conditions are applied in three dimensions.

2.2.4 MD Production Simulations

Atoms are initialised in a box to avoid overlap [176]. The initial configuration is generated through energy minimisation. The purpose is that if the starting configuration is far from equilibrium, large forces yield numerical errors in the propagation of the dynamics, which lead to failures [185]. At last, atoms are assigned initial velocities according to a Maxwell-Boltzmann distribution [180].

The system consists of the MIL-101(Cr) half-SBU isomers (or monomers) and guest molecules such as solvent and ions. Solvent atoms are treated explicitly. The TIP3P model [192] is used for water as short simulations with the more computationally expensive TIP4P model [192] did not show appreciable differences. Also, ions (Na^+ , F^-) are added explicitly and they are treated with the OPLS-AA force field. Another solvent, N, N-dimethylformamide (DMF), is treated with the OPLS-AA force field and relevant parameters were obtained from the virtualchemistry.org chemical database [146, 147].

In the case of isolated monomers (Results, Chapter 3), atoms are initialised in a cubic box of a 4 nm edge, a box size that ensures neighbouring images are not affected by each other. The overall number of atoms in the system, including solute and solvent, is 6,500 when water is selected as the solvent, and 4,000 when DMF is chosen. These simulations were performed for 0.5 μs with a 2 fs time step using the leapfrog integrator. This time step is sufficient to include the fastest motions of the atoms while constraining hydrogen bond lengths with LINCS [195], a step non-iterative algorithm that resets bonds to their correct lengths. It is more stable and

efficient than the older SHAKE algorithm and it can be used in parallel computing (P-LINCS) [196].

Dimers (Results, Chapter 4) are placed in a cube of 5 nm edge. The size of the system is now increased to around 12,000 atoms for dimers in water. In DMF, this value is lowered to 8,000 atoms in the system. Simulations were performed for 7 μs in pure water, 1 μs in water with ions. In DMF, the simulation time is 4 μs for the AA dimer, 2.5 μs for AC and 2 μs for the rest of the dimers. For the assembly of numerous monomers (Results, Chapter 5) is simulated, the edge of the cubic box is equal to 20 nm. There are 132 monomers (MLA, MLB and MLC) in solution. ML stands for “Metal-Linker” complex and isomers are numbered as “A, B and C”. These follow two different initial distributions: (1) equiprobable (44 MLA, 44 MLB and 44 MLC) and (2) only MLA (132 MLA). The system of half-SBUs in water consists of 785,000 atoms, while in DMF it has 510,000 atoms overall. Simulations were performed for 0.1 μs .

Atoms are assigned with partial charges that describe the electron distribution in the half-SBUs and these are provided from the work of Cantu et al. [107]. The solvent is modelled to have point charges as well; hence electrostatic interactions between all species present are considered. The cut-off for non-bonded interactions is 10 Å, which is slightly more than $2.5 \cdot \sigma_{LJ}^{TIP3P}$ that is considered a good compromise between accuracy and speed [180], where $\sigma_{LJ}^{TIP3P} \approx 0.315 \text{ nm}$ [197].

Long range electrostatic interactions were treated with the Particle Mesh Ewald Scheme (PME) [198]. This has been preferred as opposed to direct or Ewald sum of charges. PME is faster and more accurate than both as it assigns charges to a grid [196]. The velocity rescaling thermostat [199] and the Berendsen barostat [200] were used to sample the system at 298 K and 1 bar. Using this thermostat, the mean and fluctuations for the temperature correspond to the NVT ensemble. Regarding the barostat, the mean pressure is maintained at the reference value and since volume fluctuations in the system are negligible, it can be used to accurately represent isobaric conditions. Also, temperature effects are evaluated using the same thermostat at 493 K.

In the assembly of half-SBUs, the velocity rescaling thermostat and the Berendsen barostat [200] maintained the temperature and pressure at 493 K and 3,500 bar respectively for an equilibration period of 5 ns. Production MD simulations followed using the Parrinello-Rahman Barostat [201] with a relaxation time of 2 ps in water and 4 ps in DMF.

2.3 Enhanced Sampling Methods

One of the limitations of Molecular Dynamics is the time-scale accessible by current computational equipment. Study of processes that incorporate rare events is almost impossible. A well-documented example is protein folding that takes place in the order of tenths of milliseconds, while the time-scale accessible by MD for large systems, e.g. a protein in aqueous solution, is of the order of a few microseconds [202]. The metadynamics [203] method is used in order to sample rare events in this context.

2.3.1 Metadynamics

In this research work, metadynamics is used. More precisely, the well-tempered variant of the method, often abbreviated as WTmetaD [204]. In this method, a bias potential V' is added to the Hamiltonian of the system. Therefore, the Hamiltonian, H , is now expressed as follows,

$$H = K + U + V' \quad (2.7)$$

Where K and U correspond to the kinetic and potential energies of the system and V' to the metadynamics bias is [203], [205],

$$V' = V'(\mathbf{S}(\mathbf{R}), t) = \int_0^t \omega(t') \cdot \exp\left(-\sum_{i=1}^{ncv} \left(\frac{S_i(\mathbf{R}) - S_i(\mathbf{R}(t'))}{2\sigma_i}\right)^2\right) dt' \quad (2.8)$$

Where, the metadynamics bias potential, V' , is a function of time, t , and $\mathbf{S}(\mathbf{R})$ that is a collective variable (CV) of the atomic coordinates, $\mathbf{R}$. The quantity $\omega(t')$ is the bias deposition rate, that is the ratio of the height of the Gaussian functions (w) and their deposition stride (τ_G). Gaussians are deposited every τ_G and the time on this trajectory is t' ($t' = \tau_G$ the first time a Gaussian is deposited, then $t' = 2 \cdot \tau_G$ the second time, etc.) [206]. This rate is a metric for the accuracy versus speed of filling the free energy landscape with the metadynamics bias. The sum in the exponent runs over the number of CVs (ncv) biased during the simulation. The metadynamics bias is a sum of Gaussian functions, with a width equal to σ , centred along the CV trajectory. The width is chosen to be less than a third of the standard deviation of the CV during an unbiased simulation in order to accurately uncover all features of the free energy profile. Additional forces (the derivatives of the metadynamics bias with

respect to the CVs) act on the CVs of the atomic positions; hence the system is encouraged to visit relevant configurations along the CV trajectory.

The choice of appropriate CVs depends on the process under study and it is based on chemical intuition. These should be limited in number (at most cases less than 3) in order to avoid high computational cost, complexity and convergence issues due to calculation of additional forces between bias depositions.

In WTmetaD [204], the deposition rate of the additive bias potential is decreased inversely with time and the height of the Gaussian functions is rescaled following the form by [202], [205],

$$w = \omega_0 \cdot \tau_G \cdot \exp\left(-\frac{V(\mathbf{S}, t)}{\Delta T}\right) \quad (2.9)$$

Where, ω_0 is the initial deposition rate and ΔT is a temperature. This way the additive potential V' converges, after a long time, to minus the product of the free energy $F(S)$ and the “bias factor” (γ); a quantity that depends on temperature and is provided by the researcher (the bias factor sets the value of ΔT), modulo an irrelevant constant [202]. The choice of γ is based on the barriers present on the free energy profile. The resulting free energy profile is independent of the choice of the bias factor after convergence has been achieved. An expression that links the aforementioned quantities is provided below,

$$V'(S, t \rightarrow \infty) = -\frac{\Delta T}{T + \Delta T} \cdot F(S) + c \quad (2.10)$$

2.3.2 Reweighing bias

Reweighing the bias obtained from a WTmetaD simulation [204] is a way to obtain the unbiased probability distribution of collective variables by accounting for the effect of the bias potential deposited during the simulation on the sampling. This can be achieved using the method developed by Tiwary and Parrinello [207] which considers a time dependent bias as the one in WTmetaD [204] and calculates the time-dependent constant $c(t)$ in equation 2.10 directly as:

$$c(t) = k_B T \cdot \log\left(\frac{\int \exp\left(\frac{\gamma \cdot V(\mathbf{S}, t)}{k_B T \cdot (\gamma - 1)}\right) d\mathbf{S}}{\int \exp\left(\frac{V(\mathbf{S}, t)}{k_B T \cdot (\gamma - 1)}\right) d\mathbf{S}}\right) \quad (2.11)$$

where, k_B is Boltzmann's constant.

Then it uses this quantity to apply weights to configurations and calculates the reweighted bias as the difference between the final bias and $c(t)$:

$$\langle O(\mathbf{R}) \rangle = \langle O(\mathbf{R}) \cdot \exp(\beta(V(\mathbf{S}(\mathbf{R}, t) - c(t))) \rangle \quad (2.12)$$

where, $O(\mathbf{R})$ is an operator that depends on atomic positions, β is the inverse temperature and angular brackets are used for the ensemble average.

2.3.3 Collective Variables

2.3.3.1 Half-SBU flexibility

In the case of isolated half-SBUs in solution, the mass-weighted radius of gyration (R_{gyr}) is chosen as a CV in order to investigate conformational flexibility. An analytical form of this CV as implemented in PLUMED 2 [208] is provided below,

$$R_{gyr} = \sqrt{\sum_i m_i \cdot \frac{\left| \mathbf{r}_i - \frac{\sum_i m_i \mathbf{r}_i}{\sum_i m_i} \right|^2}{\sum_i m_i}} \quad (2.13)$$

Where, m_i is the mass and $\mathbf{r}_i$ the position of atom i . Gaussian potentials of height 0.5975 kcal/mol and width 0.1 Å were deposited every 500 simulation steps (corresponding to 1 ps). The bias factor used is equal to 10.

2.3.3.2 Association-Dissociation of SBUs

An investigation of the self-assembly of MIL-101(Cr) from its half-SBUs (Structural Building Units) [107] is performed in order to sample the configurational space of dimers, to evaluate their equilibrium distribution and to assess their connection with the development of defects in the MOF crystallisation process.

For this purpose, two CVs, M-T and M-M are biased. “M” stands for the metal centre and “T” for the terephthalate linker. These distinguish between states of interest, namely crystal-like, noncrystal-like and detached half-SBUs. The set of all distances between the chromium atoms of one metal centre (M) and the carbon atoms of the adjacent terephthalate linker (T) is constructed and then bias is deposited on the lowest component of this set, which is the first CV used, namely M-T. The other CV biased, M-M, is the lowest component of the set of all distances between chromium atoms that belong to the metal centres of the two adjacent molecules.

In WTmetaD, Gaussians were deposited every 500 steps (1 ps) with width (σ) equal to 0.1 Å, initial height 0.5975 kcal/mol and bias factors for each case as follows: 30 for AA, 20 for AB, AC, BB and 10 for BC, CC. The choice of bias factor depends on the energy barriers needed to overcome and these differ between dimers. All simulations were carried out using GROMACS 5.1 [196] with PLUMED 2.2 [208].



Figure 2-1. Collective variables used to describe relevant half-SBU and SBU states in WTmetaD simulation. M-M (metal-metal distance) is represented by the yellow line. An example for M-T (metal-terephthalate distance) is provided with a light blue line. Colour code: Cr - lime, O - cyan, H-grey, C (Monomer 1)-blue, C (Monomer 2)-red.

A schematic representation of the two CVs is provided in Figure 2-1. The distance between all possible pairs of atoms in the yellow circles are calculated in order to construct the M-M set of distances. The other collective variable set is constructed through calculation of all distances between atoms in the yellow circles and all terminal carboxylic carbons such as the atom in the blue circle. An example of a component of the set of M-T distances is provided with the blue line.

2.3.3.3 SBU Rearrangement

A separate simulation starting from an SBU configuration and exploring the phase space characterised by another CV is performed. This CV is the coordination number between terminal carboxylic oxygens and chromium atoms. The cut-off distance chosen for calculating the coordination number is 2.5 Å. Additionally, WTmetaD [204] bias was deposited also on the potential energy in order to assist convergence of the enthalpic contribution. The total simulation time is 1.5 μ s for this biased production simulation.

The WTmetaD [204] parameters include width 0.01 and 47.8 kcal/mol for the gaussians deposited on the space of coordination number and potential energy of the system. Gaussians were deposited every 1 ps and their initial height and bias factor were set to 0.598 kcal/mol and 100 respectively. A rational switching function, as implemented in [208], with parameters ($d_0=0$, $n=2$, $m=4$) was chosen in order to calculate the set of relevant coordination numbers. This switching function has the form,

$$s(c) = 1 - \frac{\left(\frac{c - d_0}{c_c}\right)^n}{\left(\frac{c - d_0}{c_c}\right)^m} \quad (2.14)$$

where c_c is the cut-off for the coordination number c . All possible coordination numbers (c) are calculated and bias is deposited on the number of those greater than $c_c = 0.5$.

A harmonic restraining potential (V_r) acted on a collective variable in order to ensure that sampling is restrained in state 2. This collective variable is the M-T distance used earlier in this text for SBU association-dissociation. The force constant for this potential was set to 35.85 kcal/mol and it was active when M-T distance exceeded values of 3.5 Å.

2.4 Enthalpy and Entropy Profiles

2.4.1 Calculation of contributions to the free energy

A WTmetaD simulation results in the computation of the free energy of the system G projected on CV space, S [204]. A linear expression relates the Gibbs free energy, $G(S)$, with its enthalpic, $H(S)$, and entropic, $S(S)$, contributions,

$$\Delta G(S) = \Delta H(S) - T \cdot \Delta S(S) \quad (2.15)$$

where Δ is the difference with respect to an arbitrarily selected reference state in S [204].

Free energy surface $\Delta G(s)$ is analysed into its contributions following the work in ref. [209]. The ensemble average of the enthalpic contribution is mapped on S , and the entropic contribution ($-T \cdot \Delta S(S)$) is obtained using equation 2.15.

The configurational transitions of the monomers in solution is associated to negligible variations in the volume of the solute. Therefore, the contribution to

enthalpy due to mechanical work is constant as this is the product of the pressure P and the change in volume mapped on $\mathcal{S}$, $V(\mathcal{S})$. Therefore, $\Delta H(\mathcal{S})$ reduces to the internal energy $\Delta U(\mathcal{S})$. Also, the kinetic energy does not depend on $\mathcal{S}$ at constant temperature; hence the internal energy contribution $\Delta U(\mathcal{S})$ reduces to the potential energy of the system $\Delta E_P(\mathcal{S})$.

Conformational transitions in half-SBUs or SBUs take place in solution. In this case, the potential energy of the system is dominated by contributions between solvent molecules. Therefore, the contributions to $\Delta E_P(\mathcal{S})$ should be further analysed as,

$$\Delta E_P(\mathcal{S}) = \Delta \langle E_P^{solute} \rangle_{\mathcal{S}} + \Delta \langle E_P^{solute-solvent} \rangle_{\mathcal{S}} + \Delta \langle E_P^{solvent} \rangle_{\mathcal{S}} + \Delta \langle E_P^{LR} \rangle_{\mathcal{S}} \quad (2.16)$$

where $\langle E_P^{solute} \rangle_{\mathcal{S}}$ is the ensemble average of the potential energy due to the presence of solute projected in $\mathcal{S}$. This considers contributions of the bonded terms (bond, angles, proper dihedrals and Ryckaert-Bellemans dihedrals [210]) of the solute. $\langle E_P^{solvent} \rangle_{\mathcal{S}}$ is the ensemble average of the potential energy due to the presence of solvent projected in $\mathcal{S}$. $\langle E_P^{solute-solvent} \rangle_{\mathcal{S}}$ considers the short-range non-bonded terms for solute-solute and solvent-solvent interactions, while long-range interactions, $\langle E_P^{LR} \rangle$, are calculated in total for the system of both solute and solvent. Furthermore, $\langle E_P^{solvent} \rangle_{\mathcal{S}}$ does not depend on the configuration of the solute projected on $\mathcal{S}$; hence it is equal to zero. At last, ensemble averages are mapped on $\mathcal{S}$ using the method of Tiwary and Parrinello discussed in ref. [207].

2.4.2 Enthalpy differences in terms of the solvation shell size

In an effort to understand how the solute-solvent interactions are affected by the number of solvent molecules present in the simulation box, enthalpy-entropy profiles are calculated with an increasing solvation shell. In this approach, contributions to the potential energy are summed only for the solvent molecules within a certain cut-off distance from the solute. The contribution due to bonded terms remains the same, but the nonbonded contribution can be significantly affected by this change. Therefore, the $\Delta \langle E_P^{Solute-Solvent}(\mathcal{S}) \rangle_{\mathcal{S}}$ term is affected only.

Solvent atoms within a certain cut-off distance from the atoms of the solute are labelled as parts of the “solvation shell”. The rest of the solvent atoms system are characterised as “not in solvation shell”. This analysis can categorise all atoms of the system including the solvent and other guest molecules, for example ions, to be part

of the set called “not in solvation shell”. Therefore, it is possible to sum interactions between the solute and only the solvent atoms in the “solvation shell”. Solvation shell sizes cover a broad range from 2.5 to 20 Å. This way it is possible to quantitatively assess the number of solvent molecules inside a simulation box that is enough to model solute-solvent interactions accurately.

This study should provide a computational framework for optimisation of the size of the simulation box for simulations in bulk solution as this is frequently decided in an empirical fashion. Moreover, the enthalpy and entropy profiles contributed to different sizes of the solvation shell are calculated. In this manner, various guest molecule environments can be evaluated and the difference in the enthalpic contribution for the same size of the solvation shell can be calculated. This should determine the effect of the size of the solvation shell on the conformational entropy of the system.

At last, it should be noted that this is a new method to quantitatively evaluate the effect of the solvation shell size on the enthalpy profile projected on collective variable space. Implementing this method, the size of the simulation box can be optimised in order to find the smallest size of the system that presents negligible differences when compared to any larger size. Therefore, the number of solvent molecules is minimised; hence the computational cost is the lowest possible that does not present considerable impact on the accuracy of the model. This analysis departs from empirically deciding the size of the simulation box. Consequently, this measure can ascertain the researcher that the size of the system is large enough to accurately consider the potential energy of a highly solvated molecule.

2.5 Calculation of the equilibrium distribution of species

The equilibrium distribution of species can be estimated by calculating the equilibrium constants of all relevant transitions. This is focused on the analysis of dimers in solution (Chapter 4). The equilibrium constant for a typical chemical reaction is given below [211],

$$aA + bB \rightleftharpoons cC + dD, \quad K_{eq} = \frac{n_C^c \cdot n_D^d}{n_A^a \cdot n_B^b} \quad (2.17)$$

where A, B, C and D are chemical species, a, b, c and d are their respective stoichiometric coefficients. The amount of each at equilibrium is n_i , $i = A, B, C, D$. This can be directly related to the difference between the standard Gibbs free energy (ΔG^0) of the dimerisation through the following equation [184], [212],

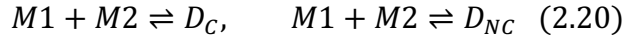
$$\Delta G^0 = -R \cdot T \cdot \ln(K_{eq}) = -(N_A \cdot k_B) \cdot T \cdot \log(K_{eq}) = -\left(\frac{N_A}{\beta}\right) \cdot \log(K_{eq}) \quad (2.18)$$

Where R is the universal gas constant, T is the temperature of the system, K_{eq} is the equilibrium constant, N_A is Avogadro's number, k_B is Boltzmann's constant and β is the inverse temperature. It should be noted that the simulation results in the calculation of the Helmholtz free energy (ΔF). Furthermore, constant temperature and pressure conditions are applied to the system. The change in volume between the systems of dimers and couples of detached monomers is negligible. This was monitored throughout the trajectories of the simulations.

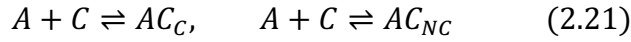
In this work, the equilibrium distribution of species in presence of ions is estimated. In this process, the free energy differences were considered by taking state 5 (detached monomers) as the reference. The probability of forming a crystal-like or noncrystal-like SBU from detached half-SBUs (reference state) is calculated for each conformer. An assumption used is that monomers (half-SBUs) form dimers (SBUs) only and that dimers are initially absent. The characterisation of crystal-like and noncrystal-like dimers is applied in order to calculate the equilibrium distribution of species. More precisely, the probabilities of these two distinct cases are summed by taking all the states, that correspond to either, into account. In other words, the ΔG of the formation of a crystal-like dimer of one type (e.g. dimer of type BC) is calculated as follows,

$$\Delta G_{BC,C} = -k_B T \cdot \log \left(\sum_i \exp \left(-\frac{\Delta G_i}{k_B T} \right) \right) \quad (2.19)$$

where i takes the values of all the states that correspond to crystal-like conformers on the free energy surface of the BC SBU and $k_B T$ is in energy units (e.g. kcal/mol) here and in the rest of this text. Furthermore, these ΔG values correspond to the transition from the detached state to every state featured in the corresponding FES. In this context, two monomers form either a crystal-like or a noncrystal-like SBU. Hence the following set of reactions occur in the system,



where $M1, M2$ are two monomers (MLA, MLB, MLC) and D_C and D_{NC} are the crystal-like and noncrystal-like dimers (or SBUs) formed from their respective building units e.g.



This results in 12 reactions (6 for crystal-like and 6 for noncrystal-like dimers) leading to 15 species being present at equilibrium (3 monomers and 12 dimers). Each one of these reactions is associated with a certain extent (λ). The equilibrium probability of species i , that can be either A, B, C, AA, AB, AC, BB, BC or CC, is then given by the following equation,

$$P_{i,eq} = P_{i,0} + \sum_j v_{ij} \cdot \lambda_j \quad (2.22)$$

where j corresponds to the reaction (e.g. 1st, 2nd etc.), v_{ij} to the stoichiometric coefficient of species i in reaction j , $P_{i,eq}$ and $P_{i,0}$ to the probability of species i initially and at equilibrium respectively and λ_j to the extent of reaction j . It should be noted that the sum of probabilities should be equal to the unity. Then, using the notation above, a relation for the equilibrium constant is derived,

$$K_{eq} = \frac{P_1^{v_1}}{P_2^{v_2}} = \exp\left(-\frac{\Delta G}{k_B T}\right) \Rightarrow \frac{\Delta G}{k_B T} + v_2 \cdot \log(P_2) + v_1 \cdot \log(P_1) = 0 \quad (2.23)$$

where 1 corresponds to reactants and 2 to products; hence $v_2 > 0$ and $v_1 < 0$. Then for the j reaction it is,

$$\beta \cdot \Delta G_j + \sum_i v_{ij} \cdot \log(P_i) = 0, \quad 1 \leq j \leq 12 \quad (2.24)$$

where $\beta = \frac{1}{k_B T}$ is the inverse temperature. Therefore, a square system of non-linear equations emerges. This system is solved numerically following the trust-

region approach with a dogleg step calculation [213], [214]. A sum of logarithms is preferred to the exponential quantities in order to assist convergence. An initial guess is provided to the solver algorithm in order to find the local solution that is relevant by considering the difference in ΔG values, consequently translated to probabilities. Therefore, initial λ values are assigned based on intuition assisted by the ΔG values. This is translated to an initial guess of a larger λ for the lowest ΔG values. The reason is that the most stable dimers have a relatively larger extent of reaction than the weaker ones.

2.6 Convergence and error analysis

The use of a time weighted average and corresponding standard deviation is used to estimate convergence in dimer simulations conducted this work (Chapter 4). Furthermore, block averages are used for simulations of monomers (Chapter 3) in order to estimate the sampling error for both free energy and enthalpy. At last, the error bootstrap method is used to calculate uncertainty in the resulting values for the equilibrium probability distribution of species (Chapter 4).

2.6.1 Time-weighted average

The time weighted average (S_{avg}) and the corresponding standard deviation ($sdev$) are used as in Berteotti et al. [215]. Calculation of free energy differences between states is performed throughout the simulation trajectory. Nevertheless, the first part of the simulation is exploratory since all relevant states are not sufficiently sampled and the last part is more accurate as all relevant states are visited. The use of time weights considers this difference thus providing larger weights to the last than the initial estimates of the free energy differences. The relevant equations are provided below,

$$S_{avg} = \frac{\sum_i t_i \cdot S_i}{\sum_i t_i}, \quad sdev = \sqrt{\frac{\sum_i t_i \cdot (S_i - S_{avg})^2}{\sum_i t_i}} \quad (2.25)$$

Where t_i are the time weights. Value S_i correspond to the measurement of the variable S at time t_i .

2.6.2 Block average

The block average analysis includes partitioning of the trajectory of a collective variable into n blocks of equal size. This method considers the correlations between neighbouring measurements resulting from MD simulations. As block size increases these correlations are lifted and statistics can be calculated using the central-limit theorem; hence the sum of measurements will approximately follow a normal distribution [216]. Afterwards, the histogram on the space of the collective variable ($H(\mathcal{S})$) is calculated in each block. The average histogram $\langle H(\mathcal{S}) \rangle$ and the corresponding error ϵ_H can be calculated for the set of blocks. Ultimately, the error is propagated in free energy in order to provide the sampling error of the free energy projected on collective variable space; hence $\epsilon_F = \epsilon(F(\mathcal{S}))$. The steps and set of equations for this method are provided below [208].

1. Calculate the error from the sample variance (numerator in the expression below) [208],

$$\epsilon_H = \sqrt{\frac{\frac{n}{n-1} \cdot (\langle H^2 \rangle - \langle H \rangle^2)}{n}} \quad (2.26a)$$

where, n is the number of blocks and H the histogram on CV space.

2. Error propagation from the histogram to the free energy,

$$\epsilon_F = \epsilon_{-F} = \epsilon_H \cdot \frac{d(-F)}{dH} = \epsilon_H \cdot \frac{d(k_B T \cdot \log(H))}{dH} = \epsilon_H \cdot \frac{k_B T}{|H|} \quad (2.26b)$$

Where, ϵ_{-F} is error of the negative free energy projected on CV space.

2.6.3 Error bootstrap method

The error bootstrap method is used to calculate uncertainties associated with the probability of each species at equilibrium. If the calculation of the probability distribution is associated only with the average values for ΔG between the reference state and the states of interest, the uncertainty will not be considered. Therefore, an error bootstrap method is performed in order to calculate the uncertainty associated with the equilibrium probabilities. In this context, the calculation of the equilibrium distribution is iteratively performed for random values in the interval $[\Delta G - sdev, \Delta G + sdev]$. Where $sdev$ is the standard deviation associated with the ΔG . This method results in an average probability and an associated standard deviation for each

species. This analysis is carried out for up to 500 iterations in order to ensure that the estimated equilibrium probability values and the corresponding standard deviations have converged. The convergence of the method was decided through monitoring the equilibrium probability values and the associated standard deviations.

2.7 Molecular properties

2.7.1 Radial distribution function

The radial distribution function is measure of the average number density between a pair of particles (or atoms in classical mechanics) divided by the density in an ideal gas at the same overall density [180]. The first peak on a typical liquid structure radial distribution function constitutes the first solvation shell, the second smallest is a measure of where the second solvation shell is located, etc. The definition of the radial distribution function is provided in the equation below [177],

$$g(\mathbf{r}_1, \mathbf{r}_2) = \frac{N \cdot (N-1)}{\rho^2 \cdot Z} \int d\mathbf{r}_3 d\mathbf{r}_4 \dots d\mathbf{r}_N \exp(-\beta U(\mathbf{r}_1, \mathbf{r}_2, \dots \mathbf{r}_N)) \quad (2.27a)$$

$$g_{AB}(\mathbf{r}) = \frac{V}{N^2} \langle \sum_i \sum_{i \neq j} \delta(\mathbf{r} - \mathbf{r}_{ij}) \rangle \quad (2.27b)$$

Where δ is a Dirac (continuous) delta function (which is zero at the origin and infinite everywhere else). V is the volume of the system of N particles and $\mathbf{r}$ is the position vector. U is the potential energy, Z is the canonical partition function and ρ is the number density. This function ($g(r)$) is equal to the unity for an ideal gas [180]. Equation 2.27b is commonly used to calculate the radial pair distribution function in computer simulations [177]. Calculation of the radial distribution function provides insight into the structure of the system (solid, liquid, gas) as it is a measure of local order around an atom. The integral corresponding to the area under the curve for a certain distance, namely the cumulative distribution function, is equal to the average number of B particles which are located at this distance away from A.

2.7.2 Rotational Inertia

Rotational inertia provides another physical property that complements the analysis performed in Chapter 3. The flexibility of MOF building units in solution is understood in more detail through identifying principal axes of rotation for each isomer and also analyse the propensity of MLA, MLB and MLC to develop rotational

acceleration around principal axes. This analysis provides a better understanding of isomer flexibility in solution as principal axes are not the same for each isomer and this cannot be observed on the space of radius of gyration that is used as a collective variable; hence the rotational movement of each isomer is evaluated in solution and this is linked with the propensity of each isomer to promote crystallinity. At last, this analysis is used to ascertain that the mass-weighted radius of gyration (employed in Chapter 3) is a good proxy to describe rotational inertia through a comparison of the relevant profiles.

Inertia is defined as the resistance to any change in the state of the system as formulated by Newton's first law of classical mechanics. As Goldstein [217] states, a linear operator that can transform the net angular velocity ($\underline{\omega}$) to net angular momentum ($\underline{L}$) is a second rank tensor known as the inertia tensor ($\underline{I}$) as it can be seen in equation 2.30a.

$$\underline{L} = \underline{I} \cdot \underline{\omega} \quad (2.28a)$$

$$\begin{vmatrix} I_{xx} - I & I_{xy} & I_{zx} \\ I_{xy} & I_{yy} - I & I_{yz} \\ I_{xz} & I_{yz} & I_{zz} - I \end{vmatrix} = 0 \quad (2.28b)$$

$$I_{xx} = \sum_i m_i \cdot (y_i^2 + z_i^2), I_{xy} = - \sum_i m_i \cdot x_i \cdot y_i \quad (2.28c)$$

This tensor is real and symmetric ($I_{xy} = I_{yx}$); hence there always exists a unique set of coordinates for which this tensor is diagonal. The three eigenvalues of the tensor are the principal moments of inertia and their corresponding eigenvectors are the principal axes of inertia [217]. The principal moments are always real and positive numbers and the corresponding eigenvectors are always orthogonal. The physical meaning of axes and moments of inertia is linked with the tendency of a body to develop angular acceleration around an axis of rotation. Its resistance to rotate around the axis is proportional to the corresponding moment of inertia.

Equation 2.28b is used to calculate these eigenvalues by finding the roots of the determinant of the inertia tensor subtracted by a unitary tensor multiplied by the moment of inertia, I . Consequently, the determinant results in a cubic equation for I and principal moments are its roots. Components of the inertia tensor on (e.g. I_{xx}) and off (e.g. I_{xy}) the diagonal are provided in equation 2.28c, where the position of a particle, i , with mass, m_i , relative to the axis of rotation is $\mathbf{r}_i = (x_i, y_i, z_i)$ [217].

The moment of inertia is inversely proportional to the angular velocity and the rotational energy [181], [218]. Calculation of all three principal axes and moments

of inertia is necessary in order to examine the effect of any force in any possible direction expressed by three component vectors in cartesian space [219].

At last, it should be mentioned that the symbols for vectors have changed only in the equations of this section in order to highlight the difference of tensors from vectors as these should not be confused by using bold letters for every quantity [217].

2.7.3 Rigidity of the half-SBU metal-centre

The mass weighted root mean square deviations of atomic positions ($RMSD_{mw}$) is calculated throughout the ab initio MD trajectory in order to assess the rigidity of the metal centre, as this is modelled as fairly rigid in the classical force field implementation.

It should be noted that the project collaborators at PNNL have developed the force field through studies at the DFT level. Also, they have setup and conducted ab initio molecular dynamics simulations. Consequently, only the trajectories are post-processed by the author of the thesis (see section A.1).

The $RMSD_{mw}$ is calculated in Visual Molecular Dynamics (VMD) software [220], using the equation below,

$$RMSD_{mw} = \sqrt{\frac{\sum_i m_i \cdot \|\mathbf{r}_{1,i} - \mathbf{r}_{2,i}\|^2}{N \cdot \sum_i m_i}} \quad (2.29)$$

where, m_i is the mass of atom i of N atoms present in structures r_1 and r_2 . The DFT optimized structure corresponds to r_2 while r_1 is calculated for every frame of the ab initio MD trajectory. Consequently, the average and standard deviations of the RMSD values are identified. RMSD values are calculated only for the metal centre as bonded parameters relevant to these atoms are added to the force field. This quantity provides a quantitative measure of the rigidity of the metal centre by evaluating the change in the positions of relevant atoms over simulation time.

Chapter 3

Conformational Flexibility of Monomers

The results are distributed over three chapters, namely Chapter 3, Chapter 4 and Chapter 5. In Chapter 3 the enthalpic and entropic drivers to conformational flexibility of isolated half-SBUs in solution are assessed. This should provide an early insight into the propensity of monomers to alter their structure under various conditions. Also, the origins of defects on the final MOF can be understood as their most probable configurations are compared to those in the crystal. Furthermore, half-SBU dimer interactions are investigated in Chapter 4 as these should provide a thorough understanding of the nature of interactions during the formation of the smallest building blocks (dimers) of a MOF. The conditions that limit the extent of defective dimers are identified and this is a significant advantage when modelling assembly of units in larger scales. The last part of results, Chapter 5, follows the assembly of several half-SBUs into an aggregate structure. Observations from the small scale studies of monomers and dimers are validated in the larger scale and this provides confidence that these should also hold on much larger scales that correspond to MOF synthesis. Overall, this bottom-up analysis is thoroughly discussed in the following chapters, starting from isolated half-SBUs in solution and leading up to large scale aggregates assembly.

3.1 Introduction

In this chapter, half-SBU monomers are investigated through MD simulations in solution. These are isomers MLA, MLB and MLC that occur during the synthesis route of the MIL-101(Cr) building unit [107] (Figure 3-1). MLA and MLB are stereo isomers, while MLC is a structural isomer of both. Production classical molecular dynamics simulations are performed in order to assess the flexibility of monomers of the MIL-101(Cr) half-SBU. The free energy profiles projected on the mass-weighted radius of gyration are evaluated (section 3.2). Calculation of the rotational inertia for each molecule follows (section 3.3), with a focus on both principal axes (section 3.3.1) and associated moments of inertia (section 3.3.2). The breakdown of free energy to entropic and enthalpic contributions follows in section 3.4. This is performed for half-SBUs in pure water (section 3.4.1), water with ions (section 3.4.2), and DMF (section 3.4.3). Furthermore, enthalpic contribution profiles are calculated for increasing

solvation shells (section 3.4.4) in order to assess convergence of profiles with the size of the solvation shell. Radial distribution functions (section 3.5) are calculated providing information on how different solvents interact with each of the half-SBUs of MIL-101(Cr). Finally, conclusions arising from the analysis of isolated half-SBUs in solution are presented in section 3.6.

3.2 Calculation of the radius of gyration

Free energy profiles are computed and mapped on the radius of gyration for all three half-SBUs under various conditions in order to gain insight into the flexibility of each monomer. The reason is that conformational isomerism of building blocks has a very important role in the flexibility of the final MOF material [221]. Furthermore, the flexibility can be fine-tuned in order to provide the final MOF membrane with cavities that can be used for separation of industrial gases [222].

At first, free energy landscapes are computed in pure water at 298 K and a higher temperature (493 K). It should be noted that experimental synthesis is carried out in water, and in presence of ions, at 493 K placed in an autoclave for 8 hours [38]. High pressures are developed in the autoclave as synthesis is carried out in the liquid state. MLA has a narrower free energy profile with its R_{gyr} oscillating around 5.5 Å; hence it is not very flexible. An interesting observation is that the metal centre is more accessible in MLA than in any other isomer. MLB is more flexible, and it fluctuates around higher R_{gyr} than MLA and MLC. At last *MLC* presents a stable structure favouring more compact configurations than the other two. This can provide a potential source of defects as half-SBUs in the crystal structure are not so compact, as seen before in Figure 1-1. An extended analysis of the dominating structures of the three isomers is provided later in section 3.4.

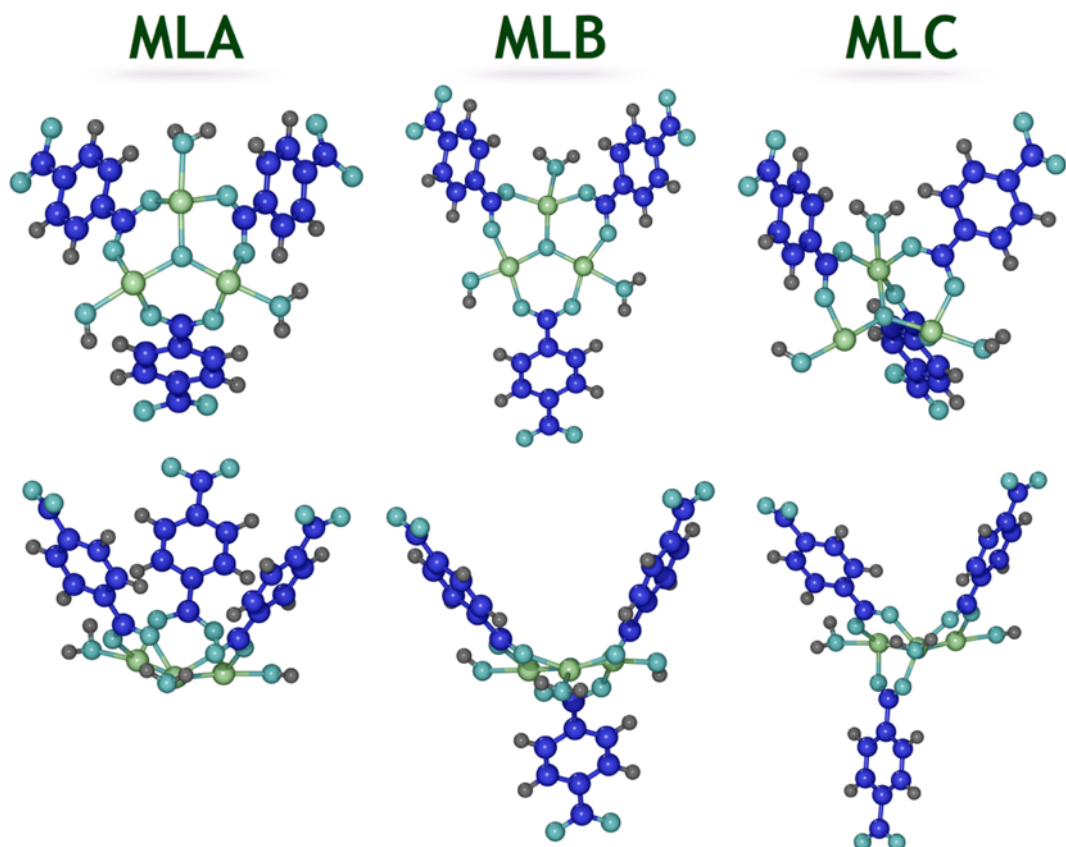


Figure 3-1. MIL-101(Cr) half-SBUs (Cr - lime, O - cyan, H-grey, C: blue).

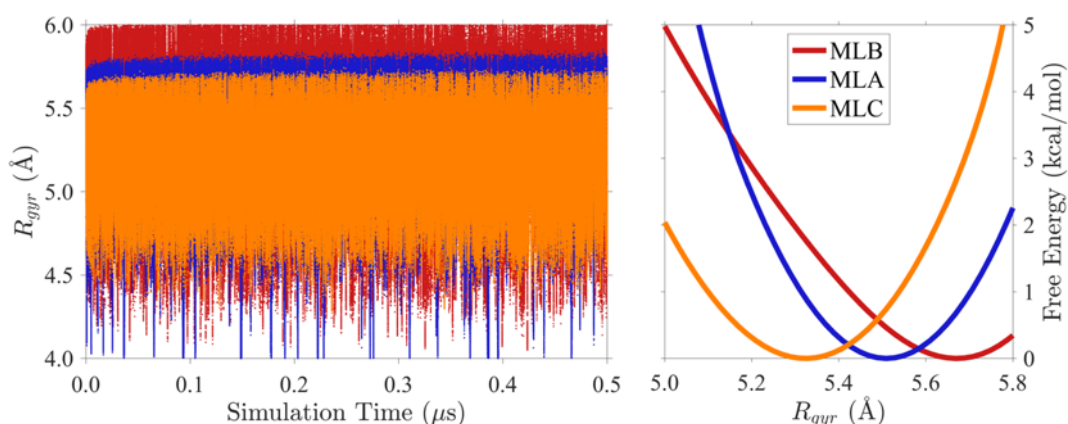


Figure 3-2. Left: Time evolution of R_{gyr} . Right: Free energy with respect to R_{gyr} for the three isomer half-SBUs. Colour code: MLA: blue, MLB: red, MLC: orange.

The structures corresponding to the three half-SBUs are provided in Figure 3-1. The time evolution of the collective variable and free energy profiles with respect to R_{gyr} are showcased in Figure 3-2. The trajectory in collective variable space is important to assess convergence qualitatively. Diffusion in this space means that frequent transitions between all relevant states occur. This can be observed on the left panel of Figure 3-2, where CV frequently visits all states of interest. A quantitative convergence analysis is carried out later in section 3.4.

3.3 Rotational inertia

3.3.1 Principal axes of inertia

In this section, the rotational inertia of the MIL-101(Cr) half-SBU isomers is assessed. The principal axes of inertia are identified, and the corresponding moments are calculated. This analysis provides significant insight into the structural flexibility of the different isomers as a measure of symmetry along principal axes of inertia.

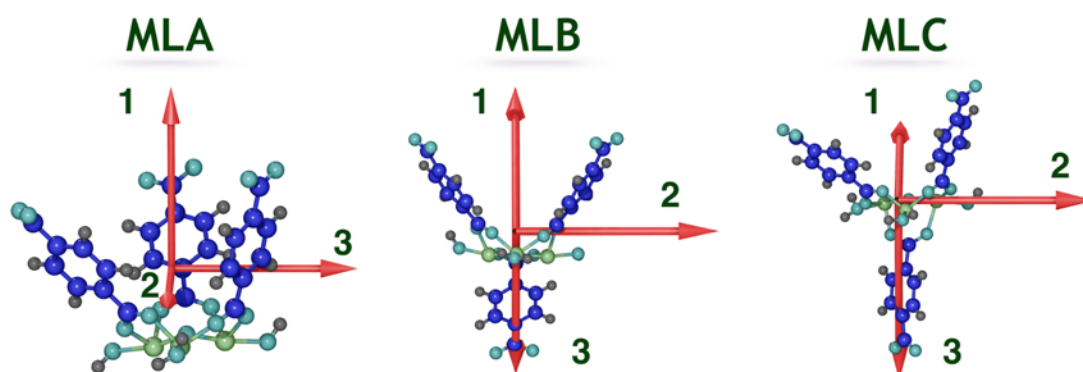


Figure 3-3. Principal axes of inertia for MLA, MLB and MLC. The major (1), middle (2) and minor (3) axes are shown.

A first observation is that the major axis does not show significant differences for the three isomers (see Figure 3-3). This passes through the metal centre of the half-SBUs and it is perpendicular to the plane of the chromium atoms for MLA, while the angle between this plane and the metal centre is decreased for MLB and it takes the smallest value for MLC.

The middle and minor axes are considerably different for MLA compared with the MLB and MLC (see Figure 3-3). The middle and minor axes for MLA are parallel to the plane containing the chromium atoms. Their direction is towards a water molecule linked with the metal centre. Nevertheless, they tend towards a different water molecule each as expected, since they are perpendicular to each other.

The minor axis for MLA is similar to the middle axis for MLB and MLC (see Figure 3-3). A difference is that in MLA, it does not pass through a terephthalate linker as in MLB and MLC. In these two, the middle axis passes through the oxygen atoms that connect the terephthalate linker with the metal centre. In both MLB and MLC, the minor axis is parallel to the terephthalate linkers that are placed on the other side than the rest of the linkers in each isomer.

To summarise, MLA shows considerably different principal axes of rotation compared to MLB and MLC; hence it behaves differently during rotational motion. Also, it does not present any principal axis that is parallel to a terephthalate linker as the other two. In MLA only, the three linkers are positioned symmetrically around the major axis; hence they are rotating in similar fashion. Another interesting observation, for both MLB and MLC, is that one linker is parallel to the minor axis; thus, it acts as an axis of rotation for the other two linkers and the molecule as a whole. The three principal axes of inertia (1: major, 2: middle, 3: minor) for each half-SBU are depicted in Figure 3-3 as red arrows starting from the centre of mass of each molecule. The ranking of the axis is relevant to the propensity of the molecule to rotate around each one. Therefore, it is inversely proportional to the corresponding moments of inertia.

3.3.2 Principal moments of inertia

The moments of inertia corresponding to the three axes of rotation are calculated for all three half-SBUs along with the total moment of inertia during the simulations in water.

