Self-Assembling Ternary Complex Stabilities and Template Ratios in Carceplex Formation

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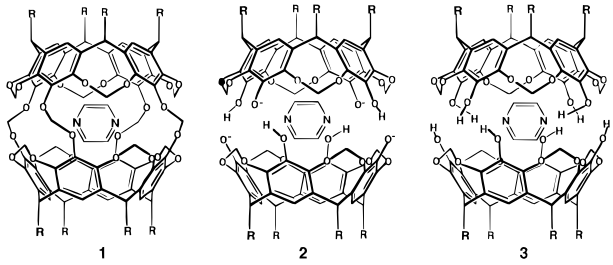
Carceplexes are container host molecules with encapsulated guest molecules.[1] The efficient synthesis of carceplexes depends on template effects: molecular recognition between a guest and the host precursors leads to self-assembly into stable complexes; subsequent ring-closing reactions can lead efficiently to carceplexes.[2] Once the container molecule is formed, it retains the guest by constrictive binding.[1] A variety of applications can be conceived for these complexes and carceplexes: drug delivery and release, orientation of magnetic and optical nanocomponents, and catalysis of reactions are among the most exciting. To develop these applications, we seek to understand quantitatively the forces controlling self-assembly, such as van der Waals and electrostatic interactions of the host and guest molecules, solvation and desolvation, and entropy. This study reports progress toward that goal.

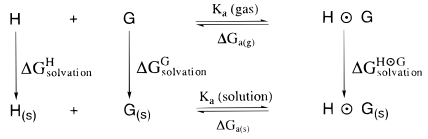
Sherman et al. have measured relative yields of formation of carceplexes (**1**) from competition reactions with a series of 24 guest molecules.[3,4] The ratios of yields, normalized to 1 for



N-methylpyrrolidone (NMP), are known as template ratios. The values are given in Table 1. The equilibrium constants (K_{rel}) for formation of ternary complexes, consisting of two methylene-bridged resorcinarene diol dioxides and a guest molecule (**2**, R = CH_3), have also been measured.[2] Template ratio differences as large as a million-fold are observed between pyrazine and NMP as guest molecules. The template ratios correlate well with the K_{rel} values of ternary complex (**2**),[2] indicating that the ternary complexes are similar to the transition states for the guest-determining step of carceplex formation.

The free energy of formation of the ternary complex, H•G, in the gas phase and in solvent are related by the thermodynamic cycle shown in Scheme 1. The absolute free energy of association in solution, $\Delta G_{a(s)}$, is expressed as follows.

Scheme 1



$$\Delta G_{a(s)} = \Delta G_{a(g)} + \Delta G^{H\bullet G}_{solvation} - (\Delta G^{H}_{solvation} + \Delta G^{G}_{solvation}) \quad (1)$$

The solvation free energy of the host is a constant, and we assume that the solvation free energy of the ternary complexes is approximately constant, since the different guest molecules are surrounded by the same host molecule. We also approximate $\Delta G_{a(g)}$ by the calculated $\Delta E_{a(g)}$. With these approximations the following applies:

$$\Delta G_{a(s)} \approx \Delta E_{a(g)} - \Delta G^{G}_{solvation} + \text{constant} \quad (2)$$

Gas phase complexation energies were calculated using Macromodel 4.5[5] with the AMBER* force field[6] from the energies of the optimized ternary complex (**3**) and the sum of the energies of empty resorcinarene dimer and a guest molecule. Relative and absolute free energies of solvation $\Delta G^{G}_{solvation}$ of the guest molecules in chloroform were calculated with BOSS 3.5,[7,8] using OPLS parameters.[9]

Table 1 summarizes the calculations performed here. Tetrol dimer complex **3** was used for the calculations as a model

