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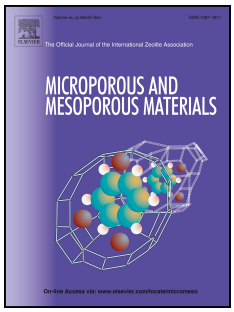

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PII: S1387-1811(20)30548-5

DOI: https://doi.org/10.1016/j.micromeso.2020.110548

Reference: MICMAT 110548

To appear in: *Microporous and Mesoporous Materials*

Received Date: 23 June 2020

Revised Date: 24 July 2020

Accepted Date: 4 August 2020

Please cite this article as: F. Habib, D.A. Tocher, N.J. Press, C.J. Carmalt, Structure determination of terpenes by the crystalline sponge method, *Microporous and Mesoporous Materials* (2020), doi: https://doi.org/10.1016/j.micromeso.2020.110548.

Credit Author Statement

Faiza Habib: Methodology**,** Investigation, Formal analysis, Writing-Original draft,

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Structure Determination of Terpenes by the Crystalline Sponge Method

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ABSTRACT: The crystalline sponge method was used to produce novel encapsulation complexes with the aim of structural determination of terpenes, such as geraniol-monoterpenoid, farnesol-sesquiterpenoid and β-damascone-tetraterpenoids. Along with the structure determination of the terpenoids, non-bonding CH-π, π-π interactions were identified in the host-guest complexes, which were responsible for holding the guests in the specific position with respect to the framework. In addition, the orientation of guests with respect to the framework was studied.

KEYWORDS: Crystalline sponge method, Structure determination, Host-guest interactions.

1. INTRODUCTION

The crystalline sponge method is a technology allowing precise, unambiguous molecular determination of a non-crystalline compound which would otherwise be not suitable for single crystal X-ray diffraction (SCXRD) analysis due to its state in isolation, such as powder, amorphous solid, liquid, volatile matter or oil. In this method, metal-organic frameworks (MOF) are used as 'crystalline sponges', which can then absorb the target sample from a solution into the pores and allow them to arrange themselves in a regular pattern with the help of specific interactions between the MOF framework and the guests. These interactions include π-π, CH-π, and charge-transfer interactions. The technique was first introduced by Fujita *et al.*[1] in 2013 and since then has grown rapidly and proven helpful in the structure elucidation of natural products[2],[3] volatile compounds[4],[5], ozonides[6], metabolites[7], in studying reaction mechanisms[8],[9] and in absolute structure determination[10],[11]. With the success of the crystalline sponge method many researchers developed alternative crystalline sponges[12],[13]. These new crystalline sponges can be searched in the crystallographic database using guidelines published by Fujita *et al.*[14] In this study

we used the most successful crystalline sponge to date [{$(ZnI_2)_3$(tris(4-pyridyl)-1,3,5-triazine)$_2$·$(CHCl_3)$}$_n$] (**1**) developed by Fujita and co-workers[1] to encapsulate terpenes, since its applicability has been tested and clearly demonstrated on multiple occasions.

Terpenes are naturally occurring organic chemicals produced by plants and some insects. Their strong aromatic qualities are valued by the perfume industry, agribusiness is interested in their potential pesticidal properties and their role in traditional herbal remedies has been used by pharmaceutical and biotechnology industries to guide the synthesis of drugs. With this motivation the guest molecules selected for this research were geraniol ($C_{10}H_{17}O$), farnesol ($C_{15}H_{26}O$) and β-damascone ($C_{13}H_{20}O$) (Figure 1). Geraniol is an acyclic monoterpene alcohol, which exhibits anti-tumour and potent chemo-preventive effects in colon cancer treatment and has proven to sensitize cell differentiation to conventional anti-colitic therapies[15]. In addition, studies of geraniol have shown anti-inflammatory and antiatherogenic properties[16]. Similarly, farnesol has the ability to selectively kill leukaemia cells and functions as a key synthetic intermediate in the mevalonate/cholesterol synthesis pathway[17],[18]. Therefore, structural information on these terpenes would be useful in understanding complex cellular processes and potentially help pharmaceutical industries to design new drugs derived from these terpenes.

