Desolvation tips the balance: solvent effects on aromatic interactions†

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The folding behaviour of the molecular torsion balance framework is rationalised by considering the effects of solvation using the *α*/*β* H-bond parameter scheme for estimating the free energies of pairwise functional group interactions in solution.

Solvent can have an enormous effect on reaction rates and chemical equilibria,[1] but our models for the molecular basis for these phenomena are not well-developed. Rather general properties like polarity or dielectric constant are usually used to classify solvents and rationalise their effects on chemical processes.[2] Detailed analyses of solvation phenomena rely on correlations of the observable with a large number of empirical solvent descriptors to generate a predictive model.[3] We recently proposed an approach that treats solvent effects on molecular interactions as the sum of pairwise intermolecular interactions that can be quantified using two parameters (α and β) to estimate the free energy of intermolecular functional group interactions (Fig. 1).[4]

$$\Delta\Delta G = -(\alpha - \alpha_S)(\beta - \beta_S) \qquad (1)$$

where α and β are the H-bond parameters of the interacting functional groups, and α_S and β_S are the corresponding parameters for the solvent.

Here, we apply this approach to the 'molecular torsion balance' originally developed by Wilcox for the quantification of aromatic interactions (Fig. 2).[5] In this system, a single bond rotation allows the molecule to adopt one of two conformations, designated the unfolded (Fig. 2(a)) and the folded state (Fig. 2(b)). The folded state contains an additional well-defined aromatic edge-to-face contact, and the position of the folding equilibrium (as determined by integration of slow exchange signals in the ^{1}H NMR spectrum) provides a direct quantitative measurement of the free energy contribution of this interaction. By changing the X and Y substituents, it has been possible to quantify the effects of substituents on the position of the folding equilibrium. Variation of the electronic properties of the 'face' aromatic ring by changing the X-substituent did not influence the position of equilibrium significantly in chloroform solution. When the 'edge' aromatic group was replaced by aliphatic esters (*e.g. i*-propyl) the population of the folded state increased. Based on these observations, Wilcox concluded that "…the electrostatic potential of the aromatic ring is *not* a dominant aspect of the aryl–aryl interaction. The results should encourage increased emphasis on the importance of London dispersion forces…", and subsequent theoretical studies supported this assertion.[6]

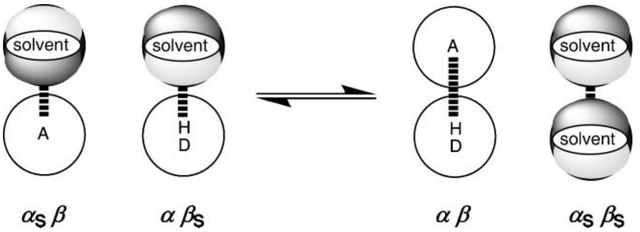

Fig. 1 The free energy of interaction between two functional groups (DH and A) in a solvent (S) can be estimated by considering the interactions in the free (solvated) and bound states.

However when Diederich harnessed the 'molecular torsion balance' framework for the experimental measurement of the interaction between organic fluorine and an amide group, he found something very different.[7] The folding free energies of a series of compounds where Y = CF_3 correlated linearly with the Hammett *meta*-substituent constants as X was varied. The conclusion was that "…the primary CH–π interaction follows a well-behaved continuum that depends on the electronic properties of the 'face' component…", *i.e.* electrostatic effects dominate the folding equilibrium in this system. So, the question is raised: how can the behaviour of such a simple system appear to be controlled by electrostatic effects in some cases, and not in others? One possibility is that desolvation holds the key to understanding the behaviour of these systems, because the Diederich measurements were made in benzene rather than chloroform. We have therefore analysed the torsion balance data using the *α*/*β* functional group interaction parameters, where α is the H-bond donor parameter for the edge ring, and β is the H-bond acceptor parameter for the face ring.

