π-Stacking Hot Paper

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Dissection of the Polar and Non-Polar Contributions to Aromatic Stacking Interactions in Solution

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Abstract: *Aromatic stacking interactions have been a matter of study and debate due to their crucial role in chemical and biological systems. The strong dependence on orientation and solvent together with the relatively small interaction energies have made evaluation and rationalization a challenge for experimental and theoretical chemists. We have used a supramolecular cage formed by two tris(pyridylmethyl)amines units to build chemical Double Mutant Cycles (DMC) for the experimental measurement of the free energies of π-stacking interactions. Extrapolating the substituent effects to remove the contribution due to electrostatic interactions reveals that there is a substantial contribution to the measured stacking interaction energies which is due to non-polar interactions (−3 to −6 kJ mol^{-1}). The perfectly flat nature of the surface of an aromatic ring gives π-stacking an inherent advantage over non-polar interactions with alkyl groups and accounts for the widespread prevalence of stacking interactions in Nature.*

Introduction

The nature of the π–π interaction has been one of the more important playgrounds for physical organic chemists.[1–3] Aromatic interactions are implicated in many synthetic and biological processes, and a number of different approaches have been used to rationalize the thermodynamic properties. A range of different supramolecular systems have been developed to experimentally quantify the relationship between chemical structure, three-dimensional structure, and interaction energy in solution,[4–12] and many theoretical investigations have been reported on idealized systems in the gas phase.[13–20] Experimental measurements of aromatic interaction energies in solution show that both electrostatic interactions with the π-electron density and dipole interactions between substituents are important in determining the overall interaction energy (Figure 1).[7,18] These observations confirm the predictions of the simple point charge models developed by Hunter and Sanders to understand the nature of π–π interactions.[1] For example, Figure 1c shows that although repulsion between the π-electron densities is reduced when the substituents are electron-withdrawing, the stacking interaction is only attractive in Orientation 2, because in Orientation 1 there are repulsive electrostatic interactions between the substituents. This view has subsequently been confirmed using higher level theory.[13,16,22] In addition, theoretical studies, which are usually carried out in the gas phase, emphasize the important contributions of dispersion or non-polar van der Waals interactions.[17] In solution, there is a competition between solvent–solvent and solvent–solute interactions, which means that dispersion contributions to intermolecular interaction energies are largely attenuated or cancel out.[23–25] Herein, we describe experimental measurements that demonstrate that in the case of aromatic stacking this cancellation is incomplete and that non-polar interactions do make a significant energetic contribution to solution phase interactions.

Substituent effects on aromatic interactions have been successfully correlated with the substituent Hammett σ parameter for many different systems.[6,10,11,26–30] The value of σ quantifies the overall effect of a substituent on the electronic properties of an aromatic ring, including both through-space electrostatic effects and through-bond resonance and inductive effects.[31,32] An analysis of substituent effects on bicyclo[2.2.2]octane-1-carboxylic acids showed that electric field effects in non-aromatic systems are also well-described

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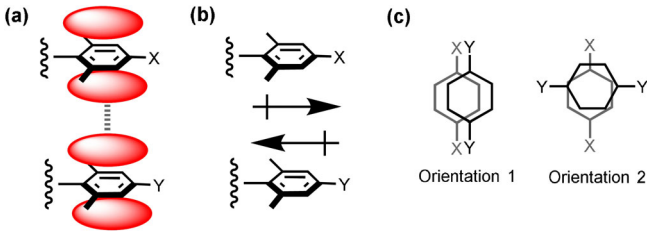

Figure 1. Electrostatic interactions between aromatic rings in a stacked geometry. a) Interactions between the two π-electron densities. b) Interactions between the overall dipoles of the two π-systems. c) Interactions between the substituents. If both substituents X and Y are electron-withdrawing, repulsion between the π-electron densities is reduced. Orientation 1 is unfavorable, due to repulsive interactions between the substituents. Repulsion between the substituents is reduced in Orientation 2, leading to a net attractive interaction. Adapted from Hunter and Sanders (1990) and Carver et al. (1998).[1,21]

by the Hammett σ_m parameter.[33] Here we use a Hammett analysis of substituent effects on aromatic stacking interactions to extrapolate the electrostatic contributions to zero and thereby measure the residual non-polar contribution to the total interaction energy.

