Non-covalent π interactions

Surfing the π-clouds for Non-covalent Interactions: A comparative Study of Arenes versus Alkenes

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Abstract: *A comparative study by NMR spectroscopy using molecular balances indicates that non-covalent functional group interactions with an arene dominate over those with an alkene and a π-facial intramolecular hydrogen bond from a hydroxyl group to an arene is favoured by ~1.2 kJ mol^{-1}. The strongest interaction observed in this study is with the cyano group and analysis of the series of Et, CH=CH$_2$, C≡CH and C≡N groups is indicative of a weak long range electrostatic interaction and a correlation with the electrophilicity of the C^a atom of the Y substituent. Changes in the free energy differences of conformers show a linear dependence on the solvent hydrogen bond acceptor parameter β.*
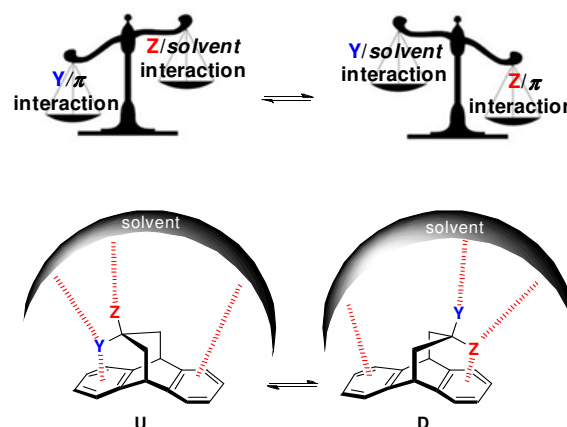
The vital role played by non-covalent interactions, and especially those involving the contribution of aromatic rings to chemical and biological recognition, continues to be a subject of intense research activity.[1] Detailed understanding and quantifiable estimates of the strength, distance, and angular dependence of such intermolecular forces is now considered to be essential, not only for the understanding of protein-ligand interactions and hence for drug design, but also for the synthesis of new asymmetric ligands, catalysts and sensors. In essence, such phenomena as π-stacking,[2] the behaviour of an aromatic ring as a hydrogen bond acceptor,[3] or cation-π interactions[4] can each be viewed as a single "Velcro like hoop and loop" of differing strength, with the combination of several of these then leading to overall binding and molecular recognition. Although a variety of techniques including structural database mining, measurement of gas phase complexes and computational modelling have all contributed to provide valuable insights, the use of designed molecular balances, relying on measurement of a conformational change, has proven to be a particularly powerful tool for obtaining data on the very small interaction energies involved. Moreover, such balances also allow the often dominant influence of solvation to be explored. The molecular torsion balance pioneered by Wilcox[2d,5] has provided the basic framework for many elegant studies which exemplify the quantitative power of this approach, and the results from a significant number of new molecular balances[6] have been summarised in an insightful review by Cockroft.[7]

Within this area, we have previously introduced the dibenzobicyclo[322]nonane framework as a useful probe for the comparative study of arene-functional group interactions in solution through systematic variation of the two substituents Y and Z on the central carbon atom of the bridge and determination of the conformational population, up (U) or down (D), of the more electronegative substituent by NMR. (Figure 1).[8] In this manner, interesting insights, such as the "preference" of a fluorine atom over a hydroxyl group for an aromatic ring, or the arene affinity of sulphur over oxygen were gained. It is important to recognise that this bicyclic scaffold is not a torsional balance but a top pan balance (or seesaw) since, for any given derivative, the influence of Y on the first aromatic ring is being measured against the counterbalancing interaction of Z with the second aromatic ring.

Figure 1. Conformational equilibrium U / D of molecular balances

In sharp contrast to the extensive body of work on aromatic systems however, relatively few studies have quantified non-covalent interactions involving the simplest fundamental π-system of all, an alkene.[9] Thus, even although the existence of π-facial hydrogen bonding of a hydroxyl group to an alkene has been recognised through infrared dilution studies[10] and X-ray

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crystallographic database mining,[10b,10d,11] a quantifiable comparison of such arene versus alkene non-covalent functional group interactions has, to the best of our knowledge, not yet been made. Herein, we now present our preliminary results to establish a basis set with a particular focus on measuring the relative strengths of a π-facial intramolecular hydrogen bond to an arene versus an alkene.

