Structure–activity relationship for quantifying aromatic interactions†

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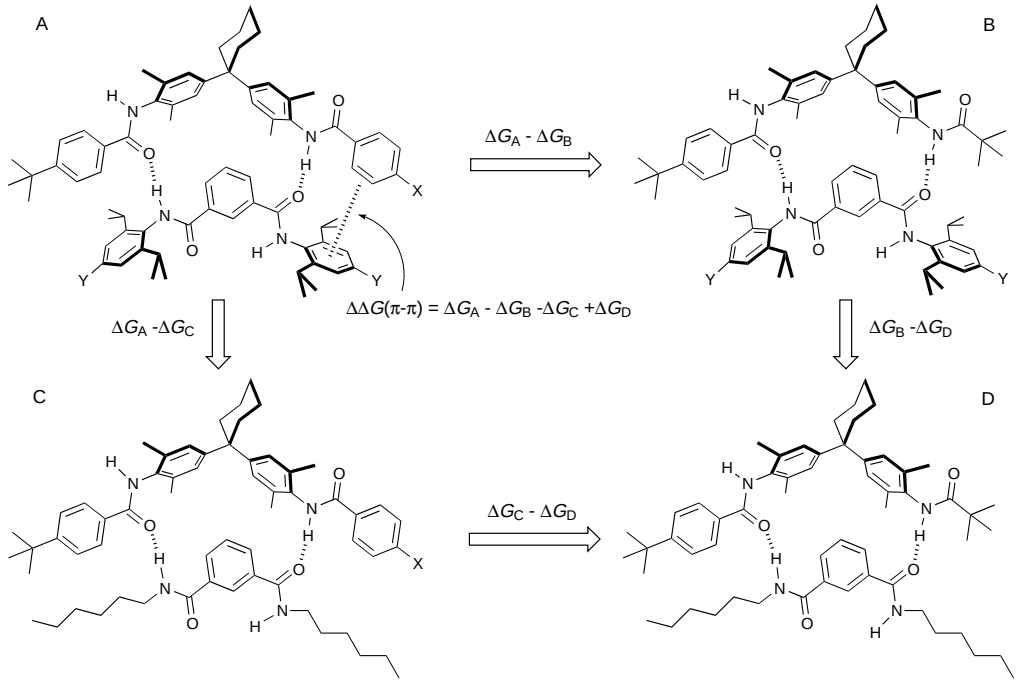
The magnitudes of a range of intermolecular edge-to-face aromatic interactions are measured using chemical double mutant cycles in synthetic H-bonded molecular zipper complexes, and good correlations are obtained with the Hammett substituent constants, suggesting that the results can be extrapolated to other functional group combinations.

Molecular recognition events are complex processes which are influenced by a large number of different factors that make it difficult to quantify the thermodynamic properties of the basic functional group interactions involved.[1–10] We have adapted the double mutant cycle approach developed to quantify side chain–side chain interactions in proteins[5] to quantify functional group interactions in a synthetic supramolecular system. Here we apply this method to derive a quantitative structure–activity relationship for aromatic interactions.[2,8,11,12] The results not only yield a molecular explanation for the properties of these interactions, they also allow us to make quantitative predictions about the influence of chemical structure on the magnitudes of aromatic interactions.

The chemical version of the double mutant cycle which enables us to dissect out and isolate the contribution of the terminal aromatic interaction to the overall free energy of binding for zipper complex **A** is shown in Scheme 1.[13,14] Chemical mutation of one aromatic ring to a Bu^t group (**A** → **B**) removes the aromatic interaction of interest, but this change also removes secondary interactions between the aromatic ring and the core of the complex. In addition, the mutation alters the strength of the neighbouring H-bond. However, the magnitude of the secondary interactions and the change in H-bond strength can be measured directly by carrying out the same chemical mutation in complex **C** (**C** → **D**). Thus by determining association constants for all four complexes and constructing the cycle in Scheme 1, we can quantify the aromatic interaction of interest. The advantages offered by this synthetic system are that the two interacting groups are attached to a relatively rigid framework which determines the geometry of the interaction, and that a wide range of different functional groups can be studied. The geometry of interaction is probably not the optimum orientation for all combinations of functional group, but it will be essentially identical in each case. This means that electronic structure–activity relationships are not buried by differences in conformation. A limitation of the approach is that we assume that the magnitudes of the core interactions in all four complexes in a cycle are insensitive to changes in the overall binding energy.[1,6] The magnitude of entropy–enthalpy compensation effects in such systems has not yet been established, but even if they are large enough to affect our measurements, they will not alter the trends in the magnitudes of the functional group interaction energies.