We recently described an experiment to quantify aromatic stacking interactions inside supramolecular cages made from dimers of tris(pyridylmethyl)amine.[34–36] Two zinc ions coordinated to the ligands provide sites for binding carboxylate ions inside the cavity of the cage. When benzoic acid guests are used, the aromatic rings of the two guests are forced into a stacked geometry (Figure 2). By measuring the relative stabilities of complexes formed with two different guests, it is possible to construct chemical Double Mutant Cycles (DMC) to measure the free energy contribution due to this aromatic stacking interaction (Figure 3).[28,29,37–40] The difference between the stabilities of complexes A and B in Figure 3 ($\Delta G°_A - \Delta G°_B$) measures the aromatic interaction together with contributions from any secondary effects, such as differences in the acidities of the guests, interactions between the guests and the cage walls, and substituent effects on the strength of the zinc–carboxylate interaction. The net contribution from these secondary effects is quantified by the difference between the stabilities of complexes C and D ($\Delta G°_C - \Delta G°_D$). Thus the DMC makes it possible to dissect out the thermodynamic contribution of the aromatic interaction between the two guests in complex A ($\Delta\Delta G°_{expt}$) from all of the other interactions that are present in these relatively complex systems.

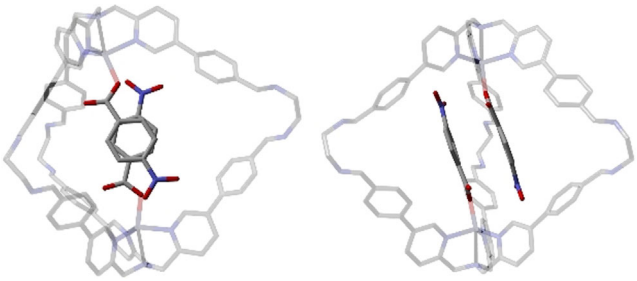

Figure 2. Aromatic stacking interactions between two *p*-nitrobenzoate guests bound inside the cavity of a supramolecular cage complex (grey). Adapted from the structure reported in reference minimized using DFT (ωB97XD/6-31G(d)).[34]

Results and Discussion

The supramolecular approach to the construction of complexes for DMC measurement of aromatic stacking interactions is particularly versatile for a number of reasons:

1. the rigidity of the cage ensures a well-defined geometry that does not change from one complex to another,
2. the aromatic rings are forced together by the much stronger coordination bonds, so that both attractive and repulsive stacking interactions can be measured,
3. the complexes are all in slow exchange on the ^{1}H NMR timescale, which means that signal integration can be used to achieve high precision in the measurement of free energies,

