Complexation of Cyclodextrins with Anion Constituents of Antigenic Determinants in Water (Axial Complexes) and in *N,N*-Dimethylformamide (Equatorial Complexes). A Thermodynamic Study

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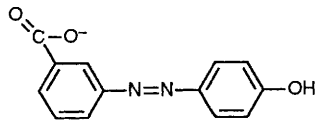
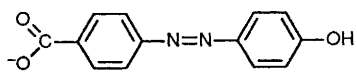
The first set of thermodynamic data on the complexation of cyclodextrins with anion constituents of antigenic determinants (4′-hydroxyazobenzene-3- and -4-carboxylate) and on the transfer of α- and γ-cyclodextrins in the water–*N,N*-dimethylformamide solvent system are reported; the data suggest the formation of axial or inclusion complexes in water and equatorial or lid type complexes in *N,N*-dimethylformamide.

Cyclodextrins (CDs) have been extensively used as models for enzymatic specificity.[1] There have been a number of recent reports on the complexation of CDs with biological membrane components in water.[2,3] The suggestion that CDs could be useful models for the study of antigen–antibody[4,5] interactions prompted us to investigate the binding properties of CDs towards anion constituents of antigenic determinants (haptens) as a first step in our research programme on the thermodynamics of binding of monoclonal antibodies with these haptens.

Our approach to the study of the CD–substrate complexation processes in different media considers transfer data for the guest and receptor between these media. We are not aware of a previous report on the transfer of CDs and their adducts between solvents, and we now report the first thermodynamic data on the complexation of 4′-hydroxyazobenzene-3- and -4-carboxylate (**1**) and (**2**) with CDs (α and



(1)



(2)

Table 1. Thermodynamic parameters of complexation of cyclodextrins with the anions (**1**) and (**2**) in water and in *N*,*N*-dimethylformamide at 298.15 K.

	Solvent: water					
	α-Cyclodextrin			γ-Cyclodextrin		
Anion	$\Delta G°_c$[a] /kJ mol^{-1}	$\Delta H°_c$[a] /kJ mol^{-1}	$\Delta S°_c$ /J K^{-1} mol^{-1}	$\Delta G°_c$[a] /kJ mol^{-1}	$\Delta H°_c$[a] /kJ mol^{-1}	$\Delta S°_c$ /J K^{-1} mol^{-1}
(**1**)	−21.23	−33.35	−40.6	−22.49	−25.18	−9.0
(**2**)	−20.72	−29.13	−28.2	−23.57	−20.44	10.5
	Solvent: *N*,*N*-dimethylformamide					
(**1**)	−19.81	−21.37 (−21.18)[b]	−5.2 (−3.7)[b]	−23.06	−22.05 (−21.18)[b]	3.4 (−3.7)[b]
(**2**)	−21.52	−15.53 (−19.30)[b]	20.8 (20.8)[b]	−23.69	−15.56 (−19.30)[b]	27.3 (20.8)[b]

[a] From calorimetric data. [b] $\Delta H°_t$ and $\Delta S°_t$ values for the anions (**1**) and (**2**) from water to methanol: refs. 8 and 9.