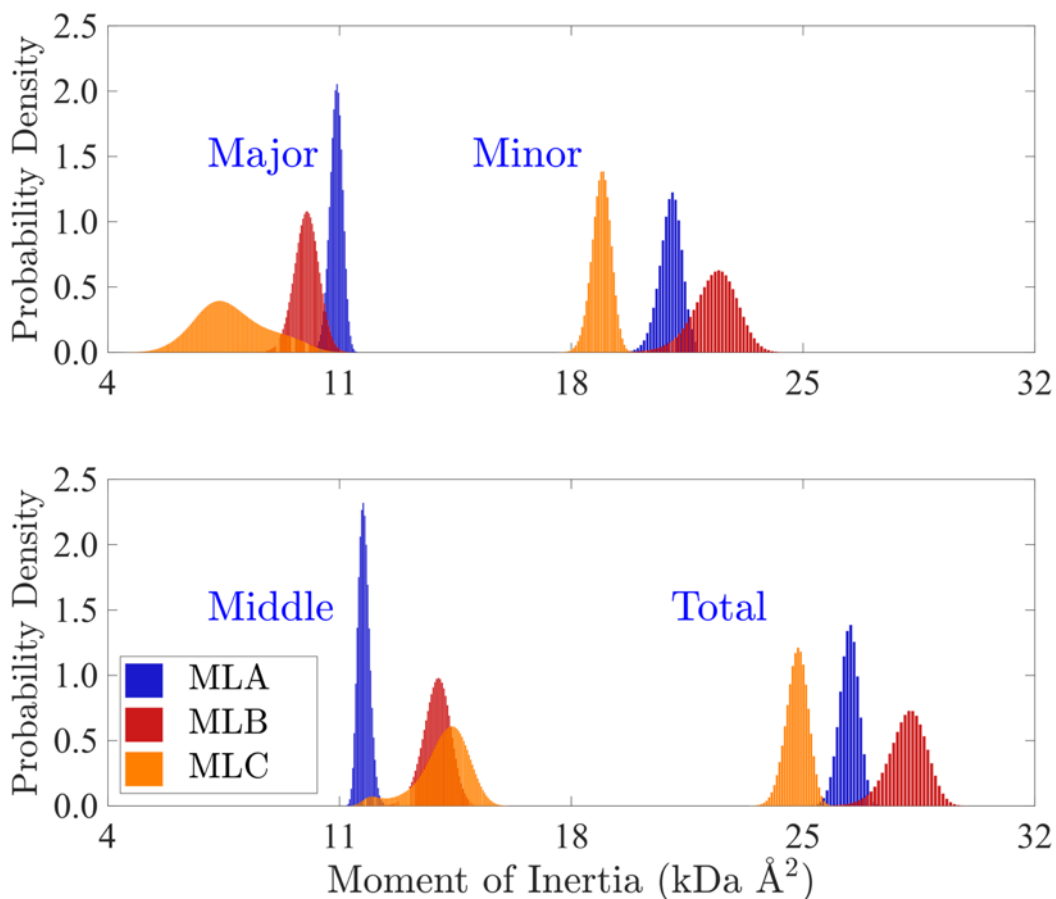


Figure 3-4. Probability density of the values for the moments of inertia, of half-SBUs in water, corresponding to rotation around the major, middle and minor axes of inertia along with the probability density of the total moment of inertia.

At first, the moment of inertia corresponding to the major axis presents higher values for MLA compared to MLB, and the lowest values for MLC. These can be seen in Figure 3-4. MLA and MLB have narrower distributions when compared with MLC that presents a wide distribution of values, but the most probable moments correspond to relatively lower values than the other two. The moment of inertia around the middle axis shows a completely different behaviour. It has the lowest values for MLA and the highest for MLC. Again, MLA and MLB present narrower ranges when compared with MLC. The distribution peaks of MLB and MLC are very close, only separated by less than $1 \text{ kDa} \cdot \text{\AA}^2$ (approximately by the $0.5 \text{ kDa} \cdot \text{\AA}^2$). It should be

noted that it is the shape and relative ranking (e.g. MLB corresponds to larger values for the total moment than MLA, MLC as on R_{gyr} space) of the densities, rather than the absolute values of the moments of inertia, that is important in this analysis (see Figure 3-4). This shows that R_{gyr} is a very good proxy as a similar behaviour with the total moments of inertia is observed. Also, the relative differences in flexibility between the isomers are understood through the width of the densities, e.g. MLA resists rotational acceleration around its major axis as its density is very narrow on moment of inertia space.

At last, the moment of inertia corresponding to the minor axis presents a narrow distribution for MLC with lower values than the rest. This is different than the behaviour of MLC during rotational movement around the major and middle axes, where distributions of moments of inertia are relatively wide (see Figure 3-4). In MLB, the opposite trend emerges as it has the highest value in a wide distribution for the moments of inertia corresponding to rotation around the minor axis. MLA has a wider distribution of moments than in the case of the major and middle axes and it is now located at the middle between the moments of inertia for MLB and MLC.

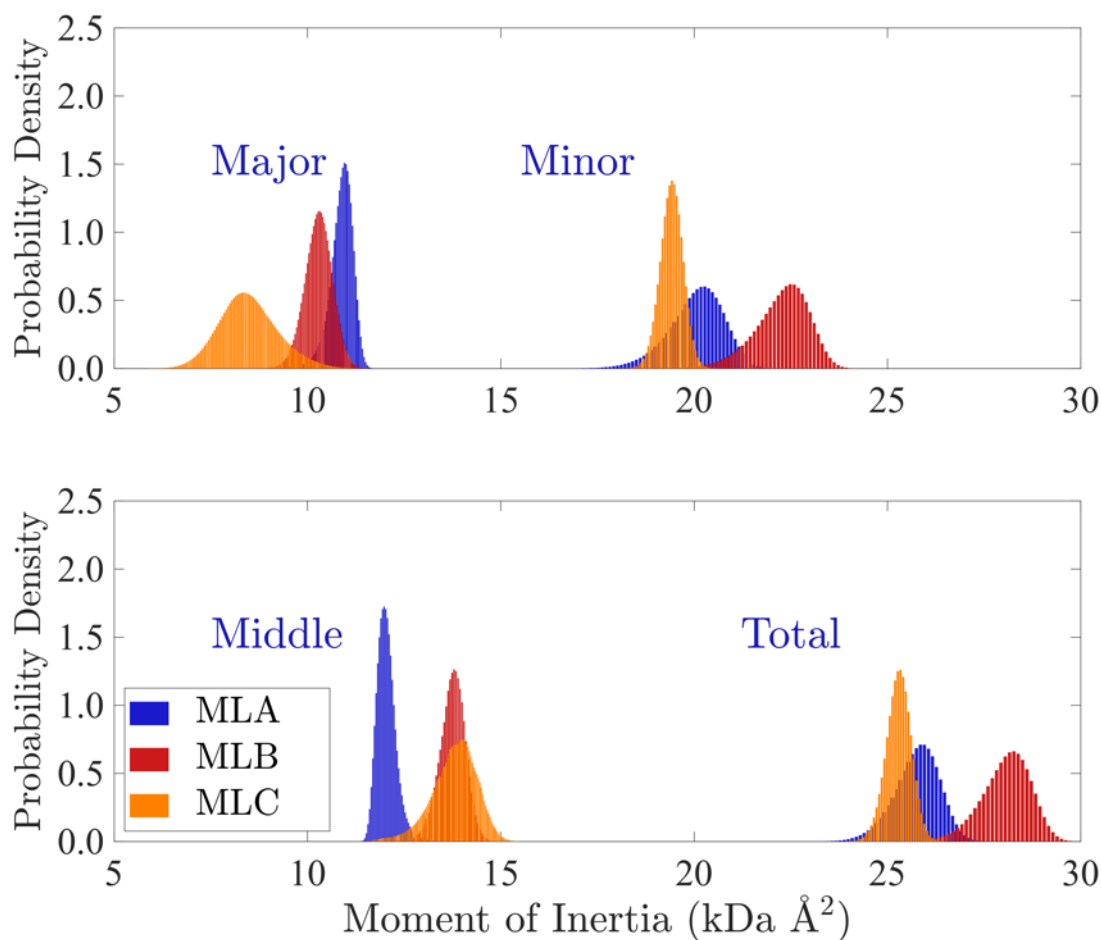


Figure 3-5. Probability density of the values for the moments of inertia, of half-SBUs in DMF, corresponding to rotation around the major, middle and minor axes of inertia along with the probability density of the total moment of inertia.

In addition to water, the probability density of moments of inertia in DMF is evaluated. The principal moments of inertia corresponding to rotation around the major and middle axes present very similar distributions of values as in water. A significant difference can be depicted during the rotational movement, especially of MLA, around the minor axis that is the source of a difference in the total moments of inertia (see Figure 3-5). Therefore, the total moment of inertia of MLA has a distribution at lower values than in water. Also, the total moments of MLA are similar to the moments of MLC in water that correspond to a rather compact configuration which allows the isomer to possess smaller rotational inertia.

Overall, there are several conclusion that can be drawn from the analysis of rotational inertia of half-SBUs in both solvents. Isomer MLA tends to resist rotational movement around the major axis, and it is more likely to rotate around the middle axis compared with the other two. Moreover, MLA presents considerably narrower

distributions for the moments of inertia around the major and middle axis when compared with MLB and MLC. MLB shows narrow distributions of moments of inertia for the major and middle axis, while it exhibits a wide distribution of moments of inertia corresponding to rotation around the minor axis. MLC shows relatively small resistance to rotation around its major axis, while it presents the widest distributions of moments of inertia corresponding to rotation around the major and middle axes.

Another important observation is that the total moment of inertia shows very similar trends to R_{gyr} for all isomers. More elaborately, MLC has the lowest values for both the total moment of inertia and R_{gyr} , MLB shows the highest values over a wide distribution and MLA corresponds to the middle values with a narrow distribution. Therefore, R_{gyr} is a quantitatively accurate metric for the conformational flexibility of the three isomers as it is in agreement with the trends of the total moment of inertia for the half-SBUs. The corresponding plots for DMF are available in Figure 3-5.

3.4 Enthalpic and entropic contributions to the free energy

Study of the enthalpic and entropic contributions to the free energy is focused on the determination of the driving forces to the structural flexibility of MIL-101(Cr) half-SBUs. This analysis is carried out for all three half-SBU isomers occurring during the self-assembly of an SBU under the various conditions studied in this section.

The analysis of enthalpic and entropic contributions to free energy is important as it highlights that static potential energy calculations describe the flexibility of monomers only in part. The potential energy landscape leads to conclusions concerning the stability of different conformers. Nevertheless, this is not enough to evaluate the probability of certain configurations in solution. Entropic contributions have an important role on the free energy landscape as they may render more stable configurations less probable than others. In other words, a configuration that belongs to a potential energy minimum is not certain that it corresponds to a free energy minimum as well. This is only the case if entropic contributions are very weak in a particular system. Nevertheless, this is not known a priori, and it should be assessed through the process described in this chapter; hence evaluating the free energy landscape as well as its underlying enthalpic and entropic contributions.

3.4.1 Half-SBUs in water

Starting the analysis from MLA, the entropic contribution drives the system towards more compact structures, while the enthalpic contribution favours more open conformations, as it presents a minimum for larger values of R_{gyr} for MLA. The R_{gyr} values dominating enthalpy and entropy are 5.87 Å and 4.77 Å respectively as can be seen in Figure 3-6. Entropy is dominated by a very compact structure with all linkers nearly parallel; resembling a cylinder. Enthalpy is dominated by an open conformer with all linkers fully extended in a Y-shape structure. The most probable configuration, dominating free energy, resembles the enthalpic minimum more than the entropic minimum. It should be reminded that experimental synthesis is carried out in water and in presence of ions at 493 K that remain in an autoclave for 8 hours [38]. Therefore, synthesis is carried out in the liquid state as the system as high pressure conditions are introduced.

Structures dominating the free energy profiles for all three half-SBUs are available in Figure 3-6 along with the corresponding free energy and its entropic and enthalpic contributions.

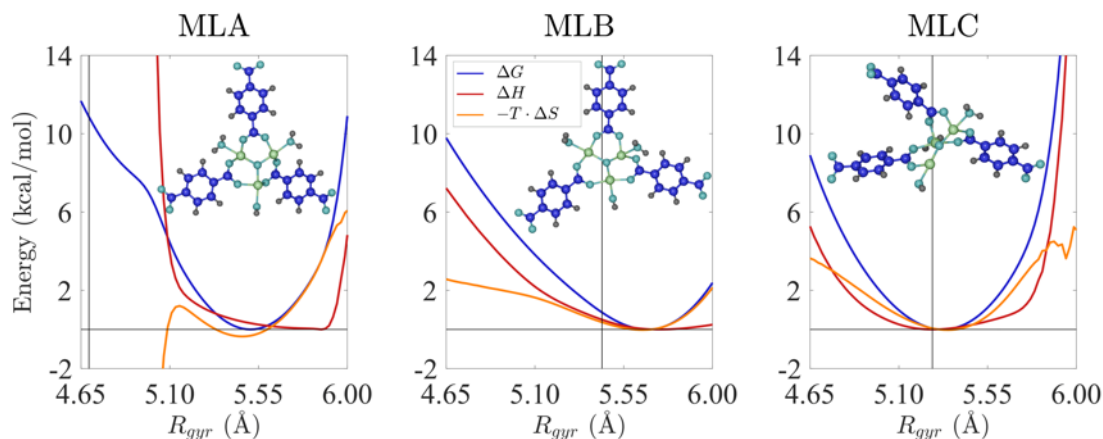


Figure 3-6. Energy profiles of the half-SBUs in water at 298 K projected on R_{gyr} . The free energy profile is represented by a blue curve, while enthalpic and entropic contributions are represented by red and orange curves respectively. Structures dominating the free energy profiles are provided for all three isomers. A thin horizontal line corresponds to zero on the vertical axis. A thin vertical line refers to the average R_{gyr} value of each half-SBU in the crystal.

In MLB, the minima of the entropic and enthalpic contributions are identified for similar values of R_{gyr} . Moreover, this isomer presents a free energy minimum for the largest value of R_{gyr} amongst all other half-SBUs; hence more open structures

are probable in solution compared to the other isomers. The respective values are 5.73 Å for enthalpy and 5.65 Å for entropy; hence the differences in the representative structures are hardly observed in Figure 3-6.

At last, MLC, has an enthalpic contribution which is dominated by low values of R_{gyr} ; hence compact structures are favoured, as seen in Figure 3-6. These are more compact than the ones corresponding to the free energy minimum. The entropic contribution presents a minimum for more open conformers. MLC presents a quite similar behaviour to MLB as entropic and enthalpic contributions are dominated by values that are not appreciably different on R_{gyr} space. Nevertheless, in MLC differences between the R_{gyr} values dominating the two contributions are not as small as in MLB. Enthalpy is dominated by values close to 5.27 Å, while the minimum of the entropic contribution is in the vicinity of 5.35 Å.

In summary, all isomers present free energy minima for R_{gyr} values that range from 5.3 to 5.7 Å. The enthalpic contribution minima are located between 5.0 to 5.9 Å. The entropic contribution presents a very large range of values of R_{gyr} dominating the respective profiles that starts from 4.8 Å and extends to 5.7 Å. The range of R_{gyr} values that present significant contributions to the free energy extends beyond the resulting range of probable values for R_{gyr} . All values for R_{gyr} have been rounded to the first decimal point.

The R_{gyr} values of each half-SBU in the crystal are calculated based on the structure in Figure 1-1. The average value (the standard deviation is provided in brackets) of R_{gyr} for MLA in the crystal is 4.69 (0.16) Å. The corresponding values for MLB and MLC are 5.44 (0.17) Å and 5.27 (0.13) Å respectively. Therefore, structures in the crystal for MLA and MLB correspond to those dominated by entropy in terms of R_{gyr} . In more detail, the R_{gyr} value of MLA and MLB in the crystal is closer to minimum of the entropic contribution than the minimum of the enthalpic contribution. In contrast, R_{gyr} values of MLC half-SBUs are closer to the minimum enthalpic contribution. Therefore, entropy is the driver of MLA and MLB to form structures similar to the ones in the crystal and enthalpy is driving MLC close to half-SBU structures that appear in the crystal. Nevertheless, it should be noted that this analysis is focused on the drivers of flexibility for the half-SBU isomers, while other factors can also affect the propensity of half-SBUs to promote crystal-like SBUs such as the nature of interactions between different half-SBUs under various conditions (temperature, solvent, ions, initial composition of the system of half-SBUs). These are discussed thoroughly in later sections (Chapter 4, 4.1.3, 4.2 and 4.3).

Table 3-1. Sampling errors (kcal/mol) in water at 298K.

Monomer	Error $F(R_{gyr})$	Error $F(U)$
MLA	0.08	0.19
MLB	0.04	0.15
MLC	0.05	0.16

The sampling errors, shown in Table 3-1, are estimated following a block analysis. Blocks of sizes range from 1 to 60 ns in order to estimate the convergence of the simulations conducted.

3.4.1.1 Temperature effects

At last, the energy profiles for MLA are investigated at a higher temperature that corresponds to the one of the experimental synthesis [38]. Nevertheless, this is carried out in an autoclave and also chemical reactions take place. Autogenous pressure is generated in the autoclave and the system remains in the apparatus for 8 hours [38]. The limitation of the time scale sampled through MD (at most a very few milli-seconds) and the classical description of the system, where bond formation is not modelled, do not allow the exact reproduction of experimental conditions.

The effect of temperature on the conformational landscape of half-SBUs and the energy profiles with respect to R_{gyr} is evaluated through an additional simulation. This is performed for MLA in water under constant temperature (NVT) at 493 K using the same thermostat as before. This simulation uses the same protocol as before, but there is no barostat acting on the system. Nevertheless, the pressure is stabilised at a high value of 4,049 bar; hence simulations are carried out at a high pressure that corresponds to the liquid state of the system at this temperature. The resulting energy landscapes are provided in Figure 3-7.

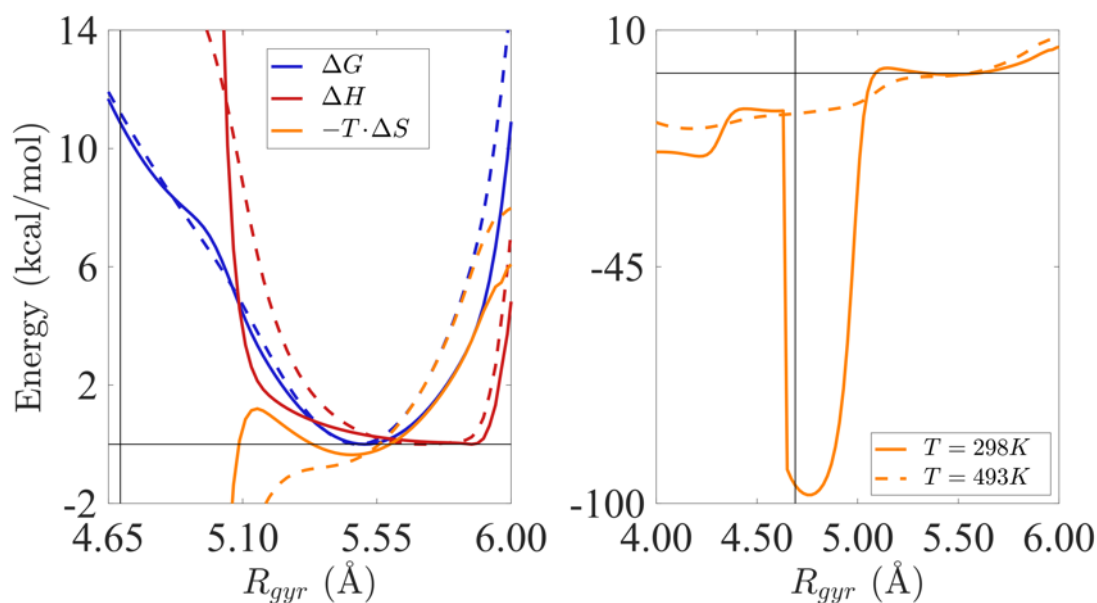


Figure 3-7. Energy profiles of MLA in water at 298 K (solid lines) and 493 K (dashed lines) projected on R_{gyr} . Left panel: The free energy profile is represented by a blue curve, while enthalpic and entropic contributions are represented by red and orange curves respectively. Right panel: Focus on entropic contributions. A thin horizontal line corresponds to zero on the vertical axis. A thin vertical line refers to the average R_{gyr} value of each half-SBU in the crystal.

The errors associated with sampling of the conformational landscape of MLA in water at 493 K are provided in Table 3-2.

Table 3-2. Sampling errors (kcal/mol) in water at 493 K.

Monomer	Error $F(R_{gyr})$	Error $F(U)$
MLA	0.09	0.28

The energy profiles at 493 K are similar to the ones obtained at 298 K, 1 bar. In more detail, the free energy profile presents negligible differences from the one at room temperature (5.51 Å at 298 K and 5.49 Å at 493 K). The enthalpy profile shows a small difference to the one obtained at 298 K. The enthalpic contribution has its minimum at the lower values of R_{gyr} in contrast with 298 K (5.87 Å at 298 K and 5.71 Å at 493 K). Nevertheless, they both present minima for larger R_{gyr} values than the ones corresponding to the free energy minima, even though structures that are enthalpically dominated at 493 K are only slightly more compact than those that are favoured by enthalpy at room temperature. A considerable difference is visible in the entropic contribution. This has a minimum at lower R_{gyr} values, than at 298 K (4.77

Å at 298 K and 4.17 Å at 493 K); hence entropy is dominated by even more compact MLA configurations. It should be noted that values for R_{gyr} have been rounded to the second decimal point for the analysis of MLA at 298 K and 493 K in water. This change in accuracy reflects the differences in the R_{gyr} values between relevant profiles that correspond to hundredths of Å.

In summary, the R_{gyr} values dominating enthalpy remain close to those that show the minimum free energy. On the other hand, the R_{gyr} that presents the strongest entropic contribution is further apart from the R_{gyr} that dominates free energy than at 298 K. As a result, free energy is more strongly dominated by enthalpy at a higher temperature resulting to open structures for the MLA half-SBU, while entropy is the most affected by this change. In more detail, the entropic contribution is dominated by even more compact structures at a higher temperature; hence its minimum is further apart on the space of R_{gyr} from the enthalpic contribution and free energy minima.

3.4.2 Half-SBUs in 0.25M NaF

Ions (Na^+ , F^-) are introduced to the aqueous solutions of MLA, MLB and MLC at a concentration of 0.25M. It should be reminded that experimental synthesis is carried out in water and in presence of ions at 493 K while the system is placed in an autoclave for 8 hours; hence synthesis is carried out under high pressure and in the liquid state [38]. Nevertheless, the free energy profile is not considerably affected by the change in temperature for MLA in pure water as seen in section 3.4.1. Ions interact strongly with the partially charged atoms of the isomers; especially the atoms located at the metal centre of each half-SBU. The effect of presenting ionic species to the system is quantified through calculating additional nonbonded interactions and their contribution to the potential energy of the system. These include van der Waals and Coulombic terms for the interaction between the solute, Na^+ and F^- . Electrostatic interactions involving the solute are appreciably stronger; hence they result in more negative values for the potential energy. Therefore, stronger enthalpic interactions are present when taking the system without ions as a reference.

3.4.2.1 MLA in 0.25M NaF

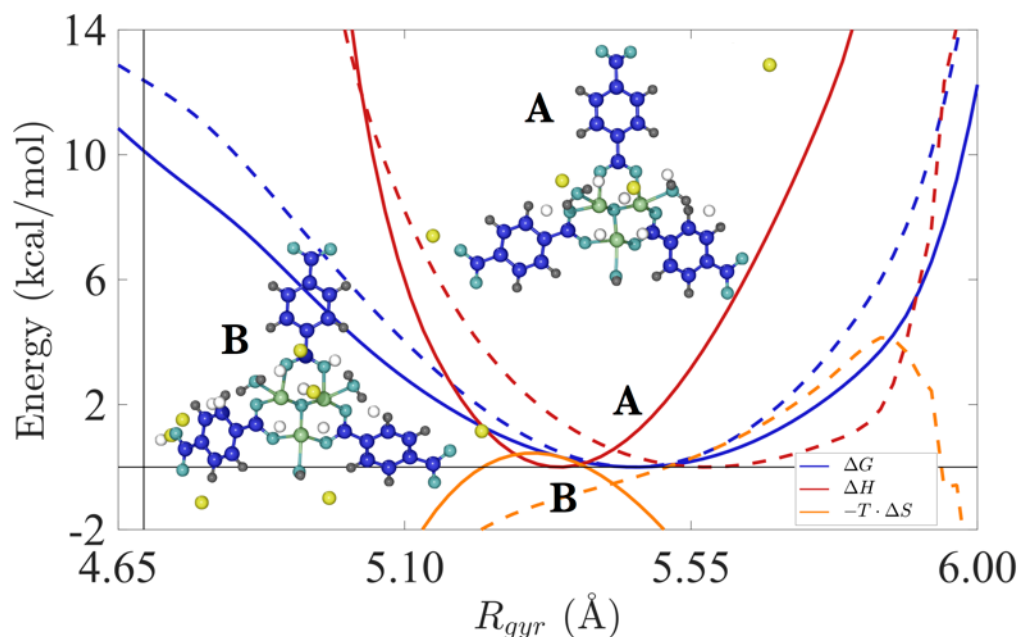


Figure 3-8. Energy profiles of MLA in water with 0.25M NaF at 298 K projected on R_{gyr} at 298 K (solid lines) and 493 K (dashed lines). The free energy (blue) profile along with enthalpic (red) and entropic (orange) contributions are shown. Structures dominating the free energy (A) and enthalpic contribution (B) profiles are provided. A thin horizontal line corresponds to zero on the vertical axis. A thin vertical line refers to the average R_{gyr} value of each half-SBU in the crystal.

Starting with MLA, free energy projected on the space of R_{gyr} presents an appreciably wider profile in the vicinity of its minimum in presence of ions when compared with the case of pure water. This is translated to an increase of the number of structures that share similar probabilities of occurrence in solution. This behaviour can be explained as ions tend to enrich the conformational landscape of half-SBUs; thus, more structures are found with similar R_{gyr} values as ions have a variety of ordering themselves on the metal centre of the molecules. This effect increases degeneracy in collective variable space.

Free energy is dominated by the enthalpic contribution while the entropic contribution and the representative structures of the free energy and enthalpy minima are very similar as they can be seen in Figure 3-8. At last a comparison of the enthalpic contribution in water in absence and presence of ions shows that when ions are present, more compact configurations are favoured. The difference between the

minima of the enthalpic contribution in the two cases (pure water, water with 0.25M NaF) is approximately 0.6 Å.

Furthermore, the trajectory in potential energy space is monitored throughout the simulation. A sharp decrease in the potential energy, calculated by summing all contributions involving the solute molecules, is identified when the chromium atoms at the metal centre are well coordinated with fluoride anions. In more detail, this rapid shift in the trajectory of the potential energy takes place when three chromium atoms are coordinated with two F^- . After this event, a third F^- approaches the metal centre and interacts strongly with the chromium atoms for the rest of the simulation time. Consequently, the anions restrict the flexibility of the molecule by hindering the movement of the linkers that become more rigid when ions are interacting with the metal centre.

In summary the entropic and enthalpic contributions to the free energy shed light to the different behaviour of molecules in absence and presence of ions. These present distinctly different minima when ions are present than in the case of pure water. Nevertheless, the free energy landscapes are dominated by structures at the same value of R_{gyr} (5.5 Å), while in presence of ions this landscape is much wider around the minimum. In agreement with the simulations in pure water, enthalpic and entropic contributions are highly contrasting. Enthalpy now favours more compact structures than free energy due to a small cluster of ions interacting strongly with the metal centre. Energy profiles for MLA in presence of ions at a concentration of 0.25M in water are available in Figure 3-8.

3.4.2.2 Temperature effects

The effect of temperature (493 K) is examined for MLA with 0.25M NaF water using the same protocol (use of thermostat and no barostat) as in pure water. The free energy profile shows negligible changes at higher temperatures when compared to the one computed at room temperature. More elaborately, the free energy minimum is located at R_{gyr} equal to 5.47 Å, at 493 K, as it can be seen in Figure 3-8, that is the same value as the one obtained at 298 K. The enthalpic contribution is dominated by less compact structures at 493 K and its minimum corresponds to larger R_{gyr} values than the free energy minimum in contrast with the simulations at 298 K. In more detail, the minimum enthalpic contribution is located at 5.57 Å (493 K) instead of 5.35 Å at room temperature (298 K). At last, the entropic contribution also presents significant changes from the one obtained at 298 K as it is dominated by more compact

structures at 493 K. More precisely, the minimum entropic contribution is located at 4.49 Å (493 K) instead of 4.65 Å at room temperature (298 K). The difference in the R_{gyr} values that dominate the entropic contribution is not as large as for the enthalpic contribution for MLA in water with ions.

The energy profiles obtained at 493 K show that enthalpy favours less compact structures and entropy more compact configurations in comparison with the ones favoured at 298 K, while the free energy profile remains unchanged. More succinctly, entropy favours configurations even further and much more compact from the free energy minimum than at 298 K. Therefore, the increase in temperature results in a stronger domination of the free energy profile by its enthalpic contribution.

Table 3-3. Sampling errors (kcal/mol) in water with 0.25M NaF at 493 K.

Monomer	Error $F(R_{gyr})$	Error $F(U)$
MLA	0.37	0.70

The sampling errors are available in Table 3-3. These are slightly larger than the errors associated with the simulation at 298 K, 1 bar.

3.4.2.3 MLB and MLC in 0.25M NaF

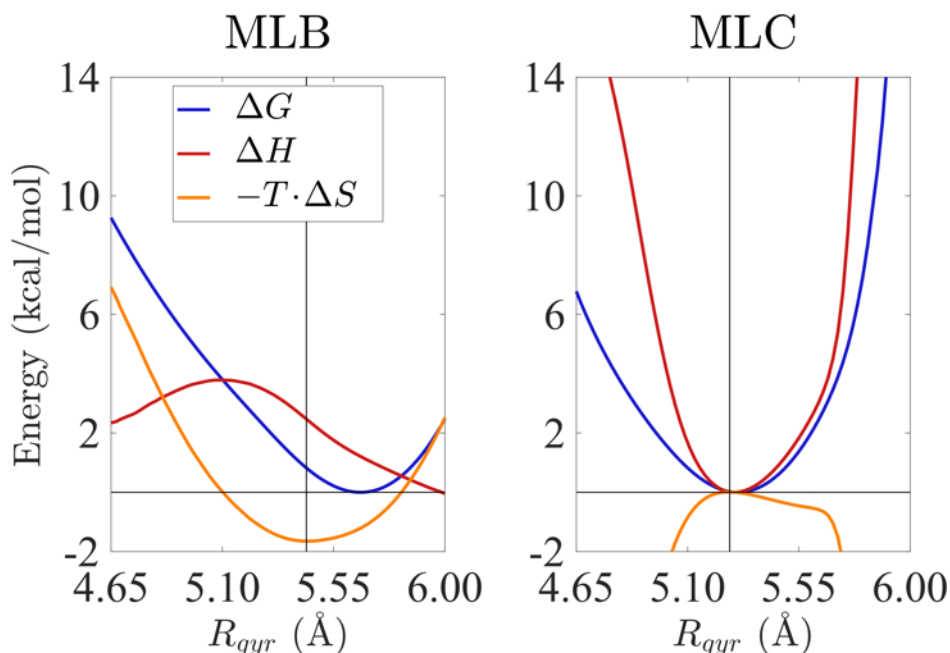


Figure 3-9. Energy profiles of MLB (left panel) and MLC (right panel) in water with 0.25M NaF at 298 K projected on R_{gyr} . The free energy profile is represented by a blue curve, while enthalpic and entropic contributions are represented by red and orange curves respectively. A thin horizontal line corresponds to zero on the vertical

axis. A thin vertical line refers to the average R_{gyr} value of each half-SBU in the crystal.

In addition to MLA, the energy profiles of MLB and MLC are evaluated on the space of R_{gyr} . Their energy profiles are depicted in Figure 3-9. The introduction of ionic species does not result in significant changes for the free energy profiles with respect to those obtained in pure water. Nevertheless, the underlying enthalpic and entropic contributions are significantly different. For MLB, enthalpy presents a minimum for values close to 6 Å. This means that the strongest enthalpic contribution is observed for larger R_{gyr} values than those dominating free energy. On the other hand, entropy presents a contribution that is dominated by compact structures due to the interaction of ions with the metal centre that enhances the structural landscape of half-SBUs. Nevertheless, these are not as compact as the ones that dominate entropy in pure water. Furthermore, the rich entropy landscape expands the well on the free energy profile around the minimum as structures with close R_{gyr} values have similar probabilities of formation due to entropy.

Ionic species affect the underlying energy profiles of MLC as they are also appreciably different than in pure water. The free energy landscape of MLC in presence of ions, at a concentration of 0.25M, is dominated by enthalpy. Also, enthalpy is less wide than free energy around their minimum. This means that their difference ($G - H$) is negative. Consequently, the entropic contribution presents a maximum at the same location of the free energy and enthalpy minima. In MLC, the ionic cluster interacts strongly with the metal centre; hence reducing number of accessible configurations due to hindering linker rotation. The terephthalate linkers are stabilised by this interaction thus rendering the entropic contribution very weak in the vicinity of the free energy and enthalpy minima. This is a different behaviour caused by the presence of ions in MLC when compared with MLB.

Overall, the behaviour of MLB and MLC is highly affected by the presence of ions. The inherent degeneracy of free energy profiles on the space of R_{gyr} is lifted by analysing enthalpic and entropic contributions. Also, the versatile behaviour of ionic species in solution is understood in MLB and MLC. In MLB, ions enrich the structural landscape resulting to a wide free energy well. Also, entropy drives MLB to the crystal structure in presence of ions as the reference R_{gyr} in the crystal is close to a minimum for the entropic contribution. In contrast, in MLC, ions interact strongly with the metal centre and the free energy and enthalpy minima are located at the reference R_{gyr} value in the crystal. Therefore, the conformer corresponding to the crystal is stabilised

by the presence of ions due to a strong enthalpic interaction between the ionic cluster and the metal centre of the half-SBU.

Table 3-4. Sampling errors (kcal/mol) in water with 0.25M NaF at 298K.

Monomer	Error $F(R_{gyr})$	Error $F(U)$
MLA	0.33	0.44
MLB	0.12	0.52
MLC	0.33	0.44

The block error analysis follows the same rationale as in water. The sampling errors are provided in Table 3-4. At last, simulations at a higher concentration of ions have been performed. Results and analysis of the aforementioned simulations are available in the appendix (section A.4).

3.4.3 Half-SBUs in DMF

Apart from ionic species, the environment of the solute can be changed by introducing a different solvent that is N, N-dimethylformamide (DMF). The same analysis is carried out in DMF and the results are compared with those obtained in water.

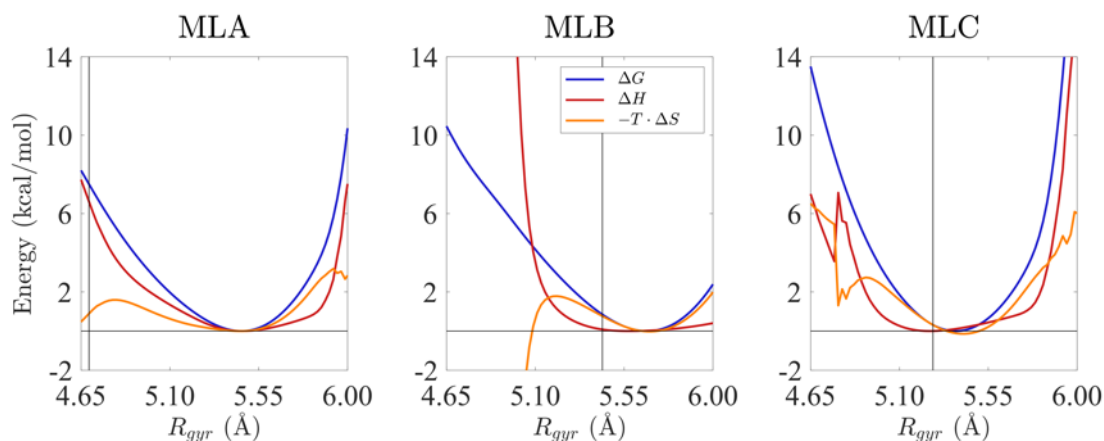


Figure 3-10. Energy profiles of MLA, MLB and MLC in DMF at 298 K projected on R_{gyr} . The free energy profile is represented by a blue curve, while enthalpic and entropic contributions are represented by red and orange curves respectively. Plot characteristics are consistent with Figure 3-6.

Starting with MLA, the entropy and enthalpy profiles are appreciably different in DMF in comparison with the ones in water. More importantly, the enthalpic and entropic contributions are not contrasting, as they are in water, but they are similar as observed in Figure 3-10. In agreement with the simulations in water, the entropic

contribution presents its minimum for low values of R_{gyr} (less than 4.8 Å). Therefore, in DMF compact conformers of MLA are entropically favoured. The enthalpic contribution presents a minimum at the same region of R_{gyr} as free energy. In both water and DMF, enthalpy favours more open conformers than entropy.

In summary, MLA in DMF presents a similar free energy profile with the one in water. Despite this fact, the contributions by enthalpy and entropy are appreciably different than in water. Also, MLA in DMF does not present deep entropic wells due to a flat entropic contribution as the low values of R_{gyr} do not present very high potential energy in contrast with water. Therefore, the number of entropically accessible states is much lower in DMF. This observation supports the fact that MLA conformers are more rigid in DMF as this solvent restricts the structural flexibility of MLA in solution when compared with water. Consequently, water offers greater flexibility of the molecule through an underlying rich entropic landscape, compared to a flat entropic profile in DMF.

Apart from MLA, the energy profiles of MLB and MLC in DMF are examined. The entropic and enthalpic contributions are highly dissimilar in DMF when compared with the ones in water. In the case of MLB, two distinct trends appear for small and large values of R_{gyr} . In R_{gyr} values less than 5.2 Å, entropy dominates the energy landscape. This behaviour is similar to MLA in pure water as the molecule has numerous ways to pack when contracted; hence, high energy configurations are present in this region of R_{gyr} . Free energy profile is dominated by entropy in the region of its minimum as the enthalpic contribution is flat around the free energy minimum; hence it is not the relative differences in the energy of the configurations that shape the free energy profile.

At last, the energy profiles of MLC in DMF are assessed. These are very similar to the energy profiles obtained in pure water. An interpretation of this behaviour is that DMF does not result in obvious changes for enthalpic and entropic contributions to the free energy projected on this collective variable. This is only the case only when comparing the energy profiles in pure water and pure DMF. It should be reminded that MLC is the conformer that is more likely to be in compact form compared with MLA and MLB. This observation leads to the conclusion, that MLC is not highly affected by solvent effects.

In summary, MLB in DMF presents an energy landscape similar to MLA in pure water as a bimodal entropic profile is observed. Entropy favours contracted conformers, but it is also the reason for the shape of the free energy profile around its

minimum. The enthalpic contribution is stronger for values greater than 5.2 Å, while below this cut-off, high energy structures emerge in the landscape as projected on R_{gyr} . Nevertheless, the enthalpic contribution is flat after 5.2 Å; hence entropy shapes the free energy well in this region. MLC presents a considerably different behaviour as, from a qualitative point of view, the energy profiles of MLC are solvent-independent for these two pure solvent environments.

Table 3-5. Sampling errors (kcal/mol) in DMF at 298K.

Monomer	Error $F(R_{gyr})$	Error $F(U)$
MLA	0.14	0.34
MLB	0.09	0.30
MLC	0.16	0.33

The block error analysis follows the same rationale as in the simulations in water. The sampling errors are available in Table 3-5.

3.4.4 Solvation shells

The manner in which the solvent affects the solute is of high importance for determining the behaviour of the solute from both dynamics and thermodynamics perspectives. This behaviour is predominantly determined by the solvent molecules that are interacting closely with the solute, usually referred to as the solvation shell. The impact that the size of the solvation shell has on the enthalpic and entropic contributions to the free energy is investigated in this section. It should be noted, that only the short-range interactions are evaluated in this analysis as the solvation shells are formed in one periodic image. The enthalpy and entropy profiles are calculated only for MLA in pure water and water with 0.25M *NaF*.

The motivation for this analysis stems from previous studies on the entropy-enthalpy compensation [223]–[229]. Enthalpic interactions involving the solute and neighbouring solvent molecules can result in considerably different entropy between the solvent molecules within a distance from the solute and other solvent molecules that are located at a large distance from the solute.

In a recent work, Schauperl et al. [230] showed that the force field choice for water does not have a significant impact on the entropy-enthalpy compensation phenomenon. Exception to this observation is the TIP3P [192] water model. This presents a lower degree of order for the solvent molecules close to the solute. Nevertheless, this observation refers to amino acids that do not present any close connection with the current work. Furthermore, this choice resulted in differences in the free energy profile in the work described in [230]. In this work, the energy profile is not appreciably affected by the change in the water model as a 170 ns simulation with the TIP4P [192] water model was used to validate that findings for the most interesting isomer, MLA, do not rely strongly on the water model. This comparison is provided in Figure A-4.

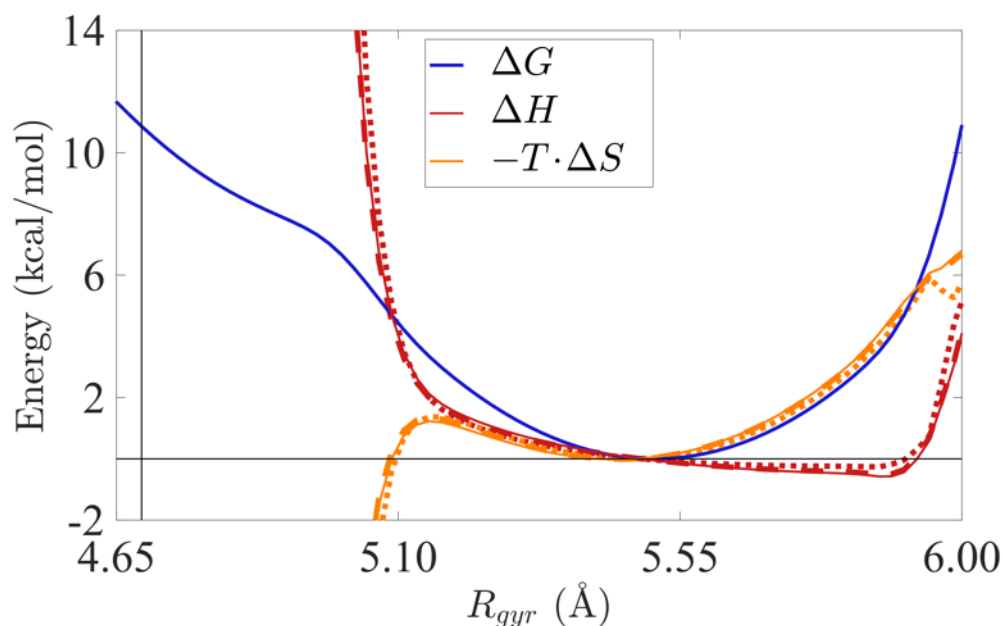


Figure 3-11. Energy profiles of MLA in pure water at 298 K in terms of R_{gyr} . Enthalpic and entropic contributions for three different sizes for the solvation shell are provided. Blue: free energy, red: enthalpic contribution, orange: entropic contribution profile. Line types distinguish between solvation shell sizes, dot: 2.5 Å, bold dash: 5 Å, solid: 10 Å. A thin horizontal line corresponds to zero on the vertical axis. A thin vertical line refers to the average R_{gyr} value of each half-SBU in the crystal.

Solvation shells range from 2.5 Å to a size equal to half the edge of the simulation box that is 20 Å. The smallest size for the solvation shell, 2.5 Å, results in considering only the very strong interactions between the solute and the solvent. More elaborately, the very strong repulsion and attraction forces result in large differences in the entropic and enthalpic contributions; hence they are inconsistent with the energy profiles obtained when the whole box is considered. Consequently, this size is very small to adequately take solvent effects into account. This is more obvious when the 5 Å solvation shell is studied. The change in the energy profiles between the two sizes is observed in Figure 3-11. Further apart, a solvation shell of 7.5 Å shows qualitatively consistent energy profiles to the ones obtained with a size of 5 Å. The same qualitatively converged behaviour is shown for sizes greater than 7.5 Å as expected. Therefore, a solvation shell of 5 Å in water can provide a qualitatively accurate energy landscape. The respective profiles for 2.5, 5 and 10 Å solvation shells for MLA in water are provided in Figure 3-11.

Furthermore, quantitative analysis is essential in order to identify the size of the solvation shell that fully converges to the energy profiles obtained in the bulk. In

this effort, three sizes for the solvation shell that are greater than 7.5 Å are evaluated. Sizes of 10, 15 and 20 Å present similar contributions to the free energy. In more detail, the average and maximum differences in the enthalpic contributions are calculated. Solvation shell sizes greater than 7.5 Å show differences that are below $k_B T$; hence this size can adequately represent the enthalpic contribution of the bulk. Further apart, for sizes greater than 10 Å, the enthalpic contributions present an average difference in the order of 10^{-5} kcal/mol. Therefore, the changes in the enthalpic contributions are negligible for size of 10 Å with respect to any larger solvation shell.

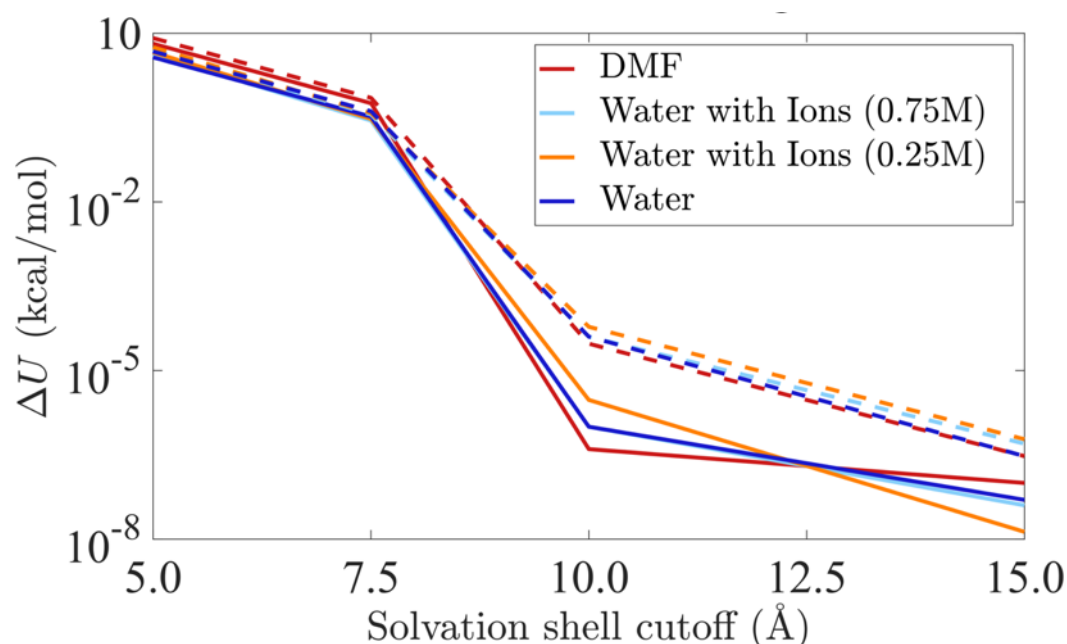


Figure 3-12. Solvation shell convergence. The maximum (dashed lines) and average (solid lines) difference in the profile of potential energy contributions, in the space of R_{gyr} , is calculated for every solvation shell size evaluated in this section. These are calculated in water (blue), with 0.25M (orange) and 0.75M (cyan) NaF and DMF (red).