As emphasised in Figure 2 consideration of the requirements for such a comparison leads to the design of four different molecular balances in order that measurements can be made relative to an identical counterbalancing interaction. In the present study for example, a comparison of the OH-arene versus OH-alkene

interaction can only be made either relative to a Y-arene interaction (**1** versus **2**), or to a Y-alkene interaction (**3** versus **4**), but not by comparing the dibenzo derivatives **1** versus the dienes **4**. As in our earlier study, the population p_D of the OH-down conformer was calculated using the observed average coupling constants from NMR spectroscopy (see Supporting Information) and the results for the twenty alcohol and three cyanohydrin derivatives prepared are compiled in Table 1.
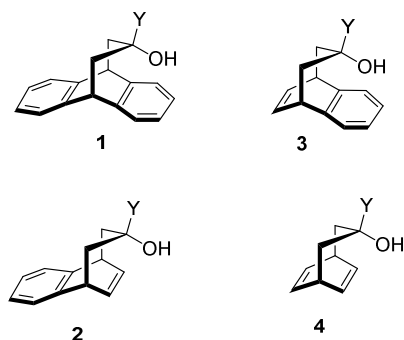

Figure 2. Molecular balances **1** - **4** (Y=H, Me, Et, CH=CH$_2$, C≡CH, C≡N)

A comparison of the results even by simple visual inspection of the conformational population reveals several features of interest. Thus, as expected, the hydroxyl group in all secondary alcohols (**1**-**4**) points towards the solvent, indicating that any π-facial hydrogen bond which can be formed in the second conformation cannot compensate for the Van der Walls radius of oxygen relative to hydrogen. By way of contrast, for all of the tertiary alcohols (Y= Me, Et, CH=CH$_2$, C≡CH) pairwise comparison of (**1**) and (**2**), clearly indicates that the OH...π-arene interaction is observed to a greater extent than the OH...π-alkene interaction. The same trend is also mirrored, but to a much lesser extent, in the pairwise comparison of the set of derivatives (**3**) versus (**4**) and this may be an indication that the counterbalancing Y…π-alkene interaction is much less favourable than the Y…π-arene interaction and decreases in the series Et > Me > CH=CH$_2$ > C≡CH. The fact that this observation is more pronounced in the more polar solvents (to which the hydroxyl group can form a H-bond) may be a consequence of the fact that hydrophobic shielding of the OH group by the aromatic ring is more efficient than by the double bond.

Whilst steric effects can certainly dominate the interaction between an alkyl group and a π-cloud, it is interesting to note that there is also a trend towards an increasing Y…π interaction as a function of the hybridisation of the α-carbon atom with $sp^3 < sp^2 < sp$, as clearly exemplified by the data for the acetylenic alcohols. Remarkably, for the cyanohydrin derivatives, the interactions of both the alkene and the arene with the cyano group completely dominate over any π-facial intramolecular hydrogen bonding from the hydroxyl group, even in non-polar solvents, possibly as a result of the increasing electrophilic character of the sp hybridised carbon atom which is ideally located to benefit from the electron density associated with the π-donors (vide infra). Once again, for all alkyne derivatives and for the cyano group, interaction with the arene is more favourable than with the alkene.

In general terms, the solvent dependence of molecular balances **1** - **4** follows the expected trend with less polar solvents favouring a much higher population p_D of the conformers featuring a π-facial intramolecular hydrogen bond.

Table 1. Populations of the OH-down conformer (p_D, in %, T= 298 K) in molecular balances **1**, **2**, **3** and **4** shown in Figure 2.[a]