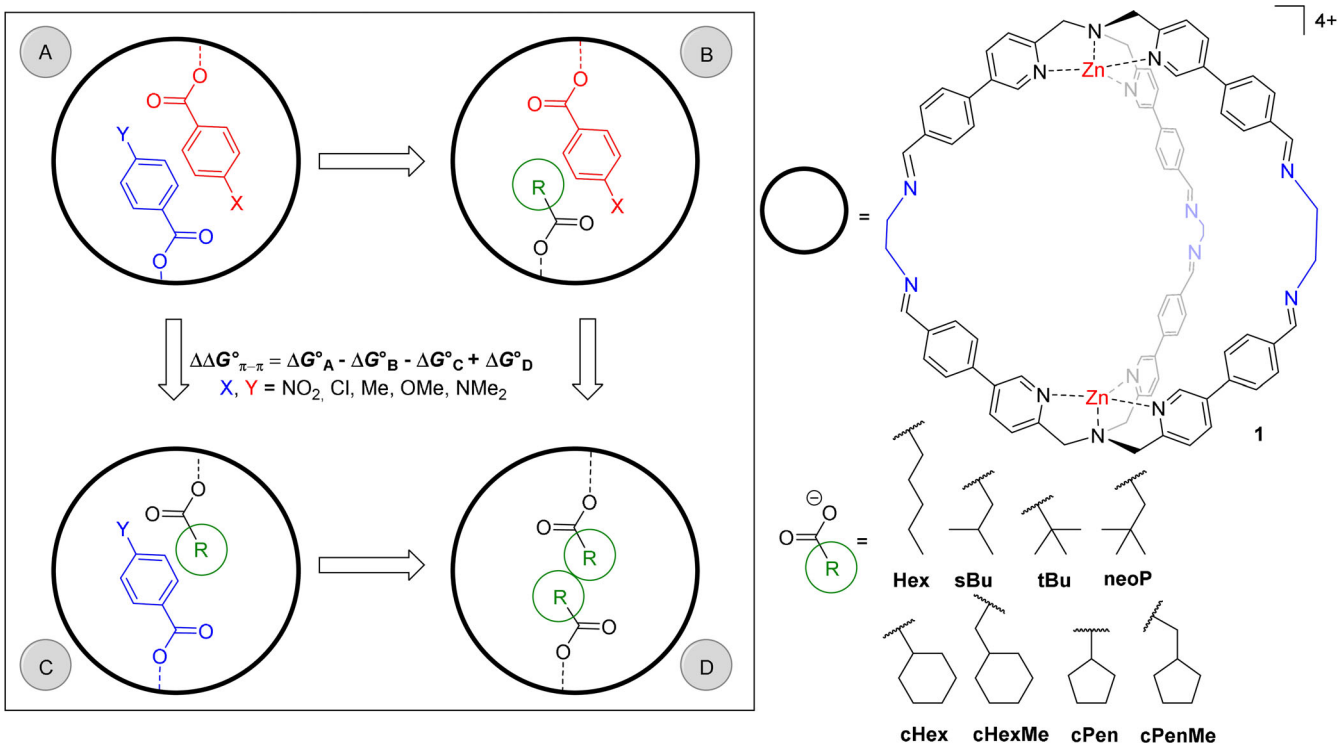

Figure 3. Chemical DMC for measuring the π-stacking interactions. Counterions are perchlorates for the cage and triethyl ammonium for the guests and they are omitted for clarity.

4. a wide range of different interactions are accessible simply by mixing the relevant benzoic acids, avoiding the need for synthesis.

Here we demonstrate this versatility by measuring 120 aromatic stacking interactions using the DMC approach shown in Figure 3. For interactions in solution, there is always a competition between desolvation and the interaction of interest. One of the interesting features of the DMC in Figure 3 is that the interactions that compete with the stacking interaction in Complex A are interactions with the R groups of the alkyl carboxylic acids in Complexes B, C, and D. The R groups in effect represent the solvent in which the aromatic interaction is measured (Figure 4).[41] Although all of the experiments were carried out in acetonitrile, any free energy contributions due to desolvation of acetonitrile from the aromatic rings cancel out in the DMC. For example, formation of complexes A and B in Figure 3 in both cases involves displacement of acetonitrile from the face of the red aromatic ring, but these free energy changes are subtracted in the DMC. Similarly, acetonitrile is displaced from the face of the blue aromatic ring on formation of complexes A and C, so these free energy contributions are also removed by the DMC. Thus the supramolecular cage complexes provide an opportunity to investigate how changing the effective solvent affects the stacking interactions, because the R group, which replaces the acetonitrile solvent on formation of the cage complexes, is a variable that is built into the experiment. Figure 3 shows the 8 different R groups that were chosen for investigation: *n*-hexanoate **Hex**, isovalerate **sBu**, pivalate **tBu**, 3,3-dimethylbutyrate **neoP**, cyclohexanecarboxylate **cHex**, cyclohexaneacetate **cHexMe**, cyclopentanecarboxylate **cPen**, and cyclopentaneacetate **cPenMe**.

Acetonitrile is a weakly solvophobic solvent (cohesive energy density of 139 cal cm^{-3}), and it is possible that the relative binding affinities of different carboxylates inside the cage complex are influenced by differences in size.[42] This solvophobic contribution would be particularly important when comparing the results obtained with different R groups, which vary significantly in volume (from 92 Å^3 for **sBu** and **tBu** to 136 Å^3 for **cHexM**). However, the DMC experiment removes any potential free energy contributions due to solvophobic effects. For example, Figure 3 shows that the R group appears once in complex B, once in complex C, and twice in complex D. Each of these binding events will be associated with a free energy contribution due to desolvation of acetonitrile from the R group when it enters the cage. In the DMC, the free energy changes for formation of complexes B and C, which each include a contribution due to desolvation of one R group, are both subtracted from the free energy change for formation of complex D, which includes a contribution due to desolvation of two R groups. Similarly, solvophobic free energy contributions due to binding of the aromatic groups inside the cage complex always appear in pairs with opposite signs in the DMC, so that they always cancel.