The effect that the presence of ions and a different solvent environment have on the size of the solvation shell is also investigated. Ionic species in water result in the addition of more interactions in the calculation of the potential energy. Electrostatic interactions dominate over van der Waals between the solute and the ions; hence the net effect of the introduction of ions favours stronger interactions involving the solute overall, when compared with the case of pure water. Nevertheless, the size of the solvation shell required to obtain a fully converged enthalpic contribution does not differ from the case of pure water.

At last, the average difference in potential energy contribution profiles is calculated in pure water, DMF and water with 0.25M and 0.75M NaF . It should be noted that, the sum of contributions does not result in profiles that are exactly equal to the potential energy in water with 0.75M NaF and DMF where long-range interactions are not negligible. Nevertheless, the aim of this section is to determine the solvation shell that results in similar contributions to the potential energy as any larger shell.

The contributions to the potential energy are calculated within 5 Å of the solute and they are compared to a very large solvation shell of 20 Å, is in the order of 4 and 6.5 kcal/mol for water and DMF respectively. These are lowered below $k_B T$ for water (0.35 kcal/mol) and close to $k_B T$ for DMF (0.57 kcal/mol), when a solvation shell within 7.5 Å of the solute is used. A further increase to 10 Å yields an average difference of 10^{-5} - 10^{-6} kcal/mol, between these profiles and the reference ones at 20 Å. At last, a solvation shell of 15 Å results in average differences in the order of 10^{-7} - 10^{-8} kcal/mol. These observations lead to the conclusion that a solvation shell of 7.5 Å represents potential energy contribution adequately, while sizes of 10 Å, or greater, can yield profiles that consider solvent effects with high accuracy.

The convergence of the potential energy differences involving the solute in terms of the size of the solvation shell is available in Figure 3-12. The energy profiles in presence of ions with respect to the size of the solvation shell are provided in Figure A-5 in the appendix.

At last, this analysis is devoted to both studying the effect of solvation and increasing the computational efficiency of the simulation that is highly dependent on the number of solvent molecules and it is usually selected empirically. In more detail, the number of solvent molecules is determined by the size of the simulation box that is usually constructed empirically to include enough solvent molecules in one image; hence the bulk behaviour of the solvent is simulated through implementing periodic boundary conditions. In this study, the required number of solvent molecules can be directly calculated by the size of the solvation shell. In other words, a box that has as many molecules as in the 10 Å solvation shell can be used to accurately represent bulk solvent behaviour. Any larger size for the box yields very similar contributions to the potential energy as the 10 Å shell, but the cost is increased in a nonlinear fashion.

3.4.4.1 Number of molecules in solvation shell

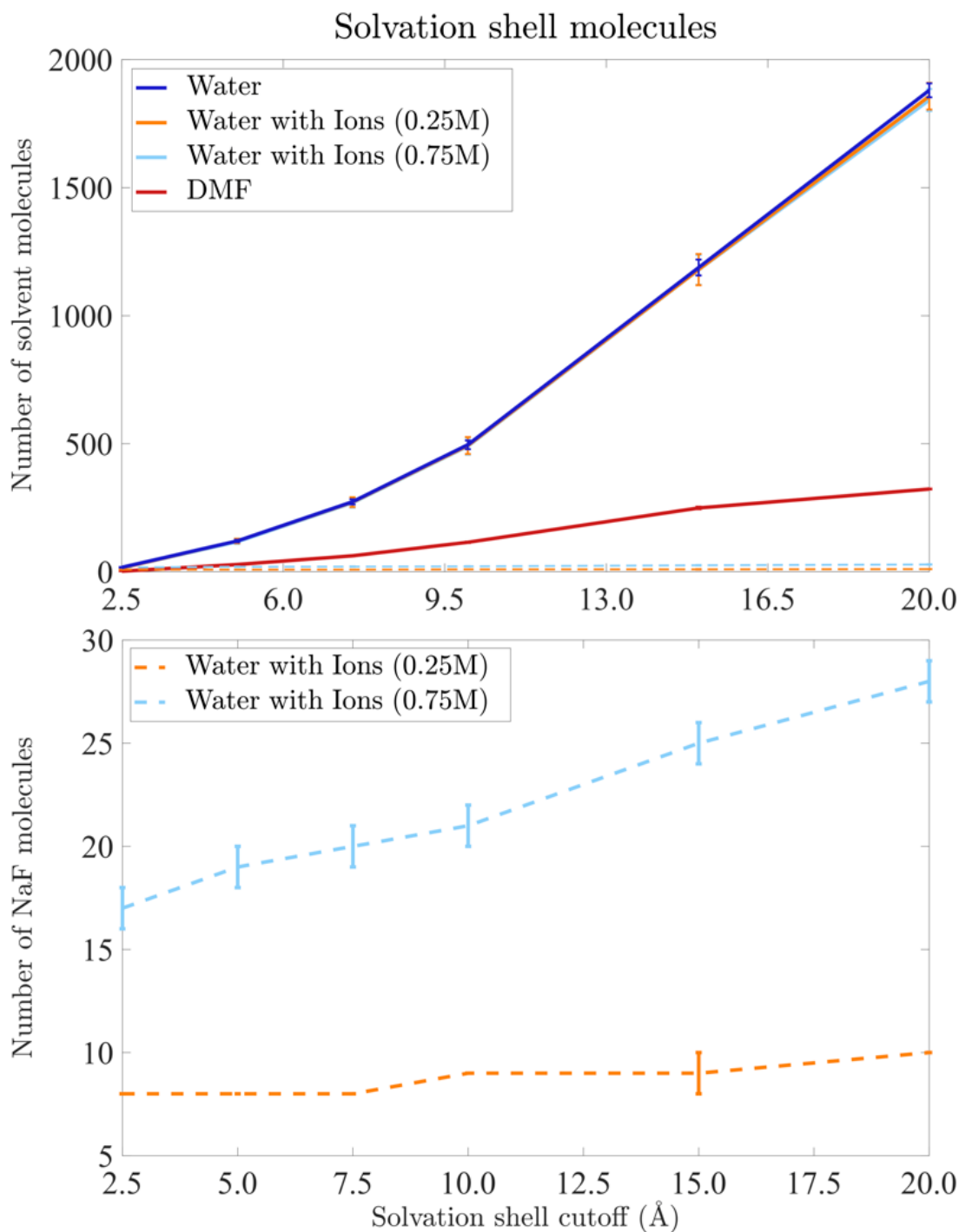


Figure 3-13. Average number of guest molecules with respect to the solvation shell size. The number of water molecules in absence (blue line) and presence of 0.25M (orange line) and 0.75M (cyan line) NaF is shown. The relevant plot for DMF is the red line. The number of NaF molecules present in the solvation shell is shown in dashed lines. Error bars result from the standard deviation.

Another important aspect is to provide a quantitative estimate of the size of the system in every solvation shell. The solute always consists of 60 atoms; hence more focus is shifted on the number of solvent molecules present in the solvation shell.

The number of solvent molecules is identified for every simulation and solvation shell size. The relevant profiles are provided in Figure 3-13. More specifically, the number of atoms or ions in each case is calculated and then divided by the number of atoms in the solvent (3 atoms for water, 12 for DMF) or ions in NaF (2 ions). Results from this analysis provide the average number of solvent molecules along with a standard deviation.

The solvation shell of 10 Å in water contains approximately 490 water molecules. In the simulations with DMF, there are only 115 solvent molecules for the same solvation shell size; hence the number of DMF molecules is approximately 4 times smaller than the number of water molecules. It should be noted that including these numbers of solvent molecules in each case can provide an accurate representation of enthalpic and entropic contributions due to the presence of solvent as in any higher number of solvent molecules.

The 20 Å solvation shell contains approximately 1880 solvent molecules when water is used. The same solvation shell has less than 350 DMF solvent molecules. Consequently, the number of DMF molecules is more than 5 times smaller than that of water molecules.

At last, the number of NaF molecules remains rather unaffected as it is 9 for 10 Å shell and 10 for 20 Å shell at a concentration of 0.25M NaF in water. At a concentration of 0.75M, the relevant numbers of molecules are 21 for 10 Å shell and 28 for 20 Å shell; hence they are slightly affected by the change in the size of the shell.

3.5 Radial distribution functions

The radial distribution functions for MLA, MLB and MLC in water, in presence and absence of ions, and DMF are calculated in order to study the solvation process for the three isomers in different environments. The reference atoms are the central oxygen at the metal centre of each half-SBU, labelled Ou, and the oxygen of water or the nitrogen in DMF.

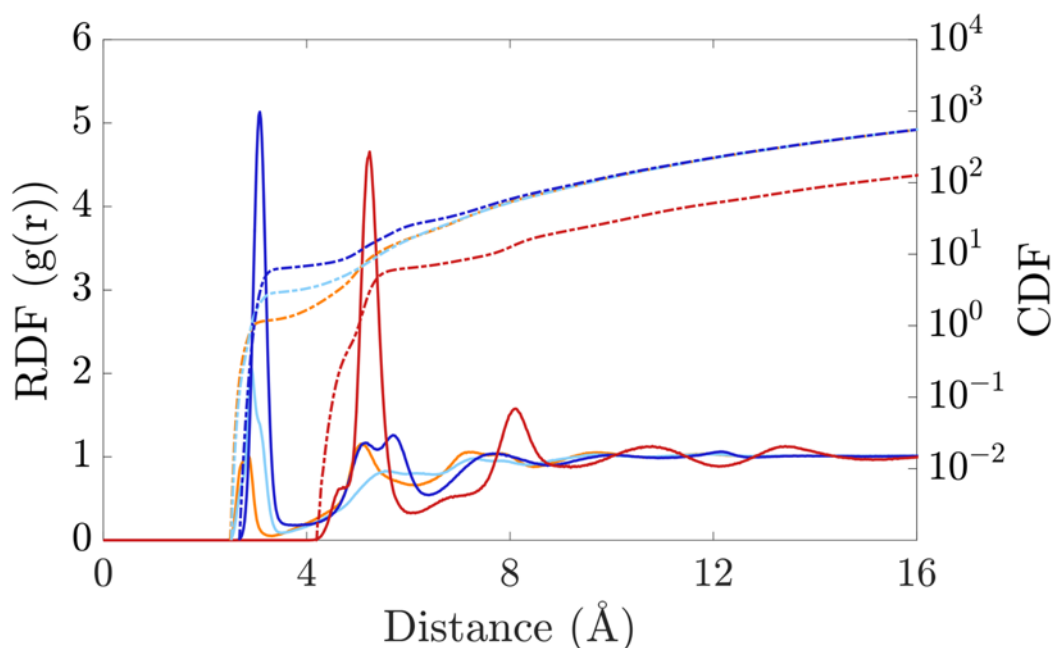


Figure 3-14. Radial (solid lines-left vertical axis) and cumulative (dot-dash lines-right vertical axis) distribution functions for central oxygen at the metal centre of MLA and oxygen of water in absence (blue line) and presence (0.25M-orange line and 0.75M-cyan line) of ions. In DMF (red line), the nitrogen atom is used instead of the oxygen in the case of water.

This analysis starts with isomer MLA in all three environments. The first solvation shell is located 3 Å away from the central oxygen of the metal centre in both pure water. This is similar (2.9 Å) in presence of ions at a concentration of 0.25M in water. Calculation of the area under the radial distribution function curve results in the cumulative distribution function from which it is observed that there are 3 molecules of water surrounding the metal centre in the first solvation shell.

The next peak in the radial distribution function curve is located at 5.2 Å in pure water as well as when ions are at a concentration of 0.25M in water. There exists a second solvation shell that consists of 13 water molecules. This is a significant increase when compared with the first solvation shell. At this distance away from Ou, the first solvation shell is observed in DMF. This consists of 3 molecules as the first solvation shell in water.

Moving to a slightly larger distance, 5.7 Å, the third solvation shell in pure water emerges with 20 molecules. At a similar distance, that is 5.5 Å, the second solvation shell of water with ions at a concentration of 0.75M is observed corresponding to a slightly lower number (18) of molecules.

The fourth solvation shell in pure water is located at 7.6 Å away from Ou consisting of 46 water molecules. The relevant shells for water with ions are located at lower distances (7.2 Å). Close to the fourth solvation shell of water, at 8 Å, the second solvation shell of DMF emerges which consists of 11 molecules.

Therefore, the number of water molecules is approximately 4 times larger than the number of DMF molecules at the same distance away from MLA. This observation is of significant importance as it can provide a reasonable explanation why a larger cut-off is needed in order to accurately consider solvent effects in water and DMF.

Both the size of the solvent molecule and the electrostatic interactions between solvent and solute atoms are responsible for these differences in the radial and cumulative distribution functions. In more detail, DMF is a larger molecule and the electrostatic interactions between the solvent and solute (MLA) atoms are weaker than in water.

Furthermore, the presence of ions in water slightly change the radial distribution functions due to the interactions between ions both with the solvent molecules and the metal centres of the half-SBUs. The first two peaks are located at very similar distances. Nevertheless, the peak after 7 Å is at smaller distances in presence of ions due to the effect that the presence of fluoride anions has on the structure of water. In more detail, Gallo et al. [231] found that F^- , an anion with high charge density, affects the hydrogen bond network of water; hence it alters the structure of the liquid and favours a higher density for the solvent as it is under pressure.

The radial distribution functions in water, in presence and absence of ions, and DMF are provided for MLA in Figure 3-14. For MLB and MLC, the corresponding plots are available in Figure A-6 and Figure A-7 in the appendix.

3.6 Conclusions on the flexibility of half-SBUs

The analysis of half-SBUs in different environments yields important observations and conclusions based on the changes of their flexibility depending on their surroundings. The evaluation of enthalpic and entropic contributions to the free energy improves the understanding on how to fine-tune the thermostructural characteristics of MOF building units.

In pure water, MLA has contrasting enthalpic and entropic contributions unlike MLB and MLC, when projected on R_{gyr} . In further detail, entropy favours compact structures unlike enthalpy for MLA at 298 K. An increase in temperature results in the entropic contribution being dominated by even more compact conformers in the case of MLA. The structures in the crystal correspond to those favoured by entropy for MLA and MLB, and enthalpy for MLC.

Introduction of ions enriches the structural landscape of half-SBUs. Ions stabilise structures due to the additional interactions that contribute to the potential energy of the system. This observation is reflected on the enthalpic and entropic contributions to the free energy, while it is indistinguishable when observing the free energy profiles only.

In MLA, enthalpy is dominated by more compact structures in presence of ions than in pure water as the rotational movement of the terephthalate linkers is hindered by strong interactions between ions and atoms of the metal centre. Also, the entropic contribution minimum corresponds to more compact structures than the free energy minimum.

The effect of temperature is more pronounced when the composition of the system is altered, and ions are present in solution. At this stage, it should be reminded that experimental synthesis is carried out in water with ions at 493 K in an autoclave for 8 hours; hence synthesis is carried out under high pressure and in the liquid state [38]. Enthalpy is dominated by more open structures at 493 K than at 298 K. Moreover, free energy favours more compact structures than enthalpy in contrast with 298 K. The enthalpic contribution is flatter at 493 K, around its minimum, as more structures possess the same energy. This is also reflected by the monotonically changing entropic contribution close to the free energy minimum. In contrast with enthalpy, entropy is still dominated by very compact structures and these are even more closely packed than in pure water.

MLB presents a different behaviour as enthalpy is highly dissimilar with respect to free energy; hence free energy is dominated by entropy. In contrast, MLC is stabilised in water with ions due to interactions between its metal centre and ions and its free energy profile is dominated by enthalpy. Also, the enthalpically favoured conformer is very similar to the reference structure in the crystal.

Solvent effects alter the enthalpic and entropic contributions while the free energy profile is similar to the one obtained in water. In particular, DMF results in a decrease of accessible states for MLA conformers than in water. This is reflected on the absence of deep wells in the entropic contribution. Conversely, compact MLB conformers in DMF are entropically favoured as the enthalpy and entropy profiles resemble those of MLA in water. MLC is stabilised by interactions with ions that result and the enthalpic contribution minimum corresponds to the reference structure in the crystal, while the free energy minimum is shifted to slightly less compact structure due to the entropic contribution.

Consequently, fine-tuning the composition of the system can lead to appreciably different entropic and enthalpic contributions. The reference structure in the crystal can be dominated by either enthalpy or entropy depending on the environment of each half-SBU. Furthermore, the degeneracy in the free energy profiles that is the result of the choice of a certain collective variable can hide certain characteristics of the profile. In fact, the free energy profiles are not appreciably affected by the change of composition or temperature. Nevertheless, the effect of these alterations on the system are visible on the enthalpy and entropy profiles. Therefore, the understanding of how certain conditions affect the flexibility of MOF building units is enhanced with the analysis of free energy into underlying contributions.

These observations lead to the conclusion that static potential energy calculations can provide a limited description of the conformational landscape of MOF building units. This can be rather inadequate in predicting the most probable structural arrangements of half-SBUs in various conditions. Furthermore, the drivers to the conformational flexibility of building units during MOF assembly can be understood when considering entropic and enthalpic contributions to the free energy.

Ultimately, the study of enthalpic and entropic contributions to free energy provides useful insights of how conditions (e.g. temperature) and changes in composition (e.g. introduction of ions, change of solvent) of the mixture affect the flexibility of MOF precursors. In more detail, the differences in free energy profiles are

insignificant with a change in either temperature or composition. Nevertheless, these changes appreciably affect the enthalpic and entropic contributions to the free energy.

Introduction of ions leads to an enriched configurational landscape around the free energy minimum, while the free energy profile is more strongly dominated by enthalpy as ions stabilise the most probable conformers. This is apparent from the trajectory of atomic positions, but it is not perceptible when observing the differences in the free energy profile when compared with the one computed in water. Also, higher temperatures shift the minimum of the enthalpic contribution as less compact conformers are stabilised. At last, a bulkier solvent, DMF, results in similar contributions to free energy as isomer flexibility is hindered in comparison with water.

This interplay of enthalpic and entropic contributions provides a mechanistic understanding of how isomer flexibility is affected by changes in synthesis conditions and mixture composition. Furthermore, entropic and enthalpic contributions can be fine-tuned in order to stabilise certain configurations of isomers. In this manner, the flexibility of isomers can be hindered or promoted under specific circumstances and this analysis can be used to evaluate these changes quantitatively on collective variable space. Thorough understanding of how isomers respond to specific changes in their environment is key to predict the optimal conditions for synthesis. Therefore, regulating configurational isomerism can be achieved through a careful setup of the synthesis mixture and conditions. Finally, this can prove beneficial for the crystallinity of the MOF as isomers can be stabilised at configurations that promote crystal-like SBUs rather than physically emerging defects.

Chapter 4

Half-SBU Dimer Interactions

This chapter is concerned with the analysis of interactions between half-SBU couples in solution. The results of this chapter have been published in the Journal of the American Chemical Society (see ref. [188]). The formation of half-SBU dimers from all possible couples of isomers MLA, MLB, MLC is investigated. For the sake of convenience, hereafter the couples are named AA, AB, AC, BB, BC, CC.

This is a step further from evaluating the flexibility of isolated half-SBUs in solution (Chapter 3). Also, it can provide useful insights on how to model assembly of multiple half-SBUs in solution (Chapter 5) at a considerably lower computational cost. In section 4.1, the attachment-detachment process is studied for half-SBUs in water. This section includes the elaborate analysis of a dimer, namely AA (section 4.1.1), estimation of convergence of differences between states featuring on the free energy surface (section 4.1.2). Study of the SBU rearrangement process (section 4.1.3) as well as evaluation of the enthalpic and entropic contribution (section 4.1.3.1) and temperature effects (section 4.1.3.2) follows. At last, conclusions from the study of dimers in pure water are presented in section 4.1.4.

Departing from simulations in pure water, ionic species are introduced in section 4.2. The AA dimer is discussed again in detail (section 4.2.1) at increasing concentrations (sections 4.2.2-4.2.7). Conclusions drawn for this dimer in water with ions are presented in section 4.2.8. Convergence analysis is conducted and presented in section 4.2.9. The rest of the possible dimers are discussed collectively in section 4.2.10. The equilibrium distribution of species is calculated in presence of ions and resulting profiles are discussed in section 4.2.11. This is followed by collectively assessing the effect of ions at increasing concentrations on the equilibrium probability of crystal-like units (section 4.2.12). At last, a comparison of findings with experiments is presented in section 4.2.13.

Finally, solvent effects are evaluated in section 4.3 through simulations of half-SBU dimers in pure DMF (section 4.3.1) as well as DMF with ions at increasing concentration (sections 4.3.2 and 4.3.3). Conclusions from the analysis of dimer interactions in this solvent are discussed in section 4.3.4; thus completing this chapter focused on the analysis of interactions between half-SBU couples in various environments in terms of guest molecules present in the system.

4.1 Half-SBU dimers in water

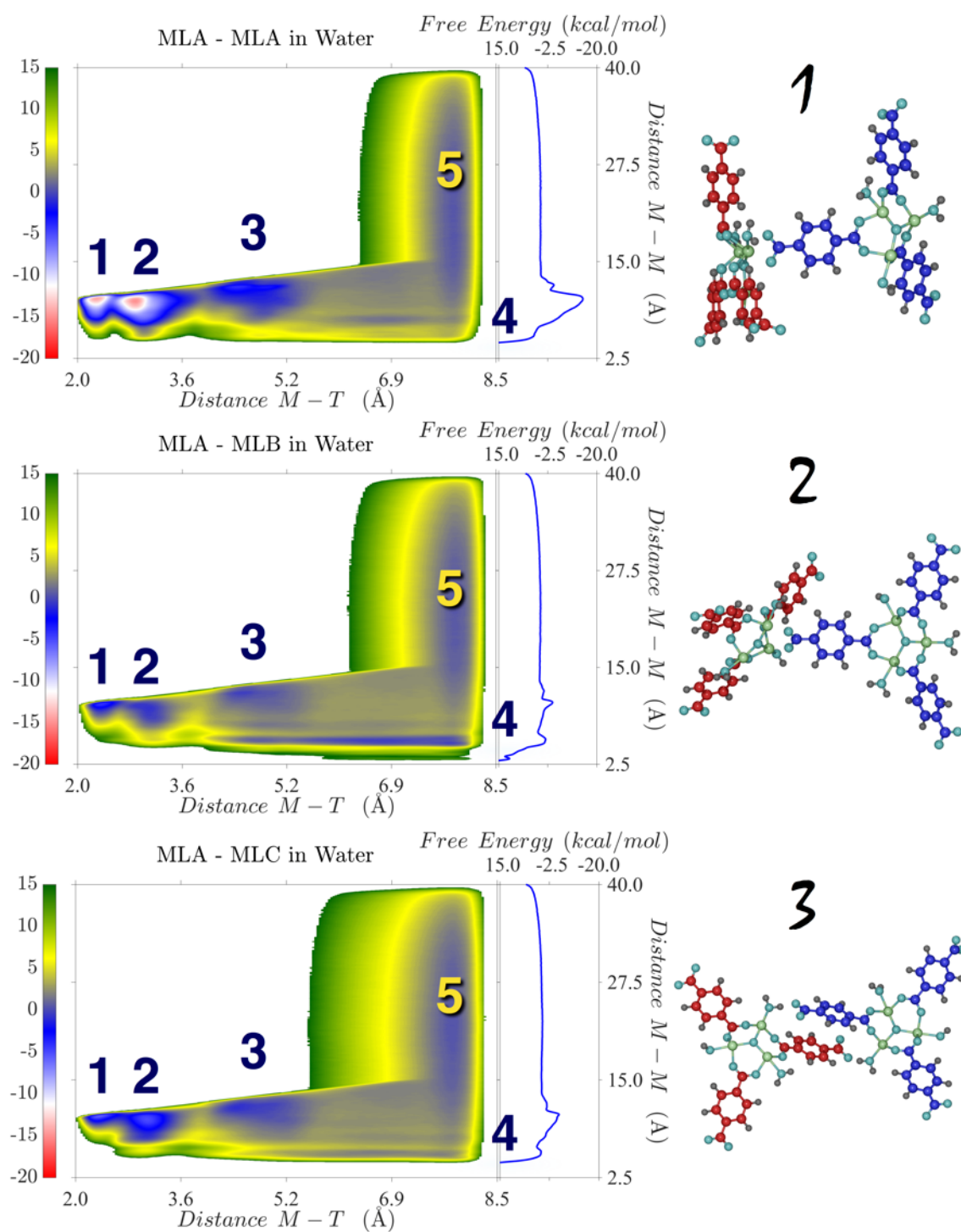


Figure 4-1. SBU Free energy surfaces of AA, AB and AC SBUs. Configurations corresponding to states 1-3 are shown on the side. The colour code for the structures is consistent with Figure 3-1 apart from carbon atoms which are coloured blue in one half-SBU and red in its counterpart. The structure shown in state 2 corresponds to 2C in AA.

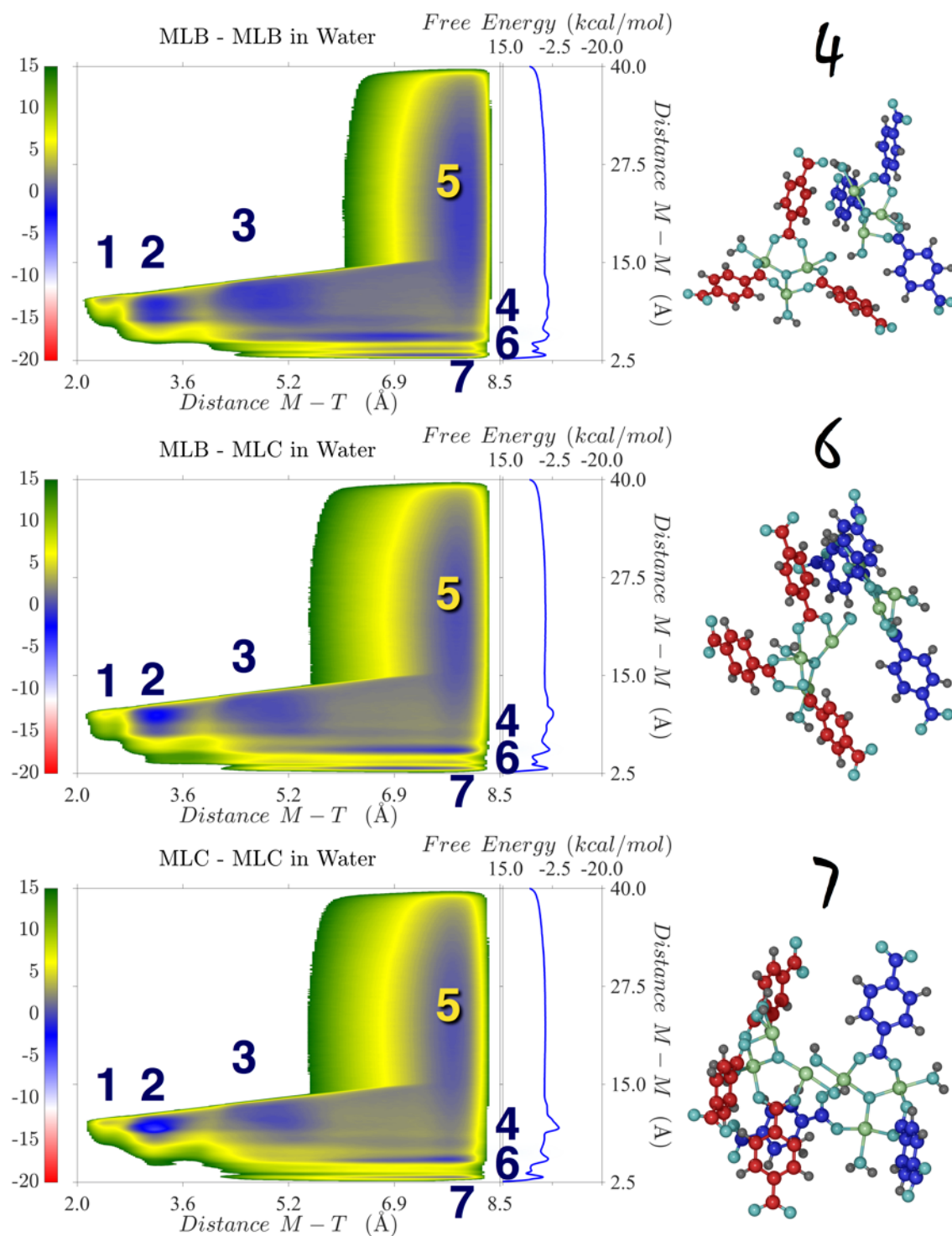


Figure 4-2. SBU Free energy surfaces of BB, BC and CC SBUs. Configurations corresponding to states 4, 6 and 7 are shown on the side. The colour code for the structures is consistent with Figure 3-1 apart from carbon atoms which are coloured blue in one half-SBU and red in its counterpart.

An enhanced sampling method, WTmetaD [204], has been employed in order to study the formation and disruption of an SBU. Free energy calculations were carried out with WTmetaD [204], for an extended simulation time (7 μ s per SBU without ions, 1 μ s per SBU with ions). It should be reminded that experimental synthesis is carried out in water, and in presence of ions, at 493 K with species placed in an autoclave for 8 hours [38]; hence synthesis takes place in liquid state in agreement with the simulations conducted in this chapter. Conclusions agree with those from simulations at a higher temperature and larger scale (see Chapter 5).

This process is studied in detail as the resulting SBUs, alternatively called dimers, exhibit different conformers. Six states of interactions between monomers (1-4, 6-7) are observed in Figure 4-1 and Figure 4-2. States 3 and 4 correspond to oxygen-hydrogen interactions, while oxygen and chromium interact in 1 (single), 2 (double), 6 (single) and 7 (double). Therefore, interactions between the terminal carboxylic atoms with the metal centre of the adjacent half-SBU are named as M-T and interactions between the metal centres of the two half-SBUs are identified as M-M. Following this approach, states 1-3 correspond to M-T interactions, while 4-7 to M-M.

All possible couples of half-SBUs are evaluated; hence a comparison of dimers in terms of stability against disruption is straightforward through comparing the relative free energy difference between each state and state 5 (detached half-SBUs). Considering all meaningful states discovered in the free energy surface, it is observed that in AB state 1 is the most stable. In BB, state 1 is not present and 4 is the most stable. Nevertheless, all states are very weak with respect to state 5; hence the SBUs are prone to disruption. States 6 and 7 are present in absence of MLA. As a result, MLA does not favour the formation of SBUs with strong interactions between oxygen atoms at the metal centre of one half-SBU and chromium of its counterpart.

In all SBUs, except from AB and AC, state 2, featuring M-T interactions, is the most stable. In CC, state 1 corresponds to three O-Cr interactions (noncrystal-like). States 6 and 7 are only present for dimers in which MLA is absent and correspond to the bottom right section of the FES. These present similar M-T values as state 4, but considerably lower M-M values. This means that in these states the adjacent metal centres are at a closer distance.

Configurations corresponding to state 1 (except AC, CC) are similar to those found in a crystal lattice. These involve two oxygen atoms interacting with one chromium atom. Also, state 2 shown in Figure 4-1 is specifically named 2C as it

corresponds to the structure of an SBU found in the bulk of the crystal. Due to the degeneracy of state 2 in the M-T, M-M space, it is difficult to sample other structures in this region as 2C is mainly sampled in the simulations. Sampling of other conformers is not sufficient using these two distance CVs; hence another collective variable, the coordination between terminal carboxylic oxygen and chromium atoms, can distinguish between 2C and other structures in state 2. This was performed in the section dedicated to study the rearrangement of the SBU (section 4.1.3). Defects correspond to the states 3, 4, 6, 7. These are physically formed defects in contrast with a missing linker or missing cluster defect. A missing linker or cluster refers to a change in chemistry of the MOF and it is commonly discussed in the literature and summarised in the review of Taddei [140]. These engineered defects should be distinguished from the physically formed defects discovered through classical MD simulations during the early stages of MOF self-assembly in this work.

4.1.1 Analysis of the AA Dimer

The AA SBU is discussed in further detail as it presents the most stable conformers. Four states of dimer interactions (states 1-4) are observed. States 1 and 2C correspond to crystal-like conformers [38], [90]. In state 2C, there are two oxygen atoms of one terephthalate linker interacting with two chromium atoms at the metal centre of the opposite half-SBU. It should be mentioned that SBUs in the bulk of the crystal have the same terminal carboxylic oxygen-chromium coordination as 2C. Crystal-like interactions correspond to the SBUs with a relative orientation that highly resembles that in the crystal structure of MIL-101(Cr) as it was presented in the introduction (Figure 1-1).

At the same M-M distance, but in larger M-T distances another state can be seen. This is state 3 and it presents a single (3s) and a double (3d) interaction between a terminal carboxylic oxygen atom and a hydrogen atom that is attached to the opposite metal centre. In 3s, there is one O-H interaction and in 3d there are two interactions of this kind.

At last, state 4 corresponds to even larger M-T distances, while the M-M distance is rather constant. In this state, a single (4s) and a double (4d) interaction between oxygen and hydrogen atoms of the adjacent metal centres. As in state 3, 4s has one O-Cr and 4d has two O-Cr interactions present in the SBU.

Overall, configurations of AA in state 2 are the most stable, considering SBU conformers resulting from all possible combinations of half-SBUs. At state 2,

configurations with three and four terminal carboxylic oxygen-chromium interactions are also present, namely 2T and 2Q. Consequently, there is a configurational degeneracy in state 2, when this is projected on these 2 CVs, M-M and M-T, as previously mentioned. This degeneracy is evaluated thoroughly in the next section. At last, convergence analysis of this 7 μ s simulation shows that states 3 and 4 fluctuate within chemical tolerance ($1/\beta$), while states 1 and 2 show larger variations (27.25% and 22.55% of the mean value respectively).

4.1.2 Convergence Analysis

Convergence analysis provides ΔG estimates for transitions of interest with error margins. Results of average values along with corresponding standard deviations are provided in Table 1. These values are the time weighted averages of the free energy differences of all states with respect to state 5 that corresponds to non-interacting half-SBUs. AB, BC and CC are close to an estimate within chemical tolerance ($k_B T$). Also, states 3 and 4 have small uncertainty for all SBUs.

The aforementioned uncertainty is calculated as the standard deviation of the time weighted average. The worst cases are AA and AC, especially states 1 and 2 where the standard deviation is the largest. All other states show appreciably better converging profiles. The reason is the exceptional stability of conformers in states 1 and 2 that renders the dissociation process a rare event. Even if the sampling of the association-dissociation process is adequate as seen through the trajectories in the space of each CV, the deep free energy minima will slow down this process; hence a larger uncertainty is associated with these states. In weaker states, as 3 and 4, the standard deviation is up to the chemical tolerance of $k_B T$.

At last, the use of time weights provides an increase in the accuracy of the estimated values. The equilibration time at the start does not count the same as the last steps as simulation progresses. The reason is that new states are discovered in the course of the simulation. The convergence of the calculated value after these new states are visited should be the key in estimating the average and the associated standard deviation. Therefore, free energy differences between states are provided within a confidence interval in order to account for this uncertainty due to the limitation of sampling time.

Table 4-1. Differences between free energy minima of states 1-4, 6-7 and state 5 (detached half-SBUs, reference state). Values are provided for states shown in the corresponding FES profiles for the ion-free cases (Figure 4-1).

SBUs in water in absence of ions						
ΔG (kcal/mol) with respect to state 5						
SBU/ State	1	2	3	4	6	7
AA	-12.88 ± 3.51	-18.13 ± 4.09	-4.95 ± 0.65	$+0.97 \pm 0.41$	-	-
AB	-4.67 ± 0.78	-2.51 ± 1.06	-1.11 ± 0.39	-1.28 ± 0.54	-	-
AC	-5.42 ± 3.07	-4.40 ± 1.04	-1.04 ± 0.37	$+1.25 \pm 0.57$	-	-
BB	-	-0.65 ± 1.27	-0.09 ± 0.23	-0.20 ± 0.63	$+2.29 \pm 1.43$	-0.35 ± 2.48
BC	$+3.90 \pm 1.20$	-2.92 ± 0.71	-0.08 ± 0.10	-1.26 ± 0.32	$+2.54 \pm 1.03$	-0.29 ± 1.43
CC	$+2.47 \pm 1.00$	-4.55 ± 0.61	-0.38 ± 0.21	-1.12 ± 0.58	-	$+2.19 \pm 1.44$

The values for the ΔG of all states with respect to the detached state (state 5) are given in Table 4-1. These are the time-weighted averages along with the corresponding standard deviation.

4.1.3 SBU rearrangement

In the case of couples of half-SBUs interacting in a pure water solution, an ensemble of configurations in state 2 is observed. In these structures, 3 or 4 terminal carboxylic oxygens interact with 4 chromium atoms of the metal centres; hence a triple and a quadruple oxygen-chromium interaction are characteristic of this state. Therefore, these states are named 2T and 2Q in contrast with 2C that corresponds to a double oxygen-chromium interaction.

A separate simulation starting from a configuration in state 2 and exploring the phase space characterised by another collective variable is able to lift the degeneracy of “sub-states” in state 2. This collective variable is the coordination number between terminal carboxylic oxygens and chromium atoms as mentioned in the methods (section 2.3.3.3).

It should be noted that a coordination number of ~ 1.65 corresponds to 2C configurations, whereas values of ~ 2.5 and 3.35 are characteristic of 2T and 2Q respectively. States 2T and 2Q are characterised as noncrystal-like as they do not resemble the relative orientation and coordination between oxygen and chromium as

the SBUs in the crystal, unlike the 2C conformer. The resulting free energy difference between 2C and 2Q ($\Delta G_{2C \rightarrow 2Q}$) is around -13.7 kcal/mol.

4.1.3.1 Enthalpic and entropic contributions to the SBU rearrangement

In this section, the enthalpic and entropic contributions to the free energy profile obtained in terms of the coordination number between chromium and terminal carboxylic oxygens, as discussed previously, are evaluated. The same model as for isolated half-SBUs in solution is used for a couple of monomers in this section. Simulations were performed for 1.5 μ s at 298 K, 1 bar. The need of enhanced sampling in order to obtain accurate estimates of the free energy differences between relevant states is explained through analysing the unbiased simulation, where the lack of sampling is obvious (see section A.3).

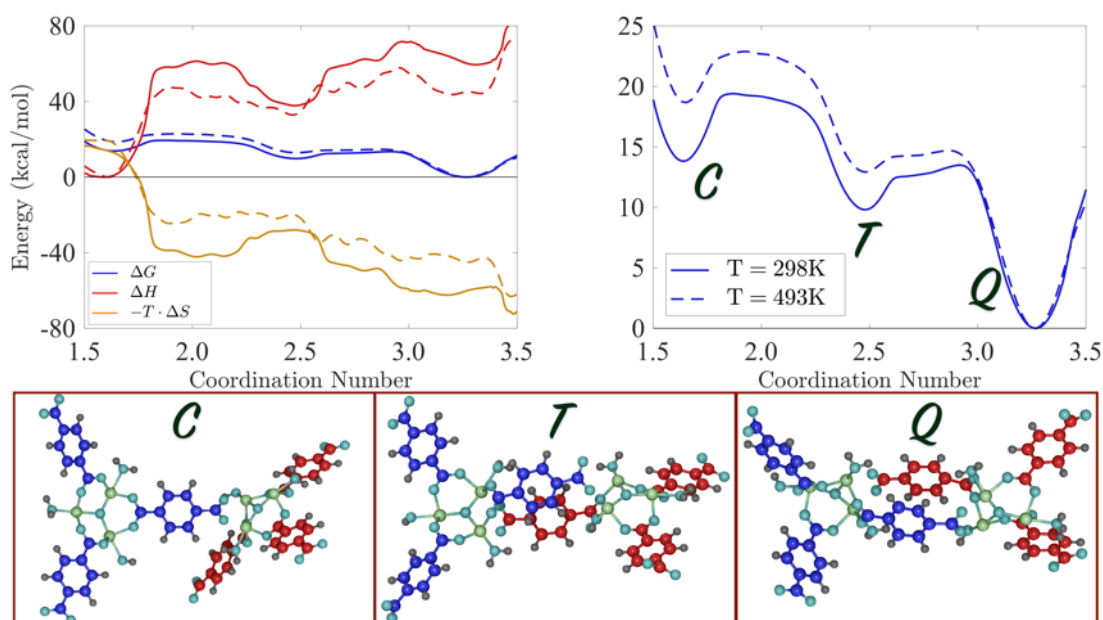


Figure 4-3. Energy profile the AA SBU rearrangement in water at 298 K (solid lines) and 493 K (dashed lines) with respect to the coordination number between terminal carboxylic oxygen and adjacent chromium atoms. Left panel: free energy along with the enthalpic and entropic contributions are represented by blue, red and orange plots respectively. Right panel: focus on the free energy landscape. Structures exhibited correspond to the 2C, 2T and 2Q states. The colour code is consistent with Figure 4-1.

The free energy profile is further analysed into enthalpic and entropic contributions. These provide insight into the nature of 2C and 2Q interactions. More elaborately, 2C is dominated by enthalpy, while 2Q is entropically favoured.

Therefore, the number of microscopic arrangements represented by state 2Q is larger than in 2T and 2C. The free energy profile shows a minimum at 2Q; hence it is dominated by entropy. The effect of the bias due to both WTmetaD [204] and V_r is negated through reweighting as mentioned in the methods section. The final bias can be used for reweighting as the bias has reached a stationary state in the simulation; hence it can be interpreted as quasi-static. Free energy profiles including enthalpic and entropic contributions and representative AA SBU conformers for states 2C, 2T and 2Q are provided in Figure 4-3.

Furthermore, the sampling error is calculated as the enthalpy and entropy profiles are not as smooth as in the isolated half-SBUs analysis. In this context, a block error analysis is carried out. The trajectory is partitioned into blocks of varying size, from 10 to 60 ns, and the average error is calculated for each block size. Then the average of all errors is calculated. This corresponds to the free energy projected on coordination number or enthalpy. As a result, the error for the free energy with respect to the coordination number is, $\epsilon(F(CN))$ is 0.07 kcal/mol. The respective error for the enthalpy, $\epsilon(H(CN))$ is 0.22 kcal/mol. These values show that the sampling error is rather small, and the enthalpy profile is inherently non-smooth. At last, this analysis provides confidence on the resulting profiles as these are generated from converged simulations.

In conclusion, the crystal-like SBU arrangement is favoured by the enthalpic contribution as it is stabilised through the interactions with water; hence it is the most stable SBU. Nevertheless, the appreciable entropic component of free energy drives the system towards 2Q, that is the most probable SBU arrangement.

4.1.3.2 Temperature effects

The same simulation and WTmetaD [204] protocol is followed for the investigation of the energy profiles at a higher temperature. This is 493 K and it has been justified earlier in this text (section 3.4). The same thermostat is used as before, but no barostat is applied. The system is in the liquid state as explained earlier (section 3.4). Simulations were performed for 1 μ s. It should be reminded that experimental synthesis is carried out in water, and in presence of ions, at 493 K with species placed in an autoclave for 8 hours [38].

State 2C is still favoured by enthalpy and 2Q by entropy at a higher temperature. A considerable change can be seen in the free energy profile, where the difference between 2C and 2Q is around -18.7 kcal/mol. Therefore, the absolute free

energy difference between the two states is about 5 kcal/mol larger than at 298 K. Furthermore, the differences between the enthalpic and entropic contributions are smaller at 493 K. The average absolute difference between the profiles is 89.3 kcal/mol at 298 K and 75.9 kcal/mol at 493 K. In further detail, the absolute difference between profiles at the region where 2C is located is around 16 kcal/mol at 298 K and 22.5 kcal/mol at 493 K. Therefore, the absolute difference between contributions is larger at a higher temperature in the region of the enthalpically dominated 2C. The absolute difference between the two contributions at the region of 2Q is 119 kcal/mol at 298 K and 87.9 kcal/mol at 493 K. In contrast with 2C, the absolute difference between contributions is smaller with higher temperature in the region of the entropically dominated 2Q. At last, the average entropic contribution is -24.4 kcal/mol at 298 K and -13.7 kcal/mol at 493 K. The respective averages for the enthalpic contributions are + 50.6 kcal/mol at 298 K and + 42.3 kcal/mol at 493 K.

In summary, the use of a higher temperature results in an increase in the absolute free energy difference between states 2C and 2Q. This is explained through the linear relationship between free energy and temperature ($\Delta G = \Delta H - T \cdot \Delta S$, explained in section 2.4.1). The enthalpic barriers are lowered with an increase in temperature as it can be seen from the respective profiles; hence enthalpy decreases from 298 to 493 K. Entropy increases with temperature leading to an overall decrease of the entropic contribution ($-T \cdot \Delta S$) to the free energy. In more detail, $\Delta G_{2C \rightarrow 2Q}$ is lowered from -13.7 kcal/mol to -18.7 kcal/mol leading to an increase in the absolute free energy difference between states 2Q and 2C. Therefore, the entropically favoured 2Q state becomes even more probable at a higher temperature than the enthalpically dominated 2C state. As a result, tuning of the synthesis temperature alone cannot lead to a change where 2C is favoured over 2Q. A change in the composition of the mixture is a possible way to change the entropy landscape in order to change the sign of the free energy difference between 2C and 2Q; hence make the crystal-like conformer more probable than 2Q. The block error analysis follows the same rationale as in the simulations in water. The sampling error $\epsilon(F(CN))$ is 0.13 and $\epsilon(F(H))$ is 0.39. All values are in kcal/mol.

4.1.4 Conclusions on the study of dimers in pure water

In the absence of ions, state 2Q for AA dominates the equilibrium distribution. The free energy difference from 2C is evaluated accurately in the simulations of the AA SBU rearrangement. State 2 of AA dominates over all FES of possible SBUs as it presents the largest absolute value for the negative free energy difference from state 5 (-18.13 kcal / mol).

AA SBUs are the most stable amongst all possible couples. Next are AC and CC. Nevertheless, both do not promote the formation of crystal-like conformers as MLC is in a structural arrangement that possibly favours defects. BB presents the weakest SBUs as MLB is very flexible; hence BB easily dissociates to the two half-SBUs.