Equation (1) was derived from studies on simple 1 : 1 H-bonded complexes in carbon tetrachloride, and it is not immediately obvious how the equation can be applied to a more complex

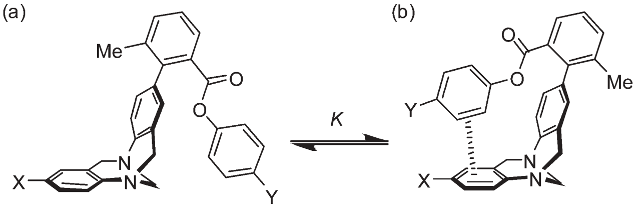

Fig. 2 The 'molecular torsion balance' developed by Wilcox for the quantification of aromatic interactions; (a) the unfolded (free) state, (b) the folded (bound) state which contains an additional edge-to-face aromatic interaction.

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system like the torsion balance, where there are multiple contacts over a larger surface area. The pragmatic approach is simply to look for correlations between the experimental free energies and the α/β parameters in the hope of obtaining some insight into how they can be applied. In this case, the properties of one of the interacting partners (the π-electron density on the face ring, *i.e.* β) has been varied in a systematic way, so we can rearrange Equation (1) to give:

$$\Delta\Delta G = -(\alpha - \alpha_S)\,\beta + c \qquad (2)$$

Fig. 3 shows plots of $\Delta\Delta G$ *versus* β for the Wilcox and Diederich experiments. The plots are not significantly affected by correcting for the small population differences that have been observed for methyl ester control compounds, so the uncorrected experimental $\Delta\Delta G$ values are used here. The β values were obtained from AM1 calculations of the molecular electrostatic potential surfaces at the centre of the face ring.‡ Fig. 3 shows quite clearly that there are almost no electrostatic effects in the Wilcox experiment and that there is a clear correlation with the H-bond acceptor parameter β in the Diederich system. However, viewed through the eyes of Equation (2), we can see the origin of this apparent discrepancy. In the Wilcox experiment, $(\alpha - \alpha_S) = 0.3$, whereas in the Diederich experiments $(\alpha - \alpha_S) = 1.7$. The substituents Y and solvents both differ. The Wilcox results imply that the edge of a phenyl ester group (Y = H) has similar H-bond donor properties to chloroform. The Diederich results imply the edge of the trifluoromethyl substituted phenyl ester is a significantly better H-bond donor than benzene. Thus we have a simple rationale for the behaviour of the two systems: electrostatic interactions between solutes that are less polar than the solvent are washed out by the effects of desolvation, but electrostatic interactions between the solutes dominate in solvents that are less polar than the solutes. It has previously been suggested that the role of the solvent on the folding equilibrium is small or favours the unfolded state to some extent.[5,6,8] The analysis presented here demonstrates that the folding of the molecular torsion balance is in fact dominated by the effects of desolvation in chloroform solution.

The magnitudes of the slopes of the correlations in Fig. 3 provide a clue to the relationship between edge-to-face aromatic interactions and conventional H-bonds. The value of α_S for chloroform is 2.2 (based on experimental data), and we can estimate the values for benzene, a simple phenyl ester and a trifluorophenyl ester using AM1 molecular electrostatic potential surfaces: α = 1.0, 1.0 and 1.8 respectively. The only way to square these parameters with the experimental values of $(\alpha - \alpha_S)$ is to assume that the face ring makes one H-bond with a chloroform molecule, whereas the edge-to-face aromatic interactions in the folded torsion balance as well as solvation of the face ring by benzene involve two CH–π H-bonds. Inspection of the X-ray crystal structure of the torsion balance indicates that there are indeed two close CH–π contacts between the aromatic groups involved in the edge-to-face interaction (Fig. 4(a)). Thus for interactions with another aromatic ring, the value of α for an aromatic CH is effectively doubled to account for the two-point interaction. The result is a large slope for the trifluoromethyl phenyl ester in benzene and a small slope for the phenyl ester in chloroform. Orozco has attributed the trends in chloroform to a change in the geometry of the interaction as the substituent X changed, but desolvation provides a more general explanation for the behaviour of these systems.[6]