Absolute structure determination of other terpenes such as astellifadiene[19], LphTPS-A - a sesquiterpene synthase[20] - and prenyltransferase-terpene synthase[3] has been previously achieved using the crystalline sponge method, demonstrating that this technique is suitable for structure determination of complex natural products.

2. EXPERIMENTAL

2.1 Crystalline Sponge Synthesis.

[{$(ZnI_2)_3$(tris(4-pyridyl)-1,3,5-triazine)$_2$·$(CHCl_3)$}$_n$] (**1**) was prepared following the modified procedure reported in the literature.[21]. Details of sponge pore dimensions and solvent accessible voids can be found in Supporting Information.

2.2 Guest encapsulation.

Initial guest encapsulation experiments crystals were attempted by soaking **1** in neat guest, however deterioration of the crystals was observed in each case. Therefore, a strategy was developed where guests were dissolved in a solvent, such as chloroform and cyclohexane prior to soaking. Several soaking conditions were investigated to obtain the best quality data and optimised guest occupancy, as detailed in the supplementary information.

For successful guest encapsulation the guest liquids (10-40 μL) were dissolved in 2 mL of cyclohexane, followed by pipetting of the solution into a vial containing well-formed rod-shaped crystals of **1**, (where mass of each crystal is approximately of the order of 10^{-6} g) and left in the incubator at 25 or 100 ^{o}C. Full experimental details are given in the supplementary information. After a few days of incubation suitable crystals were selected and subjected to SCXRD. The optimised encapsulation conditions for the inclusion complexes described in this paper are listed in Table 1.

Table 1. Specific encapsulation conditions for the crystals soaked in guest: solvent solution.

Guest	Solvent	Guest (μl)	Solvent (ml)	Soaking temperature	Incubation time/days
geraniol	cyclohexane	40	2	25°C	3
farnesol	cyclohexane	10	2	10°C	12
β-damascone	cyclohexane	40	2	25°C	5

2.3 Crystallographic Procedures.

Crystals were placed in Fomblin, and single crystals were selected and mounted onto nylon loops. X-ray diffraction data were recorded at 150 K on an Agilent Super Nova dual diffractometer (Agilent Technologies Inc., Santa Clara, CA) with Cu Kα radiation (λ = 1.5418 Å). Unit cell determination, data reduction, and absorption corrections were carried out using CrysAlisPro.[25] The structures were solved by direct methods and refined by full-matrix least-squares based on F^2 using SHELX[26] within the OLEX2.0[27] graphical user interface. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were included using a riding model. Details of the treatment of individual guest molecules in each structure can be found in the Supporting Information

3. RESULTS AND DISCUSSION

The crystalline sponge (**1**) was synthesised by following the modified procedure described in the literature[21]. To obtain higher occupancies the guest encapsulation was first attempted with neat guests which resulted in cracking of the crystals, leading to poor crystallinity of the samples, which were therefore not suitable for the X-ray diffraction experiment. Hence a strategy was developed where the guest was dissolved in cyclohexane prior to soaking. Several soaking conditions were investigated and optimisation of parameters, such as the concentration of the guest, soaking time

length and temperature were developed in each case to obtain the best and optimised occupancies as well as best quality crystals for X-ray diffraction measurements. During SCXRD analysis chemical occupancies of each guest molecule were initially refined freely which, resulted in higher occupancies than we are reporting in the paper, however, free refinement showed disorders in the guest molecules. The reported values are consistent with the best models we were able to develop modelling the disordered quests. Details of soaking experiments can be found in the Supporting Information.

3.1 Encapsulation complex with geraniol

Single crystal X-ray analysis showed the structure of geraniol within the pores of the framework Figure 2. The guest−host complex was found to crystallise in the centrosymmetric space group *C*2/*c*, showing a slight expansion in cell dimensions compared with the as-prepared crystalline sponge **1**, as expected from the specific interactions of guest within the host structure. One guest molecule was found per asymmetric unit with 40% occupancy, along with one well-characterised residual $CHCl_3$ molecule (from the synthesis of **1**). All the atoms of the guest were found and modelled; however, the hydroxyl group of the guest shows disorder evident from the larger thermal ellipsoids shown in Figure 2a.