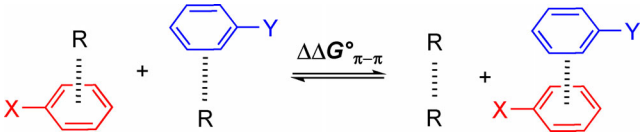

Figure 4. The DMC in Figure 3 measures the interaction between two stacked aromatic rings in an effective solvent defined by the R group of the alkyl carboxylic acid.

Experiments were carried out using 15 combinations of benzoic acids with different X and Y groups (NO_2, Cl, Me, OMe, and NMe_2) and 8 different alkyl carboxylic acids, as indicated in Figure 3. ^{1}H NMR titration experiments were performed adding sub-stoichiometric amounts of each combination of acids to the preformed cage. Under these conditions, it was possible to observe the empty cage, two cage complexes containing one of the two different carboxylic acid guests, and three different cage complexes containing two carboxylic acid guests (viz. one hetero- and the two homo-complexes), all in slow exchange on the ^{1}H NMR timescale. Integration of signals allowed direct measurement of the concentrations of the empty cage and the 2:1 complexes, and hence the equilibrium constants required for construction of the DMC in Figure 3 (see SI for details).

The results are summarized in Table 1. The aromatic stacking interactions are most attractive (−4.3 kJ mol^{-1}) when X and Y are both electron-withdrawing nitro groups and most repulsive (+2.5 kJ mol^{-1}) when X and Y are both electron-donating dimethylamino groups. This result suggests that the substituent effects on the stacking interactions are dominated by the unfavourable electrostatic interaction between the two π-electron densities, which is minimized for electron-withdrawing substituents and maximized for electron-donating substituents.

However, this rationalization does not explain why the interaction between two nitroaromatics is actually attractive, which suggests that non-polar interactions also play an important role in the observed behaviour. In addition, there are significant variations in the stacking interaction energies as a function of the aliphatic R group, the effective solvent. For example, the most repulsive stacking interaction, which was found for two dimethylaminoaromatics, falls from +2.5 kJ mol^{-1} in an effective solvent of *tert*-butyl groups **tBu** to +0.8 kJ mol^{-1} in an effective solvent of cyclopentylmethyl **cPenM** groups. These differences are well outside the experimental error (±0.3 kJ mol^{-1}), and there are consistent trends across the entire dataset in Table 1.

A Hammett analysis was used to separate the contributions due to polar electrostatic interactions from the contributions due to non-polar interactions. For each substituent X in a particular effective solvent R, the measurements in Table 1 were plotted against the Hammett substituent parameter σ_p for Y. The slopes and intercepts of these linear correlations also correlate with the Hammett substituents parameters for each substituent X in a particular effective solvent R with an average R^2 of 0.90 (See Supporting Section 3.5).

These correlations were used to derive Equation (1), and the corresponding values of the constants *a*, *b*, *c*, and *d* are listed in Table 1.

Tabelle 1: Free energy contributions ($\Delta\Delta G°_{expt}$ in kJ mol^{-1}) from aromatic stacking interactions measured using DMCs, and the corresponding constants obtained by fitting these data to Equation (1).