	1	2	3	4
**OH	H**				
CDCl$_3$	6.4	4.6	12.7	8.7
C$_6$D$_6$	3.8	3.2	7.1	5.4
CD$_3$CN	0.7	0.8	2.3	0.7
CD$_3$OD	0.0	0.0	0.0	0.0
Py-d_5	1.0	0.9	1.8	0.5
DMSO-d_6	0.3	0.3	0.6	0.2
**OH	Me**				
CDCl$_3$	93.5	92.4	98.8	98.9
C$_6$D$_6$	91.0	88.3	97.9	97.8
CD$_3$CN	76.5	67.9	94.5	93.6
CD$_3$OD	52.2	41.8	86.3	82.4
Py-d_5	46.3	46.3	83.2	82.2
DMSO-d_6	43.4	30.1	77.2	71.2
**OH	Et**				
CDCl$_3$	98.5	95.8	99.5	99.6
C$_6$D$_6$	96.7	95.1	99.3	99.1
CD$_3$CN	88.9	84.6	97.7	97.2
CD$_3$OD	75.9	66.4	94.3	92.9
Py-d_5	77.5	72.5	94.1	93.1
DMSO-d_6	64.4	53.8	89.8	88.2
**OH	CH=CH$_2$**				
CDCl$_3$	93.5	88.6	97.7	97.0
C$_6$D$_6$	91.3	86.9	96.8	96.3
CD$_3$CN	80.0	68.4	92.9	91.0
CD$_3$OD	64.6	53.3	87.0	84.9
Py-d_5	66.4	49.6	84.3	78.1
DMSO-d_6	57.4	39.9	80.2	72.9
**OH	C≡CH**				
CDCl$_3$	50.2	44.3	71.1	68.8
C$_6$D$_6$	39.3	31.1	61.0	58.1
CD$_3$CN	29.8	17.0	53.7	41.1
CD$_3$OD	17.1	9.8	35.5	23.7
Py-d_5	18.8	8.1	29.1	16.8
DMSO-d_6	20.8	11.0	31.4	19.6
**OH	C≡N**				
CDCl$_3$	24.8	17.8	29.1	-
C$_6$D$_6$	20.8	17.5	18.7	-
CD$_3$CN	2.7	1.2	7.5	-
CD$_3$OD	0.0	0.0	0.7	-
Py-d_5	2.0	0.5	-	-
DMSO-d_6	1.2	0.3	0.0	-

[a] Based on the accuracy of NMR J coupling measurements (±0.05 Hz, see Supporting Information), the error in $p_{D\%}$ values is estimated to be within ±0.9%.

For the more polar solvents CD$_3$CN, CD$_3$OD, Py-d_5 and DMSO-d_6 which can form strong but instantaneous hydrogen bonds with the hydroxyl group, the observed changes in $p_D\%$ and $\Delta G°$ (Table S4) correlate very well with the hydrogen bond acceptor parameter β as shown in Figure **3** for the series **1** - **4**, Y = Me (Table S7 provides further data). They do not correlate however with the dielectric constant ε (Table S6), and further detailed scrutiny of the solvation

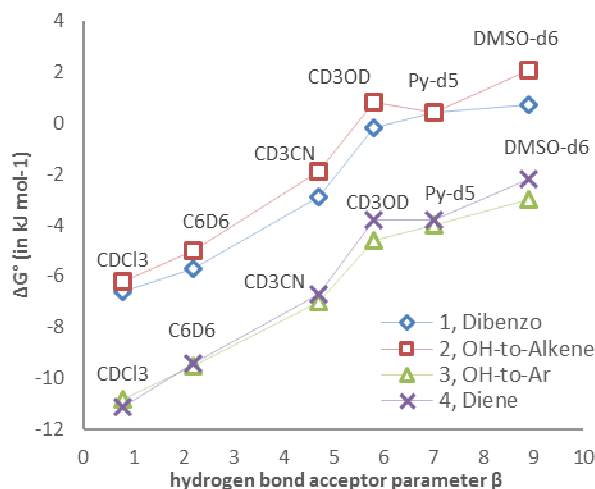data using Hunter's α/β electrostatic solvent competition model will certainly be of interest.[6b,12,13]

Figure 3. Graph of the free energy difference $\Delta G° = - RT \ln (p_D/p_U)$ vs. the solvent hydrogen bond acceptor parameter β for **1 - 4** with Y=Me, Z=OH. For linear fittings, see Table S7 and Figure S5 in Supporting Information.

Whilst inspection of the conformational populations can provide interesting insights, the interplay of the counterbalancing functional groups and a more quantitative estimate of the subtle energy difference can be appreciated by visualisation in the form of a triple mutant box,[14] as exemplified for a comparison of the two sets of tertiary alcohols (Y = Me, **1 – 4** and Y = CCH **1 – 4**) in methanol as solvent (Figure 4). The free energy differences (ΔΔG's) derived by experiment, together with those from theory (*vide infra*) and shown in parenthesis on the twelve edges of the distorted cube, can be grouped into three different subsets.
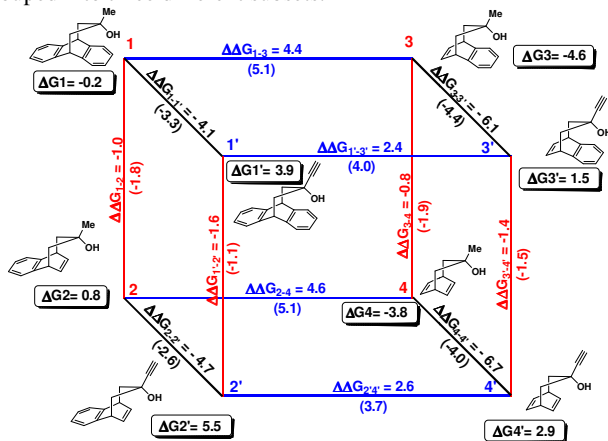