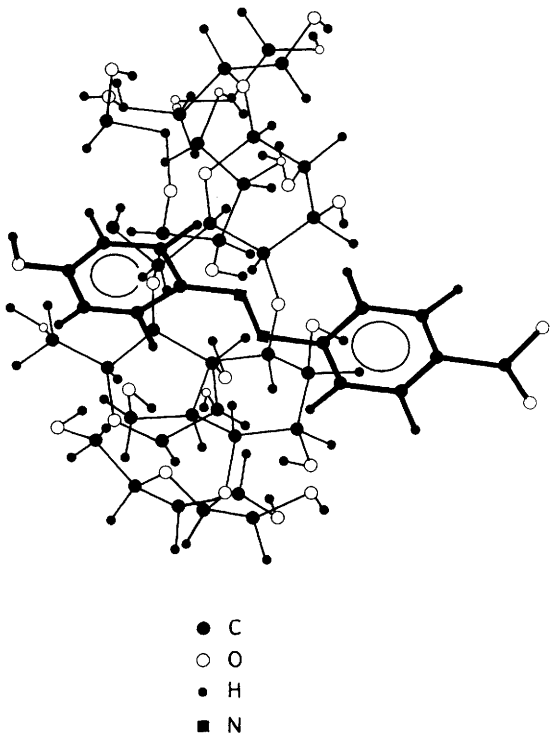


Figure 1. Computer modelling for α-CD–(**2**) (axial) complex.

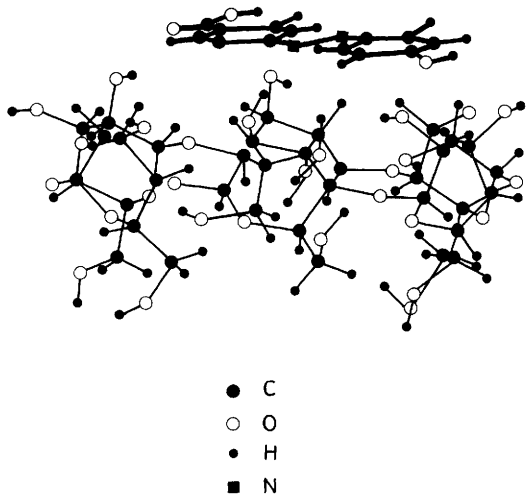


Figure 2. Computer modelling for α-CD–(**2**) (equatorial) complex.

γ) in water and in *N*,*N*-dimethylformamide (DMF) and on the transfer of CDs from H_2O to DMF.

Complexation data obtained calorimetrically are listed in Table 1. The most striking feature of these results is reflected in the enthalpy ($\Delta H°_c$) and entropy ($\Delta S°_c$) values for these anions and CDs in H_2O and in DMF. In water, these values are ligand dependent. Thus, for a given anion (**1**) or (**2**) (X^-), the differences in equations (1) and (2) are found. These data

$$\Delta H°_cX^-(\alpha\text{-CD}) - \Delta H°_cX^-(\gamma\text{-CD}) = ca.\ -8.4\ \text{kJ mol}^{-1} \quad (1)$$

$$\Delta S°_cX^-(\alpha\text{-CD}) - \Delta S°_cX^-(\gamma\text{-CD}) = ca.\ -35.0\ \text{J K}^{-1}\ \text{mol}^{-1} \quad (2)$$

suggest that, independently of the anion, substitution of α-CD for γ-CD results in an almost constant variation in the $\Delta H°_c$ and $\Delta S°_c$ values. This must be attributed to the release of water from the ligand's cavity upon complexation. In an attempt to establish the site of complexation of these anions and CDs in water, we studied the 2-carboxylate and substituted 2-carboxylate analogues of (**1**) and (**2**) with α- and γ-CDs in water. No complexation occurs between these anions and these ligands in H_2O. These observations lead to the suggestion that (a) the hydroxy substituted ring must be the active site of complexation of the anions (**1**) and (**2**) and CDs in H_2O and (b) steric effects which may be attributed to the position of the substituent group are likely to be responsible for the lack of complexation of the 2-carboxylate analogues with CDs in water. Computer calculations using the Cosmic package[5] support the interpretation that it is indeed the hydroxy substituted ring that is the active site of complexation of these anions. The structural conformation which corresponds to the minimum energy (higher stability) for the formation of inclusion complexes is that shown in Figure 1.

Unlike H_2O, in DMF no significant differences are observed between the $\Delta H°_c$ and $\Delta S°_c$ values of a given anion with α- and γ-CDs. These findings lead us to suggest that the cavity of the ligand is unlikely to provide the site of complexation for these anions in DMF. This could be attributed to (i) a strong DMF–ligand interaction with DMF molecules included in the ligand cavity or (ii) a strong interaction between these anions and the hydroxy groups of CDs (outside the cavity). Both possibilities were investigated.