Substituents		Solvating Group (R)							
X	Y	Hex	sBu	tBu	neoP	cHex	cHexM	cPen	cPenM
NO_2	NO_2	-2.8±0.1	-3.1±0.1	-2.4±0.2	-3.1±0.6	-3.9±0.1	-4.3±0.1	-4.0±0.1	-4.1±0.2
	Cl	-2.1±0.3	-1.9±0.1	-1.9±0.2	-2.0±0.5	-2.7±0.1	-3.2±0.1	-2.9±0.1	-3.1±0.1
	Me	-1.9±0.2	-1.9±0.1	-1.8±0.2	-1.9±0.5	-2.7±0.1	-3.0±0.1	-2.8±0.1	-3.0±0.1
	OMe	-1.8±0.1	-1.9±0.1	-1.5±0.1	-1.7±0.4	-2.7±0.1	-3.0±0.1	-2.8±0.1	-3.0±0.1
	NMe_2	-1.2±0.1	-1.4±0.1	-0.8±0.2	-1.4±0.3	-2.2±0.1	-2.5±0.1	-2.1±0.1	-2.5±0.1
Cl	Cl	-1.7±0.1	-1.5±0.1	-2.1±0.2	-1.6±0.2	-2.4±0.1	-2.9±0.1	-2.6±0.1	-2.9±0.1
	Me	-1.0±0.1	-0.6±0.1	-1.2±0.2	-0.6±0.3	-1.5±0.1	-1.9±0.1	-1.6±0.1	-2.0±0.1
	OMe	-0.5±0.3	-0.5±0.1	-0.6±0.2	-0.1±0.2	-1.1±0.1	-1.5±0.1	-1.3±0.1	-1.6±0.1
	NMe_2	-0.1±0.2	+0.9±0.1	0.0±0.2	0.0±0.2	-0.8±0.2	-1.2±0.1	-0.7±0.1	-1.3±0.1
Me	Me	-0.9±0.1	-1.0±0.1	-1.4±0.1	-0.7±0.4	-1.8±0.1	-2.0±0.1	-1.8±0.1	-2.1±0.1
	OMe	-0.5±0.1	-0.5±0.1	-0.7±0.1	-0.1±0.3	-1.3±0.1	-1.5±0.1	-1.4±0.1	-1.7±0.1
	NMe_2	+0.8±0.2	+0.9±0.1	+0.9±0.2	+1.0±0.2	+0.1±0.1	-0.2±0.1	+0.2±0.1	-0.4±0.1
OMe	OMe	0.0±0.2	-0.3±0.2	-0.2±0.1	+0.2±0.2	-1.1±0.1	-1.3±0.1	-1.2±0.1	-1.5±0.1
	NMe_2	+1.0±0.1	+0.9±0.1	+1.2±0.2	+1.2±0.1	+0.1±0.1	-0.1±0.1	+0.2±0.1	-0.3±0.1
NMe_2	NMe_2	+2.0±0.3	+2.1±0.1	+2.5±0.3	+2.1±0.1	+1.3±0.3	+1.0±0.1	+1.6±0.1	+0.8±0.3
Eq.1 Constants									
a		0.69±0.01	0.67±0.02	0.70±0.01	0.72±0.05	0.68±0.01	0.68±0.00	0.70±0.02	0.69±0.02
b		-1.54±0.04	-1.49±0.07	-1.45±0.03	-1.56±0.32	-1.48±0.14	-1.55±0.05	-1.60±0.01	-1.41±0.21
c		-1.54±0.04	-1.49±0.07	-1.45±0.03	-1.56±0.32	-1.48±0.14	-1.55±0.05	-1.60±0.01	-1.41±0.21
d		-1.25±0.27	-0.84±0.06	-0.81±0.35	-0.74±0.65	-1.66±0.12	-2.00±0.07	-1.70±0.04	-2.04±0.04

$$\Delta\Delta G^{\circ}_{expt}(\mathrm{kJ\,mol^{-1}}) = a\sigma_X\sigma_Y + b\sigma_X + c\sigma_Y + d \quad (1)$$

Here, σ_X is the Hammett substituent parameter σ_p for X, and σ_Y is the Hammett substituent parameter σ_p for Y.

The values of a, b, and c are practically independent of the R group, which confirms that these aliphatic groups do not make significant electrostatic interactions with the aromatic rings. The value of the constant d does however vary significantly with the solvating R group. Figure 5 illustrates how well the 120 experimental measurements of aromatic stacking energy are described by Equation (1) using the average value of $a = 0.69$, the average value of $b = c = -1.50$, and a different value of d for each R group.