A detailed examination of the packing diagram displayed in Figure 2b reveals that the guest molecule was positioned over the aromatic panel of tris(4-pyridyl)-1,3,5-triazine (TPT) and interacting with two of the pyridyl rings and a triazine ring Figure 2c, d. The formation of CH-π interactions and π-π interactions were observed between the guest and the framework. The $CH_{geraniol}$-$centroid_{pyridine}$ interactions were 3.187 and 3.374 Å, $CH_{geraniol}$-$centroid_{triazine}$ was found to be 3.839 Å, and π-π interactions between $C{=}C_{geraniol}$ and the $centroid_{pyridine}$ of the framework was observed at distances of 4.115 and 4.216 Å with a dihedral angle of 10.60˚, as illustrated in the Figures 2c and 2d. Since geraniol has a hydroxyl group it might be expected to form a hydrogen-bond with the host framework, however, the length of $O_{geraniol}$-$H_{pyridine}$ interaction was 3.053 Å, larger than that normally expected of a hydrogen bond which would be ~2.5 Å.

3.2 Encapsulation complex with farnesol

The encapsulation complex of **1** with farnesol crystallised in the centrosymmetric space group *C*2/*c*. One guest molecule was found per asymmetric unit with 30% occupancy and was found disordered about the 2-fold axis. One of the methyl groups attached to C44 was severely disordered, therefore could not be modelled, and hence is not shown in the guest structure presented in Figure 3b.

Packing details illustrated in Figure 3a show that farnesol was positioned over only one of the pyridine rings and appears to be stabilised by several interactions with that unique pyridine ring of the host and the ends of the chain are extended into adjacent pores. Each farnesol molecule forms four CH-π and one π-π interaction with the unique pyridine. Each of the three C═C bonds in farnesol interact with the host framework. The π-π interaction between $C{=}C_{farnesol}$ and the centroid of the pyridine ring was observed at 4.071 Å. The four CH-π interactions displayed in Figure 3b were 3.156 Å, 3.850 Å, 3.679 Å, and 3.449 Å. Similarly, to geraniol, no H-bonding between the hydroxyl group of farnesol and the framework was observed, because the shortest $O_{farnesol}$-$H_{pyridine}$ distance was 3.233 Å.

Since farnesol is similar in structure to geraniol but with a longer carbon chain, it was expected to show some similarity in positioning inside the pore as our previous studied had suggested for related molecules.[22] However, in this case these two guests molecules were found situated at a different site relative to the tris(4-pyridyl)-1,3,5- triazine)$_2$, TPT linker. Geraniol interacted with two pyridyl rings and a triazine ring, whereas farnesol shows interaction with that unique pyridyl ring only, with which geraniol had not shown any interaction (See Figure 2d and 3b). In addition, the molecular size of farnesol is higher than geraniol it is therefore interesting to compare the extent to which they occupy the pore space in the host. It is therefore perhaps unsurprising that the higher occupancy is observed for the smaller geraniol (40%) rather than farnesol (30%).

Other related guest molecules containing hydroxyl group have been encapsulated in sponge **1** with the chiral reference installed within the framework by Fujita *et al*.[23] Among the four guests, 2-azido-1-phenylethanol and dimethyl L-(+)-tartrate were found interacting with the framework with a hydrogen bond. In both the cases, there were four molecules present in the asymmetric unit, however only one molecule sitting in a unique site was interacting with the TPT panel through a hydrogen bond. The hydrogen bond distances were $OH\cdots N_{triazine}$ 2.308 Å and $OH\cdots HC_{pyridine}$ 2.425 Å respectively, which suggests that only specific sites allow hydrogen bonding interactions.