States 3 features weak interactions between terminal carboxylic oxygen and hydrogen atoms of the metal centre. These are present in all SBU FES and the AA conformer is still the most stable. State 4 features interactions between oxygen and hydrogen atoms as well. Nevertheless, these belong to adjacent metal centres. States 6 and 7 feature oxygen-chromium interactions between two metal centres. These are accompanied by relatively high energy barriers as seen on the projection to the M-M space in Figure 4-1. They are not probable when MLA is present; hence they are linked with the other half-SBUs.

Overall, a rich structural landscape is explored. The probability of formation for each of the conformers is evaluated through the free energy landscape. State 2 of AA is the most probable amongst all SBUs. Furthermore, it is the only state where a degeneracy in the 2 CV space can be seen as 2Q is sampled during the simulations. Conformer 2Q is not sampled for the other SBUs over the 7 μ s trajectories. This state adds to the number of possible conformational isomers to the MIL-101(Cr) SBU.

In summary, there are at least 30 ensembles of configurations that are explored through the simulations in pure water. This complexity can be a virtue of the system as this enables tuning of the conditions in which the half-SBUs interact in order to promote crystal-like configurations against defects. This is subject of study for the next sections, where an increasing concentration of ions and a different solvent are evaluated in order to understand which conditions lead to the highest probability of forming crystal-like SBUs. This is essential to understand how the extent of defects can be regulated during the early stages of MOF self-assembly.

4.2 Effect of the presence of ions

4.2.1 The AA dimer

The introduction of ions follows the simulations in pure water. These are added at increasing concentrations in order to evaluate their effect in terms of the number of ions present in the system. The addition of ions can prove beneficial for the crystallinity of MOFs as previous works [99], [165], [166] have shown. The aim of this work is to understand how ions affect the structural landscape of SBUs and the equilibrium probability of species. It should be reminded that experimental synthesis is carried out in water, and in presence of ions, at 493 K, in an autoclave for 8 hours [38]; hence synthesis takes place in the liquid state as the simulations conducted in this chapter. Furthermore, the effect of varying concentrations of salt on crystallinity is evaluated in this chapter. Conclusions agree with those drawn from simulations at a higher temperature and larger scale as it will be seen later (see Chapter 5).

In this context, MLA monomers (AA) interact in couples under increasing concentrations of ions in solution. The effect that the presence of ions has on the formation of this SBU is evaluated. The reason to study this SBU in depth is that it presents the most stable conformers in pure water. Sodium fluoride (NaF) has been added to the solution for this purpose. Fluoride was used in the original synthesis of MIL-101(Cr) [38].

Values for the concentration of NaF in the solution include 0.025M, 0.125M, 0.25M, 0.5M, 0.75M and 1M. The free energy surfaces (FES) are projected on the two collective variables (CVs) discussed in the case in absence of ions. The reason is that in this analysis CVs depend on the process of interest not the environment of the half-SBUs. Therefore, the association-dissociation of an SBU can be studied under different conditions regarding guest molecules.

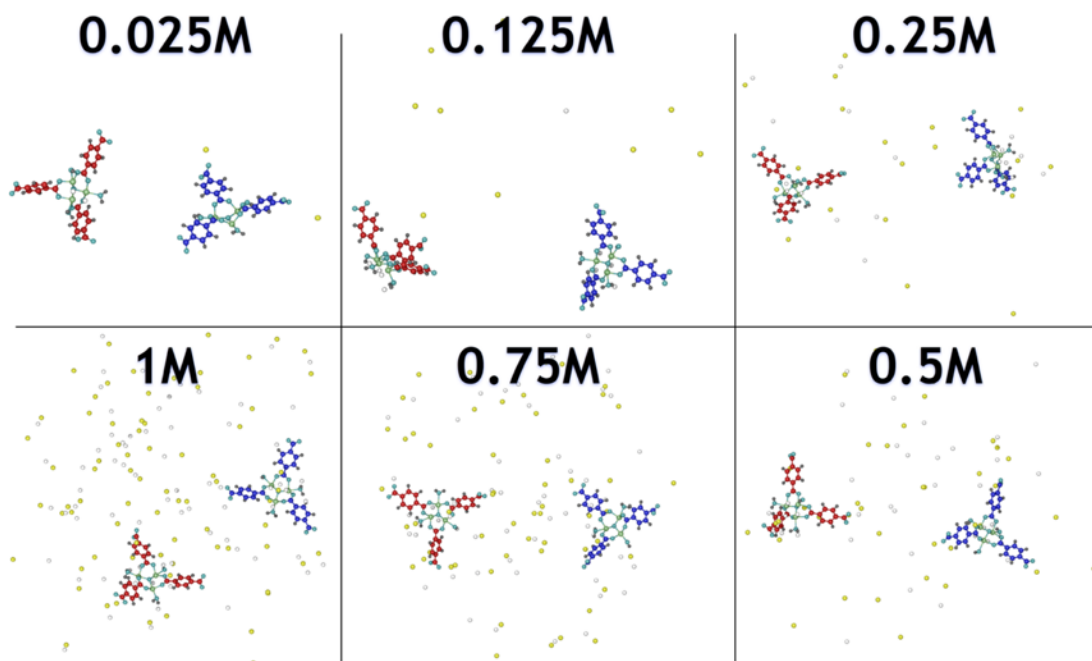


Figure 4-4. These figures correspond to the reference state (detached half-SBUs-state 5 on the free energy surface). The systems are provided in clockwise order for increasing concentration of ions starting from the top left corner. The colour code for the half-SBUs is consistent with Figure 4-1. Moreover, Na^+ is coloured yellow and F^- is white.

All systems are exhibited in Figure 4-4. These correspond to state 5 for each case. Detached half-SBUs are visible in this state. Concentration of ions can be understood better through these snapshots. Two instances have been captured. The first one includes structures at the start of the simulation. The second figure is near the end of simulation ($\sim 1 \mu s$) when ions are attached to metal centres of molecules. A whole ionic cluster can be seen connected in this manner for concentration values of 0.75M and 1M. Metal centres act as nucleation sites for the gradual development of this cluster. This can be understood as ions are attached to this site even when they are at smaller concentrations of ions e.g. 0.25M.

The case of AA has been chosen to be explained in further detail. The reason for this choice is that AA dominates the equilibrium distribution in absence of ions as it is the most stable SBU conformer. Therefore, it is reasonable to investigate how the formation of this SBU is affected by the incorporation of ions in the solution.

Analysis includes description of all structures present at the states on the relevant free energy surfaces at each concentration of sodium fluoride. After this analysis, all SBUs are discussed in a collective manner. FES for all other SBUs (AB-

CC), at every concentration of ions studied, are available in the appendix (Figure A-8 - Figure A-12).

4.2.2 Half-SBUs in water with 0.025M NaF

This case takes into account the ratio between fluoride and chromium as discussed in Berdonosova et al. [88]. This is the minimum concentration of ions in the entire analysis (2 F^- and 2 Na^+ overall).

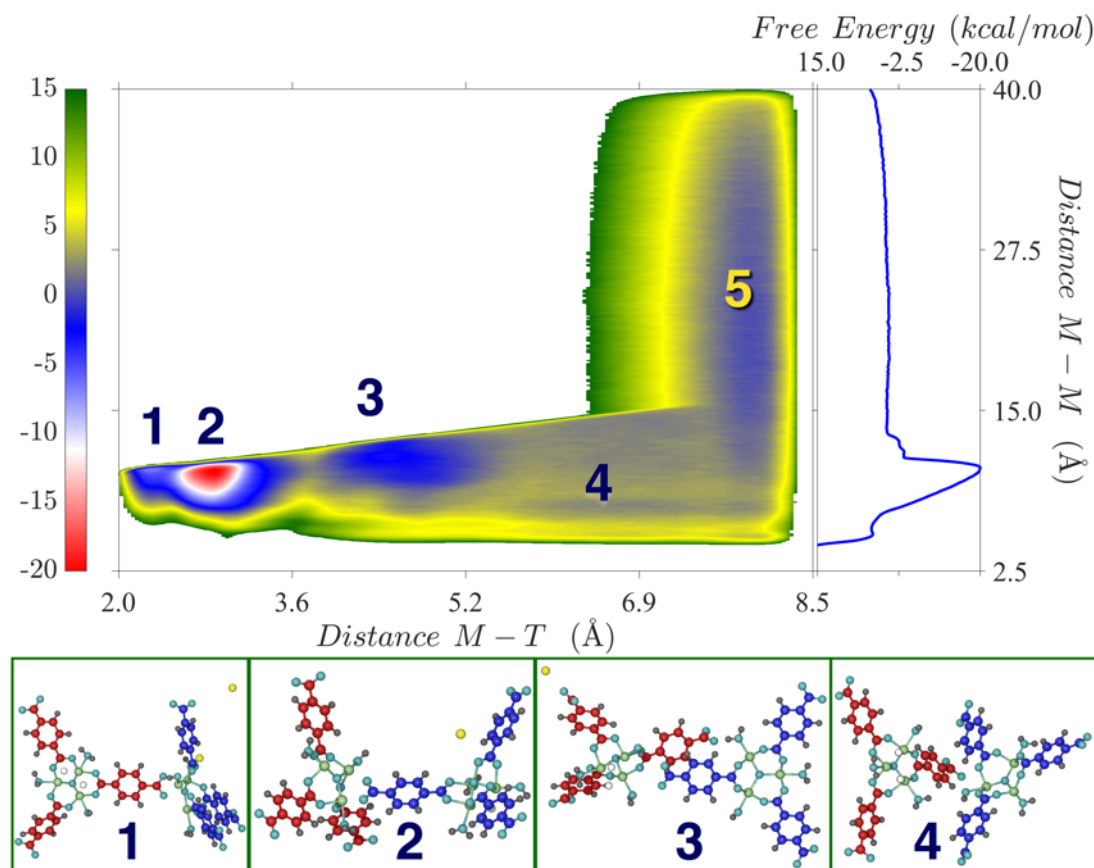


Figure 4-5. Top panel: Free energy surfaces for AA interactions in the presence of ions (0.025M). Bottom panel: Configurations correspond to states 1 - 4. Colour code: Cr - lime, O - cyan, H - grey, C (MLA 1) - blue, C (MLA 2) - red, F^- - white, Na^+ - yellow.

The free energy surface resembles the one obtained in pure water as the same states emerge. It should be reminded that experimental synthesis is carried out in water, and in presence of ions, at 493 K under high pressure generated in an autoclave for 8 hours [38]; hence synthesis takes place in the liquid state in agreement with the simulations performed in this chapter. This chapter should provide insight into the effect of varying ionic strength on the crystallinity and also explain the nature of interactions between ions and MOF precursors.

The FES is projected on the two CVs biased and it is presented along with structures corresponding to states 1-4 in Figure 4-5. State 2 dominates at 0.025M NaF as in pure water. States 1 and 4 are weaker than in the absence of ions. In min 1, a crystal-like configuration emerges. Two terminal oxygen atoms of one terephthalate linker bind to one chromium atom of the adjacent metal centre. State 2 corresponds to conformers where these oxygen atoms bind to two neighbouring chromium atoms. The previous are considered crystal-like. It should be noted that 2Q is not sampled in presence of ions as these attach to the metal centres; thus, hindering the formation of 2Q. Therefore, this FES is dominated by a very strong crystal-like interaction due to the presence of a small number of ions in solution.

In state 3, a double interaction between two adjacent oxygen atoms of one terephthalate linker to a respective hydrogen of the opposite metal centre is present. In state 4, half-SBUs are close, but they are detached. This state is very weak as expected. Moreover, in the reference state, that is state 5, half-SBUs are detached.

4.2.3 Half-SBUs in water with 0.125M NaF

Concentration of ions is slightly increased to 0.125 mol/L. Two new states are introduced (6, 7), which are present when MLA is absent in the event that ions are also absent from the solution.

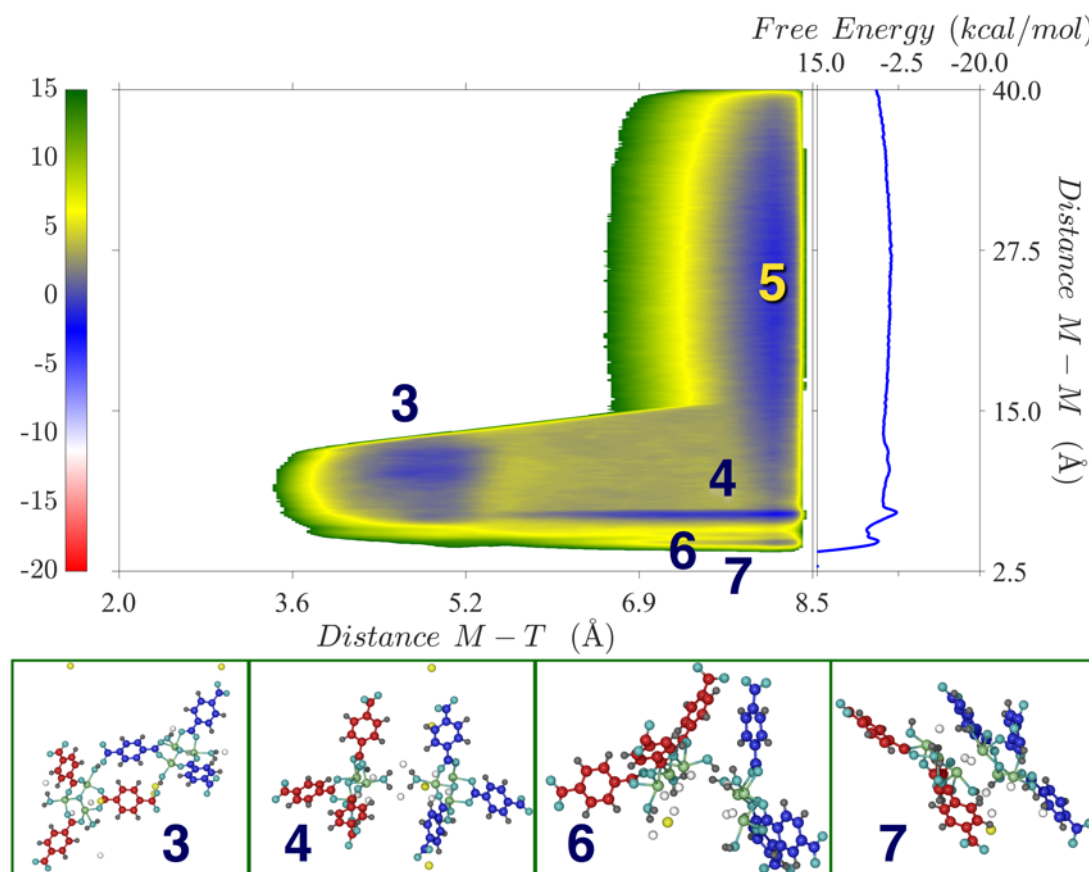


Figure 4-6. Top panel: Free energy surfaces for AA interactions in the presence of ions (0.125M). Bottom panel: Configurations correspond to states 1 - 7. Colour code: Cr - lime, O - cyan, H - grey, C (MLA 1) - blue, C (MLA 2) - red, F^- - white, Na^+ - yellow.

The free energy surface is dominated by minimum 4 (see Figure 4-6). The crystal-like region of states 1 and 2 is highly improbable in this case at this sampling time (1 μ s). The reason is that the difference in free energy between states 1, 2 and the reference state exceeds the scale of this surface. Therefore, it is highly positive that renders the formation of structures relevant to these states improbable. Therefore, no crystal-like configurations are present after this slight increase in the concentration of ions.

In state 3, a double interaction between two adjacent oxygen atoms of one terephthalate linker to a respective hydrogen of the opposite metal centre is present. This agrees with the previous analyses. State 4 is different from 0.025M and the case

in absence of ions. The two metal centres interact through two fluoride anions (F^-) acting as a bridge. Two hydrogen atoms of the same oxygen of each of the adjacent metal centres bind to the same F^- (bridge) respectively.

States 6 and 7 are also present on the FES. These correspond to stronger affinity between the metal centres. In further detail, state 6 presents a double interaction between two hydrogen atoms of one metal centre and two fluoride anions that have been attached to the adjacent metal cluster. In state 7, the structure is similar to state 6, but fluoride anions connect chromium atoms instead of hydrogen. More precisely, one fluoride anion connects (acts as a bridging ion) a chromium atom with an adjacent hydrogen atom for each monomer ($H_{M1} - F^- - Cr_2$ and $H_{M2} - F^- - Cr_1$, where $H_{M1,2}$ are hydrogen atoms of the metal centre and 1, 2 correspond to the respective monomers); hence there are two interactions of this type overall. Also, a linking fluoride anion between two adjacent chromium atoms ($Cr_1 - F^- - Cr_2$) is active here. Again, state 5 is the reference, where half-SBUs are detached. The free energy surface and the structures that correspond to each state are provided in Figure 4-6.

4.2.4 Half-SBUs in water with 0.25M NaF

Another increase in the number of ions present in solution results in a concentration of 0.25 mol/L.

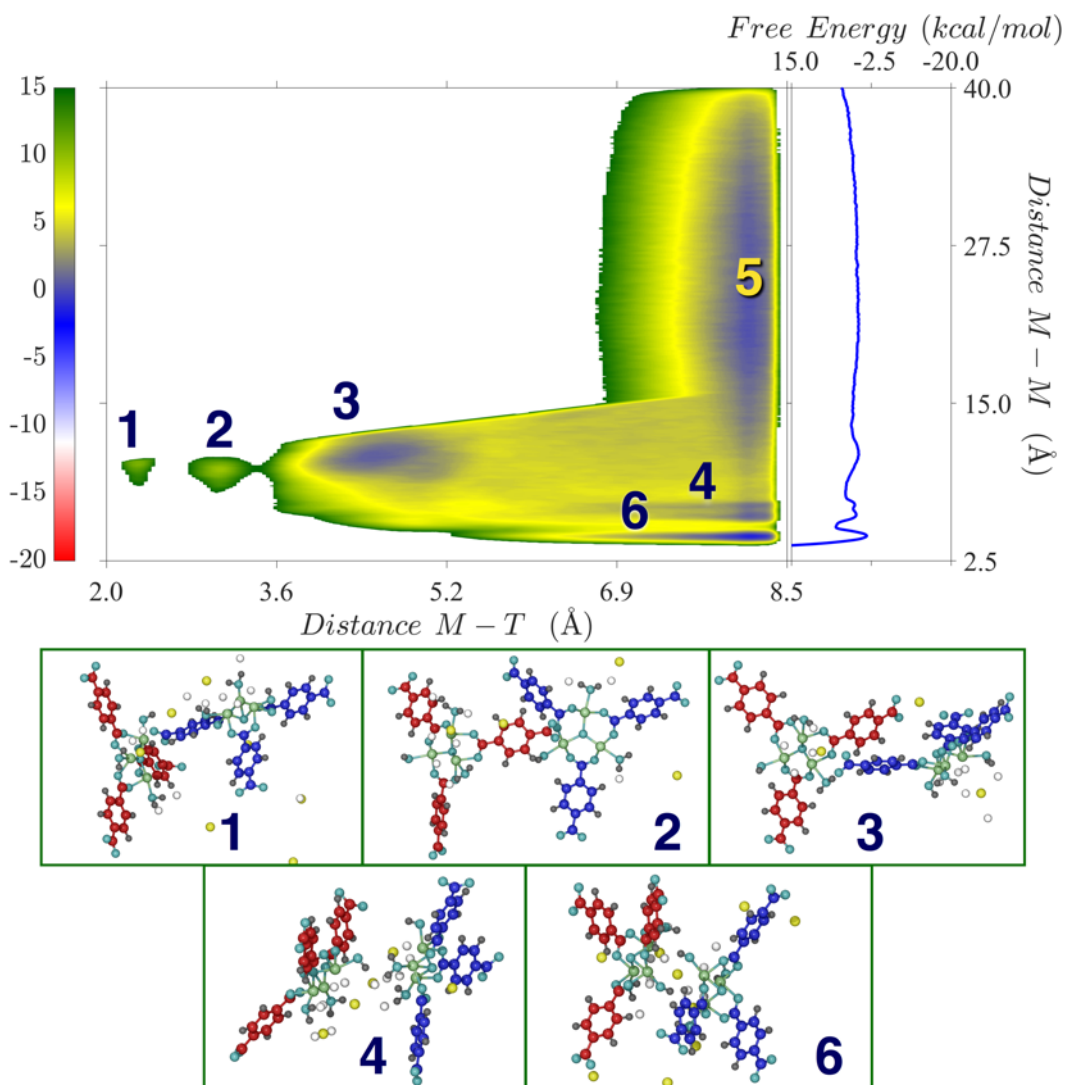


Figure 4-7. Top panel: Free energy surfaces for AA interactions in the presence of ions (0.25M). Bottom panel: Configurations correspond to states 1 - 7. Colour code: Cr - lime, O - cyan, H-grey, C (MLA 1)-blue, C (MLA 2)-red, F^- – white, Na^+ – yellow.

Analysis of the representative structures for all states featuring on the FES at this concentration of ions is provided in Figure 4-7. The free energy surface is dominated by state 6. States 1 and 2 that correspond to crystal-like configurations are improbable. State 3 is the second most probable.

State 1 corresponds to a crystal-like conformer with the typical interaction between two terminal carboxylic oxygen atoms and one chromium atom of the

opposite metal centre. State 2 is noncrystal-like in this case. The reason for that is the location it has on the FES. As opposed to previous instances, this is shifted to a lower value for the distance between the adjacent metal centres (M-M). An interaction between one of the terminal carboxylic oxygen atoms and the adjacent chromium is replaced by an interaction between the former and a neighbouring, to chromium, hydrogen atom. The other chromium-oxygen affinity stays intact. Additionally, a sodium cation intersects between two fluoride anions of the metal centre near the oxygen-hydrogen interaction.

In state 3, a double interaction is present. One of the terminal carboxylic oxygen atoms (O_{T1a}) binds to a hydrogen atom of the adjacent metal centre (H_{M2}). The other oxygen atom (O_{T1b}) connects with a sodium cation that is attached to the metal centre of the opposite monomer (Na_{M2}). Also, a triple interaction belongs to this state. This interaction occurs between an opposite, to the previous one, terminal carboxylic oxygen and an adjacent sodium linked to the metal centre added to the previously described double interaction.

State 4 presents a highly complex interaction between the metal centres. A small ionic cluster connects the aforementioned structures. In more detail, two adjacent hydrogen atoms bind to the same fluoride anion (first bridge). Also, two opposite fluoride anions, that are linked to the metal centres, connect to the same sodium cation (second bridge).

At last, in state 6, there is a double interaction between the metal centres. Two hydrogen atoms of one monomer bind to two fluoride anions of its opposite counterpart. That is the same as in the case where the concentration of NaF is 0.125M. It should be noted that state 6 dominates the FES at 0.25M; hence a noncrystal-like interaction emerging as the result of strong affinity between ions and the metal centres is the most probable for this concentration of ions in solution.

Finally, state 5 corresponds to detached half-SBUs. This is the reference for calculation of free energy differences for all states.

4.2.5 Half-SBUs in water with 0.5M NaF

At this point, the concentration of NaF is 0.5 mol/L. This results in the introduction of an additional interaction between the metal centres (state 4U). That is a new state corresponding to a noncrystal-like configuration.

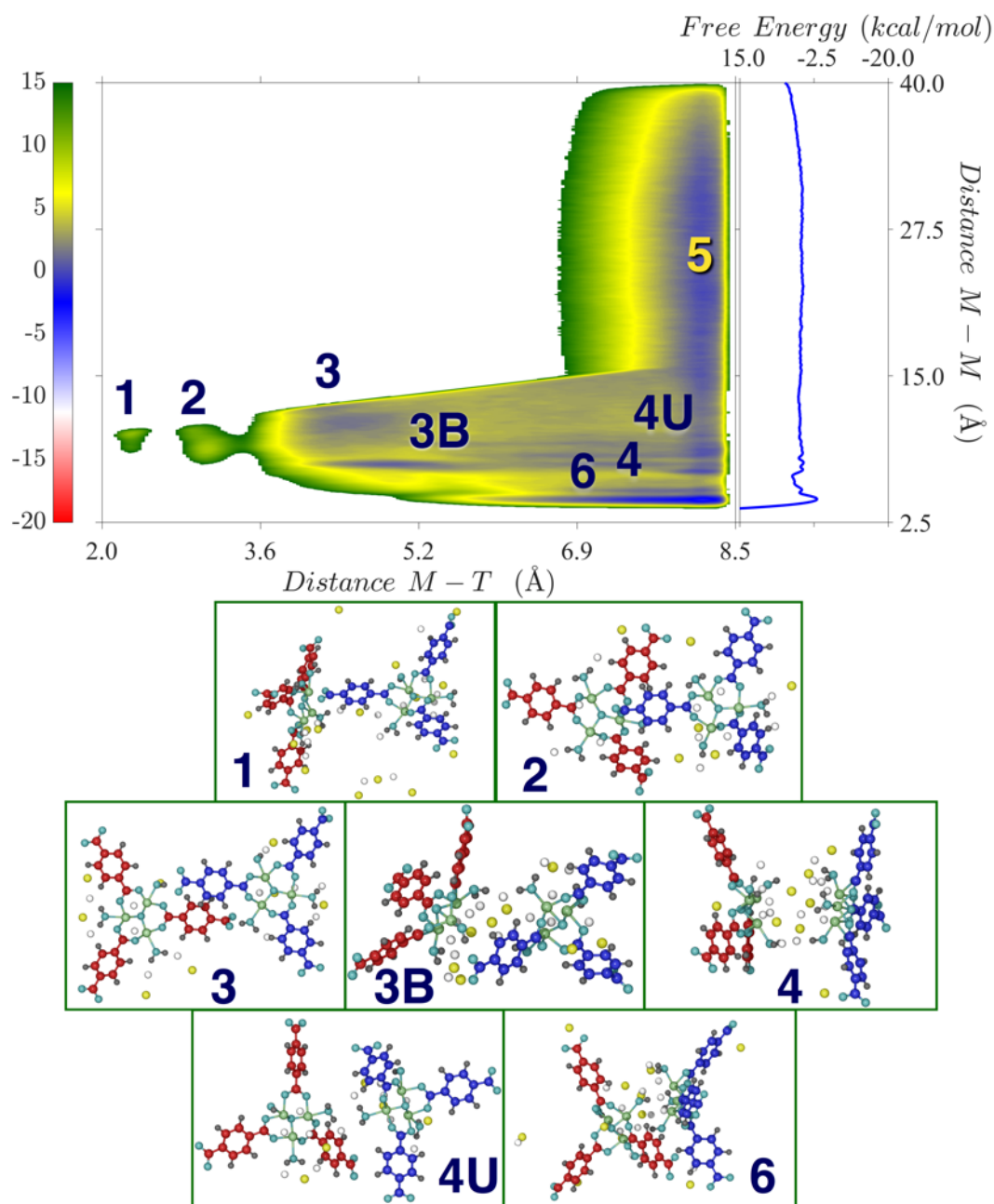


Figure 4-8. Top panel: Free energy surfaces for AA interactions in the presence of ions (0.5M). Bottom panel: Configurations correspond to states 1 - 6. Colour code: Cr - lime, O - cyan, H-grey, C (MLA 1)-blue, C (MLA 2)-red, F⁻— white, Na⁺— yellow.

As in the previous concentration of ions, at 0.5M, a noncrystal-like conformer presenting M-M interactions dominates the FES. More precisely, the most probable state on the free energy surface is 6. The free energy surface along with conformers that are representative of each state are provided in Figure 4-8. States 1 and 2 are highly improbable. This is due to their large positive difference in free energy with respect to the reference state. Moreover, states 3, 4 and 4U are close, in terms of free energy, to state 5. Analysis of the structures for each state in further detail follows.

State 1 corresponds to a crystal-like configuration, where two terminal carboxylic oxygen atoms bind to one chromium of the adjacent metal centre. In state 2, a single interaction between a terminal carboxylic oxygen and a chromium of the opposite monomer occurs. In this structure, terephthalate linkers are parallel to each other; hence this conformer is noncrystal-like.

State 3 features a double oxygen-hydrogen interaction. This occurs when a terminal carboxylic oxygen interacts with a hydrogen atom of the adjacent metal centre. This is the same as in pure water. At the bottom of state 3, there is state 3B. This corresponds to lower M-M values and the representative configuration consists of a single terminal carboxylic oxygen-hydrogen of the adjacent metal centre interaction. This is also a noncrystal-like conformer as the one representative of the normal state 3.

In state 4, a highly complex interaction between the metal centres prevails. A small ionic cluster exists between the two half-SBUs. A bridging fluoride anion connects a couple of adjacent hydrogen atoms of the metal centres. Furthermore, three sodium cations act as bridges to four hydrogen atoms (two of each metal centre) via four fluoride anions. A double interaction between sodium cations and fluoride anions is present in state 4U. Fluoride anions are attached to two hydrogen atoms of the metal centres. It should be noted that a bridge refers to the configuration where atoms of adjacent half-SBUs are linked by ions. In detail, ions (I1) interact with atoms of one half-SBU (M1) from one side and with other ions (I2) from the other side. Then these other ions (I2) interact with the former ions (I1) from one side and the other half-SBU (M2) from the other side. Consequently, a scheme of M1-I1-I2-M2 is observed in state 4 (Figure 4-8) and it is characterised as a salt bridge between half-SBUs.

State 6 is dominated by a different type of connection between the metal centres. Two adjacent hydrogen atoms bind directly to opposite fluoride anions that are attached to each metal centre. Additionally, a small cluster of three sodium cations interconnected by fluoride anions keeps the two metal centres close; hence two hydrogen atoms of the metal centre of one monomer are linked via this ionic network to one hydrogen and one chromium of its opposite counterpart.

Finally, state 5 corresponds to detached half-SBUs with small ionic clusters are attached to both metal centres.

4.2.6 Half-SBUs in water with 0.75M NaF

The concentration of ions is further increased. The value for the concentration of *NaF* here is 0.75 mol/L.

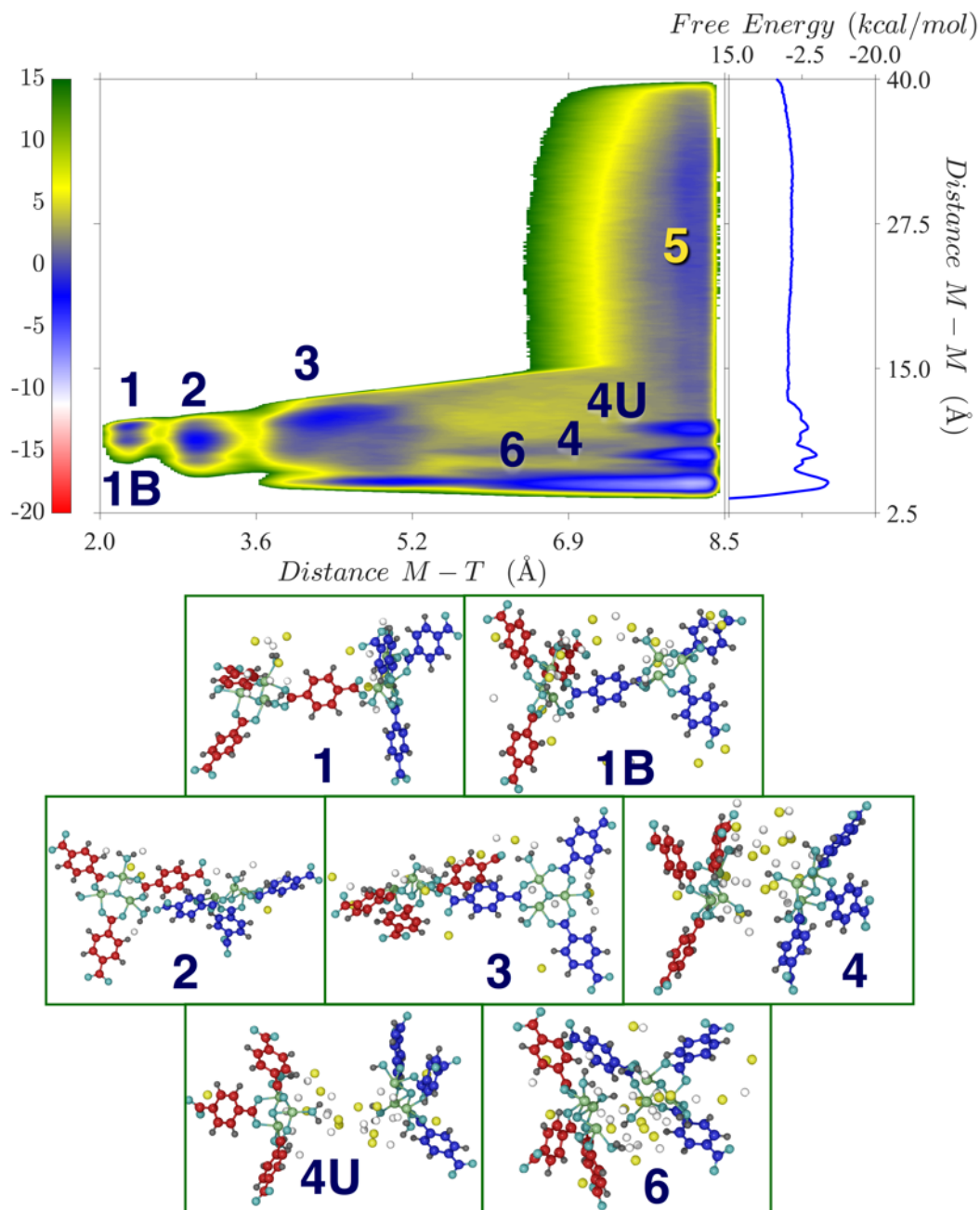


Figure 4-9. Top panel: Free energy surfaces for AA interactions in the presence of ions (0.75M). Bottom panel: Configurations correspond to states 1 - 6. Colour code: Cr - lime, O - cyan, H-grey, C (MLA 1)-blue, C (MLA 2)-red, F^- — white, Na^+ — yellow.

In this case, a new small state in the vicinity of state 1 is present (state 1B). The free energy surface shows that state 6 corresponds to the energetically strongest

interaction. Furthermore, states 1 and 2 are more probable than the detached state and this is in contrast with concentrations between 0.125M-0.5M, where states 1 and 2 are less probable than state 5. Furthermore, an analysis of the structures for each state is presented in the remaining of this section.

State 1 corresponds to a crystal-like configuration where two terminal carboxylic oxygen atoms are linked to a chromium atom of the adjacent metal centre. State 1B, is a new state that is present only in this case for the concentration of NaF. This state is located below state 1; hence it corresponds to a lower value of the M-M CV. The upper and normal state 1 dominates in terms of free energy (~ 2 kcal stronger). This is still crystal-like due to the formation of an ionic bridge. Two adjacent hydrogen atoms of the metal centres are bound to two fluoride anions respectively. These fluoride anions are connected through a central sodium cation.

State 2 is dominated by a noncrystal-like interaction. A single interaction between a terminal carboxylic oxygen and a chromium atom of the adjacent half-SBU occurs. Also, a weak interaction between a terminal carboxylic oxygen and a hydrogen atom of the opposite metal centre is present in this state. These geometrically resemble to crystal-like configurations. Finally, a noncrystal-like interaction between a chromium and an adjacent terephthalate terminal oxygen occurs. In this conformer, terephthalate linkers are parallel to each other.

The free energy surface, featuring all states discussed in this section and representative molecular structures are shown in Figure 4-9. In state 3, a triple interaction between oxygen and hydrogen atoms is present. More elaborately, terminal carboxylic oxygen atoms are involved in this interaction. At first, a terminal carboxylic oxygen atom of one half-SBU (O_{T1a}) connects to a hydrogen atom of the adjacent metal centre (H_{M2a}). Secondly, the neighbouring, to O_{T1a} , oxygen atom (O_{T1b}) is linked to a hydrogen atom close to H_{M2a} , namely H_{M2b} . At last, a terminal oxygen atom of the opposite monomer (O_{T2}) interacts with a sodium cation that is attached to the opposite metal centre. Also, another type of interaction occurs. This is between a single terminal carboxylic oxygen and a hydrogen atom of the adjacent metal centre.

State 4U is also present at this concentration of ions. This is closer to 5 than the previous cases. Also, it is higher in M-M CV than state 4U of the previous instance (concentration 0.5M). A small ionic cluster connects the two half-SBUs. Seven sodium cations act as bridges. Fifteen fluoride anions interact both with sodium cations and hydrogen atoms of the adjacent metal centres. In this manner, an interaction between

the two metal clusters emerges. Four hydrogen atoms from the metal centre of one building block and three hydrogen and three chromium atoms from its counterpart connect to this ionic network. Furthermore, a larger ionic cluster is placed between the metal centres. This consists of ten sodium cations and fifteen fluoride anions. This connects five hydrogen atoms of the metal centre of one half-SBU to three hydrogen and two chromium atoms of the opposite.

In state 4, the ionic cluster present in state 4U is shifted to the side of the two metal centres. Therefore, the metal centres are closer to each other than in 4U. Four hydrogen atoms from the metal centre of one half-SBU and three hydrogen atoms of the opposite, as well as an additional chromium, are interconnected through this ionic cluster that consists of eleven sodium cations and sixteen fluoride anions.

State 6 is dominated by a conformer consisting of a complex link between the metal centres through an ionic cluster that is located on the side of the two metal clusters as the previous cluster in state 4. There is one direct interaction between a hydrogen atom and a fluoride anion of the opposite metal centre. Also, two hydrogen atoms of one metal centre are connected to two fluoride anions of the cluster. At the opposite side, two hydrogen and two chromium atoms of the metal centre connect to the cluster via three fluoride anions overall. More precisely, one fluoride anion connects the two chromium atoms to the cluster, while two other fluoride anions connect the hydrogen atoms of the metal centre to the ionic cluster respectively. Finally, the cluster consists of seven sodium cations and ten fluoride anions.

Finally, in state 5 half-SBUs are detached in agreement with previous simulations.

4.2.7 Half-SBUs in water with 1M NaF

The final case has the maximum concentration of NaF in the solution in the entire study. The value for the concentration in this case is 1 mol/L. It should be noted that these concentrations correspond to the confined environment of the simulation box that is $125,000 \text{ \AA}^3$. Therefore, only qualitative comparison can be done with laboratory experiments.

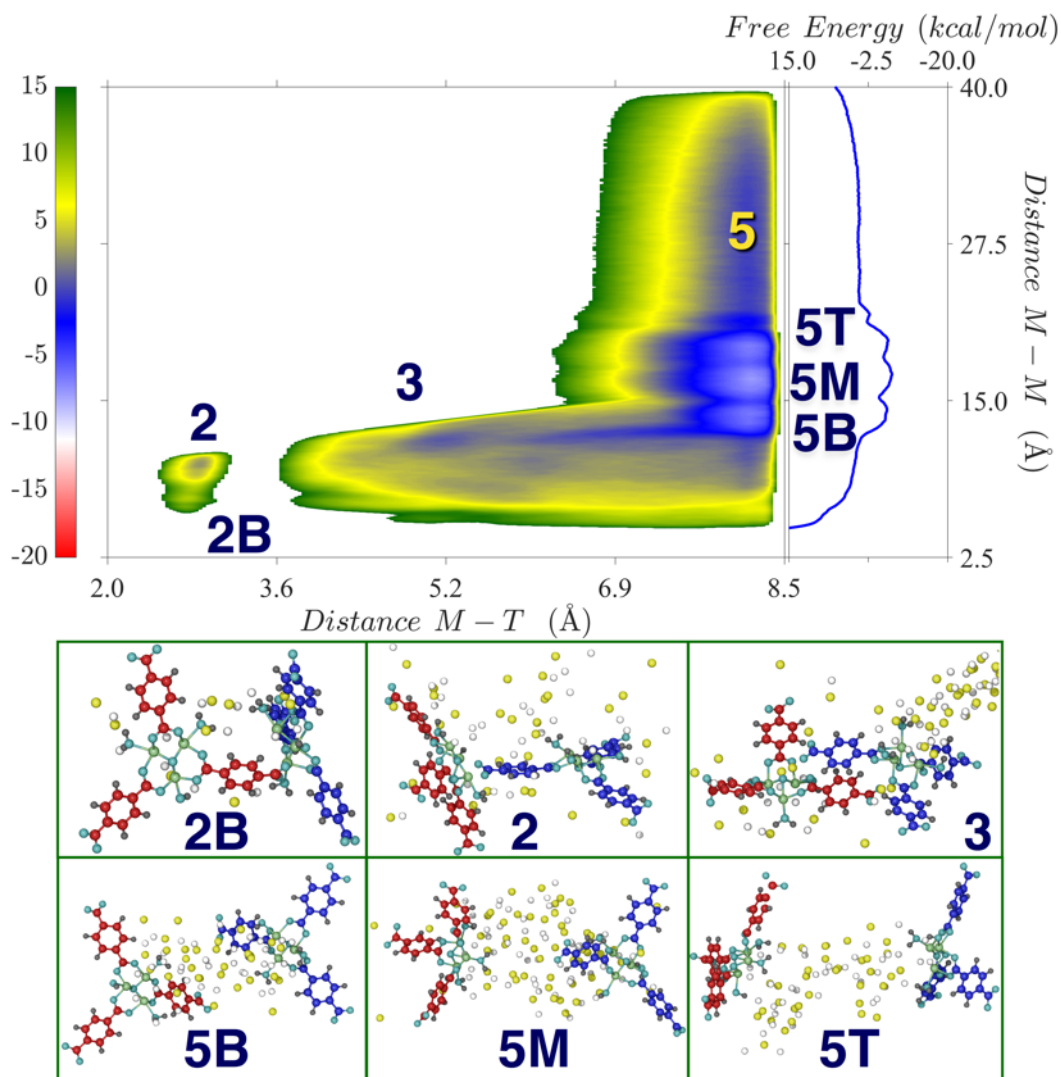


Figure 4-10. Top panel: Free energy surfaces for AA interactions in the presence of ions (1M). Bottom panel: Configurations correspond to states 1 - 4. Colour code: Cr - lime, O - cyan, H-grey, C (MLA 1)-blue, C (MLA 2)-red, F^- - white, Na^+ - yellow.

At this stage, states 1, 4, 6 and 7 are absent, minimum 2 is separated into two (2, 2B) and state 5 is split into four parts (5B-bottom, 5M-middle, 5T-top, 5). Normal state 5 is higher in M-M value than the other three as expected. That is

because half-SBUs are detached there. Whenever a letter is not used, this minimum is at the vicinity of their respective equivalents at the previous instances. The different types of state 5 (B, M, T) dominate the free energy surface. Those are stronger than the normal state 5, when half-SBUs are apart and the ionic cluster does not intervene between them.

State 2 corresponds to a crystal-like interaction and it is more favourable than the reference state. In this state, a crystal-like configuration is present. Two terminal carboxylic oxygen atoms connect to an adjacent chromium atom. Moreover, a small ionic cluster is linked to one metal centre. This consists of four sodium cations and four fluoride anions. A fluoride anion interacts with a hydrogen that is attached to one metal centre. The conformer that prevails in state 2B is also crystal-like. This one consists of two neighbouring terminal carboxylic oxygen atoms connected to two neighbouring chromium atoms of the opposite half-SBU. Furthermore, a small ionic bridge is formed between the two molecules. This consists of one sodium cation bound to two fluoride anions from each side (four connections overall). Each fluoride anion interacts with two hydrogen atoms of the metal centre of either half-SBU; hence the adjacent metal centres stay at a position that favours crystal-like configurations.

State 3 corresponds to a noncrystal-like conformer as in previous cases. A sodium cation acts as an active centre on each molecule. It is linked to three oxygen atoms. One of those is attached to the metal centre and two are the terminal atoms of the terephthalate linkers. Therefore, these three oxygen atoms are connected via this cation. A large ionic cluster is connected to one of the monomers, but this does not intersect between them.

There are four interactions between hydrogen atoms of the metal centres and fluoride anions. Furthermore, three interactions between fluoride anions attached to the metal centres and sodium cations emerge. These hold the cluster at the same position for both single and double interactions. The different parts of state 5 are ultimately presented. All of those correspond to configurations where the monomers are detached. The reason for this is that an ionic cluster intervenes between them.

At state 5B, the bottom one, an ionic cluster is on one side of the half-SBUs; hence the value of the M-M CV is the lowest among all the sub-states 5 for 5B. The cluster is held at this position via two interactions between hydrogen atoms of one metal centre and free fluoride anions, two fluoride anions attached to the metal centre and free sodium cations.

State 5M, is located in the middle of the sub-states. Here the ionic cluster is dislocated so that it intervenes when half-SBUs are closer to its long axis. The interactions of the cluster with the first molecule are the following: four between hydrogen atoms of the metal centres and free fluoride anions and two between fluoride anions attached to one metal centre and free sodium cations. The adjacent half-SBU has the same number of links with the cluster reduced by one fluoride anion.

State 5T, is the top one of the three sub-states. The ionic cluster is aligned horizontally with the half-SBUs; hence the largest distance between the half-SBUs is visible here. One half-SBU has three hydrogen atoms of the metal centre linked to two fluoride anions of the cluster (type 1). Also, one fluoride anion attached to the same metal centre connects to a sodium cation of the cluster (type 2). Its adjacent counterpart has four interactions of type 1 and two of type 2 respectively.

At last, state 5, the normal as at previous instances, corresponds to the reference state, where half-SBUs are detached. An ionic cluster is apparently attached to one of the monomers. The free energy surface along with representative SBU configurations of all relevant states is presented in Figure 4-10.

4.2.8 Conclusions on the AA dimer in presence of ions

In summary, the AA SBU structural landscape is investigated in six concentrations of Na^+ and F^- water. It should be reminded that experimental synthesis is carried out in water, and in presence of ions, at 493 K under high pressure generated in an autoclave for 8 hours [38]; hence synthesis takes place in the liquid state in line with the simulations performed in this chapter. Also, conclusions agree with those drawn from simulations at a higher temperature and larger scale (see Chapter 5). At the lowest concentration of ions, small differences with the absence of ions are observed in the FES projected on the two CVs biased. Nevertheless, the presence of ions renders 2Q improbable as it is not sampled at all in contrast with the simulation in absence of ions. This is explained by a hindrance in the relative rotation of the terephthalate linkers resulting from the strong interaction between ionic species and the metal centre. In further detail, fluoride anions interact with hydrogen atoms at the metal centres of the half-SBUs. At this concentration of ions 2C, the crystal-like AA SBU conformer, has the highest probability of formation from detached half-SBUs when compared with all other simulations in presence or absence of ions.

