Cooperativity in multiply H-bonded complexes†

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The free energy of complexation of supramolecular complexes containing phenol–carbamate H-bonds is an additive function of the number of H-bonds, with a constant increment of 6 kJ mol^{-1} per interaction in carbon tetrachloride.

Multiple intermolecular interactions between two molecules lead to cooperative stabilisation of the resulting non-covalent complex.[1] The magnitude of this stabilisation depends on the number of interactions, the properties of the functional groups, the solvent and the overall supramolecular architecture. Although it is possible to make reasonably accurate predictions of the stability of complexes that feature a single functional group interaction, extension to more complex systems with multiple interactions remains a challenge.[2] There are two key issues that must be addressed in order to achieve this: how transferrable are the thermodynamic contributions of individual functional group interactions from one system to another? And what are the thermodynamic contributions associated with geometric complementarity and conformational flexibility of the covalent scaffolds that display the interaction sites? We have previously found that free energy and enthalpy contributions of metal–ligand coordination bonds are additive in porphyrin assemblies held together by multiple interactions.[3] In this paper, we extend these studies to more weakly bound H-bonded complexes. We address the issue of transferrability by studying the properties of one type of H-bond in a variety of supramolecular contexts.

To minimise the thermodynamic contributions associated with different supramolecular architectures, we designed a set of related self-complementary covalent scaffolds containing one, two, three and four sites for functionalisation with H-bonding groups (Fig. 1). Phenol was chosen as the H-bond donor and carbamate as the H-bond acceptor, because these functional groups have relatively high H-bond parameters ($\alpha = 3.8$, $\beta = 8.3$) and so form stable complexes in non-polar solvents.[2] These functional groups do not self-associate to any significant extent, because phenol is a very weak H-bond acceptor and carbamate only has CH donors, and this greatly simplifies the experimental characterisation of systems with multiple interaction sites. In addition, the carbamates can be readily prepared from the corresponding phenols, so that complementary oligomeric scaffolds are synthetically accessible (Fig. 2). The one, two and three H-bond scaffolds are all based on a methane core, and a porphyrin core was used as the basis for the four H-bond system. Compounds **1b**, **2b** and **3b** were prepared from the commercially available phenols, **1a**, **2a** and **3a** (Fig. 2). The porphyrin tetraphenol **4a** was prepared using literature procedures,[4] and this was converted to **4b** in the same way.

Fig. 1 shows the structures of the complexes that can be formed between complementary pairs of compounds. Binding studies were carried out in carbon tetrachloride, because it is a very non-competitive solvent ($\alpha = 1.4$, $\beta = 0.6$),[2] so that even the complex with only one H-bond is sufficiently stable for accurate measurement of the association constant. ^{1}H NMR dilution experiments on the carbamates showed no evidence of self-association in carbon tetrachloride. The phenols are relatively insoluble, and for **3a** and **4a**, it is not possible to obtain ^{1}H NMR spectra in carbon tetrachloride on a timescale suitable for NMR titrations. However, mM solutions of **3a** or **4a** could be obtained in the presence of an excess of the complementary carbamate, **3b** or **4b**, respectively. The phenols are fully bound in the resulting solution, and 1 : 1 association constants were measured by dilution of the mixtures. Phenols **1a** and **2a** were sufficiently soluble in carbon tetrachloride to be used as hosts in conventional titration experiments with the complementary carbamate, **1b** or **2b**, respectively, as the guest. The dilution and titration data fit well to a 1 : 1 binding isotherm in all cases. For **1a**·**1b**, **2a**·**2b** and **3a**·**3b**, +2 ppm limiting complexation-induced changes in ^{1}H NMR chemical shift were determined for the signals due to the phenol OH protons, indicative of H-bond interactions (the phenol OH

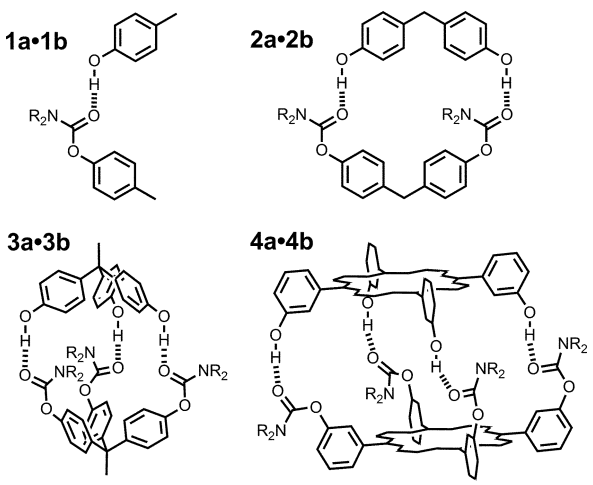

Fig. 1 H-bonded complexes containing one to four H-bonds. Some bonds in the porphyrins (**4a** and **4b**) are omitted for clarity.

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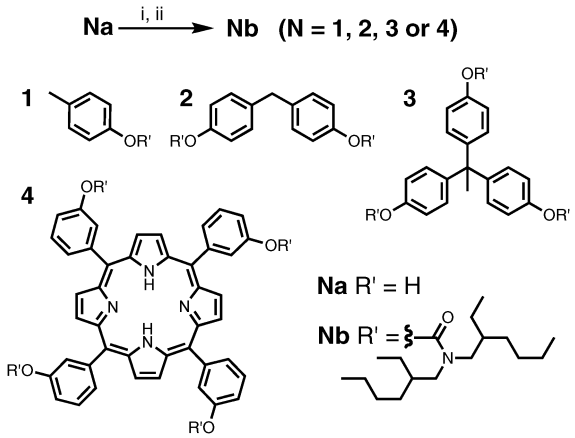

Fig. 2 Synthesis and structures of the compounds used in this study. (i) 4-Nitrophenyl chloroformate, (ii) bis(2-ethylhexyl)amine.

signal was not resolved in the spectrum of the **4a**·**4b** complex). The association constants in Table 1 show that the stabilities of the complexes increase with the number of H-bonds (N): addition of each H-bond increases the association constant by an order of magnitude.