Using the system in Scheme 1, we have carried out a quantitative study of substituent effects on the magnitudes of edge-to-face aromatic interactions. The required compounds were synthesised using standard protocols and characterised by a range of spectroscopic and analytical techniques. The complexes were characterised using ^{1}H NMR spectroscopy in $CDCl_3$. ^{1}H NMR titrations were used to determine the association constants and hence free energies of complexation for use in the thermodynamic cycles. The final results are



Scheme 1 Chemical double mutant cycles used to measure the magnitude of edge-to-face aromatic interactions, $\Delta\Delta G(\pi–\pi)$. X, Y = NO_2, H, NMe_2

Table 1 Magnitudes of edge-to-face aromatic interactions [$\Delta\Delta G(\pi–\pi)$ in kJ mol^{-1}] measured in $CDCl_3$ at 295 K using the chemical double mutant cycles shown in Fig. 1. Errors are ± 0.5–0.8 kJ mol^{-1}

Y	X = NO_2	X = H	X = NMe_2
NO_2	+1.2	−0.2	−1.4
H	−3.4	−1.4	−1.1
NMe_2	−4.6	−1.8	−0.9

summarised in Table 1. Intermolecular NOEs from ROESY experiments and the magnitudes of the complexation-induced changes in chemical shift from the titrations show that all four complexes in each of the nine double mutant cycles adopt essentially the same conformation in solution, *i.e.* the chemical mutations do not grossly alter the three-dimensional structure of the core of the complex. More detailed information about the geometry of the edge-to-face aromatic interactions under investigation was obtained from X-ray structures of model compounds such as **1** which corresponds to half of the zipper complex and crystallises with the same H-bonds and edge-to-face aromatic interactions inferred from our solution studies.[13,14]

The magnitude of the aromatic interaction, $\Delta\Delta G(\pi–\pi)$, is clearly sensitive to the nature of the substituents and varies from +1.0 kJ mol^{-1} repulsive to −4.9 kJ mol^{-1} attractive (more than an order of magnitude in binding strength). The ability to measure both repulsive and attractive interactions allows us to properly characterise the potential energy surface in this system. The trends in Table 1 are difficult to interpret, and so we have analysed the results using the Hammett substituent parameters (σ) which quantify the electronic effects of the substituents on the aromatic ring.[15] The correlation is remarkable and allows us to describe the experimental results using eqn. (1) (Fig. 1).

$$\Delta\Delta G(\pi–\pi) = 5.2\ \sigma_X\ \sigma_Y - 1.9\ \sigma_X + 1.4\ \sigma_Y - 1.5 \qquad (1)$$

This equation gives some insight into the molecular basis for the variations in interaction energy in Table 1. The last three terms in eqn. (1) are interpreted as an electrostatic interaction between the positively-charged CH groups on the edge ring and the negatively charged π-electron density on the face ring [Fig. 2(*a*)].[16] This part of the interaction is sensitive to changes in the local charge distributions on the two rings. The first term in eqn. (1) is attractive when the two groups X and Y exert opposite effects which reflects an interaction between the global charge distributions across the two aromatic rings, *i.e.* an electrostatic interaction between the overall dipoles caused by the polarising effects of the substitutents [Fig. 2(*b*)].

Eqn. (1) implies that although we have only studied nine interactions, the results can be extrapolated to a wide range of functional group combinations provided the Hammett parameters are available from the literature. It is unlikely that eqn. (1) will accurately predict ΔG values for aromatic interactions in other systems, but we expect it to provide a reasonable estimate of the magnitudes of substituent effects, *e.g.* if an edge-to-face aromatic interaction is implicated in a drug-receptor complex,[17] there is no point looking at lots of different Y groups if X is electron donating (NMe_2), because the magnitude of the interaction is relatively insensitive to Y. However if X is electron withdrawing (NO_2), the nature of Y is likely to have a dramatic effect on the interaction energy.

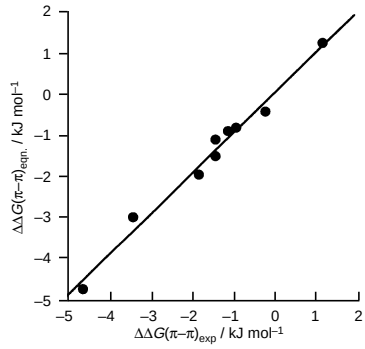


Fig. 1 Correlation of the experimental measurements of the aromatic interaction energies from Table 1 with the interaction energies calculated using eqn. (1) and the Hammett substituent parameters

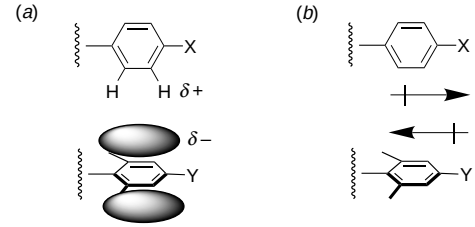


Fig. 2 Molecular interpretation of eqn. (1). (*a*) Electrostatic interactions between the CH groups of the edge ring and the π-electron density of the face ring are sensitive to changes in the local charge distributions on the two aromatic rings. (*b*) Electrostatic interactions between the overall dipoles of the π-systems are sensitive to changes in the global charge distributions on the two aromatic rings.

The generality of these results remains to be tested in different contexts, using alternative molecular frameworks and solvents, but the approach is clearly a promising method for dissecting out individual contributions to the overall thermodynamic stability of a particular molecular recognition event. By studying different interaction geometries and types, we hope to develop a database of thermodynamic measurements that can be used alongside the structural data from crystallography for understanding the chemical basis of complex molecular recognition phenomena and ultimately for rational design.

We thank the Lister Institute (C. A. H.), the EPSRC and Merck Sharp & Dohme (F. J. C.) for funding.

Notes and References

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Received in Cambridge, UK, 21st January 1998; 8/00567B