Water-soluble Cryptophane Binding Lipophilic Guests in Aqueous Solution

Josette Canceill, Liliane Lacombe, and André Collet*

Collège de France, Chimie des Interactions Moléculaires, E.R. C.N.R.S. No. 285, 11, place Marcelin-Berthelot, 75005 Paris, France

The first water-soluble cryptophane (**4**) has been synthesized in three steps from cryptophane-A (**1**); (**4**) has been found to complex chloroform and dichloromethane strongly in D_2O, with binding constants in the range 10^3—10^4 dm^3/mol.

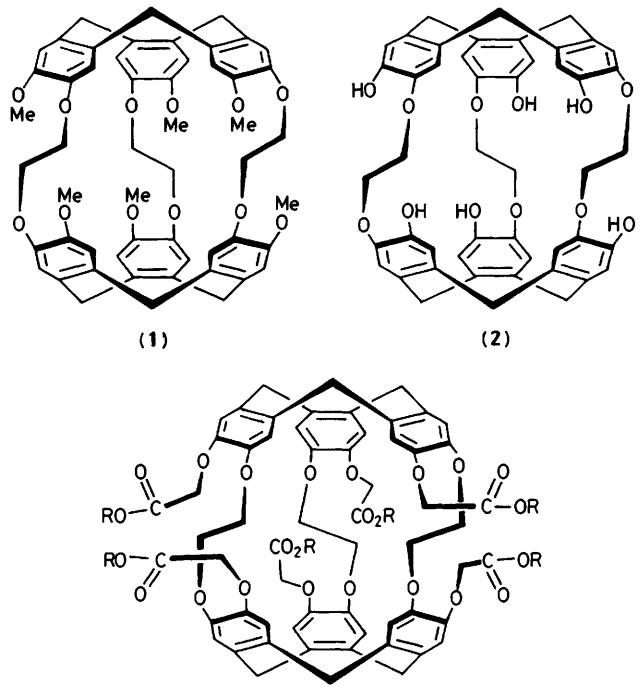
Lipophilic hosts of the cryptophane[1] family [*e.g.*, (**1**)] bind neutral molecules of complementary size and shape such as the halogenomethanes, in the absence of any hydrophobic effects, to form highly structured and very stable 1:1 complexes ($K_s > 10^2$ dm^3/mol in 1,1,2,2-tetrachloroethane).[2] In order to estimate to what extent hydrophobic forces could further stabilize these host–guest supermolecules, it was desirable to synthesize a water-soluble cryptophane.[3] Accordingly, we report here the conversion of cryptophane-A (**1**) into the hexa-acid derivative (**4**), and some preliminary experiments on the complexation of $CHCl_3$ and CH_2Cl_2 by (**4**) in D_2O.

Hexademethylation of the readily available (**1**)[4] to the hexaphenol (**2**) (cryptophanol-A) was satisfactorily achieved by using lithium diphenylphosphide[5] [2 equiv. per OMe group, tetrahydrofuran (THF), 24 h, room temp., 60%]. The latter, on reaction with Cs_2CO_3 [1.03 equiv. per OH group, dimethylformamide (DMF), 1 h, room temp.] and subsequent alkylation with an excess of methyl bromoacetate (20 h, 60 °C), gave the hexaester (**3**) in 65% yield, m.p. 195 °C (from

Table 1. Thermodynamic and kinetic parameters for guest inclusion.[a]

		CH_2Cl_2		$CHCl_3$	
Host	Solvent	ΔG_i	$\Delta G_i^{\ddagger}$	ΔG_i	$\Delta G_i^{\ddagger}$
(**1**)	$(CDCl_2)_2$	-3.7 ± 0.1	9.4 ± 0.5	-3.3 ± 0.1	9.6 ± 0.5
(**4**)	D_2O	-5.1 ± 0.5	9.8 ± 1.0	-5.3 ± 0.5	10.5 ± 1.0
Hydrophobic stabilization		-1.4 ± 0.6		-2.0 ± 0.6	

[a] ΔG_i (free energy for guest inclusion) and $\Delta G_i^{\ddagger}$ (barrier for guest inclusion) in kcal/mol at 300 K; the barrier for guest exclusion ($\Delta G_e^{\ddagger}$) was determined from the line shape of the free and complexed guest resonances and $\Delta G_i = \Delta G_e^{\ddagger} - |\Delta G_i|$.



