Amide–aromatic hydrogen-bonds in host–guest recognition

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Complexes between a macrocylic tetraamide and dicarbonyl substrates have been used to investigate the interaction of functional groups with the face of an aromatic ring; amide NH groups directed towards the π-electron density on the face of the ring produce a substantial increase in binding energy in chloroform which suggests that π-facial H-bonds can be important in molecular recognition.

Hydrogen bonding interactions between amide groups and aromatic rings have been proposed as important factors in determining the three-dimensional structure and recognition properties of proteins.[1–3] Structural evidence for interactions in which the π-electrons of an aromatic ring act as a H-bond acceptor comes from crystal structures of small molecules and proteins and from spectroscopy on molecular beams.[2,4,5] However, in proteins these interactions are extremely rare compared with the ubiquitous amide–amide H-bonds,[2] which suggests that the thermodynamic driving force for the formation of π-facial H-bonds is so small that they cannot compete with other non-covalent interactions in complex systems.[6] We present evidence that the formation of amide–aromatic H-bonds between a substrate and a synthetic receptor (Fig. 1) is associated with a substantial thermodynamic driving force which significantly stabilises the complex in non-polar solvents.

We have studied molecular recognition in organic solvents using macrocyclic synthetic molecular receptors such as **1**,[7,8] which binds a range of structurally-related dicarbonyl compounds, **2–7**. The substrates are oriented in the binding pocket by four intermolecular H-bonds which position the ring functionality (X) over the face of the aromatic side-walls of the cavity (Fig. 2). The receptor is locked into a single fixed conformation by four intramolecular H-bonds between the pyridine nitrogens and the neighbouring amides. The substrates are all conformationally inflexible and so the structures of the complexes are very well defined. This system is therefore ideally suited to the study of the interaction of functional groups on the substrate with the π-electron density of the aromatic rings surrounding the receptor binding site. Differences in the measured association constants for the various substrates complexed with **1** (Fig. 2) will reflect differences in the thermodynamic properties of the X–π interactions.

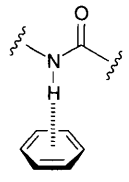
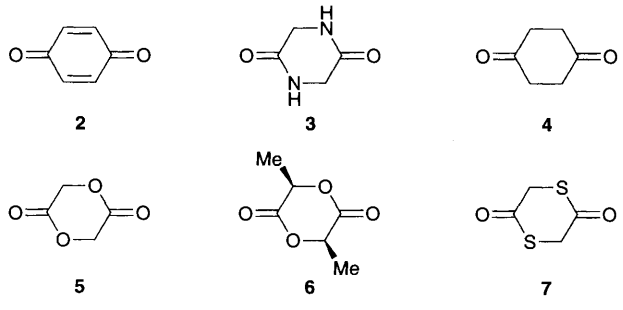


Fig. 1 Hydrogen-bonding between an amide and the π-electron density on the face of an aromatic ring



The structures of the complexes were determined using a combination of ^{1}H NMR spectroscopy and X-ray crystallography. Fig. 3 shows the X-ray crystal structure of **1** bound to substrate **3**.† The amide NHs of **3** are positioned over the aromatic side-walls of the receptor and directed towards the π-electron density on the faces of the π-systems. The substrate CH_2 groups lie over the faces of the other two aromatic side-walls but the asymmetry in the tilt of the receptor side-walls and the slight kink in the substrate means that they are not oriented directly towards the π-electron density.

^{1}H NMR titrations were used to determine the association constants for the complexes in chloroform and all gave good fits to a 1 : 1 binding isotherm (Table 1). The exception was **3** which has such low solubility in chloroform that titrations could not be performed. However, when **3** was heated with receptor **1** in chloroform, the receptor solubilised one equivalent of the substrate. The association constant for **3** was determined by a ^{1}H NMR dilution experiment on the 1 : 1 complex. As a consistency check, the association constant for **2** was also determined using this dilution technique and this experiment gave identical results to the titration method. Thus binding constants determined using the two different methods can be reliably compared. The measured complexation-induced changes in chemical shift were similar for all of the complexes studied and are consistent with the structure in Fig. 2. On