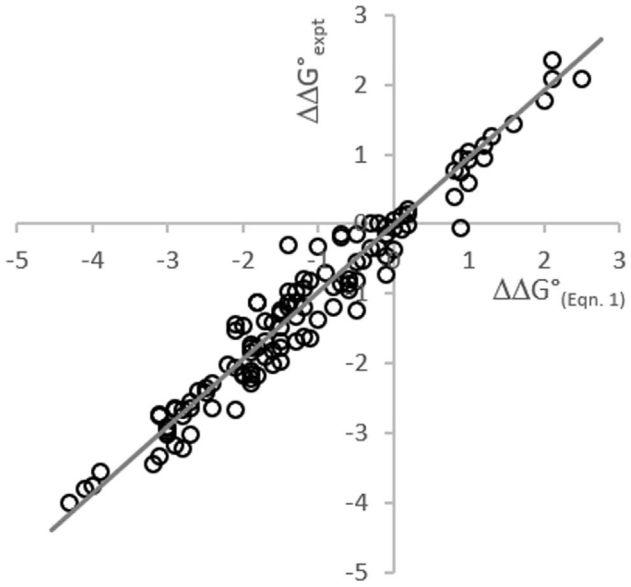

Figure 5. Comparison of aromatic stacking energies measured using DMCs with values using Equation 1 ($a = 0.69$, $b = c = -1.50$, and values of d from Table 1). The best fit straight line is shown: $y = 0.97x$ and $R^2 = 0.97$. Values are in kJ mol^{-1}.

This analysis shows that the Hammett substituent constants provide a rather good description of variations in the electrostatic contribution to the aromatic stacking interactions in this system, but that there are additional non-polar interactions, which are captured by the constant d.

The relationship in Equation (1) suggests that the total polar interaction between two stacked aromatic rings can be considered as equivalent to a Coulombic interaction between a charge on the face of one aromatic ring with a charge on the face of the other aromatic ring. The effective charge required to describe an aromatic ring with substituent X (q_X) can be expressed in terms of the Hammett constant using Equation (2) [see Supporting Information Section 3.7 for derivation of Eq. (2)].

$$q_X = q_H + \rho\sigma_X \quad (2)$$

Here, q_H represents the effective charge on the face of an unsubstituted aromatic ring, and ρ describes the sensitivity of the charge to the effects of substituents. The electrostatic interaction between the two aromatic rings is proportional to the product of the two effective charges [Eq. (3)].

$$q_X q_Y = \rho^2 \sigma_X \sigma_Y + q_H \rho \sigma_X + q_H \rho \sigma_Y + {q_H}^2 \quad (3)$$

Comparison of Equation (3) with Equation (1) provides some insight into the significance of the values of the constants listed in Table 1, which were determined using the DMC results. If we assume that the free energy change associated with the aromatic stacking ($\Delta\Delta G°_{expt}$) is due entirely to polar interactions and can be expressed in the form of Equation (3), then the constants a and d in Equation (1) should both be positive and the constants b and c should be equal. Moreover, there would be a relationship between the four constants such that the product of a and d would be equal to the product of b and c. However, although a is positive and b is equal to c, the values of d in Table 1 are all negative. This result indicates that there must be additional attractive interactions that contribute to the measured interaction energies for two stacked aromatic rings that are not captured by the simple electrostatic description provided by Equation (3). Thus, the measured values of the constant d contain contributions from both polar and non-polar interactions [Eq. (4)].

$$d = d_{polar} + d_{non\text{-}polar} \quad (4)$$

The polar contribution to d is independent of substituents on the aromatic rings, because these effects have already been factored out by the Hammett analysis, and so d_{polar} is simply the electrostatic interaction between two unsubstituted aromatic rings. By noting the relationship between the four constants in Equation (3) and that d_{polar} is proportional to ${q_H}^2$, it is possible to determine d_{polar} from the other three constants [Eq. (5)].

$$d_{polar} = b\,c/a \quad (5)$$

The values of the constants in Table 1 used in Equation (5) give a value of $+3.3 \pm 0.2$ kJ mol^{-1} for d_{polar}, which is the polar interaction energy for two unsubstituted aromatic rings. This interaction is unfavourable as expected, due to the repulsion between the π-electron densities on the faces of the aromatic rings.