3.3 Encapsulation complex with β-damascone

The crystals of β-damascone encapsulated into **1** were obtained in the *C*2/*c* space group with one guest molecule per asymmetric unit at 50% occupancy, along with one molecule of cyclohexane, and no disorder in the guest molecule was observed. The packing diagram, shown in Figure 4a, displays the structural details in which the guest molecule interestingly was positioned on the site similar to geraniol with a slight rotational difference with respect to TPT linker, which is evident by comparing CH-centroid distances. Two CH-centroid distances are comparable because the pyridyl and triazine

rings involved in interactions are common for both the guests. However, the third CH-centroid is different, since both guests were interacting with a different pyridyl ring. (See Figure 2d and 4b) In addition, the guest molecule has appeared to occupy every alternate pore, unlike the other two encapsulation complex discussed above. However, the number of guest molecules in the unit cell is the same in all three complexes. With closer examination of the packing diagram it was revealed that β-damascone was positioned in such a manner that the carbon chain of the molecule is held within the same pore. In contrast, for geraniol and farnesol the carbon chains extend into the adjacent pore, therefore geraniol and farnesol occupy a larger pore space compared to β-damascone. Since, the molecular shape of β-damascone is entirely different from the other two guests, therefore, comparing its refined occupancy with the other two guests is not useful.

The dominant host-guest interactions in this example were found to be CH-π interactions with $CH_{\beta\text{-damascone}}$ -$centroid_{pyridine}$ of 3.393 and 3.520 Å, $CH_{\beta\text{-damascone}}$-$centroid_{triazine}$ of 3.474 Å and the carbonyl group of β-damascone interacting with the triazine ring forming a contact distance $C{=}O_{\beta\text{-damascone}}$-$N_{traizine}$ of 3.025 Å. Although two C=C bonds are present in β-damascone, no π-π interactions were observed because the orientation of the side chain containing the C=C bond was in the pore, as shown in Figure 4b. In addition, the shortest $C{=}O_{\beta\text{-damascone}}$-$H_{pyridine}$ distance was 4.095 Å, suggesting that the position and orientation of β-damascone in the pore does not allow hydrogen bond formation. A similar observation was found in our previous study[22], where a *trans*-cinnamaldehyde molecule forms a hydrogen bond at one site in the pore whereas on the other site a carbon chain containing the carbonyl group of *trans*-cinnamaldehyde extends too far into the pore, therefore not forming a hydrogen bond with the framework. Furthermore, Fujita *et al*.[7] analysed a metabolite from adrenosterone within sponge **1** and observed C=O···H, hydrogen bond interactions between only one guest molecule and the framework among the three guest molecules present in asymmetric unit. This guest molecule is positioned in a unique site compared to the other two molecules. Thus, the orientation and site of the guest inside the pore plays an important role in the formation of a hydrogen bond. In all three host-guest complexes discussed above, guest ordering was dominated by CH-π and π-π interactions, and the site they occupied was not favourable for hydrogen bonding.

The dominant interactions in all three complexes were found to be comparable to previously reported non-aromatic terpenes as detailed in **Table 2**. Since the novel terpenes encapsulated in this study are non-aromatic, the pi electron density of an isolated double bond present in the guests engages in π-π interactions with the centroid of the aromatic TPT panel. The π-π and CH-π distances were compared with the reported non-aromatic terpenes, and similarity in the distances were observed. However, the

strength of the host-guest interactions cannot be compared with other non-aromatic guests because in CSM interactions are required only to be strong enough to regularly order the guest molecules in the pores, which was achieved in all the inclusion complexes reported. Additionally, this work was compared with the other functionalised terpenes encapsulated by Fujita[22], **Table 2**. Six terpene natural products extracted from *Laurencia pacifica* with a hydroxyl functional group were encapsulated and in no instance were any OH groups found to form hydrogen bonds with the framework.

These comparisons suggest, since the ordering of the guests inside the pores were dominated by CH-π and π-π interactions, that the formation of hydrogen bonds was not favoured unless the guest has occupied a unique site and orientation favourable for such a bond. This reflects the hydrophobic nature of tris(4-pyridyl)-1,3,5- triazine)$_2$, TPT link

Table 2. Comparison of CH-π and π-π interaction between non-aromatic terpenes in the pores of the host framework.

Guest	geraniol	farnesol	β-damascone	rac-camphene[24]	rac. α-pinine[24]	β-pinene[24]	astellifadiene [19]
CH-π	3.187 Å	3.054 Å	3.393 Å	3.358 Å	3.444 Å	3.291 Å	3.044 Å
π - π	4.115 Å	3.984 Å	-	4.963 Å	4.141 Å	4.484 Å	4.404 Å

4. CONCLUSIONS

We have reported three novel inclusion complexes with terpenes as guests through the crystalline sponge method, further validating the utility of this exciting new methodology and expanding the range of structures solved. The chosen guests have an important role in the biotech and agribusiness context, and further understanding of their non-crystalline low energy conformations could provide insights into biological mechanisms and potential analogue design. Along with the structure determination of the guests, their interactions with the host framework were studied. These non-aromatic terpenes have comparable host-guest interactions to the other reported non-aromatic terpenes. CH-π and π-π were identified as the dominating interactions and no interactions between the functional group in the guests and the host framework were observed.