For the former (i) the thermodynamic parameters for the transfer of CDs from H_2O to DMF were determined. These values (α-CD: $\Delta G°_t$ 1.74 kJ mol^{-1}, $\Delta H°_t$ −44.34 kJ mol^{-1}, $\Delta S°_t$ −155.9 J K^{-1} mol^{-1}; γ-CD: $\Delta G°_t$ 1.56 kJ mol^{-1}, $\Delta H°_t$ −59.79 kJ mol^{-1}, $\Delta S°_t$ −205.8 J K^{-1} mol^{-1}) are atypical for transfer of non-electrolytes from H_2O to DMF. $\Delta H°_t$ and $\Delta S°_t$ values are opposite in sign to those obtained for the transfer of other macrocyclic ligands (cryptands and crowns[7]) from H_2O to DMF. Indeed, these data reflect a strong interaction between CDs and DMF. A definite size effect is reflected in the $\Delta H°_t$ values showing an increase in stability (in enthalpic terms) in DMF as the size of the CD cavity increases. These data suggest that inclusion of the solvent in the ligand cavity is likely to occur. Therefore, it should not be surprising to find that, unless the energy requirements to remove the solvent from the cavity are met, formation of inclusion complexes in DMF will not occur.

For the latter possibility (ii), the complexation process may be visualized as the transfer of the anions (**1**) and (**2**) from DMF to a hydroxy-rich environment (the ligand). Therefore transfer data for these anions from DMF to methanol are relevant for the interpretation of the process. $\Delta H°_t$ and $\Delta S°_t$ values for (**1**) and (**2**) from DMF to methanol are given in parentheses in Table 1. The remarkable agreement found with transfer and complexation data in DMF, particularly with α-CD, strongly support the interpretation that equatorial or lid type complexes are formed in DMF. The structural conformation (obtained from computer calculations) which corresponds to the minimum energy (higher stability) for lid type complexes is that shown in Figure 2. This interpretation that axial complexes exist in water and equatorial complexes in DMF is supported by spectrophotometric measurements. Results will be reported shortly.

Finally, we stress that this work involves the investigation of the properties of cyclodextrins in nonaqueous media for which little is known, and demonstrates that the combination of thermodynamic data of complexation with transfer data for the guest species particularly to a reaction medium containing functional groups common to receptors is a powerful tool in the understanding of cyclodextrin–substrate interactions.

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References

1 M. L. Bender, Proc. First Internat. Symposium on Solution Behaviour, Theoretical and Practical Aspects, eds. K. J. L. Mittal and E. J. Fendler, Plenum Press, New York, 1982, vol. 2.
2 M. Komiyama, *Chem. Lett.*, 1988, 689; *Makromol. Chem., Rapid Commun.*, 1988, 453.
3 Y. Okahata and X. Te, *J. Chem. Soc., Chem. Commun.*, 1989, 1147.
4 F. Cramer, W. Saenger, and H. Ch. Spatz, *J. Am. Chem. Soc.*, 1967, **89**, 14.
5 J. G. Vinter, A. Davis, and M. R. Saunders, *J. Comput. Aided Molecular Design*, 1987, **1**, 31.
6 A. F. Danil de Namor and L. Ghousseini, *J. Chem. Soc., Faraday Trans. 1*, 1985, **81**, 781.
7 A. F. Danil de Namor and F. Fernandez Salazar, unpublished results.
8 A. F. Danil de Namor, R. Traboulssi, and F. H. Marquardt, *J. Chem. Soc., Faraday Trans. 1*, 1990, **86**, 1067.
9 A. F. Danil de Namor, R. Traboulssi, and M. Salomon, *J. Chem. Soc., Faraday Trans. 1*, 1990, in the press.