If electrostatic interactions were the only contributions to the observed free energy changes measured for the aromatic stacking interactions in these systems, then the value of the constant d would be equal to d_{polar}. Table 1 shows that this is clearly not the case, which implies that there is a substantial contribution from non-polar interactions to the aromatic stacking energies measured in these experiments. Since the values of a, b and c do not vary from one system to another, the value of d_{polar} is a well-defined constant that can be applied to all of the double mutant cycle measurements. Therefore the contributions of polar and non-polar interactions to the observed DMC energies can be determined for each aromatic stacking interaction using Equations (6) and (7).

$$\Delta\Delta G_{polar} = a\sigma_X\sigma_Y + b\sigma_X + c\sigma_Y + d_{polar} \quad (6)$$

$$\Delta\Delta G_{non\text{-}polar} = \Delta\Delta G°_{expt} - (a\sigma_X\sigma_Y + b\sigma_X + c\sigma_Y + d_{polar}) \quad (7)$$

The results are shown in Table 2. Non-polar interactions make a significant contribution (−3 to −6 kJ mol^{-1}) to all of the measured stacking interaction energies.[43,44] In fact, the non-polar contribution is more attractive than the total interaction energy in all cases. The net contribution from polar interactions is unfavourable in all of the stacking interactions studied. The reason is that none of electrostatic effects described by the Hammett constants, that is, dipole interactions or changes in π-electron density, are large enough to overcome the electrostatic repulsion due to the close proximity of the π-electron densities of the two stacked rings. The most

Tabelle 2: Polar and Non-Polar contributions to the total aromatic stacking interaction energy measured using DMCs.

		$\Delta\Delta G_{polar}$ / kJ mol^{-1}	$\Delta\Delta G_{non\text{-}polar}$ / kJ mol^{-1}							
Substituents			Solvating Group (R)							
X	Y		Hex	sBu	tBu	neoP	cHex	cHexM	cPen	CPenM
NO_2	NO_2	+1.4	-4.2	-4.5	-3.8	-4.5	-5.3	-5.7	-5.4	-5.5
	Cl	+1.9	-4.0	-3.8	-3.8	-3.9	-4.6	-5.1	-4.8	-5.0
	Me	+2.3	-4.2	-4.2	-4.1	-4.2	-5.0	-5.3	-5.1	-5.3
	OMe	+2.4	-4.2	-4.3	-3.9	-4.1	-5.1	-5.4	-5.2	-5.4
	NMe_2	+2.9	-4.1	-4.3	-3.7	-4.3	-5.1	-5.4	-5.0	-5.4
Cl	Cl	+2.7	-4.4	-4.2	-4.8	-4.3	-5.1	-5.6	-5.3	-5.6
	Me	+3.2	-4.2	-3.8	-4.4	-3.8	-4.7	-5.1	-4.8	-5.2
	OMe	+3.3	-3.8	-3.8	-3.9	-3.4	-4.4	-4.8	-4.6	-4.9
	NMe_2	+4.1	-4.2	-3.2	-4.1	-4.1	-4.9	-5.3	-4.8	-5.4
Me	Me	+3.8	-4.7	-4.8	-5.2	-4.5	-5.6	-5.8	-5.6	-5.9
	OMe	+4.0	-4.5	-4.5	-4.7	-4.1	-5.3	-5.5	-5.4	-5.7
	NMe_2	+4.9	-4.1	-4.0	-4.0	-3.9	-4.8	-5.1	-4.7	-5.3
OMe	OMe	+4.2	-4.2	-4.5	-4.4	-4.0	-5.3	-5.5	-5.4	-5.7
	NMe_2	+5.1	-4.1	-4.2	-3.9	-3.9	-5.0	-5.2	-4.9	-5.4
NMe_2	NMe_2	+6.3	-4.3	-4.2	-3.8	-4.2	-5.0	-5.3	-4.7	-5.5
average			-4.2±0.2	-4.2±0.4	-4.2±0.4	-4.1±0.3	-5.0±0.3	-5.3±0.3	-5.0±0.3	-5.4±0.3

attractive stacking interactions were found for two nitroaromatics, and for these systems, the contribution due to polar interactions is close to zero, so the attractive interaction observed is due almost entirely to the non-polar contribution.