Figure 4. Free energies for **1 - 4** (Y=Me and CCH). Values in parentheses are those computed at the B3LYP+D3/TZVP/SCRF=methanol level.[15]

Thus, the differences in free energy between a π-facial intramolecular hydrogen bond to an arene and to an alkene are shown on the red edges, and, even although they have been measured relative to four different molecular fragments, consistently reveal, that the OH…π arene interaction is the stronger by approximately -1.2 kJ mol⁻¹ on average. The unfavourable interactions of Y with an alkene relative to an arene are shown in blue with those for the methyl group (+4.4 and 4.6 kJ mol⁻¹) being considerably higher than for the terminal alkyne (2.4 and 2.6 kJ mol⁻¹) as noted earlier. Finally, as shown in black, the replacement of the methyl group by the terminal alkyne is favoured, both for Y…π

arene interactions (-4.1 and -4.7 kJ mol⁻¹) and even moreso for Y…π alkene (-6.1 and -6.7 kJ mol⁻¹).

Throughout our studies, the interplay of theory and experiment has always proven to provide additional insight, particularly since a molecular balance is particularly suited for computational calculation, due to considerable cancelation of systematic error in the method. Using our recently reported method[16] which minimises basis set superposition errors (BSSE) and includes dispersion terms and zero point and entropic corrections using vibrational partition functions through evaluation of solvation corrections using continuous solvent models the calculated free energy differences[17] ΔΔG's as defined in Figure 4 are in good agreement with experiment, with a mean error of 1.1 kJ mol⁻¹. It should be noted that use of the continuum model alone for solvation leads to excessive overestimation of the D conformer by 8-12 kJ mol⁻¹. A very good match with experiment, for the ''anomalous'' behaviour of methanol shown in Figure 3 can however be obtained when a model incorporating three explicit methanol molecules is used.[17]

DFT calculations have proven of value in understanding the interactions of unsaturated groups with arene and alkenes. Thus, for the vinyl group, as shown in Figure 5, the preferred conformation is indicative, either of an incipient CH...π[18] interaction or an electrostatic interaction with the sp^2 hybridised carbon atom. As expected, face to face π-stacking is disfavoured.
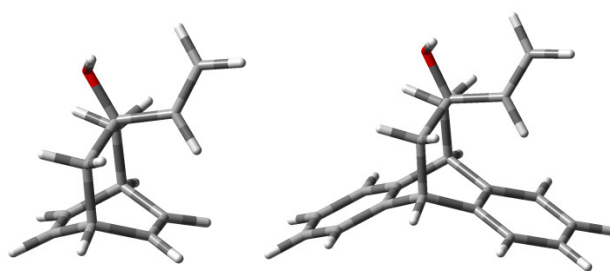

Figure 5. Geometries of **4**U-OH,CH=CH₂ (left) and **1**U-OH,CH=CH₂ (right) from DFT M06-2X/6-31+G(d) calculations. Geometries at the B3LYP+D3/TZVP level can be viewed interactively.[17]

It is, in principle, possible that the C-H...π interaction is stronger for the sp^2 C-H bond compared to the sp^3 C-H bond. However, further increase of the p_U values in molecular balances **1 - 4** for Y = C≡CH and C≡N compared to the CH=CH₂ group (Table 1) is in favour of a simple electrostatic type interaction between the C^α atom of the Y substituent and the π-acceptor, as the C^α atom becomes more positive on moving from left-to-right in the sequence of substituents $\underline{C}H_2CH_3$, $\underline{C}H=CH_2$, $\underline{C}≡CH$ and $\underline{C}≡N$. From our preliminary NBO analysis of M06-2X/6-31+G(d) calculations of **1**U conformers, the natural charges (q_C, in a.u.) of the C^α atoms are -0.49, -0.25, -0.04 and +0.31 in CH₂CH₃, CH=CH₂, C≡CH and C≡N, respectively. The corresponding energetic characteristics, ΔG° values in CDCl₃ (Table S4), show a satisfactory linear dependence (Figure S4) on these q_C values with $r^2 > 0.9$. This is in agreement with the known linear dependence of the energy of the electrostatic interaction on the charge ($E \sim q_1 q_2 / r$, where r is the distance between charges q_1 and q_2). These findings support the presence of long range (r^1 dependent) electrostatic C...π-interactions, although further investigations are required to verify the significance of the electrostatic and other interactions.

