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Thermodynamic study on supramolecular complex formation of theophylline derivates with a synthetic receptor

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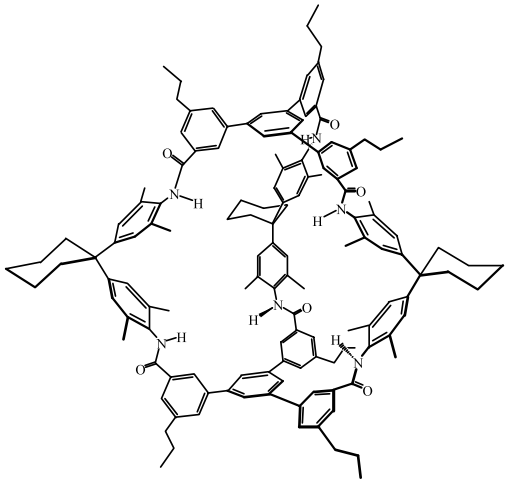
Abstract—Thermodynamic parameters for the supramolecular complex formation of macrobicyclophane with several theophylline dimers are reported. Solvation of guests plays an important role in the supramolecular complex formation. A good correlation between ΔG and guest solubility is obtained in different $CHCl_3/CH_2Cl_2$ proportions. © 2003 Elsevier Science Ltd. All rights reserved.

The xanthine derivatives theophylline **2**, caffeine **3** and theobromine **4** are small and biorelevant molecules well-known for their pharmacological properties, such as CNS-stimulation, bronchodilator, diuretic and tachycardia activity.[1] Recently, Waldvogel et al.[2] and our research group[3] have prepared, independently, new tridimensional receptors with a C_3-symmetrical structure capable of using the third dimension to surround alkylated oxopurines in a more efficient way. Our receptor **1** (Fig. 1) is a three-dimensional macrobicyclic receptor of the cyclophane type which acts as a molecular box.

In this paper, we report on the thermodynamic study of the formation of supramolecular complexes of macrobicyclophanic receptor **1** with several dimer derivatives of theophylline, in $CHCl_3$ and CH_2Cl_2 at 293 K. To this end, isothermal titration calorimetry (ITC)[4] was used to quantify the thermodynamic parameters of this association. We have found an interesting solvent effect, i.e. solvation of guests, in the supramolecular complex formation.

The rigid dimer derivatives of theophylline **5** (Table 1) were synthesised from theophylline by alkylation fol-



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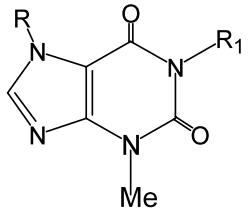

R= H, R_1 = Me **2**
R = Me, R_1 = Me **3**
R = Me, R_1 = H **4**

Figure 1. Macrobicyclophane receptor and hosts.

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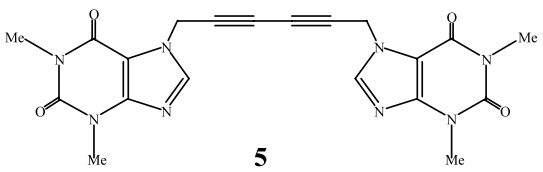
Table 1. Thermodynamic data obtained by ITC from theophylline dimers and host **1**[a]



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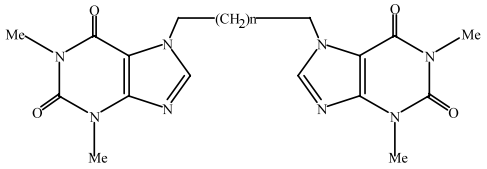

6, n = 2; **7**, n = 4; **8**, n = 6;
9, n = 8; **10**, n = 10

Guest	Solvent	n	K_{ass} (M^{-2})	ΔG (kcal mol^{-1})	ΔH (kcal mol^{-1})	ΔS (cal K^{-1} mol^{-1})
5	$CHCl_3$	0.8	923±7 (M^{-1})	−3.9	−7.5	−11.9
6	$CHCl_3$	0.9	528±61 (M^{-1})	−3.6	−7.1	−12.0
7	$CHCl_3$	0.6	9615±350	−5.3	−16.4	−38.0
8	$CHCl_3$	0.5	1114±80	−4.1	−16.4	−41.9
9	$CHCl_3$	0.5	352±13	−3.4	−12.3	−30.3
10	$CHCl_3$	0.5	293±28	−3.3	−12.9	−32.6
5	CH_2Cl_2	0.5	271500±7800	−7.3	−13.0	−19.4
6	CH_2Cl_2	0.6	1610±470	−4.3	−8.5	−14.5
7	CH_2Cl_2	0.4	1173500±24000	−8.1	−18.8	−36.6
8	CH_2Cl_2	0.4	88300±2700	−6.6	−15.8	−31.3
9	CH_2Cl_2	0.5	34350±2500	−6.1	−14.8	−29.8
10	CH_2Cl_2	0.4	12150±700	−5.5	−19.1	−46.4

[a] K_{ass}, ΔH and ΔS were obtained at 293° K by curve fitting using Origin 5.0 software as implemented by MicroCal™.

lowed by oxidative dimerization.[5] The treatment of theophylline with dihalides X-$(CH_2)_n$-X (X = Br or I, n = 2, 4, 6, 8, 10) in DMF containing potassium carbonate[5] gave the corresponding dimers of theophylline (**6**–**10**) (Table 1).