Table 1. Experimental Template Ratios, K_{rel}, Calculated Complexation Energies, and Solvation Free Energies (kcal/mol) of Guests

guest	exptl template ratio[3]	exptl K_{rel}[2]	calcd $\Delta E_{a(g)}$ for **3**	calcd $\Delta G^{G}_{(s)}$ (BOSS Monte Carlo)	calcd $\Delta G_{a(s)}$ (eq 2)
pyrazine	1000000	580	−24.3	−7.8	−16.5
1,4-dioxane	290000	71	−18.5	−5.8	−12.7
dimethyl sulfide	180000		−16.2	−1.6	−14.6
1,3-dioxolane	38000		−20.5	−6.3	−14.2
2-butanone	37000		−18.5	−5.2	−13.3
pyridine	34000	9.5	−22.5	−6.7	−15.8
dimethyl sulfone	19000		−19.9	−6.2	−13.7
furan	12000		−19.5	−6.3	−13.2
tetrahydrofuran	12000		−19.1	−5.4	−13.7
acetone	6700	0.9	−15.8	−4.1	−11.7
thiophene	5800		−21.1	−5.4	−15.7
benzene	2400	1.0	−20.7	−5.3	−15.4
2-propanol	1500		−15.6	−4.8	−10.8
pyrrole	1000		−20.9	−5.6	−15.3
tetrahydrothiophene	410		−16.6	−3.0	−13.6
1,3-dioxane	200		−15.2	−4.1	−11.1
acetamide	160		−17.6	−5.6	12.0
trioxane	100		−16.5	−5.2	−11.3
acetonitrile	73		−11.0	−3.6	−7.4
ethanol	61		−12.6	−4.0	−8.6
dimethylacetamide	20		−15.8	−8.2	−7.6
dimethylformamide	7		−16.5	−6.5	−10.0
NMP	1		−15.0	−7.0	−8.0

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(7) Jorgensen, W. L. *BOSS*, version 3.5; Department of Chemistry, Yale University: New Haven, Connecticut, 1995. The free energies of solvation were calculated by the Monte Carlo free energy perturbation method using BOSS and standard procedures.[8] All simulations include 260 chloroform molecules and one solute molecule in the NPT ensemble at 1 atm and 25 °C. A typical perturbation between two guests consist of seven windows

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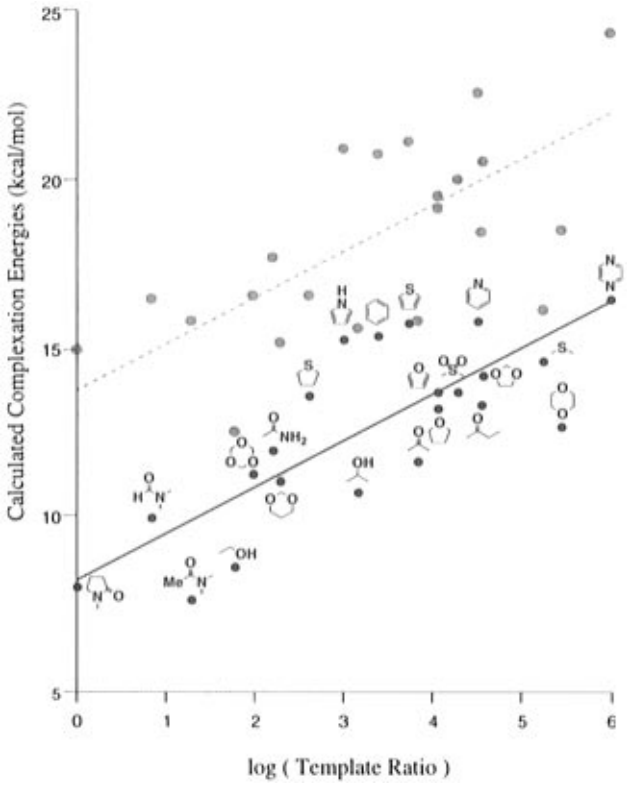

Figure 1. Correlation between experimental template ratios[3] and calculated complexation energies of ternary complexes with (red circles) and without (gray circles) calculated guest solvation energy corrections. The correlation lines are the following: red circles, $\Delta E_{a(g)} = 1.33 \log K_{rel} + 13.5$ ($r = 0.65$); gray circles, $\Delta G_{a(s)} = 1.34 \log K_{rel} + 8.0$ ($r = 0.78$).

ternary complex, since neglect of the counterion and solvent in **2** causes unrealistically strong hydrogen bonds and a ternary complex structure which is too tight.