As the number of ions is increased, new states are discovered. States 6 and 7 are present at a concentration 0.125M. State 6 is present in every other case except from the lowest and highest concentration of ions studied. State 7 is absent for all other concentrations of NaF . State 4U emerges at concentration levels of 0.5M and 0.75M. At 0.75M, in the vicinity of state 1, a weaker (~ 2 kcal/mol) interaction, compared with the normal state 1, is present, namely 1B. At 0.75M and 1M salt bridges are formed. These promote crystal-like interactions through hindering the relative rotation of the terephthalate linkers. Finally, at the highest concentration evaluates, that is 1M, most of the previously observed states are absent. These are 1, 4, 6 and 7. States 2 and 5 are split into two and four parts respectively.

Defects dominate the free energy surface at all levels of concentration of ions that are greater than 0.025M. In the absence of ions, states 6 and 7 are only present for SBUs in which MLA is absent and correspond to the bottom right section of the FES (below state 4). In the case of the AA SBU, these are rendered active when the concentration of ions is increased further than 0.025M. The adjacent metal centres are at a closer distance in the structures that dominate the aforementioned states. At concentrations of 0.025M, 0.75M and 1M the crystal-like configurations are more probable than the reference state. At last, the incorporation of fluoride decreases the free energy differences between the crystal-like and noncrystal-like conformers. Very

strong interactions are not present as in pure water. These are disrupted by ionic species that stabilise interactions when the ions access the metal centre of the half-SBUs. This is another aspect of the use of ions in solution as defects can be self-healed more easily in presence of ions.

4.2.9 Convergence of free energy differences

Convergence analysis provides estimates for the difference in free energy (ΔG) between states of interest with error margins.

Table 4-2. Differences between free energy minima and state 5 (detached half-SBUs). Values are given for minima shown in the corresponding FES profiles for the ion-free cases (Figure 4-1 and Figure 4-2). * This is the estimate of state 2 from the FES projected on the 2 CVs (M-M and M-T). ** This is state 2T that dominates state 2 overall. *** Instead of state 4, State 5B is calculated here. Crystal-like configurations are in bold text.

ΔG (kcal/mol) with respect to state 5. Dimer in solution at presence of ions.						
AA Ions Conc. / states	1	2	3	4	6	7
0	-12.88 ± 3.51	-18.13 ± 4.09*	-4.95 ± 0.65	+0.97 ± 0.41	-	-
0.025M	-10.53 ± 3.51	-15.21 ± 6.76	-2.27 ± 0.96	+1.36 ± 0.59	-	-
0.125M	-	-	+0.67 ± 0.83	-1.96 ± 2.19	-0.75 ± 2.28	+8.77 ± 6.71
0.25M	+3.93 ± 4.99	+3.0 ± 4.97	-0.11 ± 1.81	-0.75 ± 2.67	-0.55 ± 5.60	-
0.5M	+4.60 ± 5.15	+3.27 ± 5.22	+0.85 ± 0.87	-1.99 ± 2.08	+2.03 ± 4.52	-
0.75M	-1.72 ± 5.60	-3.98 ± 2.40	+0.63 ± 1.71	+0.28 ± 3.59	-0.63 ± 3.14	-
1M	-	-3.07 ± 6.36**	+1.58 ± 1.26	-0.19 ± 2.51***	-	-

Results are provided in Table 4-2. These values are the time weighted averages of the free energy differences of all states with respect to state 5. State 2 is considered crystal-like unless otherwise specified. States 3 and 4 have small uncertainty for most of the systems studied. States 6 and 7 follow 1 and 2 at the levels of the fluctuations around the nominal value for the ΔG with respect to state 5. The uncertainty is calculated as the standard deviation of the time weighted average.

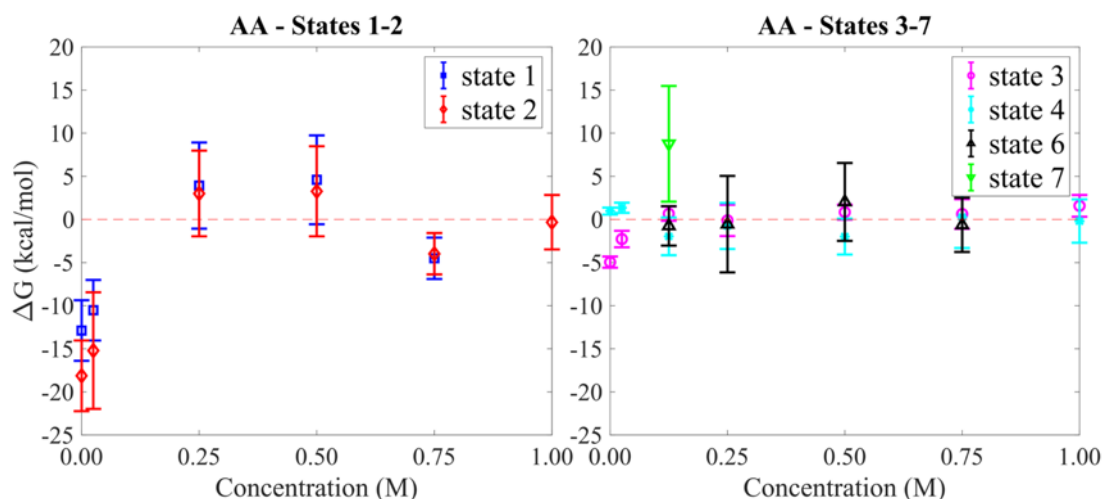


Figure 4-11. Effect of the concentration of ion on the free energy difference of all the minima with respect to state 5. The error bars correspond to the uncertainty measured through the standard deviation. Left-States 1 and 2 (crystal-like in absence of ions), Right-States 3-7 (non-crystal-like).

In the entire analysis of the SBUs, the worst cases for convergence are AA, AC where the standard deviation is the largest. The source of this uncertainty is located at states 1 (AA, AC) and 2 (AA). All other dimers show better profiles in terms of convergence. The values for the ΔG of transition from state 5 to each one of the rest are given in Table 4-2. This is followed by Figure 4-11 that exhibits the mean values and fluctuations of the data showed on the table. The trend shows the ΔG of states 1 and 2 (considered crystal-like in most cases) initially increasing with the concentration of ions. Eventually it is decreased at concentrations up to 0.5M. Under these conditions, M-M interactions are favoured.

Finally, the probability of forming crystal-like conformers is increased again as salt bridges are formed at concentrations greater or equal to 0.75M. These promote crystal-like configurations as previously mentioned. Noncrystal-like states 3 to 7 are in equilibrium with the detached state as they remain relatively unaltered by the increase in concentration of ions. These show the strength, consequently probability, of the development of defects from these monomers.

4.2.10 Overall analysis of dimer interactions in the presence of ions

Different dimers are evaluated at increasing concentrations of ions. These range from 0.025M to 1M. An extensive analysis of the free energy surfaces and interactions that these feature for the AA dimer has been conducted in the previous section. Therefore, an overview of the effect of ions in the structural landscape of SBUs in water is the purpose of this section. It should be reminded that experimental synthesis is carried out in water, and in presence of ions, at 493 K under high pressure generated in an autoclave for 8 hours [38]; hence synthesis takes place in the liquid state in agreement with the simulations conducted in this chapter, while findings are consistent with those at a higher temperature as seen in Chapter 5. Investigation of the process of SBU association and dissociation provides an evaluation of how ions affect crystallinity through the assessment of interactions between ions and MOF precursors.

Starting from a concentration of 0.025M, state 1 is crystal-like for dimers AB, BB. In the same category lies minimum 2 of AC. This dominates in terms of ΔG for this SBU at this concentration of ions. BC and CC do not exhibit any configurations of this type as terephthalate linkers are parallel to each other when the two half-SBUs are close (M-T value lower than 3 Å). This concentration is the only one in which state 1 is visible on the FES ($\Delta G < +14$ kcal/mol) of the BB SBU.

The concentration of *NaF* is further increased to 0.125M. State 1 for AB, AC is the only one that corresponds to crystal-like configurations. For AB, state 1 is probable ($\Delta G < 0$), while for AC it is improbable. This is not present on the FES of BB-CC at this concentration of ions. At 0.25M *NaF*; states 1 and 2 are not observed on the FES of AB only at this concentration. Ions do not favour many of the interacting states at this point as states 5 (detached half-SBUs) and 6 (metal centres interaction) compete closely for the domination the FES. Again, the crystal-like conformers are favourable only in AC, at state 1. In AB-CC, state 2 corresponds to the terephthalate linkers placed in parallel; hence the configuration is considered noncrystal-like.

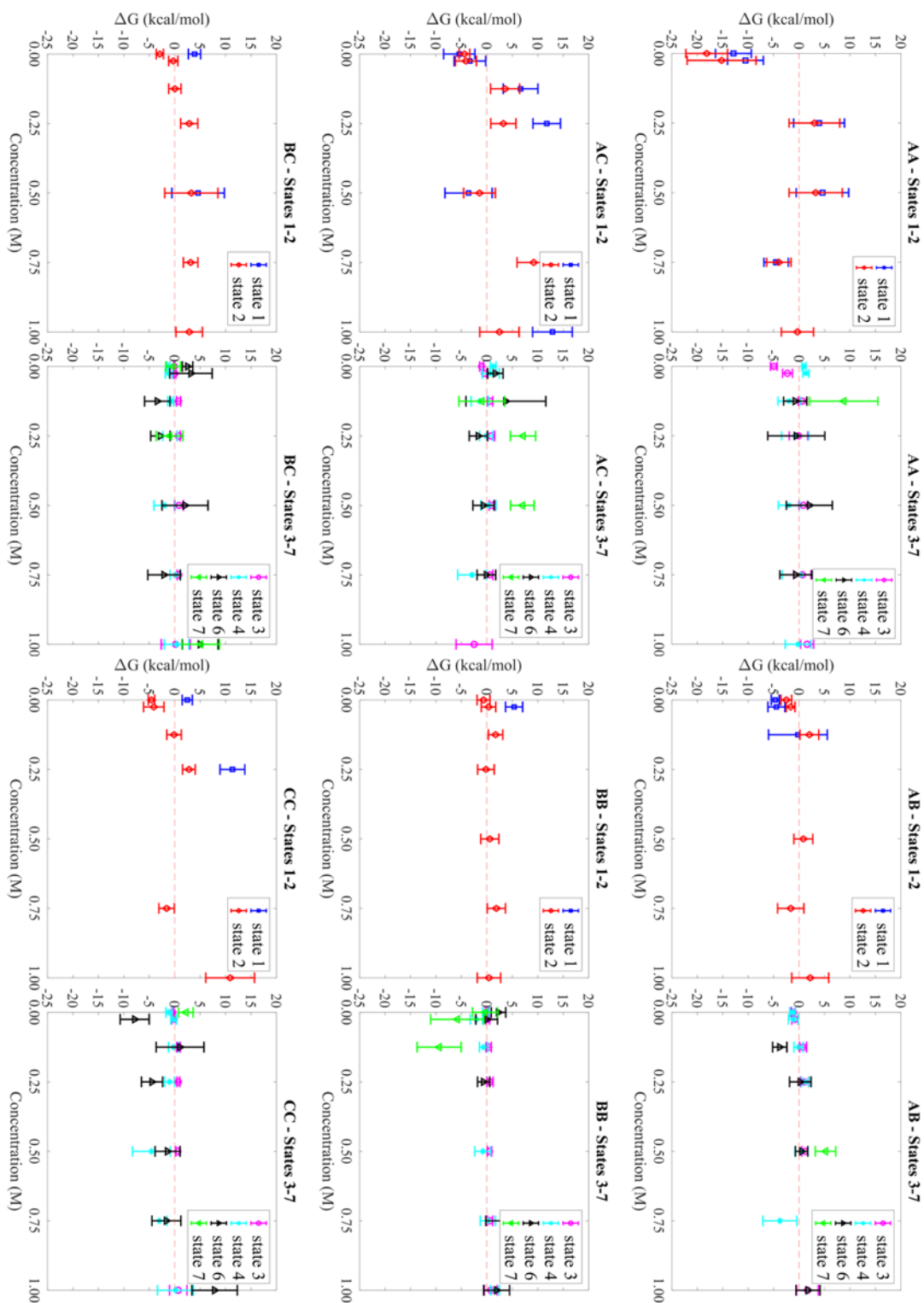


Figure 4-12. Values for the free energy differences of all states (with respect to state 5) with increasing concentration of ions. Error bars correspond to the standard deviation. Each case is split into two images. The left image corresponds to states 1 and 2 (usually crystal-like) and the right on 3-7 (non-crystal-like).

The concentration is then doubled (0.5M). At this stage, state 1 is only present for AC, but it is considered noncrystal-like due to parallel linkers. States 1 and 2 are absent from the FES of CC. State 2 is dominated by a noncrystal-like structure with parallel organic linkers as well. A concentration of 0.75M for *NaF* is considered next. State 1 is not featured in any of the AB-CC FES. State 2 corresponds to noncrystal-like interactions where terephthalate linkers are parallel to each other. In these structural arrangements, two terminal carboxylic oxygen atoms interact with one chromium and one hydrogen of the adjacent metal centre respectively. In BC, interactions occur between 1) an oxygen and a sodium cation and 2) an oxygen and a chromium atom. Therefore, all crystal-like configurations originate from AA at this concentration of ions.

At last, the highest value for the concentration of *NaF* is studied. This corresponds to 1M. The excess of ions renders interactions between adjacent half-SBUs infrequent. As a consequence, crystal-like configurations are improbable as large salt clusters are formed and consequently obstruct interactions between half-SBUs. More elaborately, these clusters develop from ions attached to the metal centres of adjacent half-SBUs. Therefore, salt intervenes between half-SBUs that are placed on opposite ends of salt clusters. In other words, half-SBUs facilitate the nucleation of salt as clusters are developed and these keep the half-SBUs apart. Nevertheless, when uncertainty is considered, crystal-like conformers due to the presence of ionic bridges emerge in AA, at a limited extent. In all cases configurations near the detached state dominate the FES. The only cases where states, apart from 5, have a negative mean free energy difference with respect to 5 are AC (state 3) and CC (state 4 and 6).

Analysis of the fluctuations and uncertainty of the values for the ΔG of transition from state 5 to each of the states featured on the different free energy surfaces is carried out. This is provided in Figure 4-12. Noncrystal-like states are at equilibrium with the detached state; hence they are not affected significantly by the addition of ions to the solution. Also, fluctuations of the free energy differences of these interactions with respect to state 5 are relatively small (around 2-3 kcal / mol).

States 1 and 2 feature interactions that are considered crystal-like for certain dimers. These are not affected appreciably for BB and BC. On the other hand, they follow the same trend for the remaining cases. At first, they are favourable, then their probability is decreased (positive change to free energy difference from state 5) and finally it is increased again.

As in AA, ions above a certain threshold promote the emergence of crystal-like SBUs through forming bridges that hinder certain noncrystal-like interactions. These are subject to the decrease of the flexibility terephthalate linkers; hence ΔG values of these states are lowered and consequently the probability of their presence at equilibrium is increased. These salt bridges are formed in a way that the half-SBUs interact in a crystal-like configuration and not in one that the linkers are parallel to each other for example. Given the presence of the ionic cluster, interactions between the half-SBUs, are less frequent than in absence of ions. Therefore, the ΔG values of the states representing crystal-like conformers are decreased but they are not of the same magnitude as in absence of ions. The data in Figure 4-12 is available in a tabular form in the appendix (Table A-5).

4.2.11 Equilibrium Distribution in the presence of ions

The evaluation of the equilibrium distribution of species is performed starting from two initial probability distributions of half-SBUs. The first is an equiprobable distribution of the three isomers. The second distribution considers the difference in energy barriers present in the synthesis of these monomers. MLC has a higher barrier than MLA and MLB; the last two have comparable barriers [107]. The new initial probability distribution, after a suggestion from the collaborators of the project, who have modelled the three half-SBU isomers, are $P_{A,0} = 45\%$, $P_{B,0} = 45\%$, $P_{C,0} = 10\%$. Two assumptions of this model include that SBUs are initially absent and half-SBUs can only form dimers. These are in agreement with the protocol followed in all SBU association-dissociation simulations. Also, the first assumption follows the observation that nucleation starts after the formation of half-SBUs. The second assumption is inherent to the treatment of the early stages of self-assembly in this work. The dimer is the smallest nucleus that can be formed out of half-SBU monomers and this leads to the understanding of which combinations of half-SBUs promote or hinder the emergence of defects in the MOF crystal lattice.

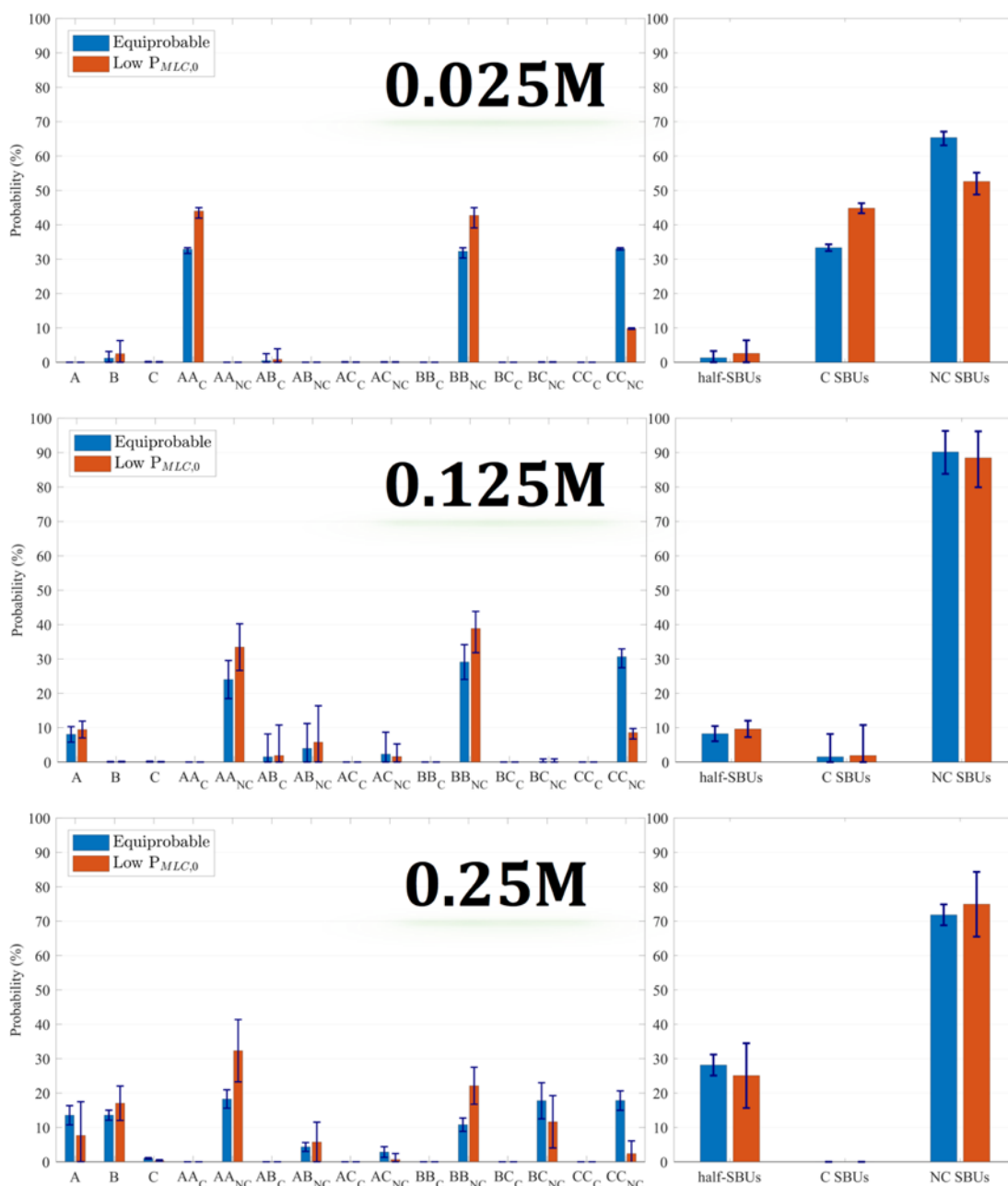


Figure 4-13. Equilibrium distribution of species at low ionic strength. Concentration of ions: 0.025M (top), 0.125M (middle) and 0.25M (bottom). Distributions are differentiated on initial condition for the probability of half-SBUs by colour (blue: first, red: second). The left panel includes the equilibrium probabilities of all species, while the right one categorizes them into detached half-SBUs, crystal-like (C) and noncrystal-like (NC) SBUs.

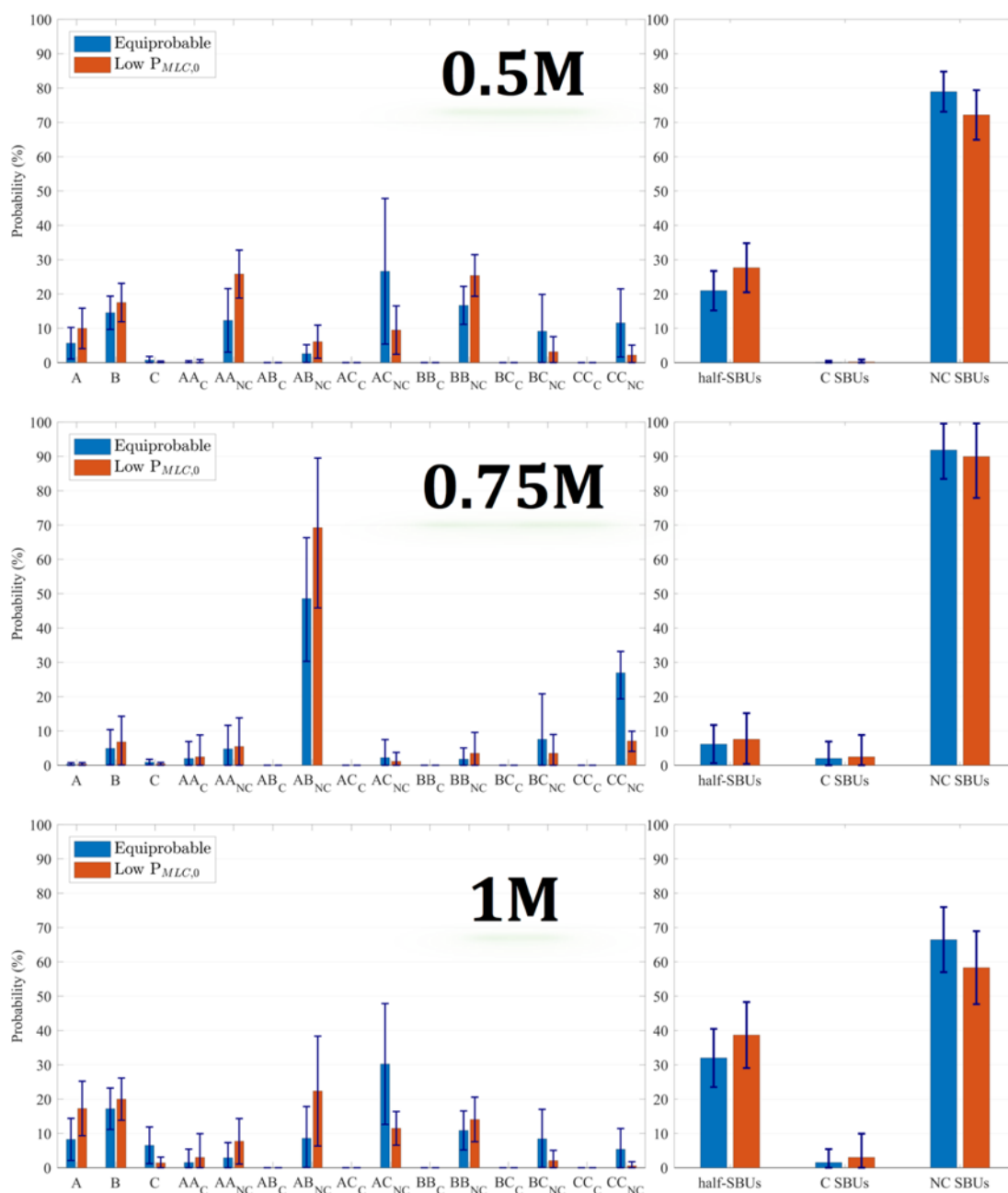


Figure 4-14. Equilibrium distribution of species at high ionic strength starting from an equiprobable initial distribution of half-SBUs. Concentration of ions: 0.5M (top), 0.75M (middle) and 1M (bottom). Distributions are differentiated on initial condition for the probability of half-SBUs by colour (blue: first, red: second). The left panel includes the equilibrium probabilities of all species, while the right one categorizes them into detached half-SBUs, crystal-like (C) and noncrystal-like (NC) SBUs.

The calculation of the equilibrium distribution of species in the system is carried out for every concentration of NaF for which a simulation was performed. The smallest concentration of NaF considered is 0.025M. Under these conditions, AA_C strongly contributes to the overall probability of crystal-like conformers at equilibrium that is $\sim 33\%$. The uncertainty of this value, calculated as the standard deviation from the error bootstrap method, is also very small ($\sim 1\%$). The detached half-SBUs have a small average equilibrium probability of $\sim 2\%$ and this does not exceed 3% based on uncertainty. The noncrystal-like conformers have an equilibrium probability of $\sim 65\%$ (uncertainty is $\sim 3\%$). It should be noted that the estimates are rounded to the closest integers in the sake of simplicity. A closer observation of these values is available through Figure 4-13 and Figure 4-14.

A difference between the weak presence against the absence of ions is that noncrystal-like configurations that are degenerate in state 2 on the FES projected on M-T and M-M are not sampled at all in presence of ions. In the simulation of the half-SBUs in 0.025M NaF , the ions interact strongly with the metal centre, promoting 2C, the crystal-like conformer, by hindering the rotational flexibility of the terephthalate linkers as previously discussed. When the second initial distribution of half-SBUs is considered, there is an increase of crystal-like conformers at equilibrium to $\sim 45\%$, with $\sim 2\%$ uncertainty, followed by a decrease of noncrystal-like configurations to $\sim 52\%$ (with $\sim 4\%$ uncertainty) and a slight increase in the presence of isolated half-SBUs ($\sim 3\%$ on average and $\sim 6\%$ at most).

A concentration of NaF equal to 0.125M is discussed next. The noncrystal-like probability is based upon the presence of AA_{NC} , BB_{NC} and CC_{NC} . These three dimers result in a sharp increase in the likelihood of observing noncrystal-like adducts ($\sim 85-90\%$). Crystal-like configurations originate from AB_C ; hence the uncertainty is calculated from this SBU. Crystal-like conformers can be at most $\sim 8-9\%$ ($\sim 2\%$ on average) at equilibrium regardless of which initial distribution is selected. Half-SBUs are $\sim 8-9\%$ at equilibrium for this concentration of ions.

Ionic strength is further increased to 0.25M NaF in solution. Half-SBUs are rather inactive ($\sim 25-30\%$ probability at equilibrium) and noncrystal-like structures dominate ($\sim 70-75\%$ equilibrium probability). Therefore, the probable dimer structures are noncrystal-like at this concentration of ions due to strong interactions between the metal centres that favour states 4, 6 and 7. More specifically, AA_{NC} , BB_{NC} , BC_{NC} and CC_{NC} are stronger than AC_{NC} and AB_{NC} .

The middle concentration of NaF is equal to 0.5M. The probability of crystal-like conformers is negligible as in the 0.25M NaF . MLA and MLB are rather inactive resulting to the overall isolated half-SBUs presence at equilibrium with a likelihood of $\sim 20\text{-}35\%$. Noncrystal-like SBUs dominate ($\sim 65\text{-}80\%$) as all SBUs are probable to be at noncrystal-like configurations at equilibrium. AC_{NC} has the highest equilibrium probability, when starting from an equiprobable initial distribution of monomers. In contrast, AA_{NC} is the most probable at equilibrium when the “low MLC” initial distribution occurs.

A different profile emerges due to further addition of ions in order to reach a concentration of 0.75M. At this level, crystal-like configurations become probable again. These are $\sim 2\text{-}3\%$ on average and $7\text{-}9\%$ at most. This is the result of AA_C , becoming probable due to the formation of salt bridges between two adjacent half-SBUs. AB_{NC} is the most probable SBU conformer, followed by CC_{NC} . It should be mentioned that MLB is not very active at this level of concentration of ions and the strength of the AB_{NC} structure is a result of large salt clusters which emerge when this SBU is in water with 0.75M NaF .

Finally, the concentration of ions is increased to its maximum value in this work; that is 1M. Salt bridges and clusters are both observed at this stage. Therefore, a versatile behaviour can be seen at the equilibrium distribution. At first, salt bridges lead to crystal-like structures ($\sim 2\text{-}3\%$ on average and $\sim 5\text{-}10\%$ at most). These originate from AA_C , as in water with 0.75M NaF . The second observation is the, an increased likelihood of isolated half-SBUs at equilibrium ($\sim 25\text{-}45\%$) due to salt clusters that inhibit interactions between them. Furthermore, noncrystal-like conformers are very strong ($\sim 55\text{-}70\%$ probability at equilibrium). AC_{NC} is the most probable SBU conformer, followed by AB_{NC} . At last, MLB is the least active monomer at this level of concentration for the ions in the system.

The choice of initial distribution of half-SBUs reflects the response of the equilibrium distribution of species to pre-determined composition of the system at the start of the assembly process. The second initial distribution that favours MLA, unlike MLC, leads to an increase for the equilibrium probability of crystal-like SBUs. This is another observation that supports the understanding that MLA promotes crystallinity and MLC is a potential source of defects. Therefore, relevant processing to sterically hinder or promote the formation of certain half-SBUs during the early stages of MOF synthesis can prove crucial for the regulation of the extent of defects in the final product.

Furthermore, the presence of ions at increasing concentrations provides a molecular-level understanding of their versatile behaviour the system. At very small concentrations, they promote crystallinity. At middle concentrations, ions favour interactions between the metal centres; hence promoting defects. Finally, at high concentrations, salt bridges promote the formation of crystal-like SBUs but interactions between half-SBUs are hindered due to salt clusters which intervene between them.

The equilibrium distribution plots for every concentration of NaF are provided in Figure 4-13 and Figure 4-14. The blue colour represents the average equilibrium probabilities of species resulting from an equiprobable initial distribution of half-SBUs. The red colour is used to show the average equilibrium probabilities of species when a low MLC initial distribution of half-SBUs is selected. The error-bars correspond to the standard deviations. Probabilities for all species are available on the left panel and these are split to three categories: half-SBUs, crystal-like and noncrystal-like SBUs on the right panel.

4.2.12 Effect of Ions on the probability of crystal-like dimers

This analysis is accompanied by the estimation of the trend that the probabilities of half-SBUs and SBUs (Figure A-13 in the Appendix) follow with increasing concentration of ions. The error-bars appearing in this figure are calculated through an error bootstrap method as discussed previously in the text. It should be reminded that experimental synthesis is carried out in water, and in presence of ions, at 493 K under high pressure generated in an autoclave for 8 hours [38]; hence synthesis takes place in the liquid state in agreement with the simulations conducted in this chapter. Conclusions agree with those drawn from simulations at a higher temperature and larger scale as it is observed in Chapter 5.

Furthermore, the relative rate of dissociation for any SBU (denoted by index i) is evaluated at every concentration of NaF . At first, the probability weighted average for the ΔG values of reaction j is calculated. This corresponds to the half-SBUs association into an SBU as calculated from each FES (ΔG from state 5). This is performed in order to provide an estimate for the tendency of SBUs to dissociate under certain conditions and compare that to their tendency to dissociate in absence of ions. After this, the relative rate of dissociation for an SBU in reaction j , $RR_{SBU,j}$, at each ionic concentration with respect to that in absence of ions is calculated. The formulas for the calculation of the aforementioned quantities are provided below,

$$\langle \Delta G_{SBU,j} \rangle = \frac{\sum_1^{12} P_{SBU,i} \cdot \Delta G_i}{\sum_1^{12} P_{SBU,i}} \quad (4.1a)$$

$$RR_{SBU,j} = \frac{e^{\beta \cdot \langle \Delta G_{SBU,j} \rangle}}{e^{\beta \cdot \langle \Delta G_{SBU,0} \rangle}} \quad (4.1b)$$

where, $\langle \Delta G_{SBU,j} \rangle$ is the probability weighted average free energy difference of an SBU; hence considering all states for SBU i ($i = AA_C, AA_{NC}, AB_C, AB_{NC}$ etc.) in reaction j ($j = 0, 0.025M, 0.125M, 0.25M$ etc.). $P_{SBU,i}$ is the equilibrium probability of each SBU i . ΔG_i is the free energy difference of SBU i from state 5. $RR_{SBU,j}$ is the relative rate of dissociation of an SBU at reaction j .

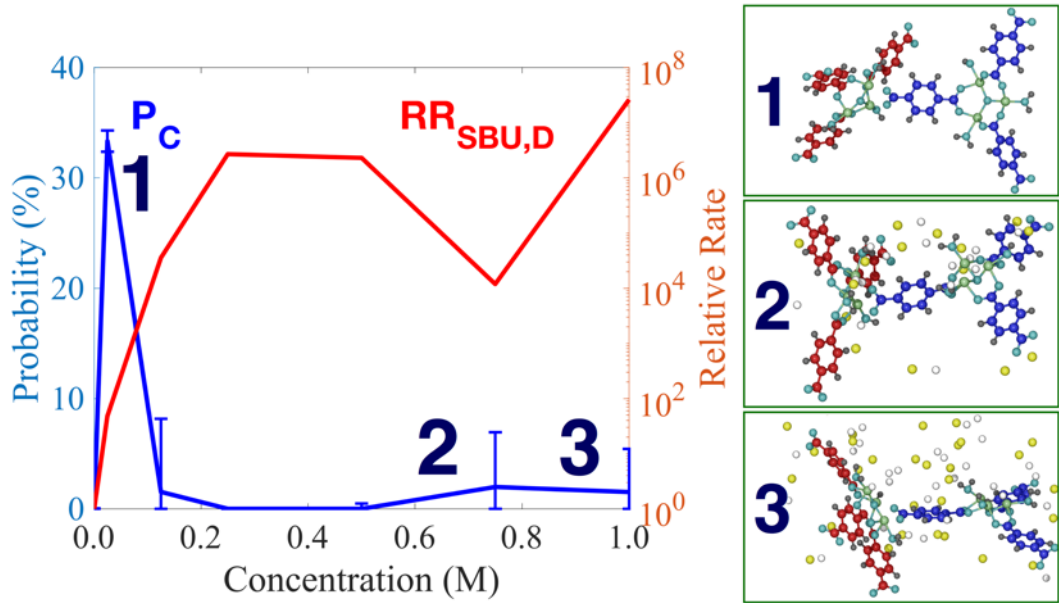


Figure 4-15. Effect of concentration of ions on the probability of observing crystal-like SBUs at equilibrium (blue line). Error-bars correspond to the standard deviation. The red plot corresponds to the relative rate of dissociation of any SBU conformer. Crystal-like configurations are shown for 0.025M, 0.75M and 1M NaF . The scale is up to 40% to show the trend in more detail.

This analysis is useful to understand how the ionic strength is linked with the propensity to self-heal defects of the SBUs. More elaborately, the relative rate of SBU dissociation is increased for concentrations up to 0.25M. In middle values of concentration, 0.25-0.5M, the relative rate is constant; hence the likelihood of SBUs to dissociate is not affected by a change in the concentration of ions within this range. The relative rate of SBU dissociation is decreased until 0.75M, where it is at local minimum, and then increased again until 1M.

In summary, the dissociation rate of SBUs is 4-7 orders of magnitude larger than in absence of ions. Consequently, clusters formed through SBU assembly become more dynamic with increasing concentration of ions. Therefore, the propensity of SBUs to potentially self-heal defects is promoted by the presence of ions in the early stages of self-assembly. The relative rate of SBU dissociation and the equilibrium probability of crystal-like SBUs are provided in Figure 4-15.

The equilibrium probability of the emergence of crystal-like and noncrystal-like SBUs as well as inactive half-SBUs follows clear trends with increasing concentration of ions. At low concentration of ions, the crystal-like conformers are favoured. In this case, isolated half-SBUs are very improbable at equilibrium. Noncrystal-like SBUs are highly probable as well. More precisely, half-SBUs are highly active resulting to a strong presence of crystal-like units as well as defects. At higher concentrations, the activity of half-SBUs is hindered by the increase in the number of ions. These bind to the metal centres; hence mostly promoting a fraction of interactions, mostly between metal centres; hence states 4, 6 and 7. This behaviour is understood through the emergence of a local maximum in the probability of half-SBUs at 0.25M and a global maximum for the noncrystal-like SBUs at 0.125M.

Ions at concentrations between 0.25M and 0.5M lead to a very small probability of crystal-like interactions. This is increased for larger concentrations, such as 0.75M. Finally, at 1M, the inactive half-SBUs are at a maximum, while the probability of both crystal-like structures and defects is lowered. Consequently, half-SBUs are less active at this concentration.

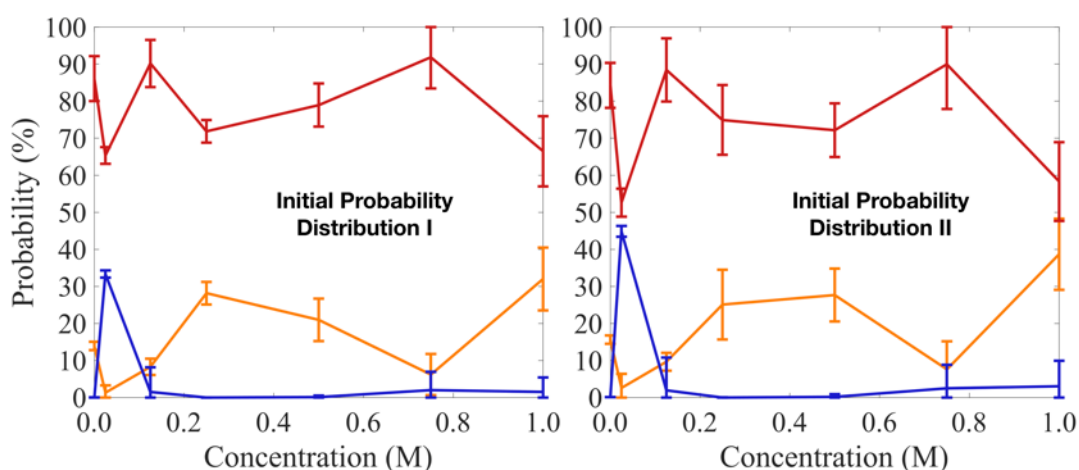


Figure 4-16. Effect of the concentration of ions on the equilibrium probability of half-SBUs (orange), crystal-like (blue) and noncrystal-like SBUs (dark red) at equilibrium. Both initial probability distributions are considered.

The trends corresponding to the second initial probability distribution of half-SBUs (low MLC), as discussed previously in the text, are evaluated as well. The pattern is similar to the other initial probability distribution assessed. Nevertheless, the strength of different types of species varies. Isolated half-SBUs at equilibrium are most probable at 1M in agreement with the other initial probability distribution. The trend changes only for the middle concentrations of ions, at 0.5M, where the equilibrium probability of half-SBUs is increased in comparison to the other initial distribution; hence a lower initial probability of MLC renders half-SBUs less active at this concentration of ions.

The probability of noncrystal-like SBUs has two peaks for 0.25M and 0.75M and it is very low for 0.025M and 1M. This means that it follows a similar pattern as the equiprobable distribution of half-SBUs, except from the case of 0.5M, as previously discussed. Overall, the equilibrium probability of noncrystal-like SBUs is greater than 50 %; hence noncrystal-like units dominate the equilibrium probability of all species in the range of concentrations studied. This result shows how important the early stages are for the formation of defect SBUs. Therefore, there is a need to thoroughly understanding the mechanism of formation for these species in order to regulate their occurrence.

At last, the crystal-like SBUs have a maximum equilibrium probability that is increased from 33 % to 40 % at 0.025M *NaF*. All other concentrations show a similar trend for the probability of crystal-like SBUs. As a result, the modification of the initial distribution of monomers can yield an appreciable change in the equilibrium probability of crystal-like configurations at low concentrations of ions. The equilibrium probability of noncrystal-like SBUs is decreased for this ionic strength as expected. The probability trends are available in Figure 4-16. The average values are plotted accompanied with error-bars resulting from the standard deviation. The error bootstrap method was performed for the calculation of the aforementioned quantities.

4.2.13 Comparison with experiments

At first, the half-SBUs are detached and interactions between them are investigated in order to explore the configurational landscape of the resulting SBU isomers. The 2C SBU configuration has the same relative orientation and structure as the SBUs in the experimentally obtained MIL-101(Cr) [38] structure as seen in Figure 1-1. Therefore, the model is able to capture the experimentally observed SBU configuration during sampling without any previous knowledge of the energy

landscape of the SBU conformers. Additionally, possible noncrystal-like SBU conformers are sampled during the association-dissociation process. This provides a thorough understanding of how noncrystal-like SBU configurations are formed during the early stages of MOF self-assembly. It should be reminded that experimental synthesis is carried out in water, and in presence of ions, at 493 K under high pressure generated in an autoclave for 8 hours [38]; hence synthesis takes place in the liquid state in agreement with the simulations conducted in this chapter. Also, conclusions agree with those drawn from simulations at a higher temperature and larger scale (see Chapter 5). This chapter provides a mechanistic understanding of the effect of ions at varying concentrations on crystallinity. Also, this chapter explains how MOF precursors interact with themselves and which interactions are promoted or obstructed at varying ionic strength.

Ions are often incorporated in the synthesis of MOFs. Moreover, fluoride has been used by experimentalists during this process. This anion promotes the crystal growth of this category of materials [99]. The interaction between fluoride and the metal centre of the half-SBU is considered to help in holding the structure of the polymer in place [166]. Furthermore, fluoride anions act as bridges between building blocks [165]. This is in accordance with the findings of this work for a concentration of NaF greater than 0.5M, where there are enough ions to form these bridges. At this point, it should be noted that at these concentrations of ions, large ionic clusters are introduced, and they render interactions between the half-SBUs infrequent.

In summary, the probability of crystal-like SBUs as well as defects is higher at low concentrations of ions as previously mentioned. Therefore, inactive half-SBUs should be considered during the interpretation of these results. More precisely, ions that exceed a concentration threshold are observed to agree with experimental findings in promoting crystal growth. Nevertheless, the equilibrium probability of SBUs is lower than in smaller concentrations of ions due to presence of large salt clusters that render interactions between the half-SBUs infrequent.

At last, different ions could be used to understand how the choice of specific ions impacts the energy landscape and the probability of forming crystal- and noncrystal-like SBUs. For example, an anion with a size larger than F^- is more difficult to approach the metal centre and it is not certain that it can fit to the inner core of the half-SBUs; hence it could be obstructed by the terephthalate linkers. Moreover, an anion with a charge that is smaller than F^- could potentially lead to weaker interactions between ions and the metal centre. Therefore, ionic effects will not be prevalent in the system and this could lead to a behaviour similar to the one in

absence of ions. It should be noted that the focus is shifted towards F^- as this is mostly responsible for the overall effect of ions on the system due to interactions with partially charged hydrogen atoms that belong to the metal centre of the half-SBUs. Nevertheless, another cation rather than Na^+ could be used to examine its effect on the system.

At last, the force field used in this work shows a good agreement with experiment concerning the solubility of NaF in water. The experimentally reported value is between 0.967 and 0.997 M [232]. The microsecond-long simulation trajectories with ions reveal a similar behaviour of the system with salt. At 0.5M NaF, there is no salt cluster observed. At 0.75M NaF, a very small bridge forms only between the half-SBUs that act as nucleation centres for salt. Finally, at 1M a very large cluster between the half-SBUs is formed and it is not disrupted as simulation progresses. Therefore, the solubility of NaF from the force field is between 0.75 and 1M showing good agreement with the experimentally observed value.

4.3 Effect of Solvent

In the last part of the analysis for the SBUs, the effect of solvent is considered. N, N-dimethylformamide, commonly abbreviated as DMF, is selected in place of water. The reasoning behind this choice is the frequent use and popularity of this solvent in MOF synthesis [158], [233], [234].

Solvent molecules are explicitly represented and the same cell size and MD parameters were used except from the solvent isothermal compressibility that was changed to $6.5 \cdot 10^{-5} \text{ bar}^{-1}$ [193] in order to correspond to DMF modelled with OPLS-AA. The OPLS-AA force field parameters and atomic positions for DMF were obtained from [193], [194]. The dipole moment of DMF is calculated as the sum of the products of the atom position vectors and their corresponding charges [235]. Then it is compared with the experimentally determined value. The dipole moment of DMF, as determined through laboratory experiments, is 3.86 D [236], [237]. The value calculated using the classical force field is 3.52 D, which is in good agreement with the experimental observation. This calculation provides further confidence in using the classical force field as it reproduces the separation of charges well within the system.

The process followed was an initial energy minimisation of the solvent molecule followed by solvation of the half-SBUs and consequent energy minimisation of the system in order to relax the initial structure. Equilibration and production simulations followed for all six possible couples of half-SBUs in DMF. WTmetaD [204] parameters remained the same as in water for consistency. MD simulations were run for 4 μs (AA), 2.5 μs (AC) and 2 μs for AB, BB, BC and CC. The bias factors used for each simulation are: 50 (AA), 40 (AC) and 30 for the rest. These differences are due to the difficulty of sampling relevant states for AA and AC with respect to the rest as these presented more stable interactions than the rest.

