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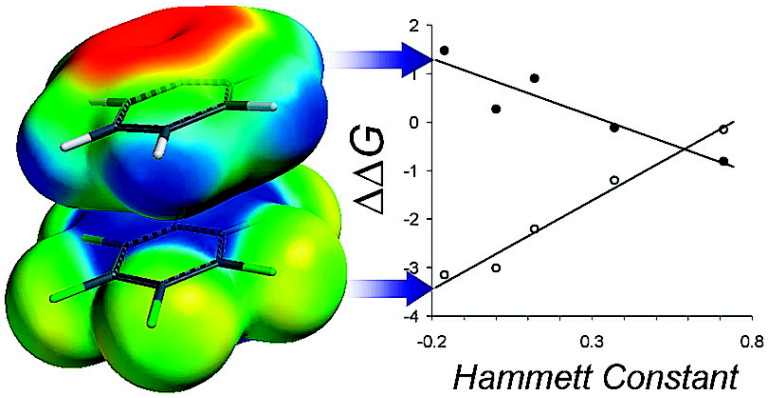


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# Electrostatic Control of Aromatic Stacking Interactions

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The stacking of aromatic rings is one of the most common noncovalent interaction motifs found in both natural and synthetic systems. DNA base stacking is important in determining structure and function;[1] aromatic interactions are widely used in template-directed and asymmetric synthesis,[2] and the properties of many crystalline solids are controlled by aromatic interactions that dictate the molecular organization.[3] While qualitative models of the factors that govern these interactions are available, and estimates are available from ab initio calculations, there is little quantitative experimental data on the magnitudes of stacking interactions and the influence of substituents.[4]

Supramolecular chemistry provides us with the tools required for a systematic study of the properties of weak noncovalent functional group interactions using well-defined synthetic systems. We have been using H-bonded "zipper" complexes in conjunction with chemical double mutant cycles to quantify noncovalent intermolecular interactions with aromatic rings in chloroform solution.[5] In this paper, we show how this approach can be used to measure the effect of substituents on aromatic stacking interactions.

Figure 1 shows the double mutant cycle used in this investigation. The stacking interaction highlighted in complex A is measured by chemical mutations that remove it. A single mutation (e.g., comparing the stabilities of complexes A and B) is not sufficient because this has secondary effects, such as changing the H-bond strength. The double mutant complex D quantifies these secondary interactions, and the free energy difference of any two parallel mutations in Figure 1 allows the interaction of interest to be dissected out of the complicated array of weak interactions present in complex A.

We assume that differences in entropic contributions cancel in the cycle, so that the method can be used to quantify the contributions of specific interactions to the free energy of complexation.

We have used this system to carry out a quantitative study of substituent effects on aromatic stacking interactions using the compounds shown in Figures 1 and 2. The syntheses of compounds **2**, **6**, and **10** have been reported elsewhere,[5] and the remaining compounds were prepared using similar methods. The complexes required to construct the double mutant cycles were characterized using $^1$H NMR spectroscopy in $CDCl_3$. $^1$H NMR dilutions and titrations were used to determine the 1:1 association constants and limiting complexation-induced changes in chemical shift ($\Delta\delta$). The $\Delta\delta$ values provide an indication of the three-dimensional structures of the complexes, and the patterns observed were similar to those reported previously for related zipper complexes (see Supporting Information).[5]

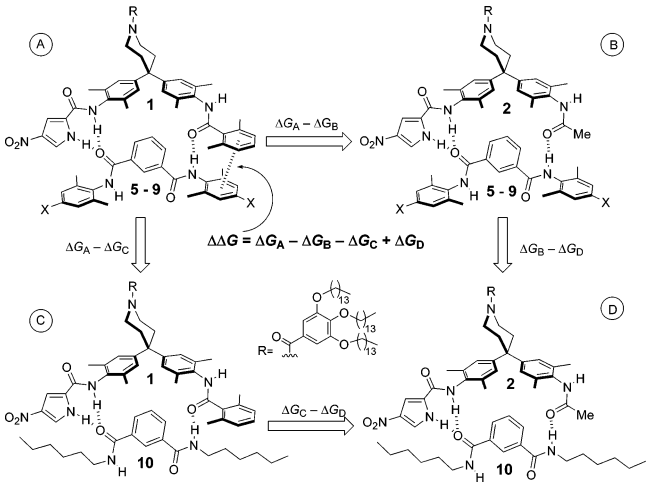


***Figure 1.*** Chemical double mutant cycle for measuring the aromatic stacking interaction in complex A; X = $NMe_2$ (**5**), H (**6**), OMe (**7**), Cl (**8**), or $NO_2$ (**9**). Compounds **1**, **2**, and **10** are labeled in the complexes.

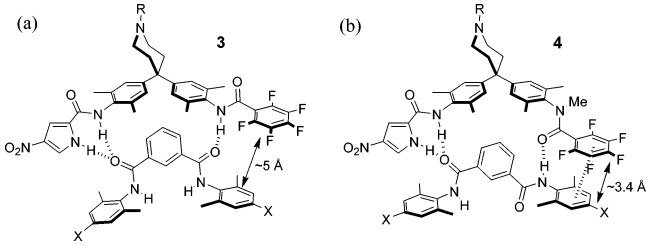


***Figure 2.*** (a) Complexes with **3** adopt a conformation where the aromatic rings are not in contact. (b) With the methylated derivative **4**, this conformation is not possible, and the aromatic rings are forced to stack. R is the solubilizing group shown in Figure 1.