The non-covalent origin of these free-energy differences can also be visualised by employing the appropriately termed and recently introduced[19] NCI (non-covalent-interaction) topological analysis (Figure 6). This analysis presents a view filtered by the

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value of the electron density to reveal only the properties of the non-covalent regions, and in this region a reduced-density gradient isosurface is colour-coded to expose stabilising regions as blue or green and weakly repulsive regions as yellow (or red). The system Z=OH, Y=CCH nicely illustrates this approach, in which the interaction between the OH group and the face of a benzo group is rendered as blue, counterbalanced by a weaker (green) surface when the alkyne group interacts with a benzo group, but now revealing a second smaller region which is not observed when the alkyne group is replaced by a methyl group.
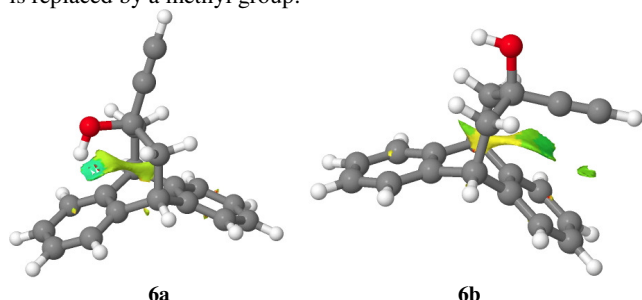

6a   **6b**

Figure 6. NCI surfaces[17] for Z=OH, Y=CCH, illustrating (a) the attractive NCI region between the OH group and the face of the benzo ring and (b) the weaker attractive region between the CCH group and the benzo face, revealing two distinct attractive regions.

An alternative and more quantitative representation of the stabilizing effect of these pendant groups is by analysis of the localized natural-bond-orbitals (NBOs). It is important to use localized orbitals, which allows each ring to be clearly differentiated from the other (molecular orbitals are delocalized over both benzo rings). Thus for the system Z=OH, Y=Me, the three highest energy NBOs can be associated with the benzo group lacking an interacting OH group (Figure 7a), whilst the next three NBOs (Figure 7b) are all electrostatically stabilized by 8-16 kJ relative to the first three due to the proximity of the OH.
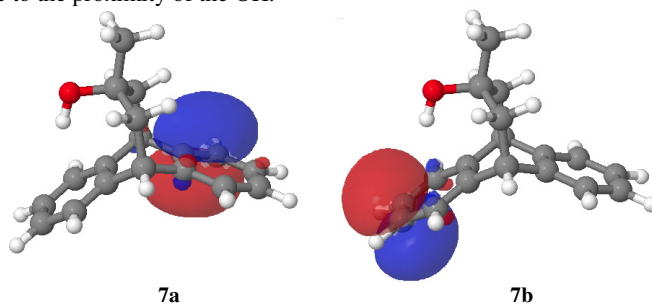

7a   **7b**

Figure 7. NBOs[17] computed for Z=OH, Y=Me for (a) the highest –energy NBO *exo* to the OH group and (b) the highest energy NBO *endo* to the OH group.

Other molecular isosurfaces such as MEPs (molecular electrostatic potential) can also be used to reveal discrimination between the effects of the non-covalent interactions.[17]

In conclusion, the forgoing results have provided quantitative data to demonstrate that a π-facial intramolecular hydrogen bond from a hydroxyl group to an arene is stronger than that to an alkene. The discovery of the remarkable behaviour of the cyano group, in forming an even stronger interaction than the hydroxyl group both for an arene and an alkene, is reminiscent of an incipient cation-π interaction, and certainly worthy of consideration for π-facial discrimination in drug and catalyst design. Interestingly, comparative analysis of data for Y = CH_2CH_3, $CH=CH_2$, $C≡CH$ and $C≡N$ groups is indicative of a weak long range electrostatic type of C...π interaction with the C^α atom of the Y substituent and the π-system.

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