In addition to assessing the effect of a different solvent on the configurational landscape of SBUs, the role of ions (Na^+ , F^-) is evaluated in DMF. Two concentrations are used 0.125M and 0.25M. These are considerably lower than in water as the solubility of ionic species is much lower in an organic solvent such as DMF; hence ionic clusters and bridges are more stable in DMF. A high concentration of ions should result in the formation of very large ionic clusters that do not promote interactions between half-SBUs. In order to avoid this undesirable effect, relatively low ionic concentrations are used. The same MD and WTmetaD [204] procedures as in DMF

in absence of ions is used, while ions are added before the energy minimisation step for the system. The only differences consist of simulation time and bias factor selection for WTmetaD. MD simulations were run for 2 μ s for *AB* (0.125M NaF), *BB*, *BC* and *CC* (0.125M NaF), 2.5 μ s for *AA*, *AC* and 3 μ s for *AB*, *CC* (0.25M NaF). Again, discrepancies occur in order to achieve good sampling (in terms of ΔG convergence) in all simulations. The bias factors used for each simulation are: 60 (*AB*, *AC*, *CC* – 0.25M NaF), 50 (*AA* at both concentrations and *AB* with 0.125M NaF) and 40 (*AC*, *BC* – 0.125M NaF, *BB* – 0.25M NaF), 30 for the rest.

4.3.1 Half-SBUs in DMF

Simulations of half-SBUs are performed in DMF instead of water. This analysis explains how a change in composition regarding the solvent affects the free energy landscape on the two CVs biased during the simulation.

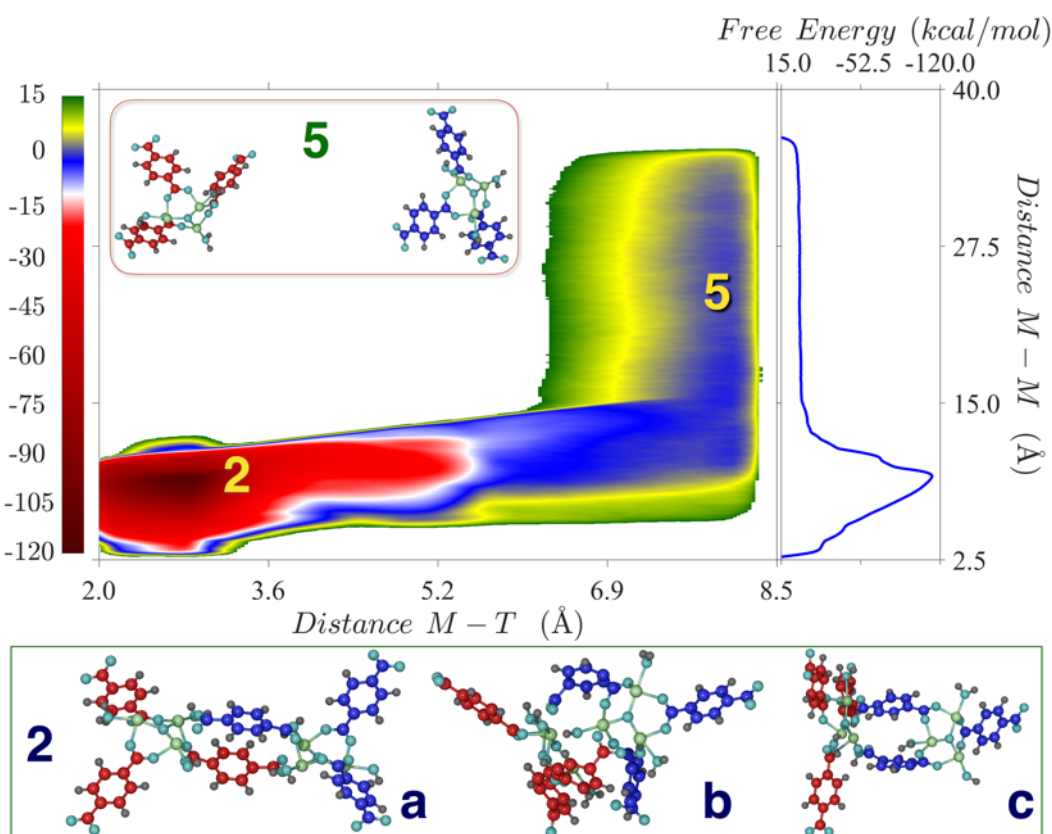


Figure 4-17. Free Energy Surface of AA in DMF. The most probable interactions featuring in state 2 are shown. The colour code is consistent with Figure 4-1.

The free energy surface (FES) of AA in DMF is exhibited in Figure 4-17. The most stable SBU in DMF is AA, as in the case of water. Nevertheless, ΔG from the

detached to the strongest attached state ($\Delta G_{5 \rightarrow 2}$) differs by almost an order of magnitude compared to water. In DMF $\Delta G_{5 \rightarrow 2}$ is ~ -120 kcal/mol while in water it is ~ -20 kcal/mol. The SBUs which prevail in DMF are more stable and compact as the most common structure consists of 4 interactions between a terminal carboxylic oxygen of one half-SBU and a chromium atom (Cr) of the metal centre in the adjacent half-SBU. Furthermore, there is a considerable degeneracy at state 2 as it can be represented by an ensemble of structures. Three characteristic structures are discussed in more detail. The first one, 2a, features two terephthalate linker parallel to each other. This is the most probable SBU conformer in DMF. This has been formed in water in absence of ions, but it is not as probable as in DMF. This means it has a higher free energy difference from state 5. In another structure, 2b, the linkers are slightly bent. The last structure, 2c, features interactions between the terminal oxygen atoms from two linkers of a half-SBU and the three chromium atoms of the adjacent half-SBU. Another important observation is that $\pi - \pi$ stacking of the benzene rings is characteristic of the isomer SBUs that are probable to form in DMF.

It should be noted that state 2 dominates the FES strongly. As a result, states that featured in the FES of AA in pure water are not highly probable in this case. Furthermore, AA is the most probable amongst all SBUs based on free energy difference from state 5 as in water. Therefore, the choice of solvent does not affect the ranking of SBUs in terms of ΔG from state 5.

4.3.2 Half-SBUs in DMF with 0.125M NaF

The addition of ions in DMF is assessed in order to investigate their role in a different solvent than water. These are added at concentrations of 0.125M and 0.25M. Free energy surfaces for all half-SBU couples in both concentrations are computed. This is followed by analysis of the resulting structures that feature on the FES of the AA SBU.

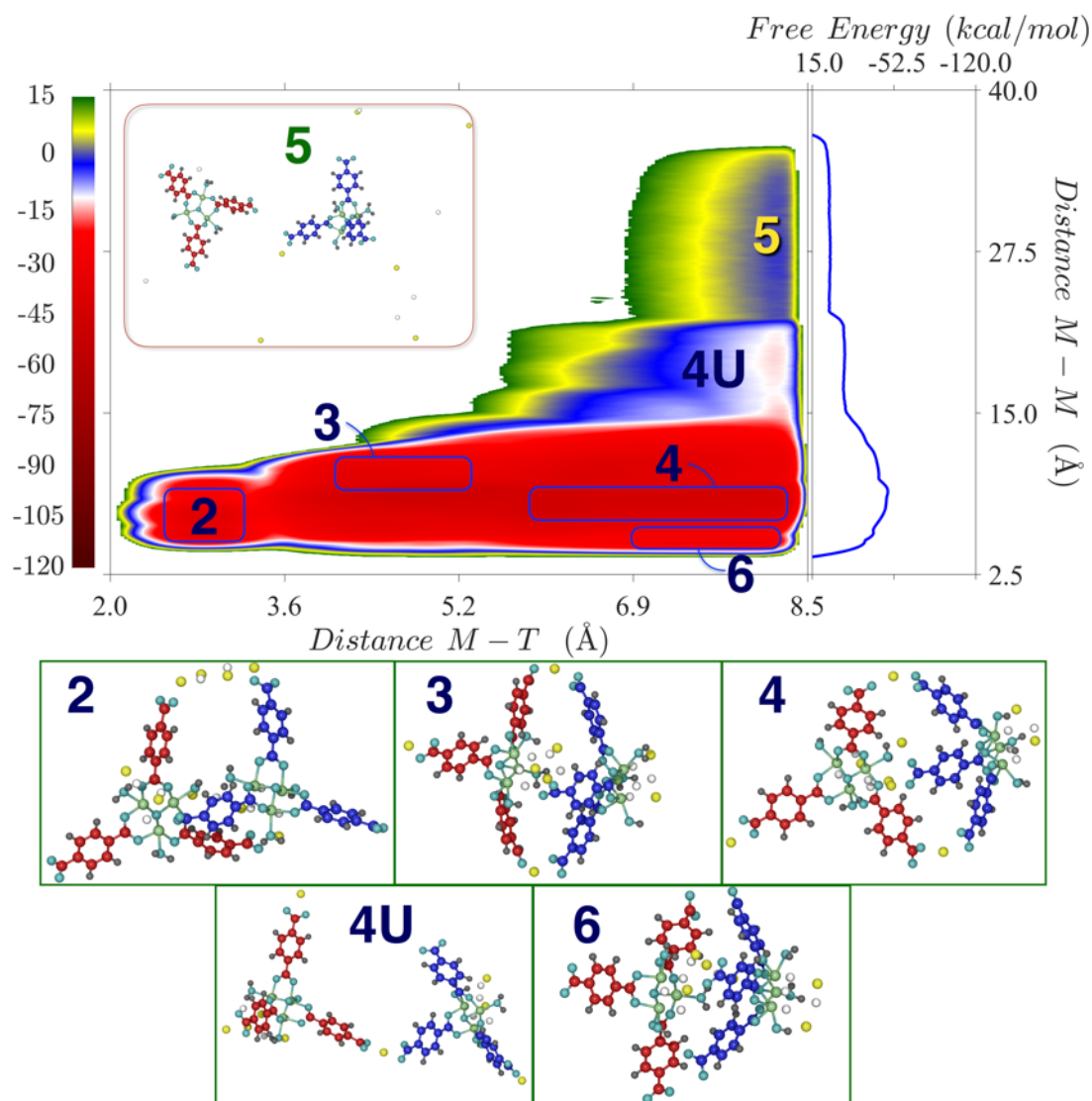


Figure 4-18. Free Energy Surface of AA in DMF with an ionic concentration of 0.125M. States are shown enclosed in designated areas on the FES. Representative structures for states on the FES are shown. The colour code is consistent with Figure 4-1.

The first situation refers to 0.125M *NaF* in DMF. The free energy surface (FES) of AA in DMF with an ionic concentration of 0.125M is exhibited in Figure 4-18. A rich configurational landscape is discovered through the FES, when compared with

the simulation in absence of ions. State 2 consists of an interaction between a terminal carboxylic oxygen (OT_1) and a chromium (Cr_2) atom of the adjacent half-SBU. Also, an oxygen of the opposite half-SBU (OT_2) interacts with a hydrogen atom of the other half-SBU (HM_1). Also, a salt bridge is formed between the terephthalate linkers; thus, hindering their rotational flexibility.

State 3 features interactions between the terephthalate linked through attached ions. More elaborately, a sodium cation intervenes between adjacent terminal carboxylic oxygen atoms which interact strongly with the cation from both sides. This situation occurs between two couples of adjacent terephthalate linkers. Another interaction that is characteristic of this state refers to a terminal carboxylic oxygen and a hydrogen of the metal centre of the opposite half-SBU.

In state 4, the terminal carboxylic oxygens of opposite linkers are attracted by sodium cations. Furthermore, terminal carboxylic oxygen atoms of a half-SBU interact with a sodium cation attached to the metal centre of the opposite half-SBU. Furthermore, another state, namely 4U, emerges on top of state 4; hence it shows a larger M-M CV value. Half-SBUs weakly interact through a sodium cation that attracts the terminal oxygens of two terephthalate linkers of adjacent half-SBUs.

Lower values for the M-M CV correspond to state 6. There are two instances where a sodium cation attracts terminal carboxylic oxygens of adjacent half-SBUs; hence linkers are closer. Also, the metal centres attach to opposite sides of an ionic cluster built between them. A terephthalate linker also interacts with this cluster through its terminal oxygens and chromium atoms of the cluster.

It should be noted that state 3 is the most probable on the current FES. This is on contrast with the FES computed in absence of ions, where state 2 dominates. Furthermore, the weak presence of ions disrupts configurations similar to 2Q in agreement with the studies in water. Also, salt bridges are formed, and these stabilise SBU conformers. Nevertheless, these are formed not only on the metal centre, but also between terephthalate linkers; hence newly discovered SBU configurations emerge through the simulations in DMF with ions at 0.125M.

4.3.3 Half-SBUs in DMF with 0.25M NaF

An increase of concentration to 0.25M results in the appearance of more stable ionic clusters that favour M-M interactions as in the smaller concentration of ions. A more elaborate analysis of the representative structures of the states featuring on the FES of AA at this concentration of ions in DMF is needed in order to evaluate how the increase in the ionic strength affects the structural landscape of SBU conformers.

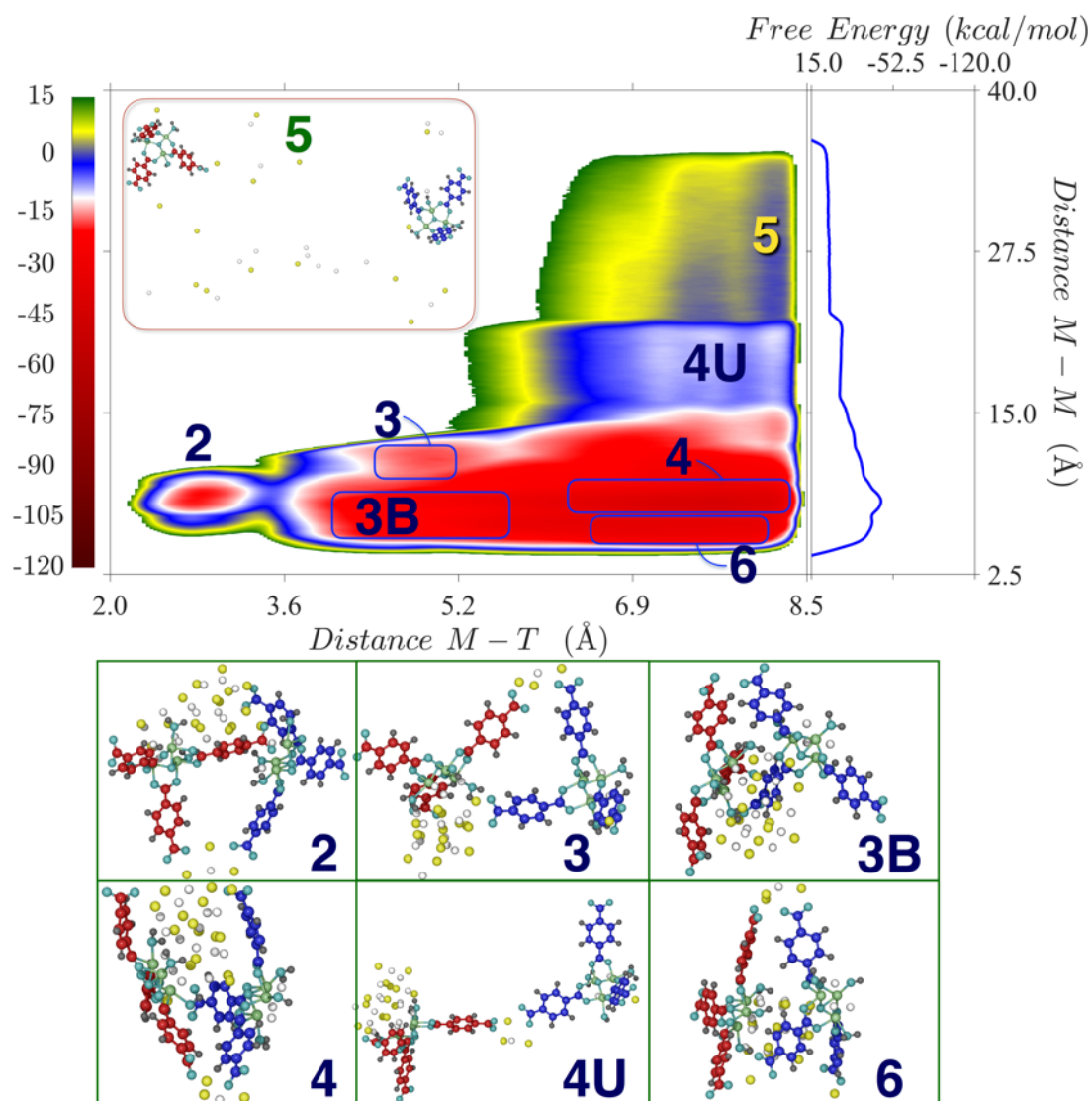


Figure 4-19. Free Energy Surface of AA in DMF with an ionic concentration of 0.25M. This is consistent with Figure 4-18.

The free energy surface (FES) of AA in DMF with an ionic concentration of 0.25M is exhibited in Figure 4-19. State 2 features a representative structure that resembles crystal-like SBUs, but it shows one terminal carboxylic oxygen-chromium interaction. Fluoride anions are also attached to chromium atoms of the metal centres. A small salt bridge is formed between the terminal carboxylic oxygens of two adjacent half-SBUs. Also, a large ionic cluster is built on the metal centre of one half-SBU and interacts on the other side with terminal carboxylic oxygen atoms of the opposite half-SBU. The salt bridge and the cluster hinder the rotational flexibility of the terephthalate linkers in this configuration.

In state 3, a terminal carboxylic oxygen interacts with a hydrogen atom of the opposite half-SBU. Also, the chromium atoms have fluoride anions attached to them at the metal centres. Furthermore, a salt bridge appears between terminal carboxylic oxygen atoms that belong to adjacent half-SBUs. At last, an ionic cluster is built on one of the metal centres, as in state 2. Nevertheless, this expands along a neighbouring terephthalate linker and it does not interact with anything else on the other side.

At the bottom of state 3, another state, namely 3B, appears. This corresponds to lower values for the M-M CV in comparison with state 3. This state is similar to state 3. All types of interactions emerging in state 3 are present in 3B as well. Nevertheless, in state 3B, two couples of terephthalate linkers that belong to adjacent half-SBUs are very close to each other; hence the SBU structure is more compact when compared with the representative configuration of state 3.

State 4 dominates the FES. This is different from the smaller concentration of ions and the case in absence of ions. A small salt bridge intervenes between terminal carboxylic oxygen atoms of adjacent half-SBUs. Furthermore, a sodium cation attracts terminal carboxylic oxygen atoms on the other side of this SBU structure. Fluoride anions attach to chromium atoms and ionic clusters are built between the two metal centres. These stabilise this noncrystal-like structure. Therefore, half-SBUs interact through the ionic cluster that has been developed between them.

Another state emerges for larger M-M CV values, namely 4U. A weak interaction compared with state 4 occurs. This features a small salt bridge between terminal carboxylic oxygen atoms of adjacent half-SBUs. Furthermore, an ionic cluster is formed on the metal centre of one half-SBU. At last, chromium atoms interact with fluoride anions in both metal centres.

At last, state 6 appears. Half-SBUs are closer as the M-M CV value is lower than in state 4. Similar interactions occur between the two states but the terephthalate linkers of adjacent half-SBUs are closer than in state 4. Terminal carboxylic oxygens that belong to opposite half-SBUs are attracted by a sodium cation on one side. On the other side, a small salt bridge is formed between those types of atoms. Also, an ionic cluster is formed between the half-SBUs as it is attached to both metal centres.

In agreement with the smaller concentration of ions, the 2Q configuration is disrupted. Noncrystal-like SBUs dominate this FES as well. State 2 is distinguished from the other states on the FES, unlike the smaller concentration of ions. At last, ions promote a rich configurational landscape for the AA SBU.

4.3.4 Conclusion on the role of solvent in the system of half-SBUs

Overall, DMF results in appreciable quantitative differences in the FES of the half-SBU couples.

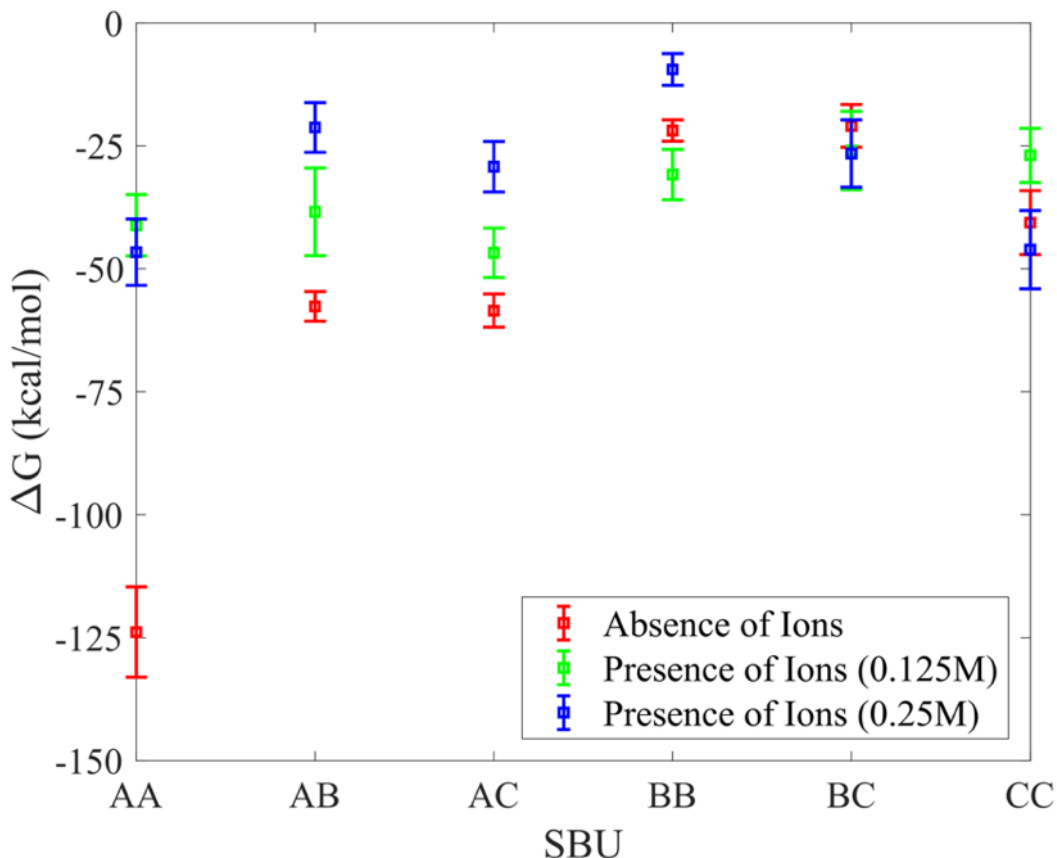


Figure 4-20. Error-bars depicting the standard deviation on the weighted average of the ΔG between the most probable state and the reference (state 5) obtained from simulations in DMF in absence and presence of ions.

The ΔG values, as calculated from the reference state (state 5), are considerably lower than in water. In particular, the time-weighted average ΔG values are provided for the most probable SBU for each type of conformer (AA-CC) accompanied with error-bars showing the standard deviation. The most probable SBU results from the lowest value for ΔG between any state on the relevant FES and the reference (state 5). These values are exhibited in Figure 4-20.

Furthermore, the most probable structures in DMF are more compact due to the existence of more chromium-oxygen interactions in absence of ions. The formation of these structures is disfavoured in the presence of ions as these interact with the terminal carboxylic oxygen atoms. Also, salt bridges are formed at both concentrations of ions. These link terminal carboxylic oxygen atoms of adjacent half-

SBU. Therefore, their rotational flexibility is hindered, and ions stabilise these structures. Furthermore, ionic clusters are formed on the metal centres at a concentration of 0.25M *NaF*.

At last, ions render SBUs more dynamic as the free energy differences of all states with respect to state 5 are less negative when compared with the ones in absence of ions. Therefore, ions in DMF can act towards the self-healing of defects during assembly, in agreement with the case of water. Therefore, the presence of these strong defects originating from the AA SBU is mediated in presence of ions as it is showcased in Figure 4-20.

The most appreciable change in the presence of ions occurs for AA. The absolute value of the negative free energy difference between the most stable state and the reference (state 5) is more than double in pure DMF (~ -120 kcal /mol) than in DMF with ions (~ -50 kcal /mol).

SBUs are more dynamic for the AB and AC SBUs in presence of ions as well. The value of ΔG becomes more positive as more ions are added for these conformers. This does not occur for BB, where SBUs are less dynamic in weak presence of ions, but they become more dynamic, than in absence of ions, when 0.25M *NaF* is added. In BC, the values of the free energy differences are very close to each other; hence this SBU is not strongly affected by the presence of ions. Nevertheless, BC is slightly less dynamic in presence of ions in DMF. The last SBU type, CC, becomes more dynamic in weak presence of ions and less dynamic when more ions are added. These are compared with the case in absence of ions.

Overall, AA is the most important to evaluate, as it presents the most probable conformers and it is a source of crystal-like SBUs in water. At last, ions contribute to the number of possible conformations for the MIL-101(Cr) SBU; hence a rich structural landscape is discovered in DMF. Newly discovered structures are identified in DMF in comparison to water. This highlights the importance of the presence, and choice, of guest molecules on the promotion of certain structural arrangements for the SBU. As a result, certain SBU structures can be hindered when the conditions, referring to the choice of solvent and the concentration of ions is fine-tuned.

4.3.5 Conclusions from the analysis of dimers

The investigation of interactions between half-SBU dimers leads to a molecular-level understanding of how conformational complexity regulates MOF self-assembly. The solvent choice promotes the formation of desired isomers, as when comparing the free energy landscape in DMF with the one obtained in water. Thermodynamic and kinetic factors indicate how solvent mixtures can be employed to regulate defect population during self-assembly. The ability of SBUs to form crystal-like configurations is strongly correlated with their structural rigidity; hence this is regulated in part through the molecular identity of dimers. It should be reminded that experimental synthesis is carried out in water, and in presence of ions, at 493 K under high pressure generated in an autoclave for 8 hours [38]; hence synthesis takes place in the liquid state in agreement with the simulations conducted in this chapter. Findings are consistent with simulations at a higher temperature and larger scale (see Chapter 5).

This system is studied using a classical all-atom force field. Therefore, a number of assumptions is inherent to this setup as discussed in Chapter 2. The differences that could be observed through an increase in the accuracy of the chemical description of the system through DFT calculations need to be addressed. In this context, *ab initio* molecular dynamics of the three half-SBU isomers in explicit water were performed by the collaborators of this project at PNNL. The author of this text analysed the trajectories and compared them with those obtained using a classical force field. This validation process shows very good agreement between the force field parameters and the behaviour of the system at the higher level of theory. This is thoroughly discussed in the appendix (see section A.1). Consequently, these observations provide confidence on the setup used for the analysis in this work.

Ionic species at varying concentrations can promote or obstruct certain pathways to self-assembly and also regulate the extent of defects. At low concentration of ions, crystal-like structures show higher equilibrium probabilities due to the presence of fluoride anions which are attached to the metal center and hinder the formation of double interactions between metal centers and terephthalate linkers (2Q conformer). Higher concentrations of ions lead to hindrance of interactions between monomers due to formation of salt clusters that intervene between them. Furthermore, qualitative trends in reaction rates are provided, as the free energy landscape inherently considers both kinetic and thermodynamic factors.

Simulations of dimers in solution unravel a remarkable ensemble of more than 300 conformer structures involved in the early stages of MOF self-assembly. This is directed by enthalpic and entropic drivers and chemical intuition is not able to determine which dominates for each SBU in solution. Free energy landscapes address these factors and their decomposition into entropic and enthalpic contributions illuminates how enthalpy and entropy are affected by varying the conditions of self-assembly. Molecular simulations are capable of discriminating enthalpic and entropic drivers and thus support a hypothesis-based approach to MOF synthesis rather than employing traditional Edisonian practices. The findings of this chapter recommend that systematic studies of theory and experiments on solvent mixtures with varying concentration of ionic species should highlight the complex nature of MOF self-assembly.

Chapter 5

Half-SBU Assembly

This is the final chapter of results obtained and analysed in this work. It follows the analysis of flexibility of isolated half-SBU monomers (Chapter 3) and interactions between their couples or dimers (Chapter 4). Now, the system under study consists of several half-SBUs in solution as it is targeted on investigating their collective assembly. The size and composition of the system is discussed first (section 5.1), followed by the evaluation of the initial distribution of half-SBUs (section 5.2). Afterwards, the post-processing of assembly trajectories is explained (section 5.3). Half-SBUs are studied in pure water (section 5.4), in water with ions (section 5.5), pure DMF (section 5.6) and DMF with ions (section 5.7). Finally, conclusions drawn from this analysis are presented in section 5.8.

5.1 System size and composition

In this chapter, the collective behaviour of the half-SBUs is assessed and this is compared with the findings from the studies with one and two half-SBUs previously examined. To this aim, several half-SBUs are dispersed in solution, under various conditions, and time evolution of the system is studied. The conditions considered are now set to 493 K and 3,500 bar for water and 353 K and 1 bar for DMF. The reason is that the hydrothermal reaction terephthalate linker (H_2BDC), chromium (III) nitrate nonahydrate ($Cr(NO_3)_3 \cdot 9H_2O$), hydrofluoric acid and water occurs under autogenous pressure in an autoclave or with the use of microwaves [38], [53], [93]. Even if simulations in this section also occur under pressure, the density of water is very similar to previous simulations.

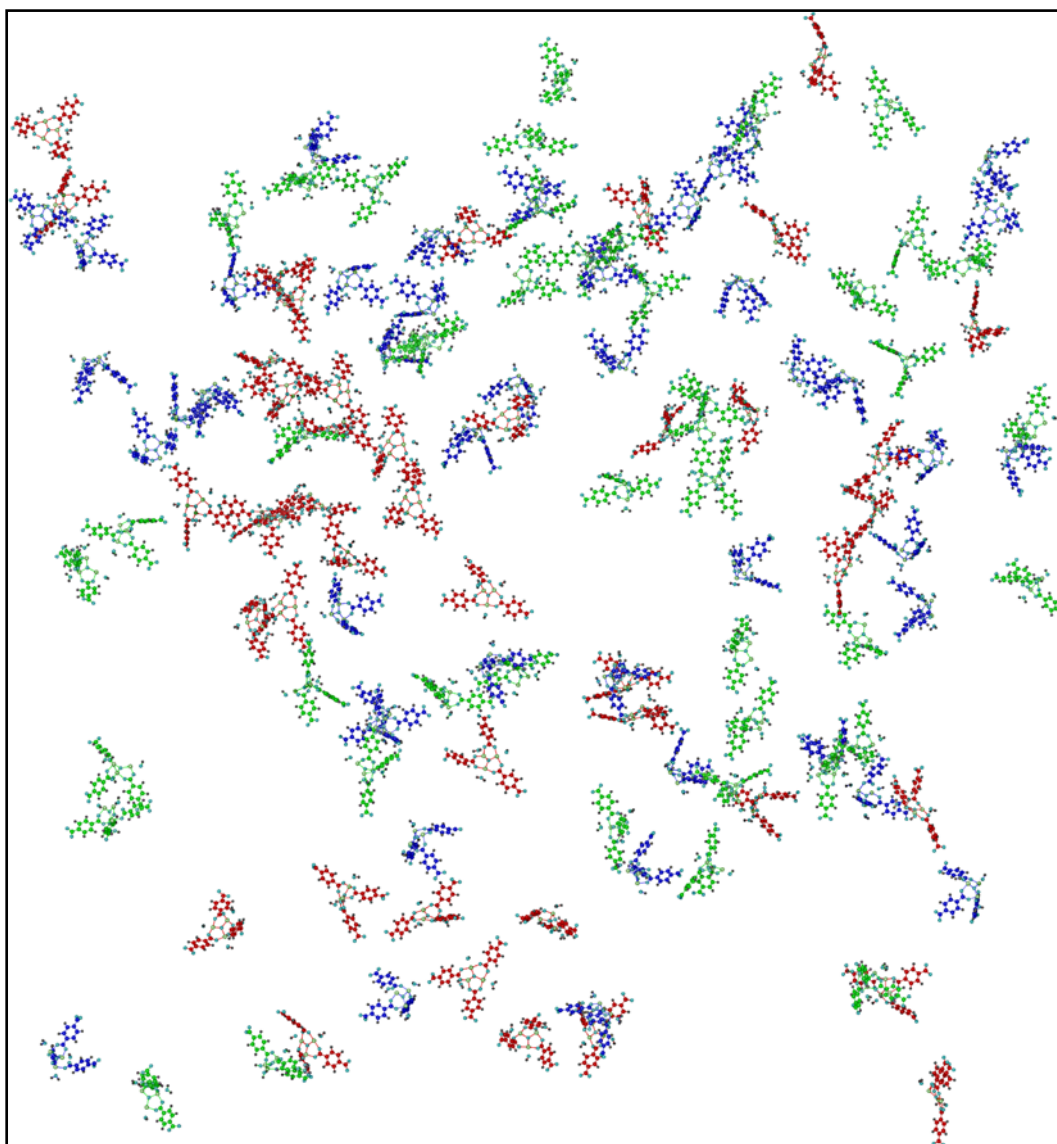


Figure 5-1. Dispersed half-SBUs at the start of the simulation. The colour code for chemical structures is consistent with Figure 1-1, except from the carboxylic carbon atoms. These are coloured blue for MLA, red for MLB and green for MLC atoms.

In order to study self-assembly, a large number of monomers is considered. This enables the system to spontaneously evolve, forming three-dimensional networks. The system studied consists of 132 half-SBUs in solution that are placed in a cubic box of 20 nm edge. Solvent molecules are represented explicitly in all simulations. The simulation box of half-SBUs in water consists of approximately 785,000 atoms. In DMF, the system is formed of about 510,000 atoms.

To investigate the role of counterions in water a regime near the maximum of crystal-like SBUs identified in Chapter 4 is considered. The concentration of ions is set to 0.035M in water as smaller concentrations tend to show almost no effect on the

outcome of half-SBU assembly. Instead, larger concentrations result in salt clusters that obstruct interactions between half-SBUs, when ionic concentrations are close to or exceed 0.1M, ionic clusters are formed and typically mediate interactions between half-SBUs. In other words, SBUs act as nucleation centres for NaF rendering and the formation of clusters consisting of MIL-101(Cr) half-SBUs is rather improbable.

It is observed that even at this scale, concentrations of ions lower than 0.1M hinder the extensive formation of 2Q SBUs, that emerged through the extensive study of the configurational landscape of SBUs in Chapter 4. At this stage, it should be noted, that the geometry and interactions in the 2Q SBU configuration were extensively discussed in Chapter 4. Therefore, findings are consistent across scales providing confidence on the behaviour of the molecular model. At last, in DMF a concentration of ions equal to 0.075M is considered as well. Large salt clusters are absent and a lattice that contains crystal-like SBUs is built from monomers initially dispersed in solution. A representation of a typical initial configuration of the system of half-SBUs in the simulation box is provided in Figure 5-1.

5.2 Evaluation of the initial probability distribution of half-SBUs

As shown in Chapter 4, differences in the initial probability distribution of half-SBUs leads to differences in the equilibrium probabilities of crystal-like and noncrystal-like SBUs as well as isolated half-SBUs. In the previous section, two initial probability distributions were evaluated. The first one consisted of equiprobable half-SBUs and the second of low MLC. The equiprobable monomer distribution is evaluated on the larger scale as well. This is now compared with an initial distribution of half-SBUs consisting only of MLA. This is a rather extreme situation, but it is meant to represent the limit case in which crystal-like SBUs are most probable (see Chapter 4).

5.3 Post-processing trajectories of assembly

In this section, the post-processing strategy of the assembly trajectories is discussed. The quantities used to investigate the dynamic assembly of half-SBUs are two coordination numbers. The first quantity corresponds to the number of coordination numbers between any couple of central oxygens (O_c) less than 0.5. In order to achieve this, a rational switching function (explained in the methods, section 2.2.4) is employed with parameters: $d_0 = 0$, $n = 16$, $m = 32$ and $c_c = 0.5$. The cut-off distance used for the coordination numbers is 15 Å. This coordination number is normalised by the number of half-SBUs present in the system.

The second quantity refers to the number of coordination numbers between chromium and terminal carboxylic oxygen (O_T) atoms more than 0.5. As in the previous collective variable, a rational switching function is used. The chosen parameters are the same as in the previous CV. Nevertheless, the cut-off distance used for the calculation of the coordination numbers is now 2.5 Å as the terminal carboxylic oxygens and the chromium atoms that belong to two different half-SBUs are very close when they interact; these are considerably closer than two adjacent central oxygen atoms. In the same manner as before, the collective variable is normalised with the number of half-SBUs in the system. It should be noted that the value obtained through the calculation of this collective variable on the crystal configuration in Figure 1-1, normalised by the number of half-SBUs in the crystal, is 2.67.

5.4 Collective Assembly in Water

At first, the assembly of half-SBUs in pure water is considered. The setup of the systems follows the two initial probability distributions of half-SBUs mentioned in the previous subsection. The systems are equilibrated for 5 ns. Afterwards, two production simulations, of 100 ns each, are performed. It should be noted, that in these simulations no external bias is added to the system.

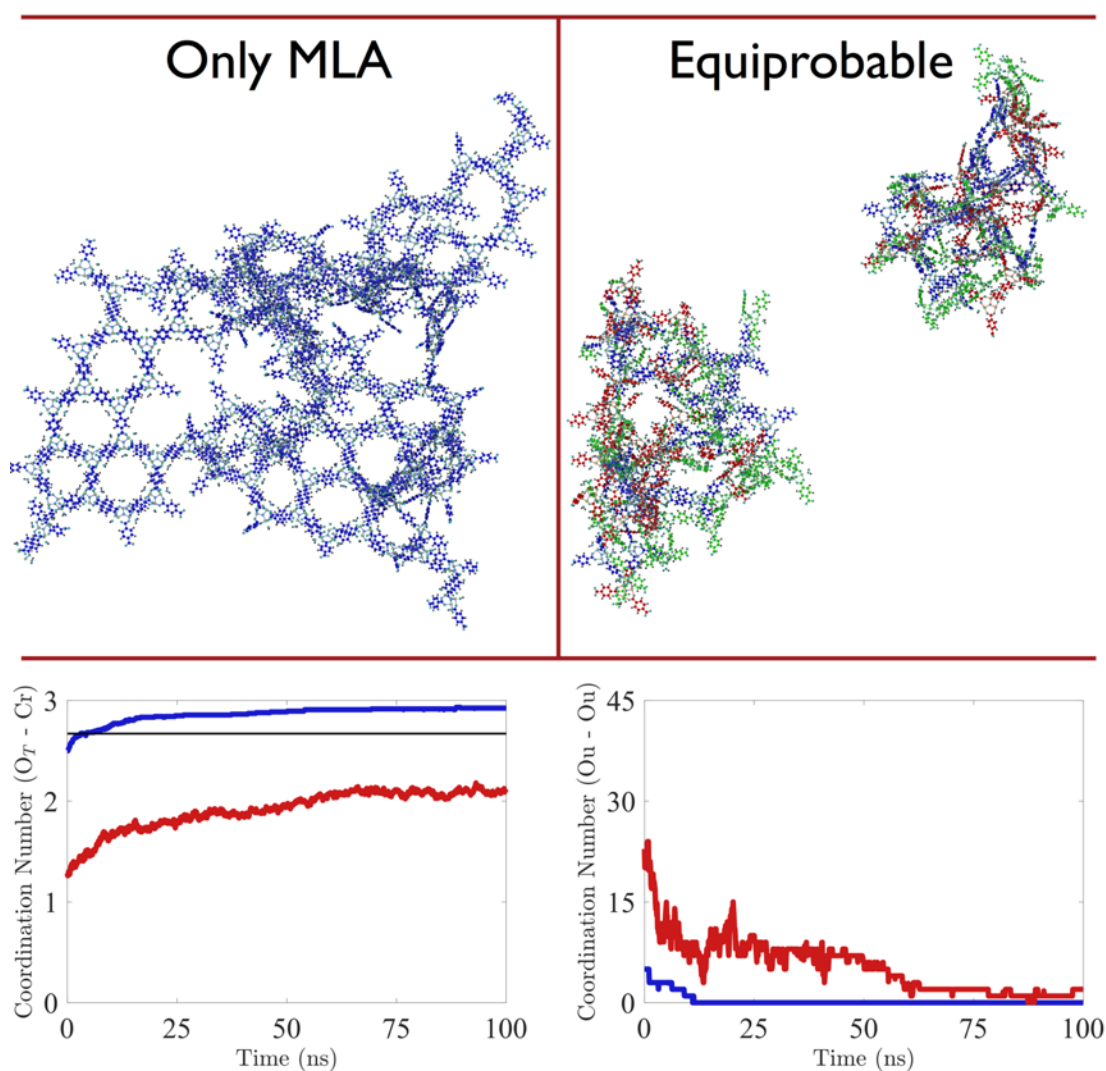


Figure 5-2. Half-SBUs assembly in water. Structures are obtained after a 100 ns production simulation starting from an “only MLA” (top left panel) or an equiprobable (top right panel) initial distribution. Coordination numbers between O_T and Cr atoms greater than 0.5 are monitored throughout the simulation (bottom left panel, blue: only MLA, red: equiprobable). The reference value of this CV in the crystal is represented by a black line. Coordination numbers between Ou atoms less than 0.5 are also monitored during the simulation (bottom right panel, blue: only MLA, red: equiprobable). The colour code for chemical structures is consistent with Figure 1-1, except from the carboxylic carbon atoms. These are coloured blue for MLA, red for MLB and green for MLC atoms.

The half-SBUs interact and form lattices rather quickly in both instances. This is observed through monitoring the first collective variable (see section 5.3); this refers to coordination numbers between any couple of central oxygens less than 0.5. This is a measure of the number of free half-SBUs in solution. This CV is quickly decreased

as it can be seen in Figure 5-2. It reaches a value close to zero after 15 ns and it remains constant for the rest of the simulation. In contrast with the previous situation, an equiprobable initial distribution of half-SBUs results in a much slower decrease to the number of free half-SBUs as the coordination number does not reach zero after 100 ns. Nevertheless, it is stabilised after 65 ns less than three half-SBUs stay detached from the two nuclei for the rest of the simulation.

Moreover, the coordination number between chromium and terminal carboxylic oxygen atoms is calculated over the simulation time. The “only MLA” initial distribution results in a sharp increase in the coordination between oxygen and chromium. This is translated to a proportional increase in the interactions between different half-SBUs. This CV reaches a plateau at 2.92 after 55 ns. This value is above the characteristic value for the crystal (2.65). The 2Q configurations (see Chapter 4) prevail at this point and these result in a large value for this CV. In contrast, an equiprobable initial distribution results in a value that is below both the one corresponding to “only MLA” and the crystal. The value that the CV reaches after 65 ns is around 2.1. This structure is characterised by interactions that does not resemble to the ones in the crystal; hence nuclei with a small degree of order emerge as they can be seen in Figure 5-2.

It should be noted that the coordination number is not close to zero at the start of the simulation as this is a production run. The system of dispersed half-SBUs was simulated for 5 ns in order to equilibrate temperature, pressure and density as mentioned previously. Half-SBUs interact during this period and they have already formed small nuclei when the production run is initiated.

In the case where only MLA is present, one large nucleus is formed and there are no isolated half-SBUs at the end of this simulation. The majority of SBUs in the lattice appear in the 2Q configuration (see Chapter 4). This is in agreement with the analysis of the SBU association process, discussed in Chapter 4, where 2Q is the most probable SBU configuration in pure water. Furthermore, pores can be distinguished in the nucleus formed after 100 ns.

This case is compared with an equiprobable distribution of half-SBUs. In the equiprobable case, two nuclei are formed and free half-SBUs appear even after 100 ns. Furthermore, the half-SBUs form clusters more slowly than in the case where only MLA is present. Pores are not formed in the same extent as in “only MLA”, and the lattice does not contain an ordered structure. The structure that the equiprobable initial distribution of half-SBUs form after 100 ns is provided in Figure 5-2.

In summary, the simulations of half-SBUs in water highlight the importance of the initial conditions for the morphology of the lattice generated by the assembly of these units. An “only MLA” initial probability distribution provides a structure with pores and a high degree of order. In contrast, an equiprobable initial distribution results in two distinct nuclei. The degree of order is considerably lower than in “only MLA” as MLA is a potential source of order for the lattice during the self-assembly process. The structures and plots corresponding to this analysis are available in Figure 5-2.

The structure obtained after 100 ns simulation of “only MLA” half-SBUs resembles another MOF, MIL-68 [238]. Synthesis of MIL-68 takes place at a lower temperature and much longer times (100 °C and 120 h) than MIL-101 (220 °C and 8 h) [38]. Aqueous hydrofluoric and aqueous hydrochloric acid in DMF (instead of hydrofluoric acid in water for MIL-101) are used in the original synthesis of MIL-68 [238]. MIL-68 [238] is also a polymorph of the equilibrium product MIL-53 [108].

It is remarkable that parts of the structure of the lattice formed of MLA half-SBUs resemble a polymorph of the equilibrium product. In other words, this polymorph can emerge early during assembly of building units. Nevertheless, ions are not present in this simulation and the most probable conformer, 2Q, is responsible for this behaviour. This analysis shows that the introduction of ions is very important during MIL-101 assembly [38], [188]. In pure water, metastable states characterised by polymorphs that slow down further rearrangement to the crystal structure can emerge. These metastable states can be avoided by changing the composition of the mixture. In this effort, the following section investigates how ions can affect assembly during the early stages by hindering 2Q while promoting 2C conformers (see also Chapter 4).

5.5 Effect of ions in water

Ionic species are added to the aqueous solution of half-SBUs. A different behaviour than in pure water is observed for both initial probability distributions. This is expected from the study of half-SBU interactions (see Chapter 4).