However, some differences were observed for complexes involving **3**. In particular, large downfield changes in chemical shift were observed for the pentafluorophenyl amide proton,[6] suggesting that these complexes adopt a different conformation from that shown in Figure 1. The electron-withdrawing pentafluorophenyl group makes the amide a poor H-bond acceptor and a powerful H-bond donor, and as a consequence, complexes involving **3** favor a conformation in which the aromatic rings are not in contact (Figure 2a). When double mutant cycles were constructed using the data for **3**, we correspondingly found interaction energies close to zero.[7]

The conformational problem can easily be solved by methylating the offending amide (Figure 2b). With compound **4**, the patterns of $\Delta\delta$ values were practically identical to those obtained with **1** and **2**, indicating that all of the complexes adopt similar conformations, and reliable double mutant cycles can therefore be constructed. Solution structures of the complexes were determined using

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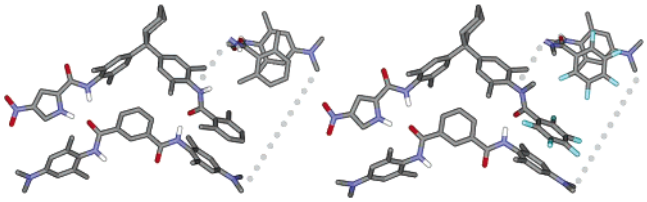

***Figure 3.*** Solution NMR structures of complexes **1•5** and **4•5** (X = $NMe_2$) with a top view of the geometry of the stacking interaction in each case.

***Table 1.*** Double Mutant Cycle $\Delta\Delta G$ Values (kJ $mol^{-1}$) for Aromatic Stacking Interactions[a]

| X | phenyl | pentafluorophenyl |
|---|---|---|
| $NMe_2$ | +1.5 | −3.2 |
| H | +0.3 | −3.0 |
| OMe | +0.9 | −2.2 |
| Cl | 0.0 | −1.2 |
| $NO_2$ | −1.0 | −0.2 |

[a] Values measured in $CDCl_3$ at 293 K, and errors are ±0.7−1.1 kJ $mol^{-1}$.

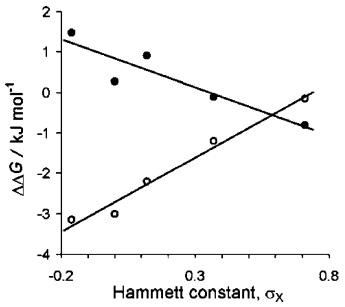


***Figure 4.*** Experimental aromatic stacking interaction energies (ΔΔG) correlate with the Hammett substituent constant for X ($\sigma_X$). Interactions with phenyl (●) and pentafluorophenyl (○) are shown.

the NMR $\Delta\delta$ values (see Supporting Information) and provide an average representation of the conformational ensemble.[8] The terminal aromatic rings in complex A are in a stacked geometry regardless of whether the stacking interaction is attractive or repulsive (Figure 3).[9]

The stacking free energies ($\Delta\Delta G$) for phenyl and pentafluorophenyl rings with various substituted aromatics were determined using the equation in Figure 1 and are shown in Table 1. In general, the pentafluorophenyl interactions are attractive, and the phenyl interactions are repulsive, but the magnitudes of the stacking interactions are clearly sensitive to the nature of the X substituent. The data correlate well with the corresponding Hammett substituent constants for X (Figure 4), which provides some insight into the origin of the variations.[9] For stacking interactions with the simple phenyl group, the more electron-withdrawing the X substituent, the less repulsive the interaction, until eventually, when X = $NO_2$, the interaction is slightly attractive. For stacking interactions with the pentafluorophenyl group, the trend is inverted, and the interactions become increasingly attractive as X becomes less electron-withdrawing. These trends are consistent with a simple electrostatic explanation: the stacking interaction reflects the electrostatic potentials on the surfaces of the aromatic rings that are sensitive to the nature of the substituents. The symmetry in Figure 4 is consistent with the observation that the quadrupole moments of benzene and hexafluorobenzene are approximately equal in magnitude but of opposite sign. Thus, the pentafluorophenyl group has a positive surface that interacts attractively with electron-rich aromatics, and phenyl has a negative surface that interacts attractively with electron-poor aromatics.[10]

The quantitative structure-free energy relationships derived here demonstrate that aromatic stacking interactions in chloroform are dominated by electrostatic effects in exactly the same way as we have shown previously for the corresponding edge-to-face geometry. The trends are in accord with those observed for intramolecular stacking interactions in organic solvents,[11] but distinct from measurements in water where the interaction is dictated by desolvation.[12]

The net contribution of the stacking interactions to the overall free energy of binding is surprisingly small in this system. The geometrical constraints of the zipper architecture probably prevent the aromatic groups from reaching the minimum energy arrangement, but the ability to fix the geometry of the interaction has allowed us to examine the subtleties of substituent effects that would otherwise be obscured by structural differences. Although the absolute values of the interaction energies are not directly transferable to other systems, the simple trends observed clearly have some generality. We hope that this work will contribute to the broader understanding of aromatic stacking interactions in other systems and solvent environments.

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**Supporting Information Available:** Tables listing experimental and calculated complexation-induced changes in chemical shift $\Delta\delta$, binding constants, and $\Delta G$ values. Experimental details of solution NMR structure determination. Spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Mean $\Delta\delta$ values for the pentafluorophenyl amide proton were +1.1 ppm for complexes involving **3**, compared to +0.3 ppm for the corresponding protons in complexes involving **1** and **2**.

(7) We previously reported that the stacking interaction in the **3•5** complex was −0.4 ± 0.9 kJ $mol^{-1}$, which is gratifyingly close zero, as expected for two noninteracting groups.[5b]

(8) The structures were determined from the $\Delta\delta$ values and intermolecular NOEs using the software described in: Hunter, C. A.; Packer, M. J. *Chem.—Eur. J.* **1999**, *5*, 1891−1897.

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