The non-polar interactions in Table 2 do not vary significantly with substituent on the aromatic ring, but there are clear trends depending on the solvating R group. The interactions between the aromatic rings are all slightly more attractive in an effective solvent of cyclic hydrocarbons ($-5\,kJ\,mol^{-1}$) than in acyclic hydrocarbons ($-4\,kJ\,mol^{-1}$). This result suggests that the more flexible acyclic hydrocarbons are better able to solvate the aromatic rings, thereby providing more competition for the non-polar van der Waals component of the interaction. However, it is clear that in all cases these interactions between stacked aromatic rings are more favourable than with aliphatic hydrocarbons. This result presumably reflects the fact that the perfectly flat surface of aromatic groups allows intimate contact over a larger surface area than is possible with the corrugated surface of aliphatic groups (Figure 6).[19,43,45]

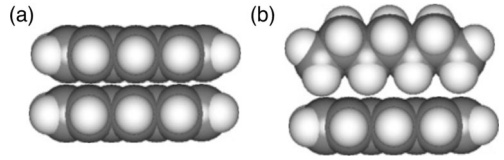

Figure 6. Space filling models of aromatic stacking and solvation of an aromatic ring by an alkyl group. The perfectly flat surfaces of two aromatic rings allow close contact over a larger surface area than is possible with the corrugated surface of an alkyl group.

Conclusion

A supramolecular cage complex has been used to carry out an extensive experimental survey of aromatic stacking interactions in solution. Chemical double mutant cycles have been used to measure the free energy contributions due to 15 different aromatic stacking interactions in 8 different effective solvent environments. The results show important contributions from both electrostatic and non-polar interactions between the aromatic rings. There is a strong correlation between the experimentally measured stacking interaction energies and the Hammett substituent constants, and this correlation can be extrapolated to separate the polar and non-polar contributions to aromatic stacking in this system. The electrostatic interactions between two unsubstituted aromatic rings in a stacked arrangement contribute $+3\,kJ\,mol^{-1}$, and this repulsion is ascribed to the interaction between the π-electron densities on the faces of the π-systems. Electron-withdrawing substituents reduce the repulsion by up to $2\,kJ\,mol^{-1}$ (for two nitro groups), and electron-donating groups increase the repulsion by up to $3\,kJ\,mol^{-1}$ (for two dimethylamino groups). Thus the polar component of the stacking interaction is repulsive in all cases for the systems studied here.

Non-polar interactions contribute between -3 and $-6\,kJ\,mol^{-1}$ to the stacking interactions. As a result, the net stacking interaction is attractive for aromatic rings with electron-withdrawing substituents and repulsive for aromatic rings with electron-donating substituents. In the DMC approach used here, the stacking interactions compete with solvation by alkyl groups that represent an effective solvent environment. For measurements carried out using 8 different alkyl solvating groups, the polar terms in the Hammett correlation were identical, confirming that the alkyl groups do not make any significant polar interactions with the aromatic rings. However, the non-polar contribution to the stacking interaction energy does depend on the nature of the solvating group. Stacking interactions were more favourable by about $1\,kJ\,mol^{-1}$ for acyclic solvating groups compared with cyclic solvating groups. This result suggests that the way in which molecular surfaces can pack together is an important parameter. Dispersion or van der Waals interactions have been shown to be important in gas phase calculations, but in solution, competing interactions with the solvent usually attenuate these contributions to the extent that they cancel out. Aromatic stacking is special in that the perfectly flat surfaces of two π-systems allow for more intimate contact than is possible with the corrugated surface of an alkyl group. Our measurements suggest an imperfect cancellation of the non-polar interactions with solvent, which leads to a substantial non-polar contribution to the aromatic stacking energy. This effect is exacerbated when the solvating alkyl groups are cyclic and lack the flexibility to optimize intermolecular contacts with the face of the π-systems.

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Conflict of Interest

The authors declare no conflict of interest.

Stichwörter: Hammett analysis · non-covalent interactions π–π interactions · supramolecular cages

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Forschungsartikel

π-Stacking

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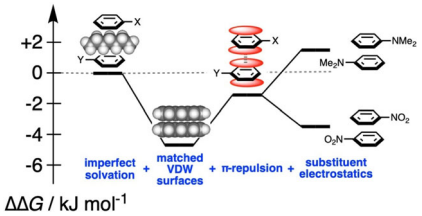
Dissection of the Polar and Non-Polar Contributions to Aromatic Stacking Interactions in Solution



A double-Hammett approach has been used to dissect out the polar contributions to the total aromatic stacking energy.