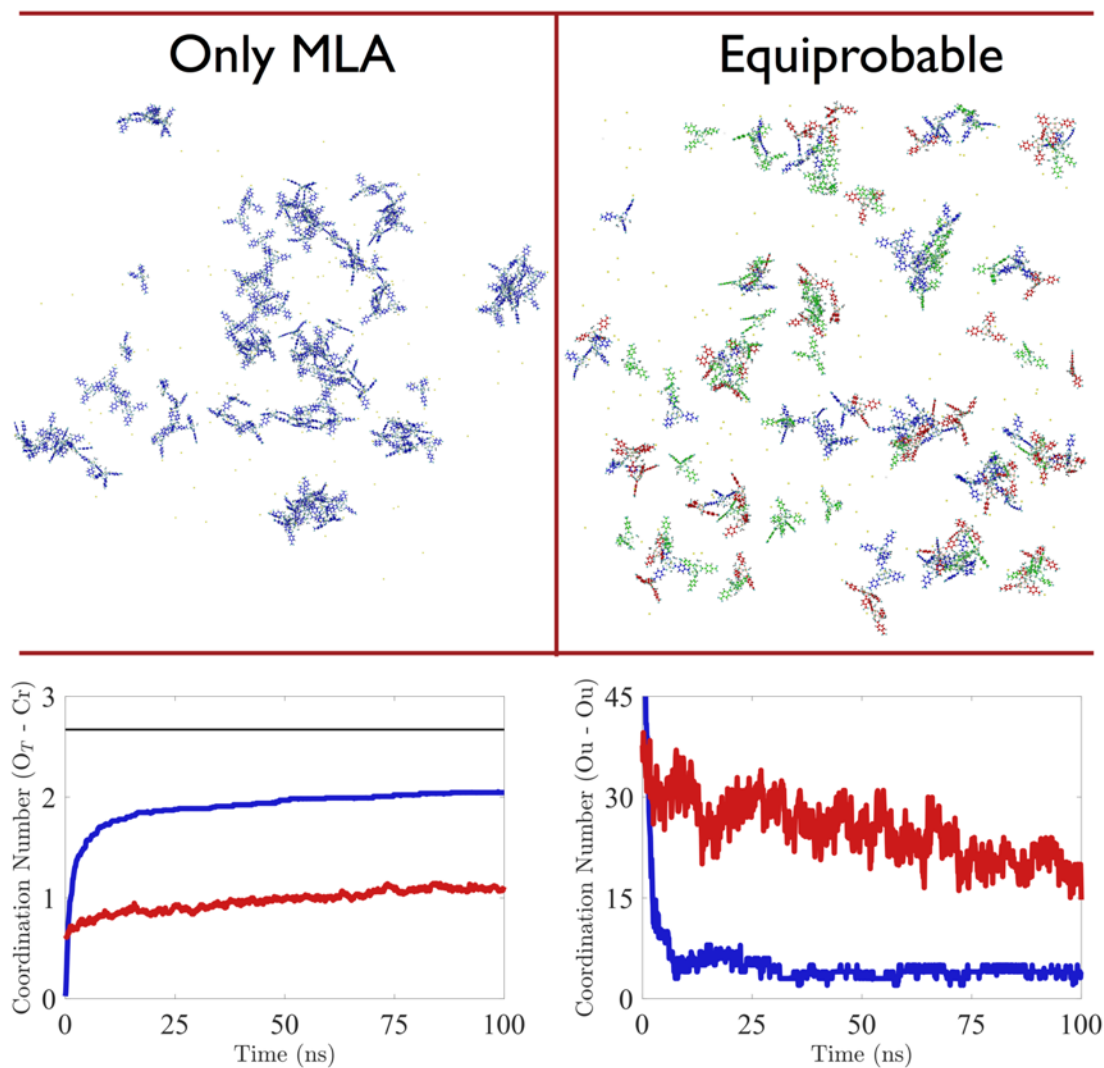


Figure 5-3. Half-SBUs assembly in water with 0.035M NaF . Structures are obtained after a 100 ns production simulation starting from an “only MLA” (top left panel) or an equiprobable (top right panel) initial distribution. Characteristics of this figure, concerning plots and colours, are consistent with Figure 5-2.

Nevertheless, investigation of the collective behaviour of half-SBUs in solution should provide further evidence on how ionic species affect the assembly towards the lattice of MIL-101(Cr). Comparison of the results from the two initial distributions shows that the interactions which originate from MLA present appreciable differences in the structures obtained after 100 ns. When the “only MLA” condition is used, there is a larger number of half-SBUs that belong to a cluster than in the case of an equiprobable initial distribution. Nevertheless, isolated half-SBUs are present in both situations. This is apparent through monitoring the trajectory of the coordination number between central oxygen atoms. The CV that corresponds to the coordination numbers that are less than 0.5 is decreased to a value less than 6 after 10 ns. This is a rapid change in the number of free half-SBUs as in absence of ions. Nevertheless, the CV remains constant to this area of values and it fluctuates between 4 and 5 after 30 ns and for the rest of the simulation; hence there are free half-SBUs in solution even after 100 ns in contrast with the simulations in pure water.

The structures formed after a 100 ns production simulation starting either from “only MLA” or equiprobable distributions and the trajectories in the space of the two collective variables monitored throughout the simulations are exhibited in Figure 5-3.

The equiprobable initial distribution results in appreciably larger values for this CV. These are first decreased to a set of values close to 30 after 25 ns. As the simulation progresses, more half-SBUs interact with nuclei and the value of the CV is gradually lowered as it fluctuates between 17 and 23 after 70 ns and for the rest of the simulation. Therefore, the number of free half-SBUs is 4 times larger in the equiprobable than the “only MLA” distribution.

Another important finding is that the coordination number between terminal carboxylic oxygen and chromium atoms is larger in “only MLA” than in the equiprobable distribution. This is in agreement with the simulations in pure water as the coordination number between central oxygen atoms. Therefore, the propensity of MLA to decrease the number of detached half-SBUs and increase the number of interactions between oxygen and chromium is not affected by the presence of ions as much as the other half-SBUs. The coordination numbers between terminal carboxylic oxygen and chromium atoms that are more than 0.5 plateau to a value close to 2.05 for an “only MLA” and 1.10 for an equiprobable initial distribution. This observation is in agreement with the finding from the study of interactions between couples of half-SBUs. Ions tend to hinder configurations where the coordination number between oxygen and chromium is high such as the 2Q conformer (see Chapter 4). On the other

side, the values for the CV from the simulations in presence of ions in water are both lower than the characteristic value for the crystal. This means that further fine-tuning of conditions such as concentration of half-SBU isomers, solvent and ions as well as temperature and pressure, to name a few, is needed to achieve a coordination number close to the characteristic value of the crystal. Another potential explanation is that the system has not yet overcome an energy barrier associated with the formation of the crystal from isolated half-SBUs.

In summary, ions appreciably affect the collective behaviour of half-SBUs that form nuclei much more slowly than in pure water. There exist fewer interactions between oxygen and chromium; hence the probability of observing 2Q configurations (see Chapter 4) is significantly decreased compared to simulations in pure water. Nuclei are formed more rapidly in the “only MLA” than the equiprobable distribution. Structures are more stable in “only MLA” than in the equiprobable distribution in agreement with the simulations in absence of ions.

5.6 Solvent effects

Half-SBUs are dispersed in another solvent, DMF, and the results are compared with the simulations in pure water. The same initial probability distributions are used in pure DMF.

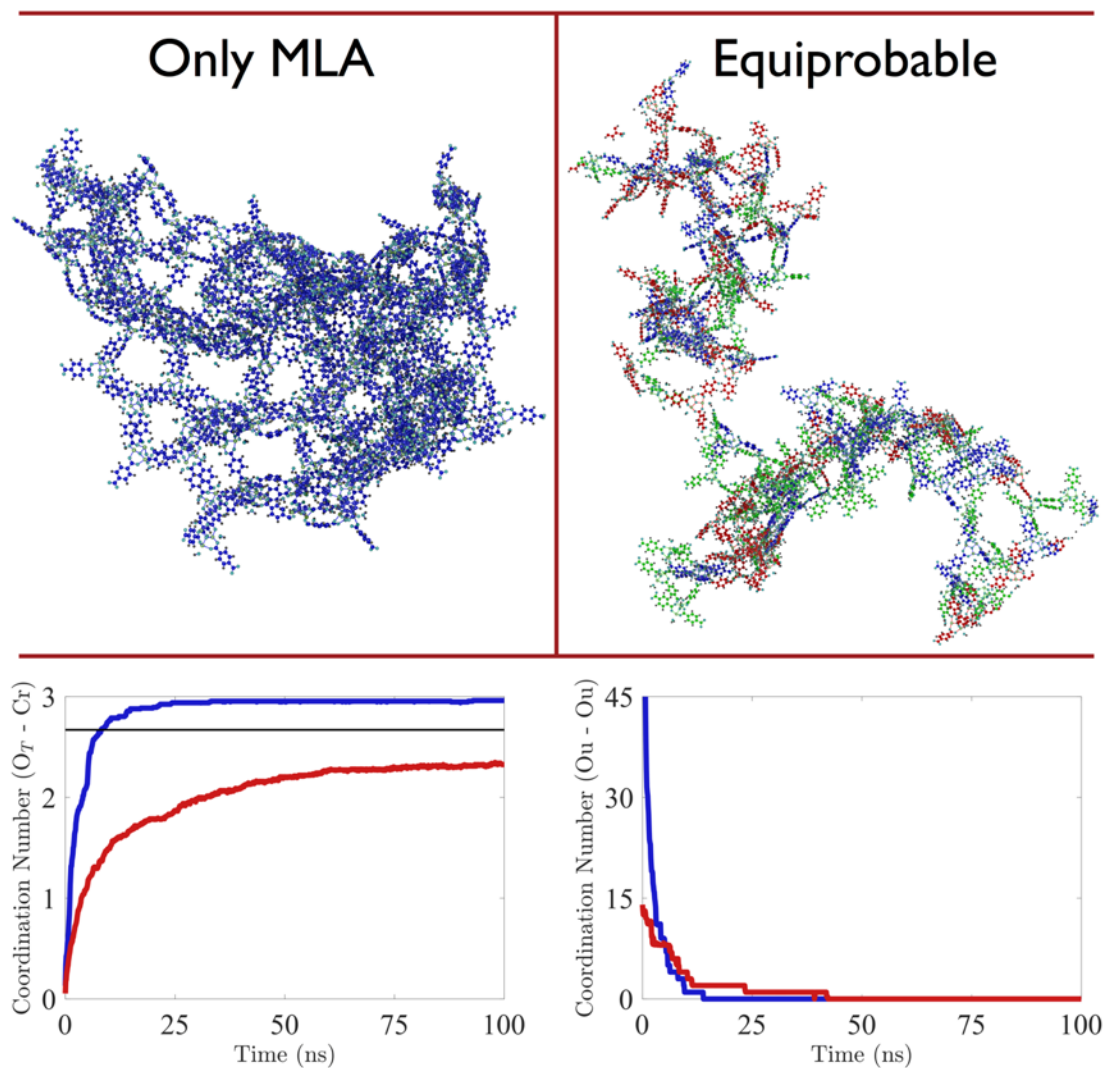


Figure 5-4. Half-SBUs assembly in DMF. Structures are obtained after a 100 ns production simulation starting from an “only MLA” (top left panel) or an equiprobable (top right panel) initial distribution. Characteristics of this figure, concerning plots and colours, are consistent with Figure 5-2.

As seen in Figure 5-4, an equiprobable distribution of half-SBUs leads to a structure which does not exhibit pores or high order in general in the same extent as in “only MLA” in pure water. This is in agreement with the equiprobable distribution in pure water. Nevertheless, the opposite behaviour is apparent when the number of

formed nuclei is evaluated. In the equiprobable distribution in DMF a single nucleus is formed in contrast with the result in water where two distinct nuclei emerge. In “only MLA”, the lattice that is formed presents higher order than the structure obtained from the equiprobable distribution. This is in agreement with the relevant simulations in pure water.

A very interesting observation is that in both instances, there exist no free half-SBUs in solution after 100 ns. This is monitored also through analysing the trajectory of the coordination numbers between central oxygen atoms that are less than 0.5. This CV is rapidly decreased, and it reaches a set of values very close to zero after 15 ns for the “only MLA” and 45 ns for the equiprobable initial distribution. Therefore, this solvent promotes the interactions between all types of half-SBU isomers. Lattices are formed as quickly as in pure water for “only MLA” and much quicker for the equiprobable distribution.

The coordination numbers between terminal carboxylic oxygen and chromium atoms that are more than 0.5 are monitored as well. The trajectory of this CV shows that shortly after all half-SBUs have attached to the lattice, the coordination number reaches its plateau at 2.95 after 35 ns. This is the highest value for this CV when compared with all other simulations. Nevertheless, it is very close to the value at which it plateaus in pure water as discussed previously. The equiprobable distribution results in an appreciably slower increase of the value of this CV that reaches a plateau at 2.31 after 80 ns. This is considerably higher than the value that the CV reaches in pure water starting from the same initial distribution. This is in agreement with qualitative analysis of the structure obtained after 100 ns, where a single nucleus with a small extent of order can be seen through the pores formed in the lattice. Nevertheless, both initial distributions in DMF result in coordination numbers that are far from the reference value for the crystal. It should be noted that in the equiprobable case the value of the CV obtained in DMF is closer to the reference than in pure water; hence a higher degree of order through oxygen-chromium interactions can potentially emerge due to the different solvent environment.

The collective behaviour of half-SBUs in DMF is different than in pure water where the equiprobable distribution results in two nuclei. In contrast, in DMF, both initial distributions result in the formation of one large nucleus. The number of free half-SBUs is decreased very rapidly; hence DMF promotes interactions between half-SBUs towards the formation of a lattice. The coordination number between oxygen and chromium atoms in the crystal is between the obtained values in “only MLA” and

the equiprobable distributions; hence fine-tuning of the initial distribution of half-SBUs can result in a coordination number very close to the reference.

5.7 Effect of ions in DMF

Ions are introduced to the solution of half-SBUs in DMF. The concentration of ions is 0.075M. In agreement with water, the concentration of ions is smaller than 0.1M. It should be noted that larger concentrations result in emergence of salt clusters that obstruct interactions between building units.

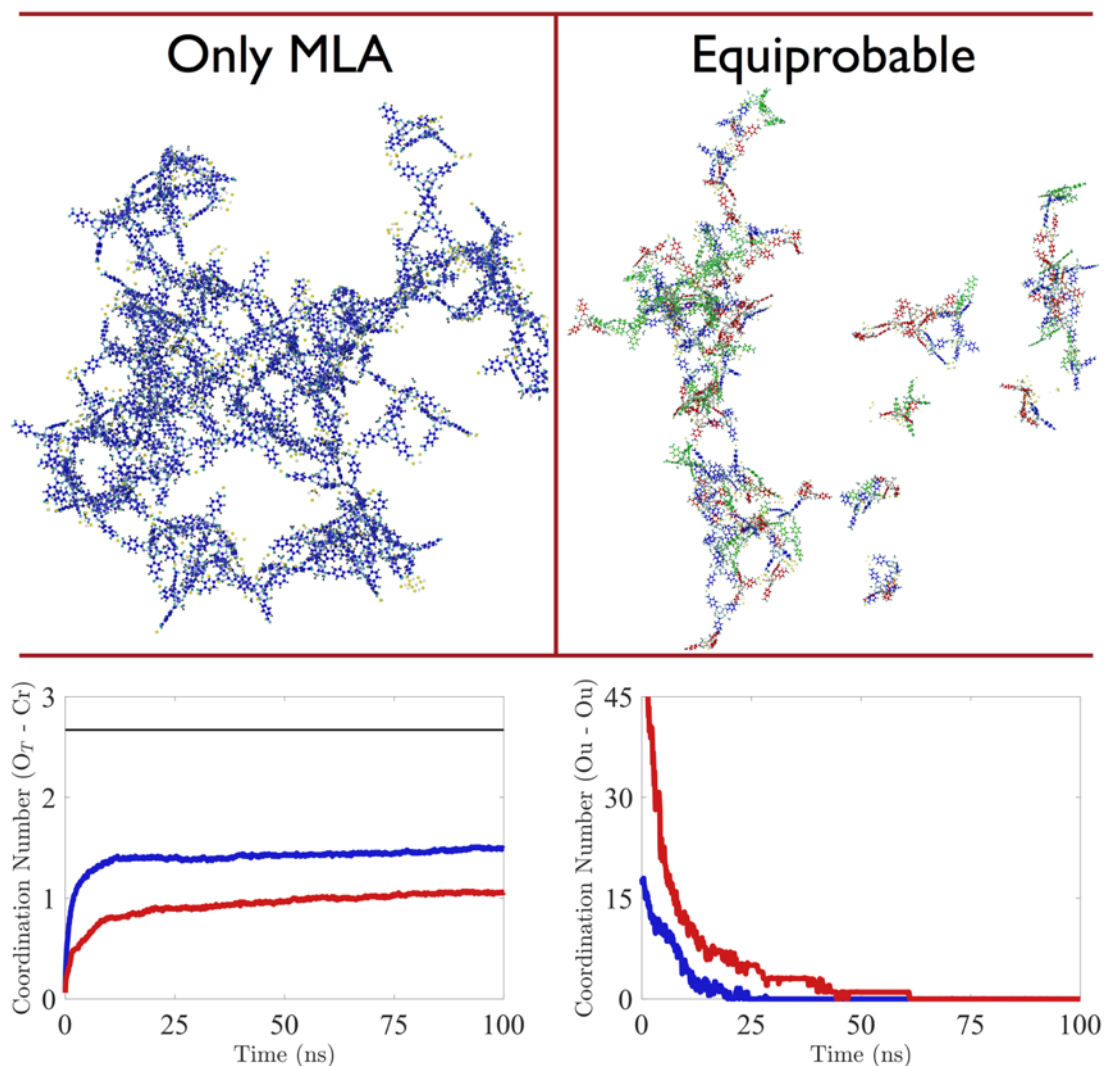


Figure 5-5. Half-SBUs assembly in DMF with 0.075M NaF . Structures are obtained after a 100 ns production simulation starting from an “only MLA” (top left panel) or an equiprobable (top right panel) initial distribution. Characteristics of this figure, concerning plots and colours, are consistent with Figure 5-2.

The structures obtained after 100 ns present appreciable differences for the two initial probability distributions. The “only MLA” initial distribution results in a single nucleus with pores and a relatively high degree of order. On the other hand, the equiprobable initial distribution leads to a system that is characterised by a large nucleus and a couple of small nuclei. Another interesting observation in contrast with the simulation in water with ions is that in both distributions there are almost no free ions in solution. Therefore, the majority of ionic species interacts with the half-SBUs as it can be seen in Figure 5-5.

The coordination numbers between central oxygen atoms that are less than 0.5 are calculated as in previous systems. This CV is decreased very rapidly in “only MLA” and it reaches a set of values very close to zero after 28 ns. Therefore, there are no free half-SBUs in solution after this time and for the rest of the simulation. In the equiprobable distribution, values close to zero are reached after 62 ns and the CV stays in this area for the rest of the simulation. This is in agreement with the simulations in pure DMF; hence this solvent promotes interactions between the half-SBUs both in presence and absence of ions.

The second CV monitored refers to the coordination numbers between chromium and terminal carboxylic oxygen atoms that are more than 0.5. This is increased sharply to 1.35 after 10 ns of the simulation and it plateaus at 1.49 after 90 ns. This is a considerable difference with respect to the simulations in water in presence of ions. The CV is almost 1.4 times higher in water with ions than in this environment. Nevertheless, the concentration of ions is slightly higher in this case when compared with the concentration studied in water. Furthermore, this value is lower than the reference for the crystal. In contrast, the SBUs formed resemble the ones in the crystal as ions hinder the formation of the 2Q configuration (see Chapter 4). This is further explained due to the lower value of this CV, but further investigation should be carried out to quantify how much the SBUs resemble to the ones in the crystal in this case.

The corresponding CV for the equiprobable initial distribution reaches 0.80 after 10 ns and it plateaus at 1.05 after 78 ns. In contrast with the finding for the “only MLA” distribution, the value for the CV obtained for the equiprobable distribution is very close to the one from the simulation in water with ions. Therefore, in presence of ions, the choice of water or DMF as solvent does not appreciably affect the number of interactions between chromium and terminal carboxylic oxygen atoms, when the system follows an equiprobable initial distribution of half-SBUs.

In summary, the presence of ions in DMF, lowers the number of interactions between chromium and terminal carboxylic oxygen atoms through hindering the formation of 2Q (see Chapter 4). Large nuclei are formed with the one in “only MLA” featuring open pores and SBU configurations that resemble the ones in the crystal with respect to their relative orientation. The equiprobable distribution results in a number of interactions between oxygen and chromium that is very close to the value obtained in water with ions. Nevertheless, the number of free half-SBUs in solution reaches a set of values close to zero before 100 ns in contrast with the simulation in water with ions. Therefore, ions favour interactions between the half-SBUs in both instances. In this case, SBUs are more dynamic and self-heal defects during the process of assembly due to interactions with ionic species. Therefore, ions tend to drive the system towards the formation of a lattice with limited presence of 2Q conformers (see Chapter 4) as the interactions between ions and half-SBUs tend to stabilise dimers at configurations that resemble the ones found in the crystal lattice.

5.8 Conclusions from the assembly of half-SBUs

Despite the use of different conditions, mainly higher temperature, the observations from the collective behaviour of half-SBU assembly agrees with conclusions drawn from the studies of monomers and dimers that were previously conducted. At a larger scale numerous observations stemming from the study of monomers and dimers can be validated. These include the finding that MLA is a source of crystallinity and order. Also, ions promote crystal-like SBUs through hindering the over-coordinated 2Q configuration (see Chapter 4). Nevertheless, a large concentration of ions leads to counterion nucleation effects rather than the formation of a lattice.

Distinguishing between only MLA and equiprobable MLA, MLB and MLC initial distributions shows that the composition of the system of half-SBUs has a very important role. This can potentially regulate the extent of defects in the final product. This is apparent in all simulation conditions and environments. When MLA is in abundance and MLB, MLC are hindered, the system is driven towards a rapid formation of a lattice that presents remarkable order. This can be quantitatively explained through monitoring the coordination between terminal carboxylic oxygen and chromium atoms. This CV takes large values in the “only MLA” case; hence interactions between the terephthalate linkers and the metal centres of neighbouring half-SBUs are promoted. Nevertheless, this CV exceeds its characteristic value for the crystal in pure solvent as 2Q configurations prevail. Ions tend to lower the values of the collective variable and drive it towards the reference for the crystal. This is the result of hindering 2Q configurations. The values of this collective variable in the case of an equiprobable distribution are below the reference for the crystal. This leads to the observation that when MLB and MLC are equiprobable to MLA, there exist fewer interactions between metal centres and neighbouring terephthalate linkers than in the crystal.

Furthermore, when the only isomer present in pure water is MLA, the lattice formed resembles MIL-68 [238] that is a polymorph of the equilibrium product. This is an excellent example of how flexibility of building units can lead to a rich conformational landscape during the early stages of assembly. This analysis shows that changes in composition can be key in the early stages as they can potentially promote polymorphs, which emerge after long times of assembly, earlier than expected. It is remarkable that the most probable conformer in pure solvent, 2Q (a noncrystal-like SBU when the MIL-101 [38] lattice is the reference crystal), is

responsible for the formation of a lattice consisting of parts which resemble another MOF, MIL-68 [238]. Nevertheless, further analysis should be performed in projects focused on the synthesis of these MOFs (e.g. MIL-68 [238]).

A different behaviour is observed in presence of ions which tend to obstruct the emergence of this metastable structure as they hinder the formation of the 2Q conformer (see Chapter 4). In this manner, this analysis highlights the importance of introducing ions during the early stages of MIL-101 [38] assembly. The reason is that the flexibility of building units can result in different products arising in pure solvents. Nevertheless, the assembly of MIL-101 is studied in this project; hence the composition of the mixture should be adjusted accordingly in order to promote the 2C rather than the 2Q conformer (see Chapter 4). Therefore, the introduction of ions is needed in order to proceed in a pathway that MIL-101 is the kinetically favoured product as in the experimental synthesis [38].

The propensity of half-SBUs to form, or attach to already formed, nuclei is assessed through monitoring the coordination number between Ou atoms less than 0.5. This collective variable is a measure of free half-SBUs in solution. This analysis shows that in pure solvent the number of free half-SBUs is rapidly decreased, whereas in presence of ions this is lowered at a slower pace. Furthermore, this CV does not approach zero only in water when an equiprobable distribution is used and in water with ions for both initial distributions of half-SBUs studied. This observation highlights the difference in the collective behaviour of half-SBUs in water. Also, the number of free half-SBUs can be regulated through fine-tuning either the initial distribution of half-SBUs or the number of ions present in the system.

In summary, the analysis of simulations where large systems are studied supports the validation of the findings from the analysis of half-SBUs (Chapter 3) and SBUs (Chapter 4). It is straightforward that MLA results in ordered structures, whereas this order is highly disrupted when an equiprobable distribution is selected. The role of ions is more versatile in these large-scale simulations as ions affect not only crystallinity but also the collective behaviour of half-SBUs. Since 2Q (see Chapter 4) is disrupted with a small number of ions in the system and larger concentrations lead to the formation of salt clusters which inhibit interactions between half-SBUs, low ionic strengths were chosen in both solvents. The propensity to self-heal defects in the 2Q-abundant “only MLA” distribution is the result of weaker interactions between half-SBUs in presence of ions. Furthermore, DMF leads to ordered and more stable lattices for both initial distributions in absence and presence of ions.

At last, there is a large number of pores in clusters generated by MLA half-SBUs. This supports the observation that MLA promotes crystallinity as the MIL-101(Cr) is also porous. This situation can be seen especially in pure water, where the number of pores is dramatically decreased in the presence of MLB and MLC. Furthermore, the number of pores is larger in water than pure DMF, where configurational flexibility of monomers is hindered by the solvent. In presence of ions in water, clusters and pores form slowly and cannot be observed through the simulations conducted. Finally, MLA presents a more ordered structure with more pores in DMF with ions compared to the equiprobable monomer distribution case.

Chapter 6

Final Remarks

This is the final chapter of the text. Final remarks summarise what has been done in this work (section 6.1), what are the main findings of this research (section 6.2) and what are the possible future directions for the topic discussed in this text (section 6.3). In the end, the overall contribution of this work to research is evaluated in section 6.4.

6.1 Summary

In this work, the behaviour of MOF (MIL-101(Cr)) building units is evaluated under various conditions and at different scales in order to provide a molecular-level understanding on the MOF self-assembly process. Isomers of the MIL-101(Cr) half-Secondary Building Unit (half-SBU): MLA, MLB and MLC are considered in order to study the assembly process. Their physical behaviour is examined through all-atom classical molecular dynamics simulations. Consequently, the effect that their flexibility and interactions, with other half-SBUs and guest molecules, has on the formation of crystal-like units against defects is evaluated. It should be noted, that the accuracy of the FF is validated through dynamic and static simulations at the DFT level in order to provide further confidence on the results obtained using this classical model.

At first, the flexibility of half-SBU isomers in solution is examined. This is achieved by using enhanced sampling methods to investigate the fluctuations in the mass-weighted radius of gyration (R_{gyr}) of half-SBUs. Enthalpic and entropic drivers to the free energy landscape of half-SBU with respect to R_{gyr} are also calculated. The effect of temperature (298 K and 493 K), solvent (water and DMF) and ions (Na^+ , F^-) on the free energy profiles is evaluated in order to understand how these factors affect the flexibility of half-SBUs and their propensity to form crystal or noncrystal-like units.

Afterwards, the association-dissociation of half-SBUs into SBUs is investigated for all possible SBU conformers. Two collective variables that correspond to the lowest components of the distances between (1) terminal carboxylic carbon and chromium atoms, and (2) chromium atoms that belong to adjacent half-SBUs are biased in order to sample all states that are relevant to the SBU association-dissociation process. The resulting free energy surfaces are able to distinguish

between several configurational states. These are further categorised as crystal-like and noncrystal-like based on the similarity of the relative orientation of the SBU conformers that dominate each state with the SBUs in the crystal. Consequently, calculation of the equilibrium probabilities of these species is possible. This is performed in different solvents under varying ionic strength in order to estimate the concentration of ions that mostly promotes crystal-like SBUs. The rearrangement of an SBU is also assessed. This is achieved through biasing the coordination number between terminal carboxylic oxygen and chromium atoms. The enthalpic and entropic drivers to this rearrangement are calculated at different temperatures (298 K and 493 K).

At last, a large system of 132 half-SBUs dispersed in solution is studied under different conditions (solvents, presence or absence of ions). Two initial distributions of half-SBUs are considered in order to evaluate the effect of the solute composition on the assembly process and the resulting structure. The collective behaviour of half-SBUs is evaluated through calculation of the coordination between terminal carboxylic oxygen and chromium atoms and the number of free half-SBUs in solution throughout the simulations.

6.2 Conclusions

There are several conclusions that can be drawn out of this work. Nevertheless, this section will focus only to the ones related to MOF synthesis and assembly processes based on flexible units in general.

At first, as discussed in Chapter 1, the state of the art in the computational studies focused on the early stages of MOF self-assembly lacks an understanding of how different factors affect the formation of defects through analysing the energetics of this process. Furthermore, the role of ions which are ordinarily used in MOF synthesis is not investigated further; hence the theoretical background of the introduction of ions is rather limited. More importantly, the design of MOF synthesis usually relies on Edisonian practices. Ultimately, this study makes a leap forward through providing a thorough understanding of the free energy landscape along with a detailed analysis of the nature of interactions in metastable states emerging during the early stages of MOF self-assembly. Nevertheless, as in any research work there are limitations in this study and the opportunities to build upon this work are discussed in the following section (section 6.3).

The half-SBUs are considered in this work as nucleation rapidly follows their formation. Half-SBU species are relevant as there is experimental evidence that the SBUs incorporated in the final MOF are determined by the interactions of these neutral precursors that aggregate to form a lattice [144]. The R_{gyr} collective variable is a very good proxy for rotational inertia that is directly linked with the flexibility of molecules. Consequently, it is possible to assess entropic and enthalpic drivers to flexibility using R_{gyr} . As a result, MLA and MLB structures that are dominated by entropy are similar to those corresponding to the crystal as well as the enthalpically favoured MLC conformers. Addition of ions leads to a richer configurational landscape, while the use of another solvent (DMF instead of water) alters the entropic landscape. In more detail, DMF disfavours the state that corresponds to the minimum in the entropic contribution in water. This analysis enhances the understanding of how enthalpy and configurational entropy affect the flexibility of each isomer and how states favoured by entropy become more probable at higher temperatures.

The entropic and enthalpic contributions are calculated also for the rearrangement of an SBU in pure water. The entropically favoured 2Q configuration, a conformer consisting of four chromium-terminal carboxylic oxygen interactions, is even more stable at a higher temperature than the enthalpically favoured 2C conformer, consisting of two chromium-terminal carboxylic oxygen interactions consistent with the SBUs in the crystal. Furthermore, the $\Delta G_{2C \rightarrow 2Q}$ is negative; hence the free energy landscape in water is dominated by the entropically favoured 2Q conformer. Ultimately, the study of underlying enthalpic and entropic contributions to the free energy is important as it provides strong hypotheses on how to proceed with the regulation of defects. For example, if the most probable conformer is favoured by entropy, the way to proceed in order to render it improbable is a change in composition. Current limitations in the literature also include the lack of understanding the nature of crystal- and noncrystal-like conformers (if they are favoured by entropy or enthalpy) incorporated during the early stages of MOF self-assembly.

It should be noted that 2Q and 2C are structures found at the most probable state during the association-dissociation of an SBU from interactions between couples of half-SBUs. Study of the association-dissociation process leads to the discovery of a complex configurational landscape of possible SBU conformers. These are further categorised as crystal and noncrystal-like based on their relative orientation. This is compared with the one corresponding to SBUs in the crystal. Consequently, 2C is characterised as crystal-like, while 2Q as noncrystal-like.

The calculation of the equilibrium distribution of species shows that there is a 30% probability of forming crystal-like dimers from non-interacting monomers in water with a small concentration of NaF (0.025M). The only contributor to this is AA_C that dominates the distribution due to its relatively strong crystal-like interactions. This is due to the disruption of the 2Q conformer in presence of ions; a change in composition that can alter the entropic landscape of the system. Also, salt bridges are formed at higher concentrations of ions due to the interactions between fluoride anions and hydrogen atoms of the metal centre. These hinder the relative rotation of the terephthalate linkers that leads to the 2Q structure; hence crystal-like conformers are favoured. Nevertheless, excess of ions leads to large salt clusters formed in solution which obstruct interactions between half-SBUs. These disfavour interactions between half-SBUs overall. Furthermore, a different solvent, DMF, results in 2Q strongly dominating the equilibrium distribution of SBUs, even more than in water. Also, in this case the addition of ions disrupts this structure due to the formation of salt bridges.

Therefore, a fine-tuning of the concentration of ions and choice of solvent has a crucial role in regulating of the ratio between crystal and noncrystal-like SBUs at equilibrium. In more detail, a small concentration of ions that is considerably below the solubility of the resulting salt is understood to promote crystallinity in the early stages of assembly. Furthermore, the flexibility of half-SBUs can be crucial to regulate the extent of defects. A prominent example is MLC that is more rigid, and it remains at noncrystal-like configurations and this leads to a low probability of crystal-like CC SBUs compared with other isomers (e.g. AA, AB, etc.).

Consequently, the probability of incorporating defects early in MOF synthesis is calculated through estimating the free energy landscape. Changes in composition strongly affect the nature of interactions thus promoting crystal-like conformers through hindering linker rotation when adding ions at small concentrations. This is a plausible rationale on why ions are used in MOF synthesis. Also, it provides experimentalists with a qualitative measure on the concentration of ions that promotes crystallinity.

A system of several half-SBUs (132 in total) in solution is investigated in order to observe interactions between them at a considerably larger scale. This provides validation of findings across scales that is essential in order to scale up the methodology suggested in this work. Furthermore, the collective behaviour of half-SBUs is evaluated under different conditions. In agreement with the analysis of half-SBU couples, 2Q dominates in pure water and DMF. Lattices are formed as half-

SBU rapidly attach to an expanding nucleus, when the solute consists of MLA half-SBUs only. This lattice presents several pores and a relatively high degree of order due to promoting interactions between terminal carboxylic oxygen and chromium atoms. Modifications regarding the composition of the system highly affect the collective behaviour of half-SBUs. An equiprobable distribution of MLA, MLB and MLC leads to the formation of small nuclei with a lower degree of order and a number of free half-SBUs in solution. Furthermore, the addition of ions results in slower formation of small nuclei and more dynamic SBUs; hence the probability of forming 2Q conformers is decreased. Therefore, in this case SBUs are prone to self-heal defects. Also, the number of interactions between terminal carboxylic oxygen and chromium atoms is closer to the one in the crystal. This is consistent with the observation from the analysis of half-SBU couples that ions favour crystallinity. This study covers the early stages of MOF assembly from flexible building units. Early insights can be used to determine synthesis conditions in order to regulate the extent of defects in MIL-101. The nature of interactions with the solvent and ionic species is understood through this analysis and findings are consistent across scales. Therefore, this work provides a rationale on how composition and synthesis conditions affect the emergence of defects in the early stages of MOF assembly.

Finally, this project should provide the basis for understanding and manipulating the synthesis of MOFs. Fine-tuning of conditions and composition of the mixture of solute, solvent and ions should enable the regulation of the extent of defects. These are responsible for the stability of the MOF under industrial conditions of high temperature and pressure. Therefore, tuning of the number of defects in the final product is the way to make MOFs robust for many applications including and not limited to processes of the chemical industry. At the same time the remarkable attributes of MOFs including porosity and surface area will provide the industry with a material that can be used for a plethora of applications much more efficiently than competition, such as zeolites. A prominent application that will benefit from this approach is carbon storage and sequestration, as more CO₂ will be stored per unit mass of material when compared with currently used zeolites.

6.3 Future development

Research is a field of open-ending and mostly never-ending problems. As this piece of work is focused on research, there is always space for further development. Most importantly, this study is focused on the early stages of MOF self-assembly. The later stages of self-assembly are not considered here. A computational model that could lead to extensive sampling between the dispersed half-SBU phase and the crystal lattice can elucidate the thermodynamically and kinetically important stages of this process. The initial conditions for this analysis can be decided carefully after considering the results of this work as they have a very important role in regulating the extent of defects in the final crystal. The size of the system, the length of the simulation and the enhanced sampling protocol should be carefully tuned in order to perform this process.

Furthermore, there is a number of other projects that can arise out of this work. The effect of different ionic species such as Cl^- , OH^- or Br^- (amongst others) instead of F^- should provide further insight on the effect of ions on the systems studied. The choice of solvent can be modified and include other commonly used solvents in MOF synthesis such as methanol, ethanol, dimethyl sulfoxide (DMSO) and tetrahydrofuran (THF) to name a few. At last, a detailed review on the use of different ions and solvents during the early stages of the synthesis of various MOFs is provided in reference [154].

The lattices in Chapter 5 arise from the assembly of building blocks and they incorporate physically occurring defects, in contrast with removing linkers during assembly. These lattices can be compared with experimentally engineered MOFs with defects such as missing linkers. In more detail, a comparison of structures can be achieved via analysing their X-Ray Diffraction patterns.

The critical size of the lattices formed in Chapter 5 that is large enough to sample bulk properties of the MOF can be determined as well. Consequently, the different lattices that are formed under various conditions regarding the composition of the solution as well as the initial distribution of building units can be tested for a plethora of applications. More elaborately, the lattice that incorporates defects can be compared with the perfect crystal for adsorption and separation of certain molecules (e.g. CO_2 , CH_4) as in the comprehensive review conducted in reference [157] or xylenes as in the study in reference [239]. These were discussed in more detail in Chapter 1. Consequently, the effect of defects on several applications can be evaluated in detail following this approach.

6.4 The Epilogue

Hybrid organic-inorganic frameworks with high porosity and large surface area with a potential to enhance a plethora of applications. This could be another definition for Metal-Organic frameworks; novel materials that aim to enhance a plethora of industrial applications. Nevertheless, their fragility at high temperature and pressure render them inadequate for use in the industry. Still it is understood that their lack of robustness is linked with the presence of defects in the crystal lattice. The question to ask then would be: how can we control the presence of defects in the final MOF?

This is the motivation for this study as it is not yet fully understood how, and under which conditions these defective units form. The factors that limit or promote the occurrence of defects during the early stages of MOF self-assembly are thoroughly evaluated under various synthesis conditions. Therefore, a framework on how the occurrence of defects can be regulated is provided. This should eventually lead to the manufacturing of more robust MOFs to be used in the industry.

This study should contribute precious knowledge on modelling MOF synthesis overall as it presents a computational model that explains processes occurring at the molecular level during MOF self-assembly.

Finally, this work focuses only on the early stages of assembly. At this point, I would like to remind the reader that *“the beginning is the most important part of any work”*, as Plato taught us in *“The Republic”* [240].

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Appendix

A.1 Force Field Parameters

The force field is a modification of OPLS-AA in order to consider chromium atoms. In this manner, two atom types are added, one for the chromium atoms and the other for the central oxygen of the metal centre. Non-bonded interactions of these atoms are modelled through a DFT-obtained structure (consisting of two MLA, one MLB and one MLC molecule) replicated by the force field. These include van der Waals and electrostatic interactions in the OPLS-AA form that define the structure as there do not exist bonds between the molecules in the optimisation with the classical force field. Bonded interactions were modelled by considering each isomer isolated. The equilibrium values for bonded interactions involving chromium atoms and the central oxygen were assigned to be consistent with the optimised structures at the DFT level.

The accuracy of the classical force field is evaluated through comparison with ab initio MD (AIMD) simulations of half-SBUs in explicit water. These simulations were carried out for 10 ps with a time step of 0.5 fs following the protocol explained in [107] and only the post-processing of the trajectories has been performed in the research work and presented in this thesis.

An assumption used in the force field is that the metal cluster is treated as fairly rigid. The root mean square deviation (RMSD) of the atomic positions is used to assess rigidity. Two mass-weighted RMSD values are calculated during the AIMD simulation with respect to the optimised structure at the DFT level. RMSD1 consists of the chromium and the central oxygen atoms. In RMSD2, the coordinatively bonded oxygen from the terephthalate linkers are added to the calculation.

Table A-1. Root mean square deviations (Å) weighted by atomic masses. Statistics for the values of RMSD are calculated throughout the AIMD simulations.

	MLA		MLB		MLC	
	Average	St. Dev.	Average	St. Dev.	Average	St. Dev.
RMSD1	0.098	0.030	0.074	0.022	0.182	0.060
RMSD2	0.224	0.052	0.159	0.045	0.345	0.091

As a result of this analysis, the metal clusters of all half-SBUs are fairly rigid during AIMD simulations as they are consistently below 0.2 Å for the RMSD1 metric. Furthermore, MLB presents the highest rigidity and MLC the lowest amongst all isomers. As expected, RMSD1 is lower than RMSD2 while RMSD2 is below 0.35 Å. Standard deviations of the RMSD values are below 0.1 Å showing the rigidity of the isomers during the AIMD simulations. This study provides confidence on the classical description of the system in this work. It is remarkable that RMSD2 values remain relatively low and constant at a higher level of theory. At last, the RMSD1 and RMSD2 values for all isomers are presented in Table A-1 along with the respective standard deviations.

In the current force field implementation, the harmonic oscillator force constants for bonded interactions involving chromium and the central oxygen atoms are set to high values. This setting ensures that the half-SBU topology features are maintained close to their equilibrium values.

Table A-2. Average bond lengths (Å) throughout the AIMD simulation trajectory along with their standard deviations (St. Dev.). The values inside the brackets are those used in the classical MD simulations.

	MLA		MLB		MLC	
	Average	St. Dev.	Average	St. Dev.	Average	St. Dev.
Cr-O _U	1.97 (1.97)	0.06	1.97 (1.97)	0.05	1.92 (1.97)	0.05
Cr-O _{water}	2.12 (2.12)	0.09	2.19 (2.12)	0.10	2.09 (2.12)	0.07
Cr-O _{OH}	2.09 (2.09)	0.09	1.91 (2.09)	0.04	2.10 (2.09)	0.07
Cr-O _{ligand}	1.98 (1.98)	0.06	2.00 (1.98)	0.06	1.99 (1.98)	0.06

Table A-3. Average bond angles (Å) throughout the AIMD simulation trajectory along with their standard deviations (St. Dev.). The values inside the brackets are those used in the classical MD simulations.

	MLA		MLB		MLC	
	Average	St. Dev.	Average	S. Dev.	Average	S. Dev.
Cr-O _U -Cr	119.03 (119.71)	3.62 (2.37)	119.85 (119.88)	3.26 (2.28)	117.96 (119.91)	4.16 (2.36)
O _H -Cr-O _U	173.02 (164.62)	3.96 (2.87)	172.74 (176.11)	3.73 (2.09)	172.39 (171.51)	3.72 (2.80)
O _{water} -Cr-O _U	173.16 (166.45)	3.60 (2.83)	172.91 (174.70)	3.58 (2.33)	171.61 (172.20)	4.43 (2.70)
Cr-O _{water} -H _{water}	119.89 (112.70)	8.03 (3.96)	118.29 (115.77)	9.03 (4.00)	119.18 (114.85)	7.68 (3.97)
Cr-O _{OH} -H _{OH}	115.91 (113.09)	7.58 (4.12)	111.70 (115.54)	7.33 (4.12)	114.65 (112.30)	7.52 (4.14)
O _{water} -Cr-O _{ligand}	83.66 (80.01)	4.57 (3.19)	83.42 (82.51)	4.33 (2.97)	85.88 (82.22)	4.36 (2.99)
O _{OH} -Cr-O _{ligand}	84.24 (80.16)	5.01 (3.11)	85.24 (83.47)	4.04 (2.75)	86.88 (76.36)	4.33 (2.95)
O _{ligand} -Cr-O _U	96.37 (90.60)	4.02 (2.67)	95.74 (95.44)	3.79 (2.46)	94.70 (94.63)	3.88 (2.51)
Cr-O _{ligand} -C _{ligand}	132.19 (128.26)	4.72 (3.59)	131.74 (128.04)	5.14 (3.80)	128.80 (126.62)	4.24 (3.70)

Average bond lengths and their respective standard deviations are calculated throughout the AIMD trajectory. Bond lengths are compared with the classical force field estimates. The average values obtained from AIMD simulations are very close to those used in the classical force field. Furthermore, the standard deviations are very small, less than 0.1 Å in most cases; hence showing agreement between AIMD and the force field. The resulting values for the three half-SBUs are available in Table A-2.

In addition to bond lengths, average values and standard deviations of angles (or three-body interactions) are compared between AIMD and classical MD for the three half-SBUs. The resulting values for all isomers are presented in Table A-3.

A first observation is that the O_{ligand}-Cr-O_{ligand} angle has different values for MLA, MLB, and MLC. This is an effect of the difference in orientation of the terephthalate linker with respect to the plane of the metal centre. More elaborately, all angles of this category are of one type in MLA (the three terephthalate linkers face

upward), two types in MLB (upward or downward), and different two types in MLC (below a linker, different from MLB). In the case of MLA, this angle has an average value of 87.83 (88.98) degrees with a standard deviation of 4.65 (4.12) in AIMD (classical MD values inside brackets). For MLB the first type has an angle of 86.18 (89.36) with a standard deviation of 4.16 (4.14). The second type is 166.88 (166.01) with a standard deviation of 4.11 (2.50). At last, for MLC, the first type shows an average value of 86.30 (86.80) with a standard deviation of 3.96 (3.53) and the second type 93.07 (87.66) with 4.52 (2.88). Ultimately, intramolecular interactions including bond lengths and angles show a very good agreement across different levels of theory for all half-SBUs.

A.2 Imposing constraints for bond lengths

In this section, the effect of imposing constraints on bond lengths is assessed. In classical MD simulations of dimers, where the two collective variables (M-T and M-M) were biased (see Chapter 4), bond lengths were constrained using the LINCS algorithm [195] as previously discussed. This approximation can be used in simulation studies of metal-ligand complexes [169].