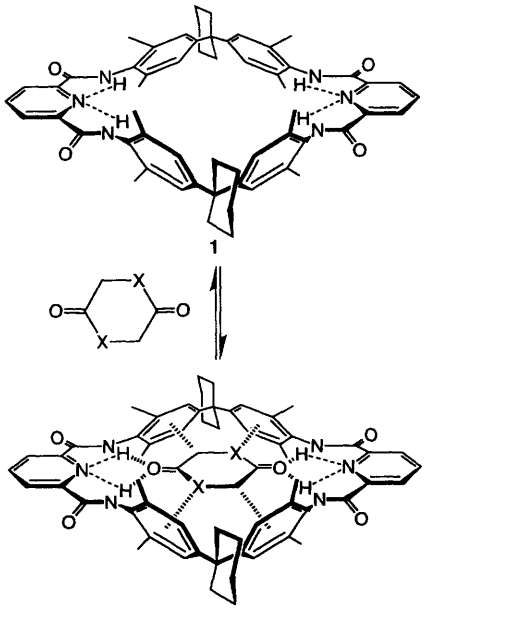


Fig. 2 Structure of the complexes formed between receptor **1** and dicarbonyl substrates **2–7**

binding, the signal due to the receptor amide protons showed a large downfield shift indicative of H-bonding interactions with the guest carbonyl oxygens (Table 1). The signals due to the protons of the guest all showed large upfield shifts (>1 ppm) which indicates that they lie over the face of the aromatic side-walls in the complex. Thus the complexes have essentially identical structures. Cyclohexanone, which has only one carbonyl group, binds to receptor **1** with an association constant of *ca.* 2 dm^3 mol^{-1} which shows that both carbonyls in substrates **2–7** must hydrogen-bond to the receptor to form a stable complex.

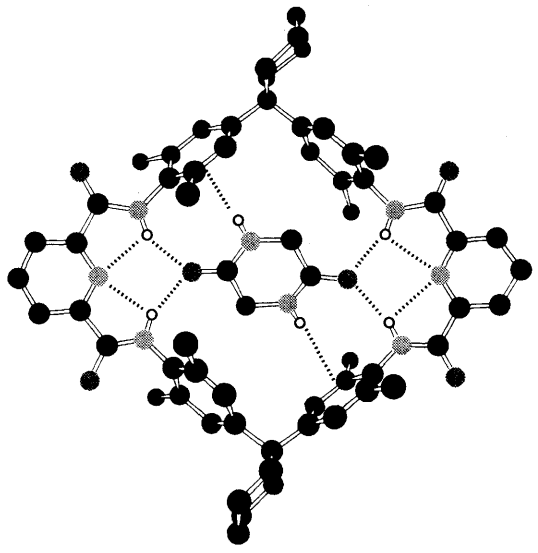


Fig. 3 X-Ray crystal structure of the **1·3** complex. The amide NH groups of **3** are directed towards the faces of the aromatic side-walls of the cavity, and the shortest nitrogen–aromatic carbon distances are 3.06, 3.32 and 3.34 Å. The hydrogen atoms were not located in the electron density map but were added using standard bond length and bond angles. However, the planarity of the amide groups requires that the substrate and receptor amide hydrogens lie in the same plane as the O, C and N atoms.

Table 1 ^{1}H NMR data for complexation by receptor **1** in chloroform

Substrate	Association constant/ dm^3 mol^{-1}	$\Delta\delta$ on complexation for amide NH of **1** (ppm)
2[a,b]	$2.3 \pm 0.4 \times 10^2$	+1.1
3[b]	$1.0 \pm 0.5 \times 10^6$	+1.5
4[a]	$8.5 \pm 0.4 \times 10^2$	+1.2
5[a]	$3.4 \pm 0.6 \times 10^2$	+0.8
6[a]	$2.6 \pm 0.4 \times 10^3$	+0.8
7[a]	$1.1 \pm 0.2 \times 10^2$	+0.8

[a] Determined using non-linear curve-fitting of ^{1}H NMR titration data. [b] Determined using non-linear curve-fitting of ^{1}H NMR dilution data.

The measured association constants show substantial variations (Table 1). Comparison of the different substrates is complicated by the fact that, although similar, they are not identical in shape and size and the basicity of the carbonyl groups is different so that the H-bond strengths are not uniform. Nevertheless, one result clearly stands out from the rest. The amide substrate **3** binds three orders of magnitude more strongly than the others. Accurate quantitation of individual interactions is not possible with this system[9] but the results show that the two π-facial H-bonds make a significant contribution to the free energy of complexation and implies that these interactions are large in magnitude. Substrates **5**, **6** and **7**, which have lone pairs directed towards the receptor aromatic side-walls, might be expected to have much reduced binding constants due to unfavourable electrostatic interactions between the lone pairs and the π-electron density, but the effect is relatively small (Table 1). This is due to the asymmetry of the complexes (Fig. 3) which allows the substrate lone pairs to avoid direct contact with the receptor π-systems.

These experiments show that amide–aromatic H-bonding interactions can have a significant effect on the molecular recognition properties of host–guest complexes in chloroform. There is a large thermodynamic driving force for the formation of such π-facial H-bonds in a non-polar environment. The fact that π-facial interactions are not common in proteins probably reflects the imbalance in the ratio of H-bond donors to acceptors in the centres of proteins rather than the thermodynamic favourability of the interactions.[4,6] H-Bonding to the face of aromatic rings may therefore play a significant role in molecular recognition phenomena in different environments.

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Footnote

† Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and reference no. 182/213.

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