APPENDICES

Supplementary information includes details of disorder and the restrains and constraints used to fix it of the individual guest molecule in each structure.

Accession Codes CCDC 1991537−1991539 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes: The authors declare no competing financial interest.

ACKNOWLEDGEMENT

The authors thank the overseas research scholarship UCL and the Faculty for the Future Fellowship for research funding.

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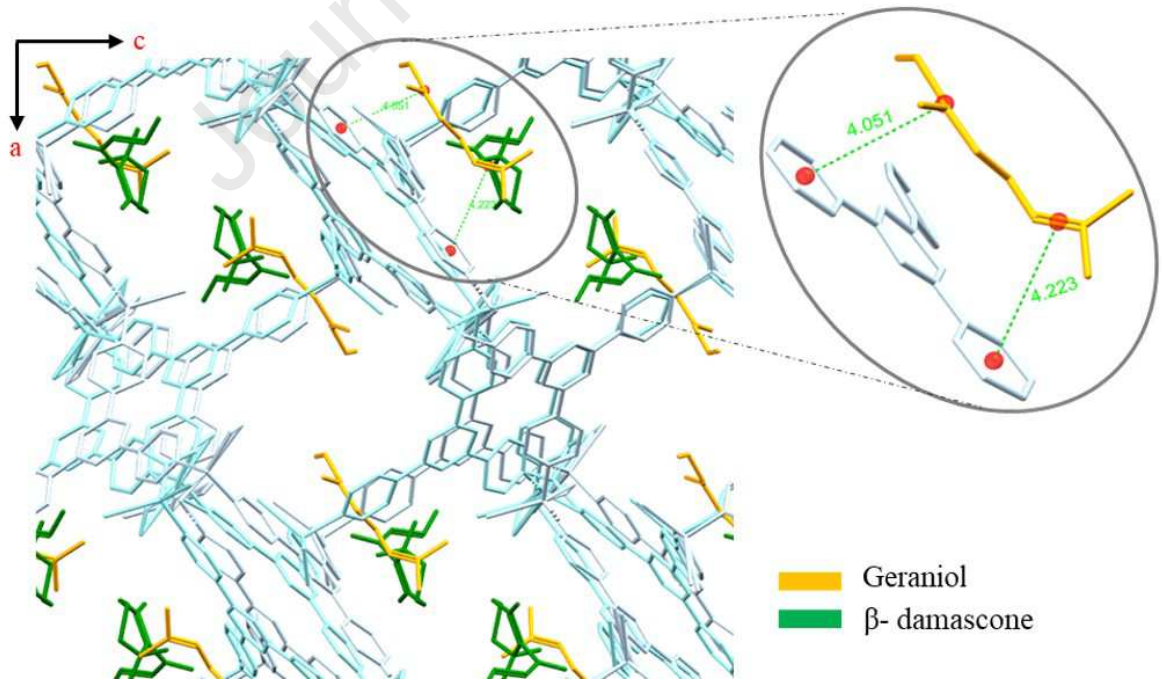
Graphical abstract