A more detailed analysis of the cooperativity in these systems requires consideration of their symmetry, because there is a statistical factor (N) that biases the equilibrium in favour of multiply H-bonded complexes.[5] In systems that make more than one intermolecular interaction, effective molarity is usually used to quantify the degree of cooperativity associated with the intramolecular contacts.[6] Effective molarity is the ratio of the equilibrium constants for intramolecular and the corresponding intermolecular interactions. In the complexes described here, it is difficult to separate individual effective molarities for each of the intramolecular contacts.[7] Thus we estimate the average effective molarity for all of the intramolecular interactions in a complex that makes N H-bonds, EM_N, using eqn (1)

$$K_N = NK_0^N EM_N^{N-1} = NK_0(K_0 EM_N)^{N-1} \quad (1)$$

where K_0 is the microscopic association constant for the formation a single H-bond (in principle, equal to K_1). Eqn (1) can be used to express the free energy of complexation, ΔG_N, as a function of N (eqn (2)).

$$\Delta G_N = -RT \ln K_0 - (N-1)\, RT \ln(K_0 EM_N) - RT \ln N \quad (2)$$

The first term in eqn (2) represents the free energy contribution of the first intermolecular H-bond, the second term is the free energy contribution of the subsequent $N - 1$ intramolecular H-bonds, and the third term is the statistical factor. Thus plotting the statistically corrected free energy of complexation ($\Delta G_N + RT \ln N$) *versus* the number of intramolecular H-bonds ($N - 1$) should give a straight line with a slope of $-RT \ln(K_0 EM_N)$, the free energy contribution of an intramolecular H-bond, which is concentration-independent, and an intercept of $-RT \ln(K_0)$, the free energy contribution of an intermolecular H-bond, which is concentration-dependent.

Table 1 Association constants measured using ^{1}H NMR titrations and dilutions in carbon tetrachloride at 298 K

Complex	N	K_N/M^{-1}	Error[a] (%)
1a·**1b**	1	18	20
2a·**2b**	2	260	10
3a·**3b**	3	7200	60
4a·**4b**	4	50 000	40

[a] The values of K_N are the average of at least three experiments and errors are quoted at the 95% confidence limit.

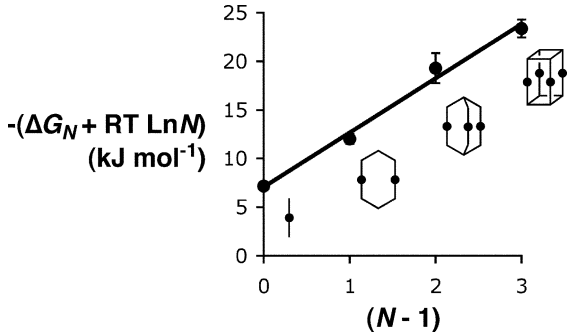

Fig. 3 The statistically corrected free energy of complexation $-(\Delta G_N + RT \ln N)$ *versus* the number of intramolecular H-bonds ($N - 1$) for the complexes in Fig. 1. The best fit straight line is shown ($r^2 = 0.99$).

Fig. 3 shows that a plot of ($\Delta G_N + RT \ln N$) *versus* ($N - 1$) does indeed give a straight line, which is consistent with eqn (2), if K_0 and EM_N are constants for all of the complexes and independent of N. In other words, these experiments indicate that the cooperativity associated with the formation of intramolecular H-bonds does not depend on the overall stability of the complex or on the degree of conformational restriction imposed by the formation of a (poly)macrocyclic architecture. The functional groups involved in H-bonding, phenol and phenyl carbamate, are attached to their central scaffold (methane or porphyrin) by a single rotatable bond in all cases, and so statistical or entropic factors associated with changes in rotameric states are unlikely to vary significantly from one system to another. The observed value of EM_N includes these contributions, but this factor appears to be similar for each intramolecular interaction in the complexes studied here. The best fit straight line in Fig. 3 has a slope of 6 kJ mol^{-1}, which is the contribution of each intramolecular H-bond to the overall stability of the complex. The intercept is 7 kJ mol^{-1}, which allows determination of the values of $K_0 = 17$ M^{-1} and $EM_N = 0.5$ M.

The complexes described here span a range of stability of more than three orders of magnitude, due to cooperativity in the multiply H-bonded systems. By attaching increasing numbers of identical H-bonding groups to rigid scaffolds, it is possible to quantify the thermodynamic contribution of individual H-bond interactions to the overall stability of the complexes. A phenol–carbamate H-bond increases the stability of a complex by 6 kJ mol^{-1} in carbon tetrachloride. This contribution is the same for all of the systems studied and is independent of the overall stability of the complex or number of interactions. This suggests that it is possible to understand the thermodynamic properties of multiply H-bonded complexes based on free energy increments associated with the individual H-bonds using a simple additive approach.[2,3,8] The H-bonding sites in these complexes have been deliberately selected to be

remote in order to minimise secondary electrostatic interactions, but in systems where the H-bonding sites are very close in space, there may be additional free energy contributions due to secondary interactions.

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