The results of complexation—average of three independent runs—of dimer derivatives of theophylline are summarised in Table 1, showing that all equilibria are exothermic. The thermodynamic analysis reveals that the association is enthalpically favoured and entropically disfavoured. This type of binding forces are basically of enthalpic origin and their effects can be compensated entropically. In this way, when the entropy decreases (more negative) the attractive interaction, ΔH, between host and guest decreases (more negative). A linear correlation between ΔH and ΔS has been obtained for all theophylline dimers in $CHCl_3$ and CH_2Cl_2—see Figure 2—which can be explained in terms of the existence of a real isoequilibrium relationship[6] between ΔH and ΔS, verified by the fact that the free energy, ΔG, did not vary considerably when measured at three different temperatures: 279 K, $\Delta G = -7.6$; 293 K, $\Delta G = -7.3$ and 308 K, $\Delta G = -6.5$ Kcal mol^{-1} in the complexation of host **1** with the rigid dimer **5** in CH_2Cl_2. This compensation relationship suggests the important role the restriction of freedom of movement of macrobyciclophanic receptor **1** and the guests plays in the complexation process.

In general, our receptor **1** is sparingly soluble in common organic solvents except $CHCl_3$ and CH_2Cl_2. Therefore, our thermodynamic study has been carried out in these solvents. In all cases, better results were achieved in dichloromethane with regard to chloroform, the former giving the highest binding constant values. Thus, when comparing the association constants obtained in the complexation of CH_2Cl_2 and $CHCl_3$, a significant increase was observed, as in the case of receptors **5** and **7**—up to two orders of magnitude. The strongest interaction, that of host **1**, in dichloromethane and chloroform takes place with the flexible guests **7**, **8** and the rigid guest **5**.

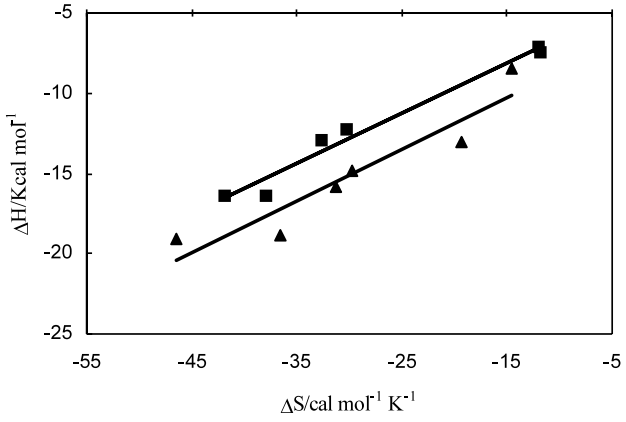

Figure 2. Plot of ΔH versus ΔS for complexation of **1** with hosts (■, $CHCl_3$, $R^2 = 0.974$; ▲, CH_2Cl_2, $R^2 = 0.890$).

In general, see Table 1, the stoichiometry parameter 'n' was in the range 0.4–0.6—except in complexation **5** and **6** in $CHCl_3$. The above observations can be accounted for through the formation of a maximum of two pairs of three tridentate hydrogen bonds between the rings of theophylline dimers and the two macrobyciclophanes **1** NH amide systems.

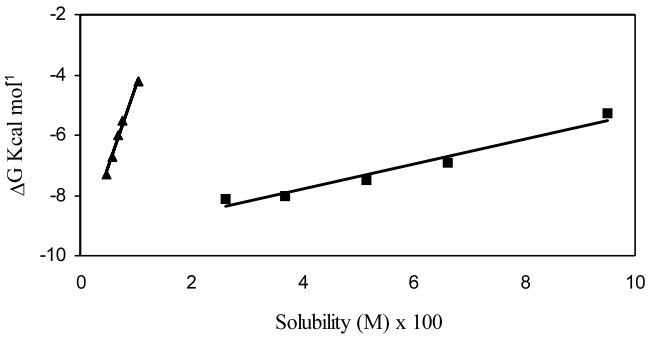

Figure 3. Correlation between binding free energy and guest solubility at different proportions of $CHCl_3/CH_2Cl_2$: 0, 25, 50, 75 and 100% vol. (▲, **5**, $R^2=0.996$; ■, **7**, $R^2=0.973$).

The binding constants of the supramolecular complexes of macrobicyclophanic receptor **1** host and the dimers of theophylline are, thus, solvent dependent. In these cases the study of the solubility of a compound measures somehow the extent of the solvent–substrate interaction.[7] Therefore, the solubilities of the rigid guest **5** and the flexible guest **7** have been experimentally obtained in different proportions of $CHCl_3/CH_2Cl_2$: 0, 25, 50, 75 and 100% in volume.[8] When plotting these experimental values, solubility against free energies, ΔG, obtained by ITC at the proportions above-mentioned, two excellent linear straight are attained (see Figure 3) both with a strong correlation ($R^2=0.996$ for **5** and $R^2=0.973$ for **7**). Thus, complex formation competes with solvation of the guest in $CHCl_3/CH_2Cl_2$. These linear correlations are indicative of the important role of guest desolvation. As depicted in Figure 3, solubility of the flexible dimer **7** is approximately 10 times higher than that of the rigid dimer **5**. This rigid dimer presents a remarkable slope, thus, resulting very sensitive to the different proportions of the $CHCl_3/CH_2Cl_2$ mixture. These experimental results show that guests are less solvated (less solubility), as in CH_2Cl_2, and present a greater binding strength (higher K_{ass}) than that in $CHCl_3$ (higher solubility). In summary, we have demonstrated a good association strength in $CHCl_3/CH_2Cl_2$ between receptor **1** and theophylline dimers. The binding strength of a supramolecular complex depends on attractive host–guest interactions, $-\Delta H$, and on unfavourable changes in entropy, due to the important restriction of freedom of movement of host and guest during the supramolecular complex formation. We have also observed a strong solvent effect and the significant role of guest desolvation in CH_2Cl_2 in relation to $CHCl_3$.

Acknowledgements

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