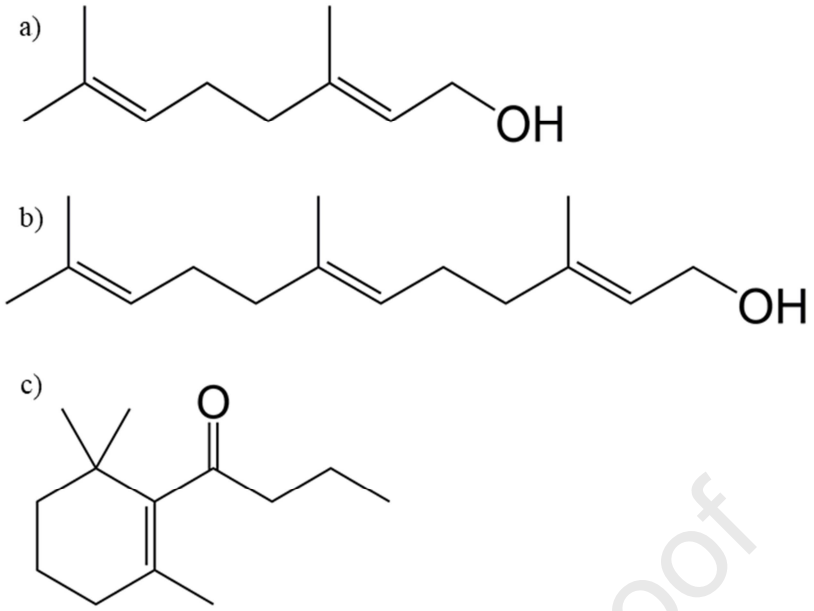


Figure 1. Structures of the guest molecules **a)** geraniol **b)** farnesol **c)** β-damascone.