One of the striking findings of Wilcox's original experiments was that the interactions with *i*-propyl groups were stronger than the interactions with the edge of an aromatic ring, despite the lower polarity of alkyl *versus* aryl protons. Fig. 4(b) suggests a possible explanation. In the folded state of the *i*-propyl ester torsion balance, energy minimisations suggest that the *i*-propyl group prefers to orient a methyl group directly towards the centre of the face aromatic ring making three CH–π contacts. The additional CH–π contact could account for the increase in interaction free energy for alkyl groups compared with aryl groups in chloroform.

The key revelation from this analysis is that in benzene, the solvent is less polar than the edge of a *p*-trifluoromethylphenyl ester ring, so the trend in folding free energy is dominated by the properties of the edge-to-face aromatic interaction. In chloroform, the solvent effectively has the same H-bond donor properties as a phenyl ester or *i*-propyl ester group, so the interactions are independent of the properties of the face ring. A second important observation is that for interactions with extended surfaces, such as the face of an aromatic ring, different functional groups may present different numbers of binding partners. Thus chloroform can only make one H-bond to the face of an aromatic ring, whereas aromatics make two H-bonds in an edge-to-face interaction and methyl groups can make three H-bonds. Thus

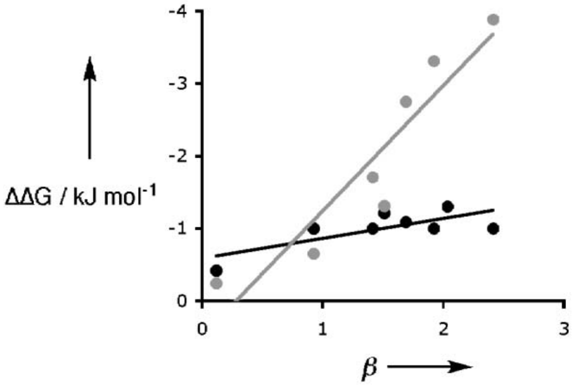

Fig. 3 The experimental edge-to-face aromatic interaction free energies plotted as a function of β of the face ring (grey: Y = CF_3 in benzene, black: Y = H in chloroform). The best fit straight lines are shown.

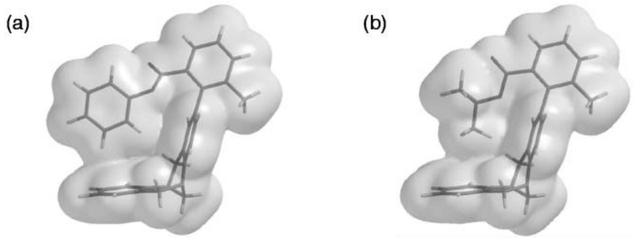

Fig. 4 AM1 molecular surfaces of models of (a) phenyl ester and (b) *i*-propyl ester torsion balance molecules. Models were built from a crystal structure (X = Me and Y = NO_2) by deleting X and Y (a) and replacing the phenyl group with an isopropyl group constructed using standard bond lengths and angles (b).

we can rationalise the apparently contradictory behaviour of a range of different systems based on electrostatic interactions and the effects of desolvation, without the need to invoke differences in dispersion interactions that should cancel out for molecular surfaces that fit well together.[4] Clearly as solvents and molecular systems become more complicated, the simple model described in this work will become more difficult to apply, but correlations with the α/β scale provide a straightforward approach that may help to rationalise the molecular basis for the properties and behaviour of a variety of chemical systems.

Notes and references

‡ The experimental data show a significantly better correlation with DFT/B3LYP/6-31G* electrostatic potential surfaces (see Supplementary Material), but the AM1 derived parameters are used here for consistency with previous work.

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