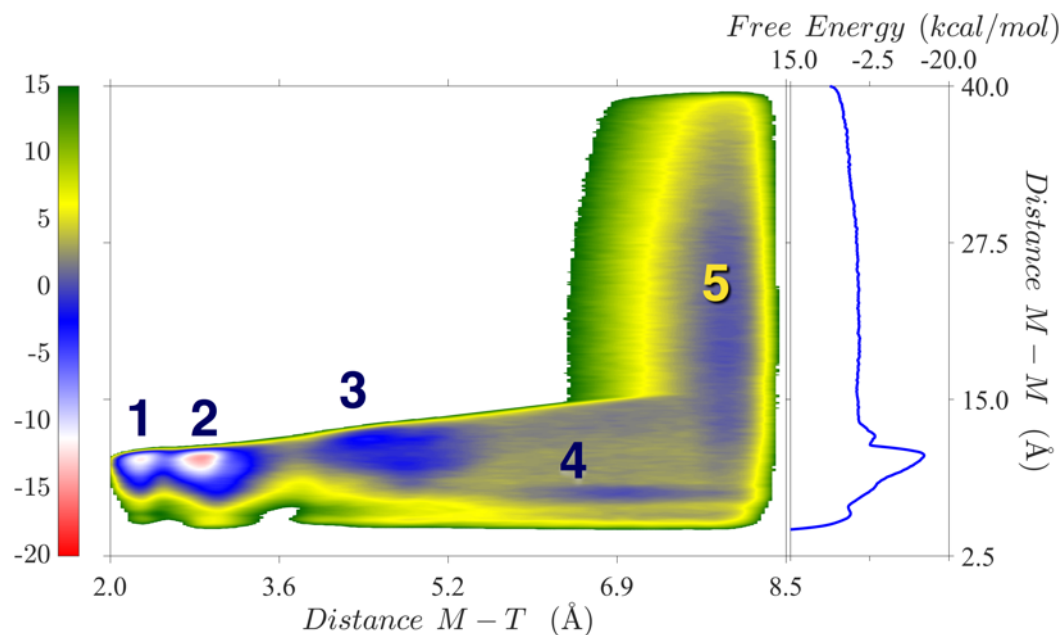


Figure A-1. Free energy surface of MLA-MLA in water at 298 K, 1 bar projected on the two distance collective variables (M-T, M-M) biased throughout the WTmetaD simulations. These are performed for 0.5 μ s, while constraining only the bond lengths involving hydrogen. States 1-5 are identified on the FES.

Additionally, a simulation is carried out while constraining the lengths of only those bonds that involve hydrogen atoms as these fluctuate faster than the time step of the simulations. Accordingly, the FES is calculated for the instance of MLA-MLA interactions in explicit water after carrying out a 0.5 μ s WTmetaD [204] simulation using the same setup as before. Although this simulation is considerably shorter than the production simulation (7 μ s), the resulting FES, presented in Figure A-1, is quantitatively consistent with the long production simulation constraining internal bonds. Therefore, it is explicitly shown that LINCS [195] constraints have negligible effect on the production simulation results and more importantly on the features of the FES.

At last, the average bond lengths, and their standard deviations, concerning atoms in the metal centre, when only bonds involving hydrogen are constrained, are calculated. This analysis is performed in order to provide the values of bonded interactions when less degrees of freedom are constrained in the system with the current force field implementation. Concerning the chromium-central oxygen bond for MLA and MLC, this is 1.96 Å (1.98 Å for MLB) on average with a standard deviation of 0.03 Å (0.04 Å for MLB). For chromium-oxygen of water the relevant statistics for MLA are 2.14 Å (2.13 Å for MLB and MLC) and 0.03 Å (0.04 Å for MLB and MLC). The same values are identified for the oxygen of hydroxide instead of water for MLA and MLB, while for MLC these are 2.02 Å and 0.04 Å. In the case of chromium-oxygen of the terephthalate linker, these values become 2.01 Å (the same for MLB and 2.02 Å for MLC) and 0.04 Å (0.03 Å for MLB and MLC). Expectedly, these values are very close to the equilibrium values modelled in the force field and fluctuations of these bonds are less than a twentieth of an Å.

Overall, from this analysis it is apparent that the values for bonded interactions are similar to both the ab initio and classical MD values discussed previously. Therefore, the force field, including bond length fluctuations, is also in good agreement with a higher level of theory; thus, it is able to represent physicochemical properties of the solutes with increased accuracy.

A.3 Unbiased Simulation of AA

Molecular dynamics simulation of the AA couple of half-SBUs in explicit water has been performed in order to initially investigate interactions between them. The half-SBUs interact very strongly leading to the observation that the SBU dimer has a significant energy difference from the detached half-SBUs state. At first, two molecular dynamics simulations at 298 K, 1 bar in a box with approximately 4,000 water molecules and 2 half-SBUs were carried out without adding any external bias.

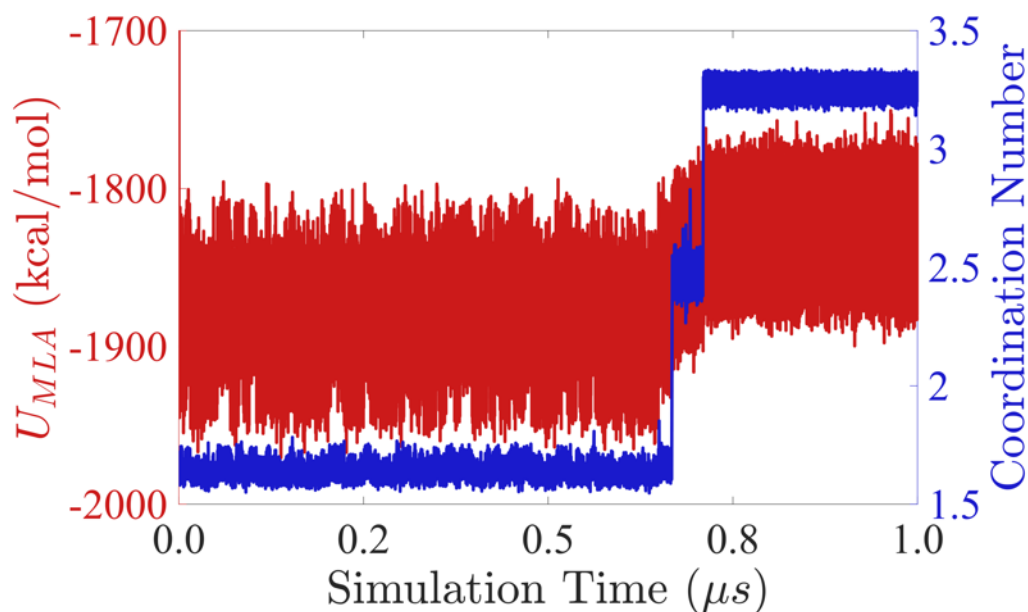


Figure A-2. MLA-MLA in water. Trajectory of the coordination number between terminal carboxylic oxygen and chromium atoms (blue line) and contribution to the potential energy due to the presence of MLA (red line).

The first simulation started from the detached state and the half-SBUs interact very rapidly to form a dimer. Then, this SBU dimer rearranges to a state that exhibits 4 interactions between terminal carboxylic oxygen and chromium atoms at the metal centres (2Q). The second simulation was initiated from a different state, namely the crystal-like SBU configuration (2C), where there are 2 interactions between the terminal oxygen atoms of a terephthalate linker and the chromium atoms of an adjacent metal centre. The rearrangement simulation is carried out for 1 μ s and at 665 ns a rapid change from 2C to 2Q occurs (see Figure A-2). The conformer will stay at this structure until the simulation is brought to an end.

This analysis shows that conformer 2Q has lower energy than 2C for interactions between two MLA molecules. Nevertheless, 2C has lower energy for interactions between MLA and water molecules. Overall, 2C has slightly lower energy than 2Q in all interactions involving MLA. Therefore, 2C is favoured in potential energy space in water, whereas 2Q is favoured in the gas phase. A shift in the trajectory of potential energy is observed in Figure A-2 when the system departs from state 2C (this can be seen in Figure A-2 around 0.7 μ s). Nevertheless, the error associated with these observations is large due to sampling only one transition (there are more than 80 transitions between 2C and 2Q in the biased simulation over 1 μ s). Consequently, enhanced sampling is needed in order to quantitatively assess the energetics of the SBU association-dissociation process. Also, following this pathway

it is possible to uncover the conformational landscape of possible SBUs, both crystal-like and defects.

A.4 AA in Water with 0.75M NaF

A further increase in the concentration of ions in solution is discussed in this section as half-SBUs are simulated in water with 0.75 M NaF.

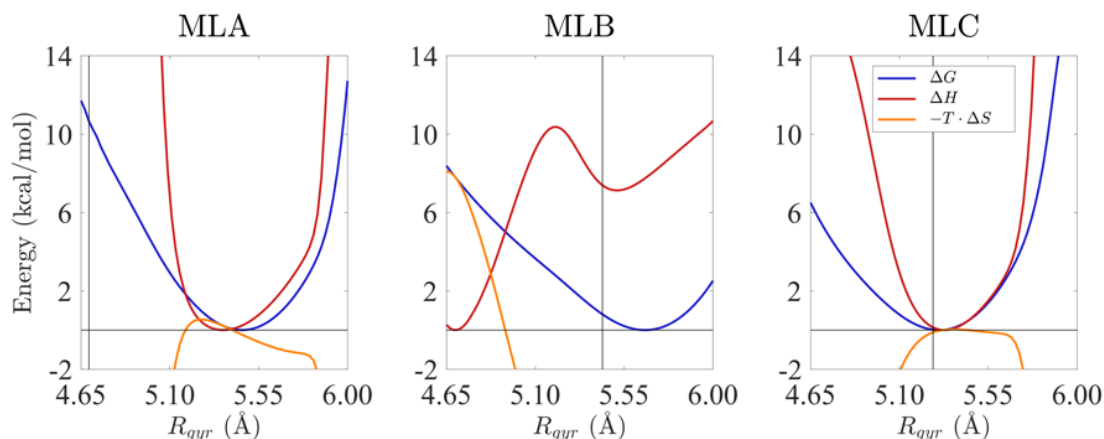


Figure A-3. Energy profiles of MLA (left), MLB (middle) and MLC (right) in water with 0.75M NaF at 298 K projected on R_{gyr} . The free energy profile is represented by a blue curve, while enthalpic and entropic contributions are represented by red and orange curves respectively. A thin horizontal line corresponds to zero on the vertical axis. A thin vertical line refers to the average R_{gyr} value of each half-SBU in the crystal.

In MLA, the free energy profile is dominated by the enthalpic contribution due to the interaction between ions and the metal centre in a similar manner as with 0.25M NaF. Enthalpy favours more compact configurations than free energy as with a smaller concentration of ions. It should be noted that MLA with 0.75M NaF is simulated for 1 μ s (instead of 0.5 μ s for MLB and MLC) in order to decrease the uncertainty of findings.

The free energy profile computed for MLB is very similar to that obtained in the smaller concentration of ions. Nevertheless, enthalpic and entropic contributions change significantly. The enthalpic contribution is dominated by very compact configurations as its minimum is located for R_{gyr} values close to 4.7 Å. Entropy favours even more compact structures that correspond to R_{gyr} of 4.1 Å. These regions are highly improbable as the free energy difference on the space of R_{gyr} with respect

to the most probable state are around +8 kcal/mol for the R_{gyr} corresponding to the enthalpic minimum and +18 kcal/mol for the minimum of the entropic contribution.

The main interest of the enthalpic and entropic contributions is concentrated in the vicinity of the free energy minimum where the most probable structural configurations are located. These are characterised by high potential energy structures; hence they are entropically dominated. Bimodal distributions can be seen for both enthalpy and entropy on the whole space of R_{gyr} , but in the vicinity of the free energy minimum, enthalpy presents a unimodal profile with a minimum for slightly smaller R_{gyr} than the one corresponding to the free energy minimum.

In more detail, in the vicinity of the free energy minimum for MLB, the enthalpic contribution is dominated by R_{gyr} values of 5.5 Å, while free energy by 5.7 Å. Entropy has two minima, one for values around 5.2 Å and one for 5.85 Å. Therefore, the overall conclusion for MLB in water in presence of ions is that the enthalpic and entropic contributions are appreciably different in the whole accessible space projected on R_{gyr} as the change in composition appreciably affects the enthalpic and entropic contributions to the free energy.

At last, MLC presents very similar energy profiles at 0.75M NaF with respect to the ones obtained at 0.25M NaF. Therefore, this half-SBU is practically unaffected by the alteration of its environment; a behaviour that can be explained by the fact that MLC presents stable compact configurations. The introduction of ions does not force the half-SBU to visit more compact configurations that could potentially result in collapse of the structure of the molecule.

Table A-4. Sampling errors (kcal/mol) in water with 0.75M NaF at 298K.

Monomer	Error $F(R_{gyr})$	Error $F(U)$
MLA	0.05	0.40
MLB	0.06	0.43
MLC	0.11	0.44

The block error analysis follows the same reasoning as in previous cases. The sampling errors are provided in Table A-4. The energy profiles of MLA, MLB and MLC in water with 0.75M NaF are provided in Figure A-3.

A.5 Supplementary Figures

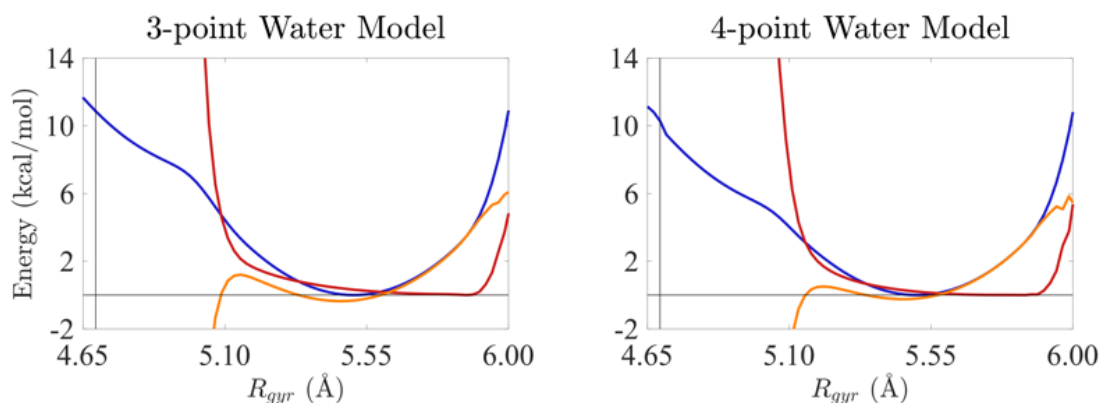


Figure A-4. MLA energy profiles using TIP3P (left) and TIP4P (right) water models [192] at 298 K projected on R_{gyr} . Free energy: blue, enthalpic and entropic contributions: red and orange respectively. A thin horizontal line corresponds to zero on the vertical axis. A thin vertical line refers to the average R_{gyr} value of each half-SBU in the crystal.

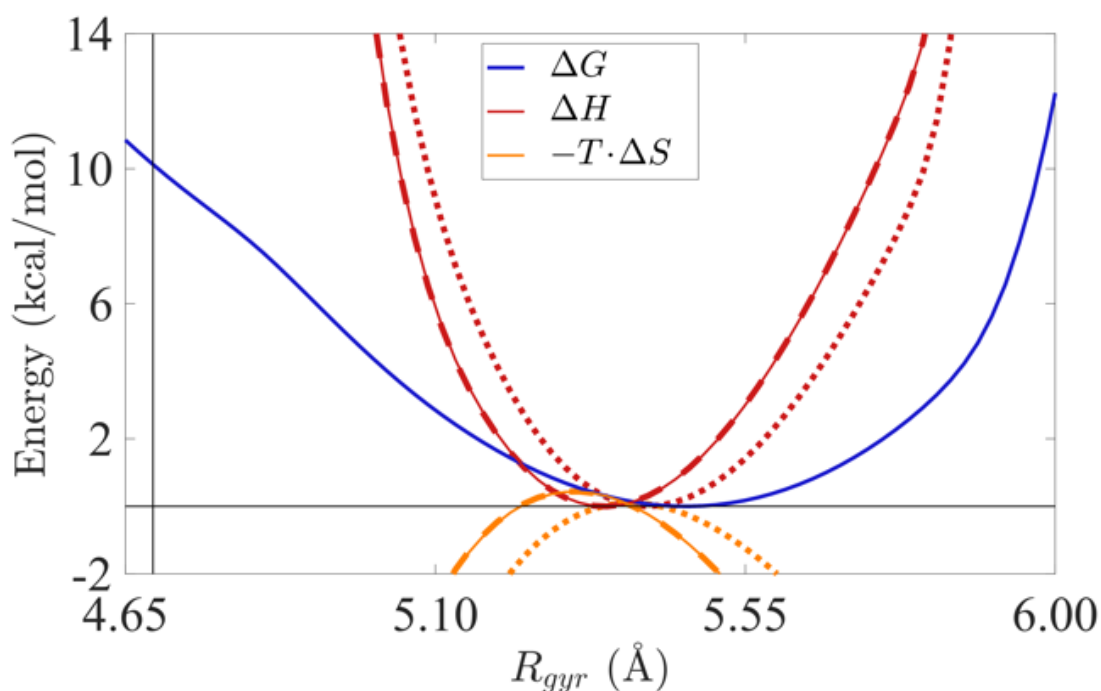


Figure A-5. Energy profiles of MLA in water with 0.25M NaF at 298 K projected on R_{gyr} . Enthalpic and entropic contributions for three different solvation shell sizes are provided in agreement with Figure 3-11.

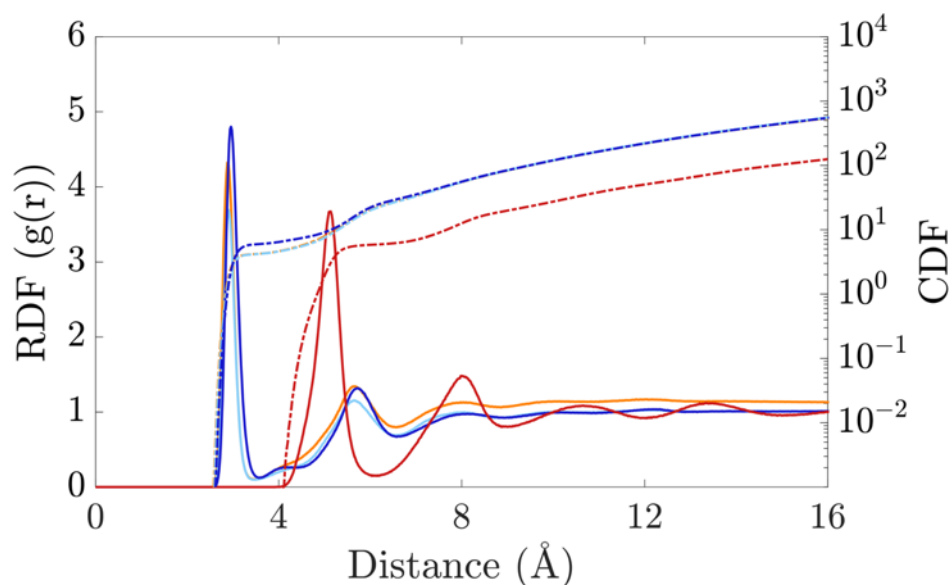


Figure A-6. Radial (solid lines-left vertical axis) and cumulative (dot-dash lines-right vertical axis) distribution functions for central oxygen at the metal centre of MLB and oxygen of water in absence (blue line) and presence (0.25M-orange line and 0.75M-cyan line) of ions. In DMF (red line), the nitrogen atom is used instead of the oxygen in the case of water.

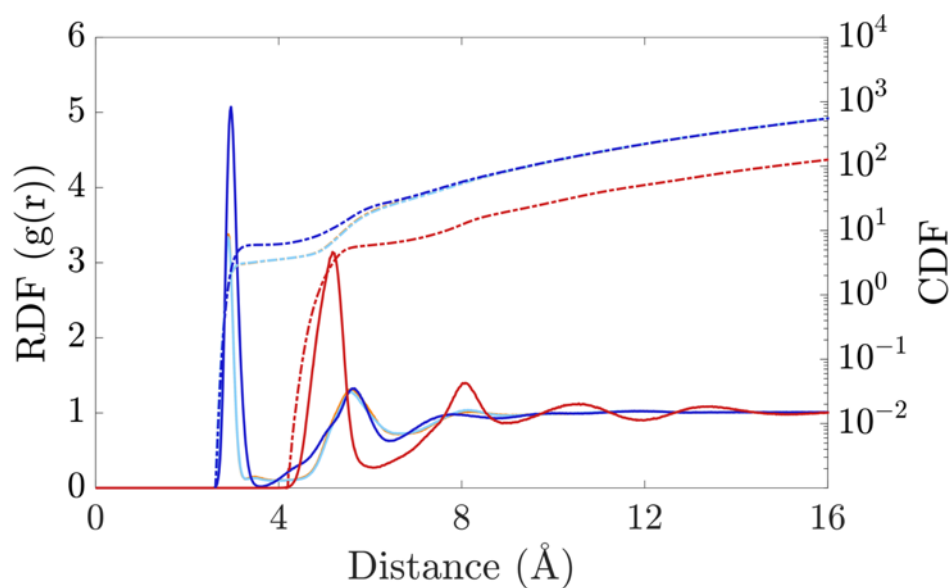


Figure A-7. Radial and cumulative distribution functions of MLC in water and DMF. The same rationale as in Figure A-6 is followed.

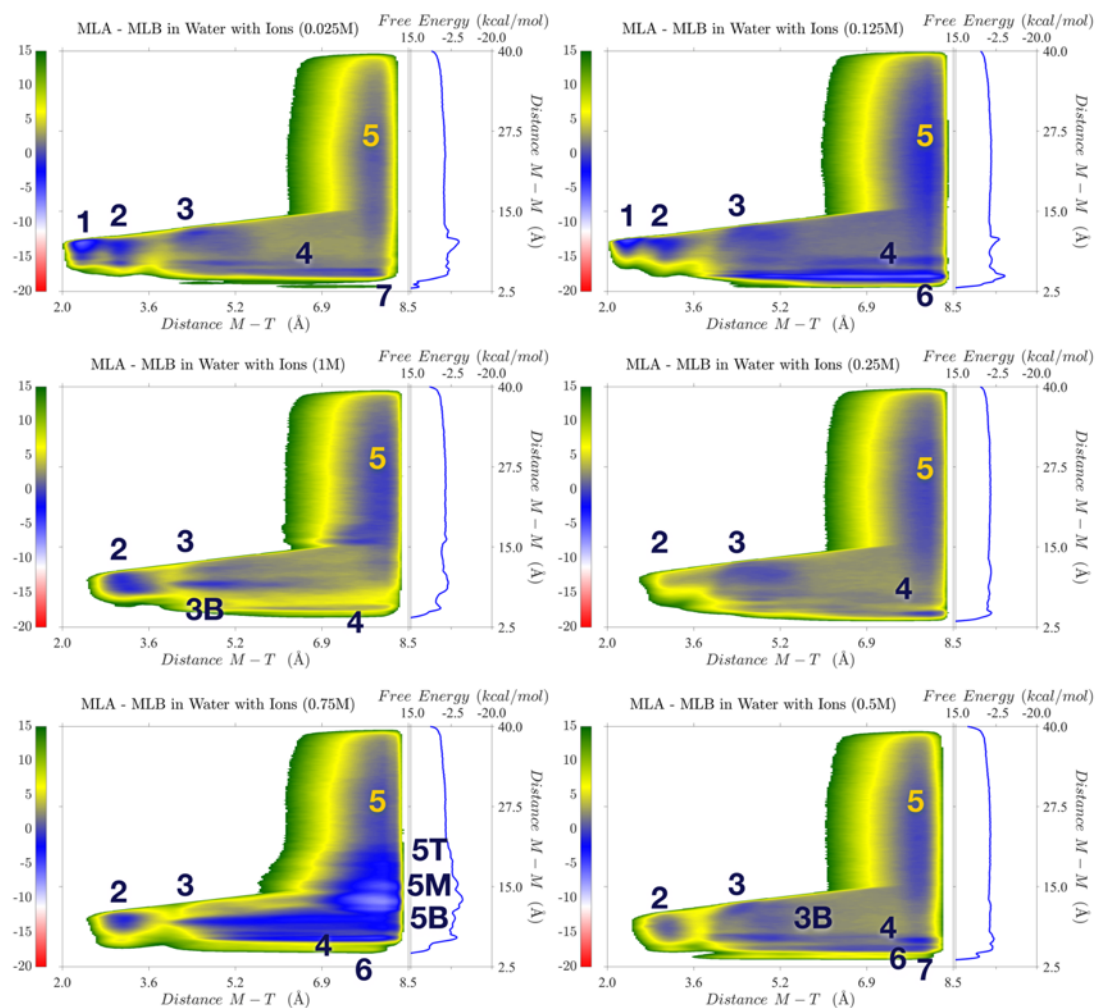


Figure A-8. AB FES for different concentrations of Ions in Solution. The small windows inside the figures show the trends of convergence for the different states of each FES.

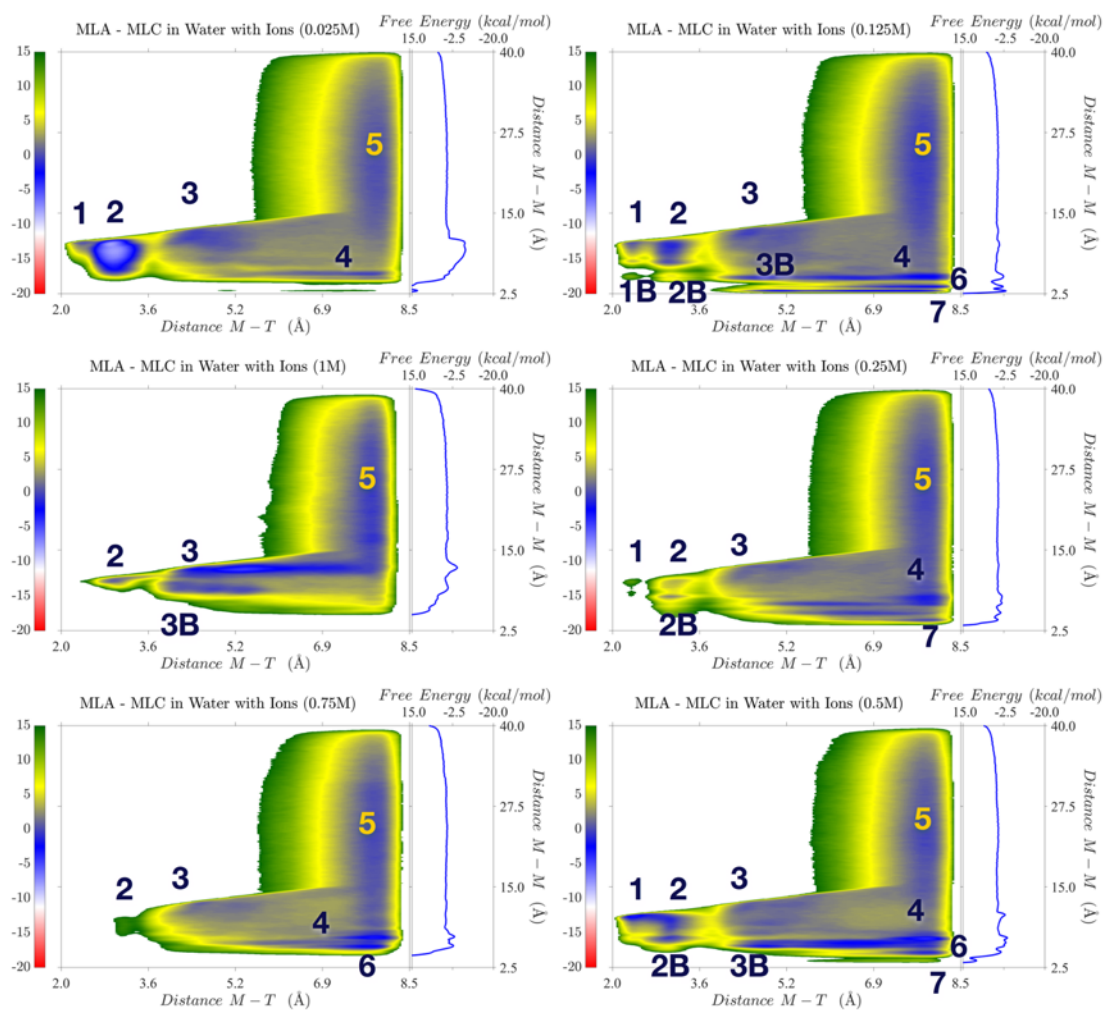


Figure A-9. AC FES for different concentrations of Ions in Solution. The small windows inside the figures show the trends of convergence for the different states of each FES.

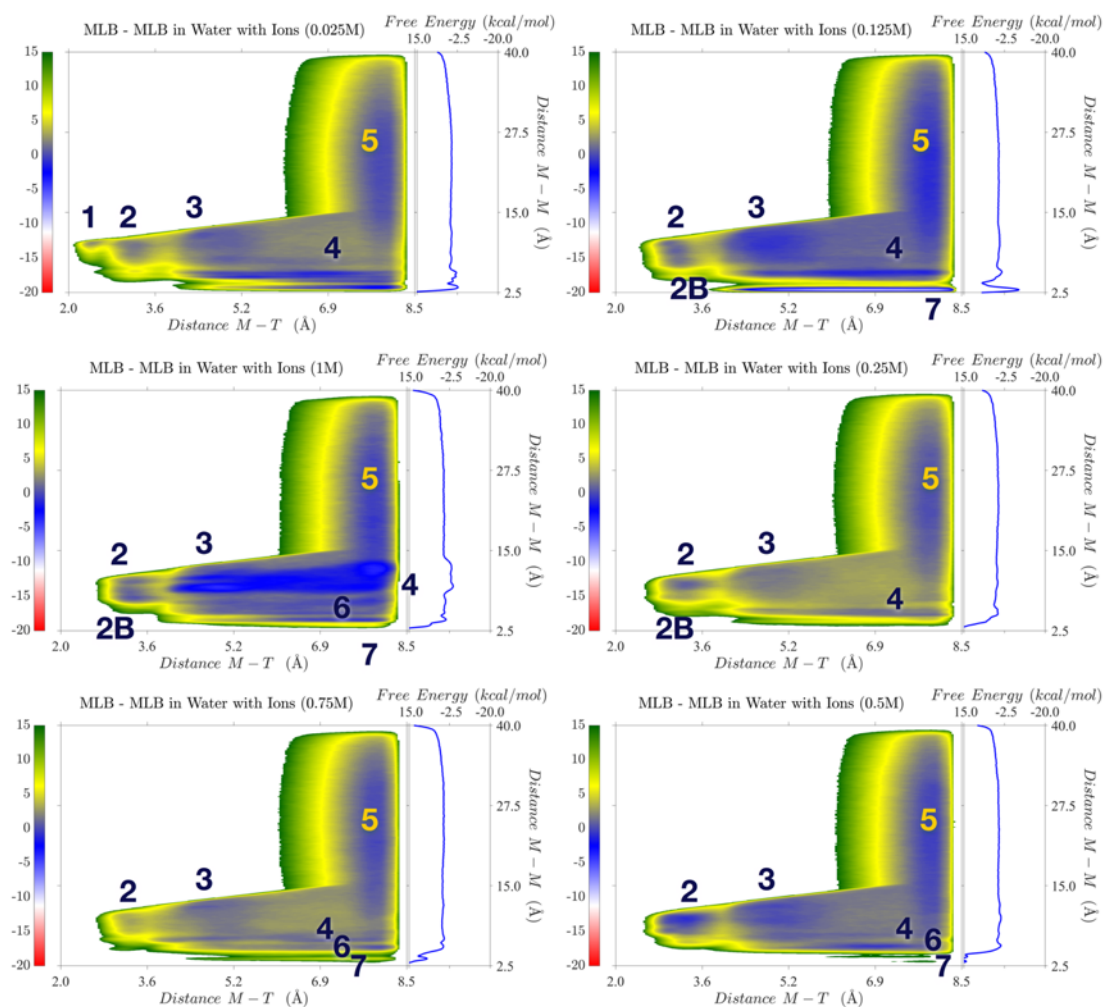


Figure A-10. BB FES for different concentrations of Ions in Solution. The small windows inside the figures show the trends of convergence for the different states of each FES.

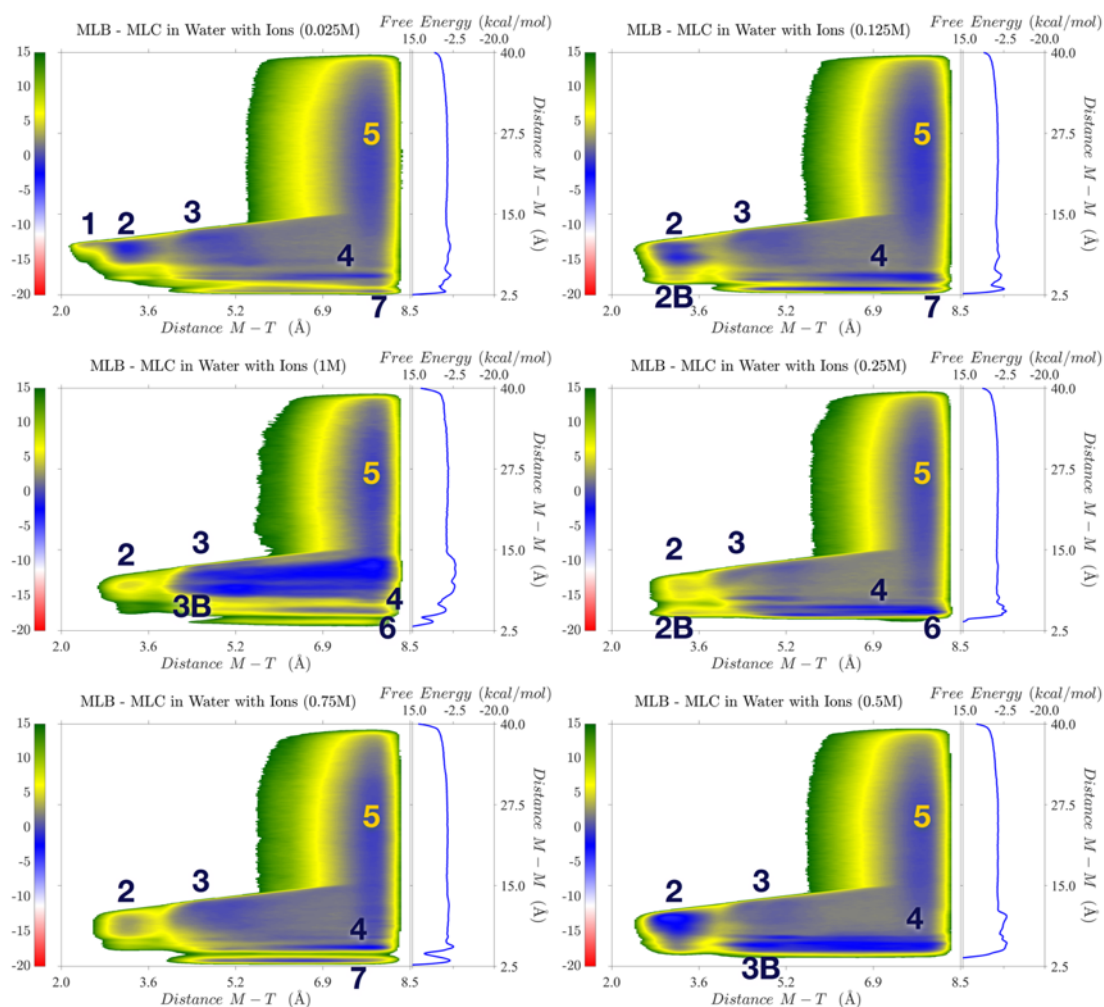


Figure A-11. BC FES for different concentrations of Ions in Solution. The small windows inside the figures show the trends of convergence for the different states of each FES.

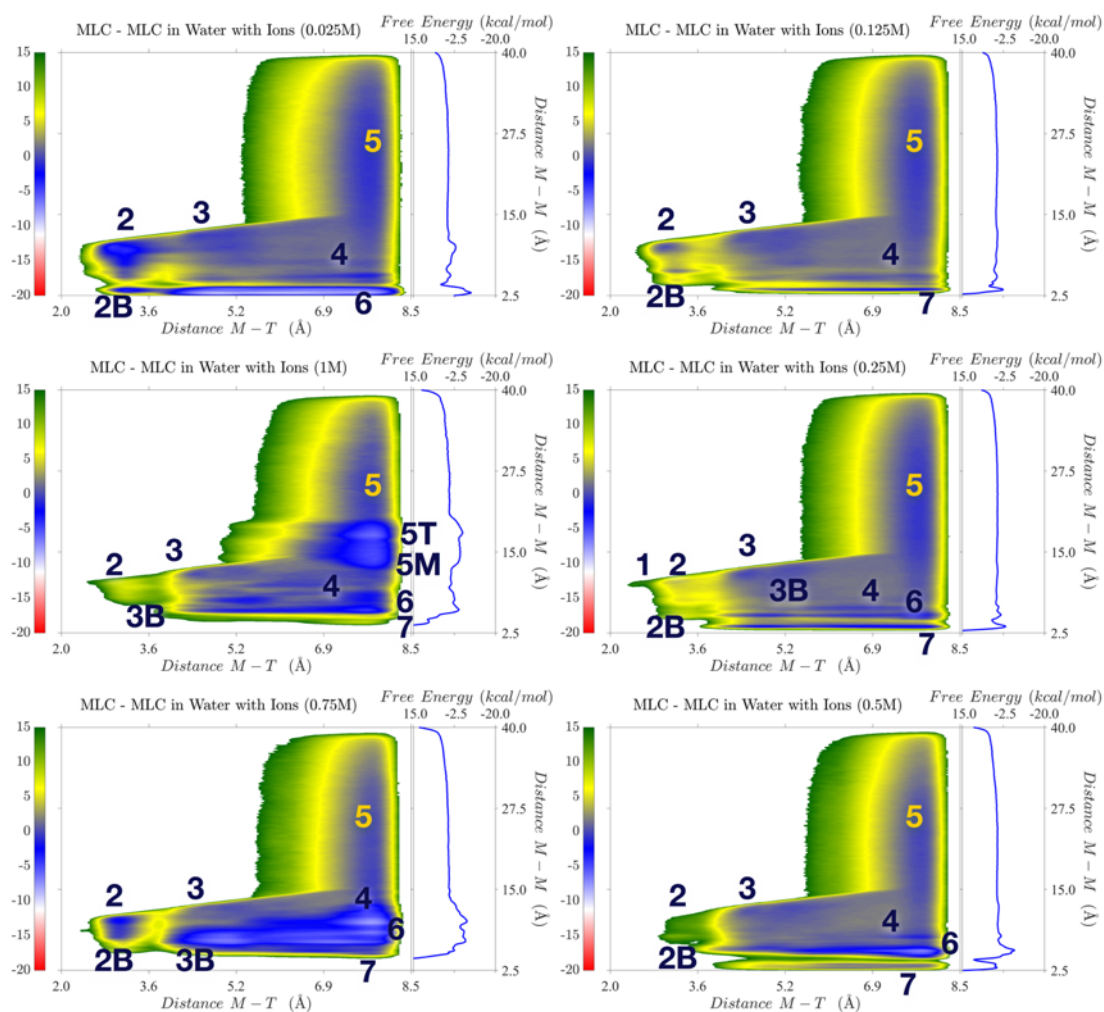


Figure A-12. CC FES for different concentrations of Ions in Solution. The small windows inside the figures show the trends of convergence for the different states of each FES.

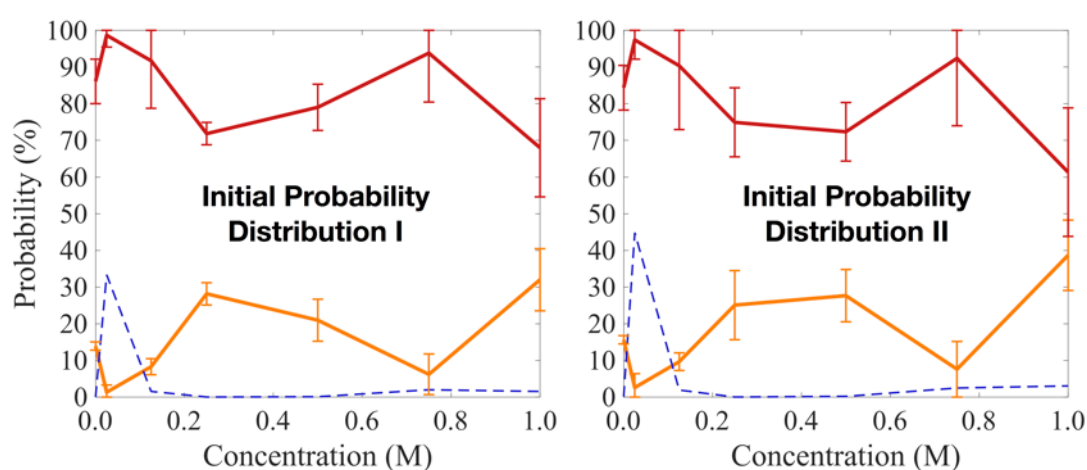


Figure A-13. Average equilibrium probability of free monomers (orange) and dimers (red) (dashed blue line: crystal-like dimers). Error-bars correspond to the standard deviation. A low MLC initial distribution of half-SBUs is assumed.

Table A-5. ΔG estimates for the transition of state 5 to the different states that feature on the FES. SBUs AB-CC and all values for the concentration of NaF are considered.

ΔG (kcal/mol) with respect to state 5. SBU in solution at presence of ions.						
Conc./state	1	2	3	4	6	7
AB						
0	-4.67 ± 0.78	-2.51 ± 1.06	-1.11 ± 0.39	-1.28 ± 0.54	-	-
0.025M	-4.45 ± 1.67	-1.66 ± 0.87	-0.81 ± 0.61	-1.14 ± 0.96	-	-
0.125M	-0.23 ± 5.77	+2.02 ± 1.85	+0.78 ± 0.69	-0.12 ± 0.89	-3.80 ± 1.40	-
0.25M	-	-	+1.09 ± 0.81	+1.24 ± 0.75	+0.24 ± 2.11	-
0.5M	-	+0.84 ± 1.86	+1.15 ± 0.61	+0.49 ± 1.28	+0.50 ± 1.21	+5.20 ± 2.01
0.75M	-	-1.64 ± 2.59	-	-3.77 ± 3.34	-	-
1M	-	+2.19 ± 3.63	+1.65 ± 2.13	-	+1.76 ± 2.36	-
AC						
0	-5.42 ± 3.07	-4.40 ± 1.04	-1.04 ± 0.37	+1.25 ± 0.57	-	-
0.025M	-3.32 ± 3.10	-4.11 ± 2.06	-0.45 ± 0.46	+0.77 ± 1.69	+1.67 ± 1.52	-
0.125M	+6.63 ± 3.41	+3.58 ± 2.85	+0.64 ± 0.54	-1.40 ± 1.71	+3.74 ± 7.84	-0.98 ± 4.51
0.25M	+11.77 ± 2.70	+3.24 ± 2.48	+0.85 ± 0.69	-0.11 ± 1.31	-1.67 ± 1.77	+7.11 ± 2.47
0.5M	-3.59 ± 4.64	-1.44 ± 3.12	+1.04 ± 0.57	+0.34 ± 1.48	-0.66 ± 2.08	+6.98 ± 2.32
0.75M	-	+9.20 ± 3.27	+0.57 ± 0.63	-2.89 ± 2.85	-0.09 ± 1.82	-
1M	+12.89 ± 3.90	+2.47 ± 3.86	-2.49 ± 3.56	-	-	-
BB						
0	-	-0.65 ± 1.27	-0.09 ± 0.23	-0.20 ± 0.63	+2.29 ± 1.43	-0.35 ± 2.48
0.025M	+5.36 ± 1.68	+0.34 ± 1.42	+0.17 ± 0.35	-2.04 ± 1.21	-	-5.81 ± 5.24
0.125M	-	+1.72 ± 1.41	+0.36 ± 0.51	-0.67 ± 0.78	-	-9.38 ± 4.33
0.25M	-	-0.18 ± 1.64	+0.63 ± 0.62	-	-0.64 ± 1.20	-
0.5M	-	+0.58 ± 1.78	+0.53 ± 0.42	-0.79 ± 1.59	-	-
0.75M	-	-1.87 ± 1.79	+0.63 ± 0.53	+0.19 ± 1.49	+3.52 ± 3.72	-
1M	-	+0.41 ± 2.30	+0.76 ± 1.26	+1.60 ± 0.87	+1.93 ± 2.54	-
BC						
0	+3.90 ± 1.20	-2.92 ± 0.71	-0.08 ± 0.10	-1.26 ± 0.32	+2.54 ± 1.03	-0.29 ± 1.43
0.025M	-	-0.29 ± 0.91	+0.02 ± 0.22	-1.14 ± 0.69	+3.20 ± 4.17	-
0.125M	-	+0.04 ± 1.22	+0.76 ± 0.41	-0.78 ± 0.56	-3.41 ± 2.50	-
0.25M	-	+2.85 ± 1.68	+0.78 ± 0.32	-0.91 ± 1.41	-2.81 ± 1.90	-1.02 ± 2.64
0.5M	-4.60 ± 5.15	+0.84 ± 1.86	+1.15 ± 0.61	+0.49 ± 1.28	+0.50 ± 1.21	+5.20 ± 2.01
0.75M	-	+3.13 ± 1.42	+0.82 ± 0.33	+0.12 ± 1.03	-2.10 ± 3.18	-
1M	-	+2.85 ± 2.61	+0.21 ± 2.85	+0.37 ± 2.42	+5.01 ± 3.51	+5.10 ± 3.70
CC						
0	+2.47 ± 1.00	-4.55 ± 0.61	-0.38 ± 0.21	-1.12 ± 0.58	-	+2.19 ± 1.44
0.025M	-	-4.11 ± 2.01	-0.14 ± 0.48	-0.21 ± 0.56	-7.86 ± 2.84	-
0.125M	-	-0.12 ± 1.43	+0.75 ± 0.34	-0.22 ± 1.01	+1.05 ± 4.70	-
0.25M	+11.34 ± 2.44	+2.80 ± 1.25	+0.71 ± 0.28	-1.03 ± 0.97	-4.45 ± 2.08	-
0.5M	-	-	+0.61 ± 0.38	-4.57 ± 3.71	-1.40 ± 2.44	-
0.75M	-	-1.59 ± 1.51	-	-3.03 ± 1.49	-1.62 ± 2.85	-
1M	-	+10.89 ± 4.79	+0.70 ± 1.71	+0.15 ± 3.53	+7.84 ± 4.46	-