(1) (2)

(3); R = Me
(4); R = H

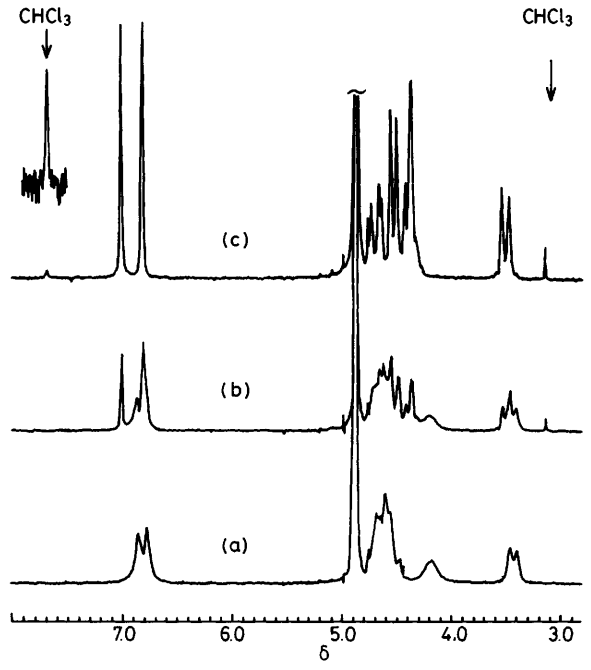


Figure 1. ^{1}H N.m.r. spectra of hexa-acid (**4**) (0.009 M) in D_2O with *ca.* four of the CO_2H groups ionized by addition of NaOD (see text); (a) original solution; (b) *ca.* 0.5 equiv. of $CHCl_3$ added; (c) *ca.* 1.1 equiv. of $CHCl_3$ added; the DOH peak was taken as the reference (δ 4.700).

$CHCl_3$–MeOH), *m/z* (f.a.b.m.s.) 1243.54. Saponification with a slight excess of NaOH (MeOH–H_2O 1 : 1, 3 h, reflux) and acidification (HCl) eventually afforded (**4**), m.p. 220—230 °C, in quantitative yield. New compounds (**2**)—(**4**) displayed expected ^{1}H n.m.r. spectra.†

Addition of *ca.* four equivalents of NaOD was sufficient to solubilize the hexa-acid (**4**) in D_2O (pD *ca.* 6).[6] Small-angle *X*-ray scattering experiments did not reveal the presence of aggregates at 10^{-2} M concentration, and such solutions were used for all binding studies.

The 200 MHz ^{1}H n.m.r. spectrum of the 'empty' host (Figure 1a) showed broadened signals probably due to the presence of trace amounts of small organic molecules‡ (solvent residues) undergoing reversible complexation. On addition of less than one equivalent of $CHCl_3$ (Figure 1b), a new set of sharp resonances appeared for the host while no signal was detected for $CHCl_3$ at the expected position; instead, a peak at δ 3.15 was present, and ascribed to complexed $CHCl_3$. Only when slightly more than one equivalent of the guest was added did the free $CHCl_3$ become observable at δ 7.69, and then all the host resonances simplified into a single set of sharp peaks that we ascribe to the [(**4**)–$CHCl_3$] supermolecule (Figure 1c). The peak at δ 3.15 vanished on irradiation at δ 7.69 (saturation transfer) thus confirming the above assignment and indicating that (**4**) reversibly binds $CHCl_3$ in water. The upfield shift induced by the host on the guest resonance (Δδ 4.54) is similar in magnitude to that induced by the other cryptophanes, and especially by (**1**) binding $CHCl_3$ in $(CDCl_2)_2$ (Δδ 4.33).