We have performed calculations on the entire series of molecules studied by Sherman, and here, we compare our results to the experimental template ratios.[2,3] Template effects were measured in NMP instead of chloroform, but we assume here that the solvation energies of guest molecules are similar in the two solvents. Calculation of solvation energies for a few guests in NMP supported this assumption.[10] Figure 1 shows two plots of the calculated complexation energies vs the log of the experimental template ratios. Gray circles show the gas phase complexation energy (the first term of eq 2) and red circles include the free energies of solvation for guest molecules (eq 2).

The observed million-fold variation for the template ratio from pyrazine to NMP corresponds to an 8 kcal/mol range in complexation energies at room temperature. The ideal slope, $2.3RT$ (1.36 kcal/mol), is very well reproduced on both plots in Figure 1. The vertical distance between two plots is the guest solvation energy, which reduces the magnitude of the association energy. Pyrazine has not only the most favorable solvation energy (−7.8 kcal/mol) but also the largest intrinsic binding energy. The association constant is large in spite of the favorable solvation. NMP is one of the poorest binders intrinsically, and its favorable solvation (−7.0 kcal/mol) also contributes to its poor complexation in solution. Dimethyl sulfide is a poor binder intrinsically, but its free energy of solvation (−1.5 kcal/mol) is the least favorable, so it forms a relatively stable complex.

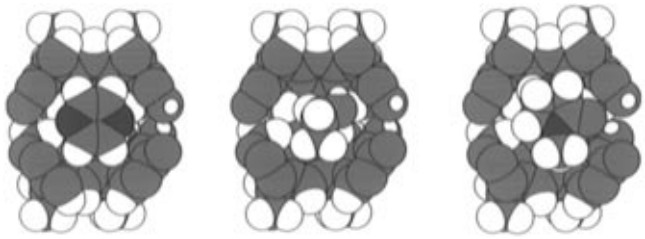

Figure 2. Cut away space-filling models of tetrol ternary complexes (**3**) of pyrazine, ethanol, and NMP.

While there is considerable scatter in Figure 1, the data seem to be grouped into two correlations, one for the aromatics and the other for the remaining molecules. This might be due to some of the approximations in eq 2. First, the free energy of solvation of the ternary complexes of polar or large molecules could be more favorable than for less polar aromatics. Second, the inclusion of entropic effects on complexation free energies might decrease the predicted free energies of binding of the tight-fitting nonaromatic molecules. To check those factors, calculations on the relative solvation free energies of the ternary complexes and free energy perturbation calculations for the conversion of one ternary complex to another will be performed. Some of the deviations from linearity in Figure 1 may also result from inaccuracies in the force field.

The calculations do faithfully reproduce the trends, aiding the analysis of the origin of the widely different complex stabilities and template ratios. The most stable complexes are those in which the guest molecule fits snugly into the cavity, with van der Waals contacts in the "polar" regions of the carceplex and electrostatic interactions in the "equatorial" regions. Pyrazine appears to fulfill these criteria perfectly; the goodness of fit is demonstrated in the cutaway of the space-filling model of the pyrazine−ternary complex shown in Figure 2.[4] Pyridine and benzene are progressively poorer because the polar nitrogen is replaced by the larger, and less polar, CH bonds. The remaining hydrogens should become less negative and have less stabilizing interactions with the host aromatic rings along the series of pyrazine, pyridine, benzene. The poorest binders are either somewhat too large, such as *N*-methylpyrrolidone (NMP), or are too small to have many favorable contacts, as with ethanol (see Figure 2).

We have shown that it is possible to calculate relative free energies of the complexation of ternary complexes and thus to understand the factors that govern template effects for these carceplexes. Calculations of this type are of major significance for the design of self-assembling molecular complexes in solution and for the understanding of molecular recognition.

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with 1 million configurations for equilibrium and 2 million configurations for sampling. For guest molecules with no OPLS parameters available, CHELPG atomic charges (Breneman, C. M.; Wiberg, K. B. *J. Comput. Chem.* **1990**, *11*, 361.) from RHF/6-31G* calculations were employed[11] along with standard van der Waals parameters.[8]

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