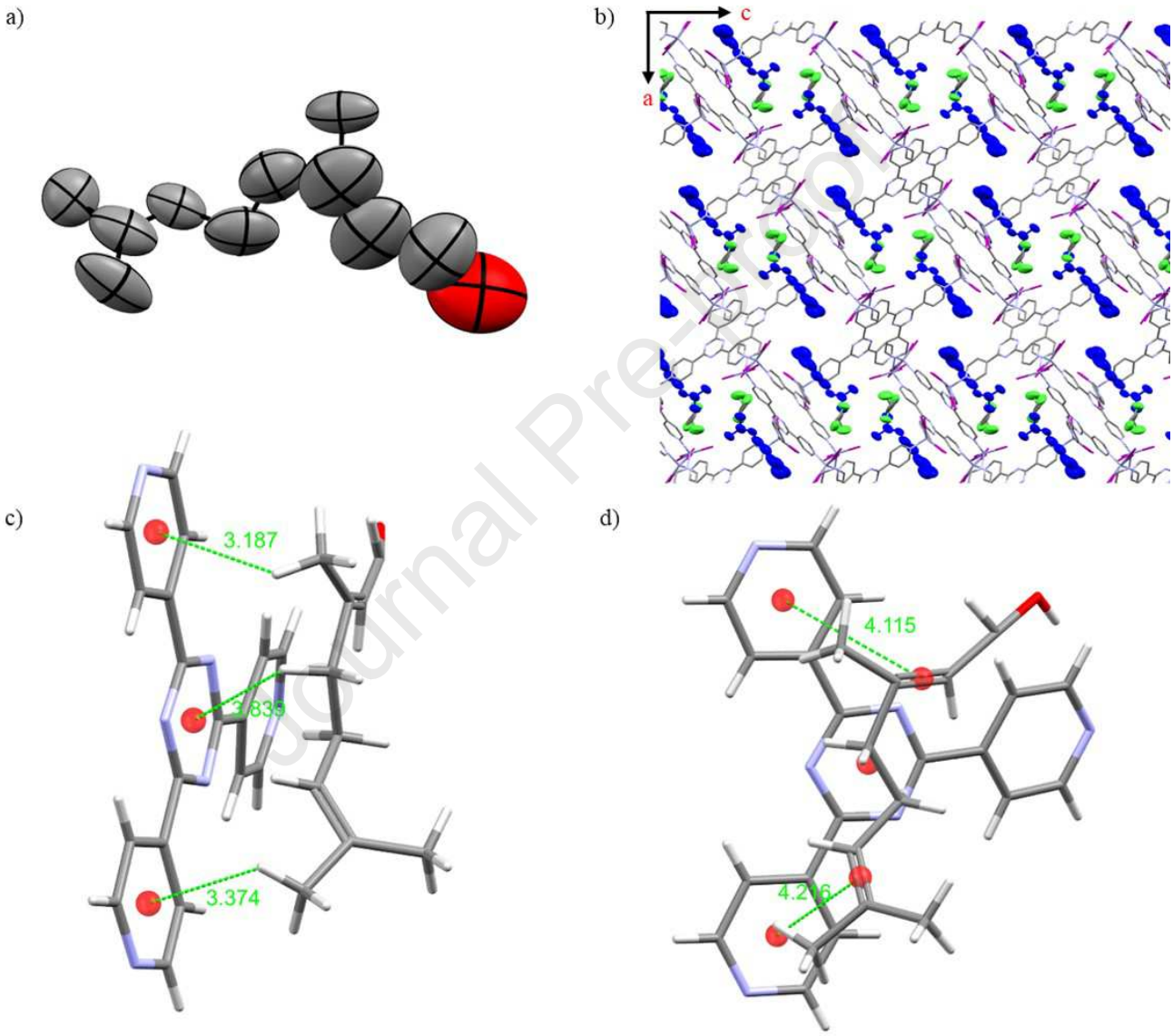
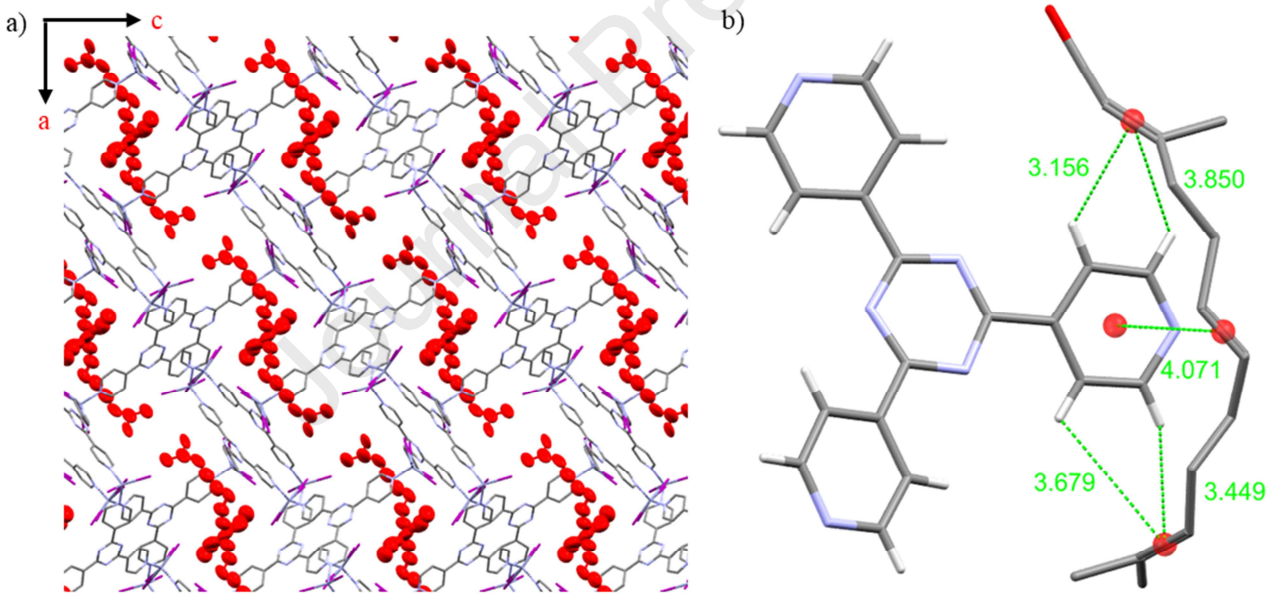


Figure 2. a) Thermal ellipsoids of guest molecule; **b)** Packing diagram of geraniol inclusion complex viewed down the b axis. Framework shown as capped stick model, geraniol as ellipsoids shown in blue colour, residual chloroform in green colour. Hydrogen atoms have been omitted for clarity; **c)** CH-π interactions between part of the host framework and geraniol **d)** π-π interactions of part of host framework and geraniol.

Figure 3. **a)** Packing diagram of farnesol inclusion complex viewed down the b axis. Framework shown as capped stick model, farnesol as ellipsoids shown in red colour, Hydrogen atoms have been are omitted for clarity; **b)** CH-π and π - π interaction between host framework and farnesol.