The complexation of CH_2Cl_2 by (**4**) followed the same trend, the complexed guest resonance being observed at δ 1.15, instead of 5.50 for the free species. Competition experiments showed that $CHCl_3$ was preferred over CH_2Cl_2 by *ca.* 0.25 kcal/mol (1 cal = 4.184 J) (stability constants ratio 1.54 ± 0.1 at 300 K). The actual stability constants were roughly estimated (±60%) to be $K_s \sim 7.7 \times 10^3$ and $\sim 5 \times 10^3$ dm^3/mol for $CHCl_3$ and CH_2Cl_2, respectively. For comparison, the complexation of the same guests by lipophilic host (**1**) was studied in $(CDCl_2)_2$, and it showed reversed selectivity, dichloromethane [K_s 475 dm^3/mol (±20%)] being preferred over chloroform (K_s 230 dm^3/mol) by 0.43 kcal/mol.

As previously discussed in the case of cryptophane-E,[2] the ΔG_i values (Table 1) for (**1**) complexing CH_2Cl_2 and $CHCl_3$ principally originate from overall attractive host–guest interactions§ and hence should represent the 'lipophilic forces' responsible for the stability of the complexes. On going from (**1**) in $(CDCl_2)_2$ to (**4**) in D_2O, the barrier ($\Delta G_i^{\ddagger}$) for entrance of the guests shows little variation, and we presume that the difference in the ΔG_i values in both solvents at least in part corresponds to the 'hydrophobic forces' that enhance the stability of the complexes in water. As would be expected, the hydrophobic contribution is larger for chloroform, which is *ca.* 30% bulkier in volume than dichloromethane, and therefore might account for the inversion of the selectivity of (**1**) and (**4**) *vs.* these guests on going from a lipophilic to a hydrophilic

† Positive ion fast atom bombardment mass spectra (f.a.b.m.s.) were taken on a ZAB HF spectrometer, n.m.r. spectra were recorded on a Brucker AM200SY instrument operating at 200.13 MHz; cryptophanol-A (**2**) (δ from internal $SiMe_4$ in CD_3COCD_3): 3.16 (d, H_e) and 4.40 (d, H_a, *J* 13.5 Hz), 4.40 (s, OCH_2CH_2O), 6.63 and 6.73 (s,s, ArH), 7.70 (s, OH); hexaester (**3**) (δ from internal $SiMe_4$ in CD_3COCD_3): 3.34 (d, H_e) and 4.55 (d, H_a, *J* 13.7 Hz), 3.82 (s, OCH_3), 4.41 (m, OCH_2CH_2O), 4.78 (q, OCH_2CO_2), 6.82 and 6.89 (s,s, ArH); hexa-acid (**4**) (δ from internal $SiMe_4$ in CD_3SOCD_3 + CF_3CO_2D): 3.25 (d, H_e) and 4.48 (d, H_a, *J* 13.3 Hz), 4.20 (s, OCH_2CH_2O), 4.56 (s, OCH_2CO_2), 6.77 and 6.81 (s,s for ArH). Satisfactory elemental analyses were obtained for (**2**) and (**3**).

‡ A small amount of acetone was identified by n.m.r. spectroscopy after it had been displaced by addition of $CHCl_3$; thus acetone must be weakly bound, compared to the halogenomethanes.

§ This view is supported by the large exothermal ΔH values measured for host (**1**) complexing CH_2Cl_2 (−3.3 kcal/mol) and $CHCl_3$ (−8.2 kcal/mol) in $(CDCl_2)_2$ (values obtained from the variation of K_s with *T*).

medium. However, a number of important parameters, with regard to the solvent–host and solvent–guest interactions, as well as the complexation enthalpy and entropy values, have yet to be measured, and such data will provide valuable information as to the relative contributions of 'lipophilic' and 'hydrophobic' effects in the formation of the cryptophane–halogenomethane complexes, and in general, in the formation of neutral host–neutral guest supermolecules.

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