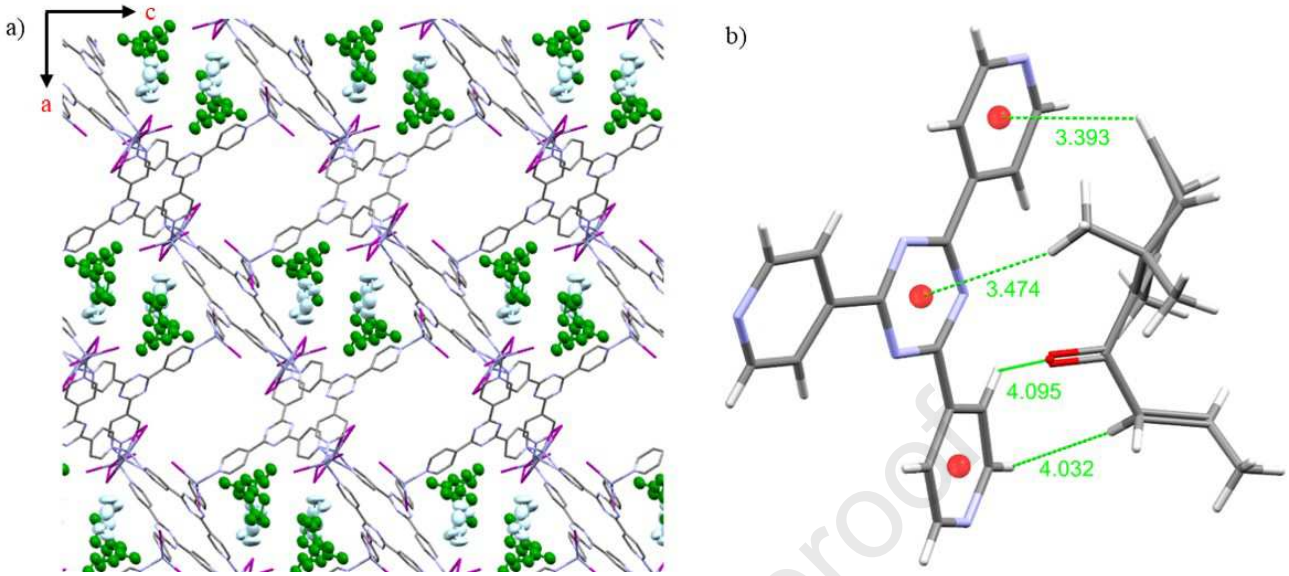


Figure 4. **a)** Packing diagram of β-damascone inclusion complex viewed down the b axis. Framework shown as capped stick model, β-damascone as ellipsoids shown in green colour, residual cyclohexane in light blue colour. Hydrogen atoms have been are omitted **b)** CH-π interaction between host framework and β-damascone.

Captions for the figures in the manuscript

Figure 1: Structures of the guest molecules **a)** geraniol **b)** farnesol **c)** β-damascone.

Figure 2: a) Thermal ellipsoids of guest molecule; **b)** Packing diagram of geraniol inclusion complex viewed down the b axis. Framework shown as capped stick model, geraniol as ellipsoids shown in blue colour, residual chloroform in green colour. Hydrogen atoms have been omitted for clarity; **c)** CH-π interactions between part of the host framework and geraniol **d)** π-π interactions of part of host framework and geraniol.

Figure 3: a) Packing diagram of farnesol inclusion complex viewed down the b axis. Framework shown as capped stick model, farnesol as ellipsoids shown in red colour, Hydrogen atoms have been are omitted for clarity; **b)** CH-π and π - π interaction between host framework and farnesol.

Figure 4: a) Packing diagram of β-damascone inclusion complex viewed down the b axis. Framework shown as capped stick model, β-damascone as ellipsoids shown in green colour, residual cyclohexane in light blue colour. Hydrogen atoms have been are omitted **b)** CH-π interaction between host framework and β-damascone.

Highlights

- Crystalline sponge method provides the opportunity to determine crystalline structure of non-crystalline compounds.
- Terpenes are naturally occurring organic chemicals produced by plants and some insects.
- Structural information on terpenes would be useful in understanding complex cellular processes and help pharmaceutical industries to design new drugs.
- Three novel inclusion complexes through the crystalline sponge method with interesting host-guest interactions.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: