Thermochimica Acta, 162 (1990) 155–161 155
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

CALORIMETRIC AND DIFFUSIONAL BEHAVIOUR OF THE SYSTEM α-CYCLODEXTRIN–L-PHENYLALANINE IN AQUEOUS SOLUTION *

L. PADUANO, R. SARTORIO, V. VITAGLIANO and G. CASTRONUOVO
Dipartimento di Chimica dell'Università di Napoli, Via Mezzocannone 4, 80134 Napoli (Italy)

(Received in final form 20 September 1989)

ABSTRACT

The interaction of L-phenylalanine with α-cyclodextrin in aqueous solution has been studied by calorimetry at 25 ° C.

The results indicate that inclusion occurs: the value of the association constant is in very good agreement with that obtained from diffusion measurements.

INTRODUCTION

The peculiar ability of cyclodextrins (cycloamyloses) to form inclusion complexes with a variety of organic and inorganic compounds, either in solution or in the solid state, has aroused the interest of many researchers, and much has been written about their chemical, physico-chemical and biological properties [1].

The thermodynamics of the inclusion of several organic compounds in α-cyclodextrin has been recently studied in our laboratory [2], as well as the isothermal diffusion of α-cyclodextrin in binary and ternary aqueous solutions [3,4]. The effect of the inclusion equilibrium upon the cross-diffusion terms has been described for the system α-cyclodextrin–L-phenylalanine–water.

This paper presents a calorimetric study of this system. The value of the binding constant is shown to be in very good agreement with that given by diffusion measurements.

EXPERIMENTAL

Materials

The α-cyclodextrin (CD) and L-phenylalanine (L) used were Sigma products. The CD water-content was determined by drying a sample to constant

---

* Presented at the 10th AICAT, Pisa, Italy, 11–14 December 1988.

TABLE 1

Calorimetric results

m_{IC} (mol kg^{-1})	m_C (mol kg^{-1})	m_{IL} (mol kg^{-1})	m_I (mol kg^{-1})	$\Delta H^{\star}/m_C$ (J mol^{-1})
0.01154	0.00562	0.1374	0.0705	−3776
0.01154	0.00564	0.1274	0.0652	−3632
0.01154	0.00563	0.1094	0.0560	−3339
0.01154	0.00537	0.0957	0.0512	−3065
0.01154	0.00562	0.0820	0.0420	−2698
0.01154	0.00562	0.0686	0.0352	−2404
0.01154	0.00560	0.0541	0.0279	−2028
0.01154	0.00560	0.0408	0.0210	−1640
0.01154	0.00561	0.0271	0.0139	−1177

$h_{CC} = -3920$ J mol^{-1} (mol kg^{-1})$^{-1}$ (eqn. (4)) [2]; $h_{LL} = +1174$ J mol^{-1} (mol kg^{-1})$^{-1}$ (eqn. (4)) [9] (the higher order h terms in eq. (4) were negligible).
$\Delta H_B^{\ominus} = -7700$ J mol^{-1} (enthalpy of binding reaction).
$K_B = 13.6 \pm 1$ kg mol^{-1} (equilibrium constant).

weight: $6H_2O$ molecules per CD molecule were found [3,4]. This was taken into account when preparing the CD solutions.

All solutions were prepared by weighing, using double-distilled water.

Calorimetry

Calorimetric measurements were performed at 25 ° C with an LKB 10700-1 microcalorimeter by mixing CD solutions of initial molality m_{IC} with L solutions of initial molality m_{IL}.

The experimental heat values were obtained from the following expression

$$\Delta H = -(\mathrm{d}Q/\mathrm{d}t)/P_w \tag{1}$$

where $\mathrm{d}Q/\mathrm{d}t$ is the heat flow and P_w is the total mass flow-rate of water flowing through the calorimeter. The experimental results are collected in Table 1.

Calorimetric experiments are described in detail in the literature [2,5–7].

PROCESSING OF THE DATA

The inclusion of a guest molecule in the cyclodextrin cavity is schematised by the following expression, assuming that 1 : 1 complex is formed

$$\mathrm{CD} + \mathrm{L} = \mathrm{CD} \cdot \mathrm{L} + \Delta H_B^{\ominus} \tag{2}$$

where L indicates any guest molecule (L-phenylalanine in this case) and $\Delta H_B^{\ominus}$ is the standard molal enthalpy of inclusion.

The enthalpy of interaction between the two solutes, $\Delta H^{\star}$, is given by the enthalpy of mixing of two binary solutions, ΔH_M, minus the enthalpy changes due to the dilution of each solute in the mixing process [6]

$$\Delta H^{\star} = \Delta H_{\mathrm{M}}[(m_{\mathrm{IC}})(m_{\mathrm{IL}}) \rightarrow (m_{\mathrm{C}}, m_{\mathrm{L}})] - \Delta H_{\mathrm{DC}}(m_{\mathrm{IC}} \rightarrow m_{\mathrm{C}}) - \Delta H_{\mathrm{DL}}(m_{\mathrm{IL}} \rightarrow m_{\mathrm{L}}) \qquad (3)$$

where m_{IC} and m_{IL} are the initial, and m_{C} and m_{L} are the final molalities of the two solutes, and ΔH_{DC} and ΔH_{DL} are the enthalpy changes due to the dilution (J kg^{-1} of solvent) of each solute from the initial to the final molality

$$(1/m)\ \Delta H_{\mathrm{D}s}(m_{\mathrm{I}s} \rightarrow m_s) = h_{ss}(m_s - m_{\mathrm{I}s}) + h_{sss}(m_s - m_{\mathrm{I}s}) \qquad (4)$$

where s represents CD or L. The h coefficients in eqn. (4) are evaluated from the experimental heats of dilution of binary aqueous solutions.

The standard molal enthalpy of inclusion is given by

$$\Delta H_{\mathrm{B}}^{\star} = \Delta H^{\star}/m_{\mathrm{C \cdot L}} \qquad (5)$$

where $m_{\mathrm{C \cdot L}}$ is the molality of the complex present in solution.

When a large excess of the guest molecules is present $m_{\mathrm{C \cdot L}} \rightarrow m_{\mathrm{C}}$, so that

$$\Delta H_{\mathrm{B}}^{\ominus} = (\Delta H^{\star})_{\mathrm{SAT}}/m_{\mathrm{C}} \qquad (6)$$

where $(\Delta H^{\star})_{\mathrm{SAT}}$ is the enthalpy of interaction measured at CD saturation.

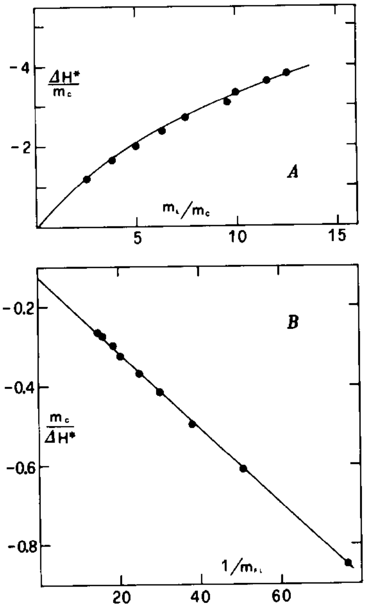

Fig. 1. A, Enthalpies of interaction for the system CD–L–water at 25 °C (kJ mol^{-1}) as a function of the ratio between the phenylalanine and the cyclodextrin molalities; B, Graph of eqn. (8): the free ligand molality was computed by iteration from eqns. (8) and (9).

The enthalpy of interaction (eqn. (3)) is related to the molality of the free guest molecules, m_{FL}, and to the binding constant, K_{B}, through the following expression [8]

$$\Delta H^{\star}/m_{\mathrm{C}} = \Delta H_{\mathrm{B}}^{\ominus} K_{\mathrm{B}} m_{\mathrm{FL}}/(1 + K_{\mathrm{B}} m_{\mathrm{FL}}) \tag{7}$$

Equation (7) is similar to a Langmuir isotherm and can be rewritten in a linear form

$$m_{\mathrm{C}}/\Delta H^{\star} = 1/\left(\Delta H_{\mathrm{B}}^{\ominus} K_{\mathrm{B}} m_{\mathrm{FL}}\right) + 1/\Delta H_{\mathrm{B}}^{\ominus} \tag{8}$$

where, for each value of ΔH^*, the molality of the free ligand is given by

$$m_{\mathrm{FL}} = m_{\mathrm{L}} - m_{\mathrm{C}}\ \Delta H^{\star}/(\Delta H^{\star})_{\mathrm{SAT}} \tag{9}$$

m_{L} being the total stoichiometric molality of the guest molecule.

Neither the molality of the free ligand nor the enthalpy change at saturation can be measured directly. $\Delta H_{\mathrm{B}}^{\star}$ and K_{B} are therefore obtained from eqns. (8) and (9) by iteration. However, in the absence of any information concerning the solute activity coefficients, only an apparent binding constant can be obtained.

The numerical values of $\Delta H_{\mathrm{B}}^{\ominus}$ and K_{B} for the present system are given in Table 1. Figure 1 shows $\Delta H^{\star}/m_{\mathrm{C}}$ versus $m_{\mathrm{C}}/m_{\mathrm{L}}$ and eqn. (8) plotted using our data.

COMPARISON WITH DIFFUSION DATA

The isothermal diffusion process in a three-component system (solute 1, solute 2 and solvent s) is described by Fick's equations

$$-J_1 = D_{11} \text{ grad } C_1 + D_{12} \text{ grad } C_2 \tag{10a}$$

$$-J_2 = D_{21} \text{ grad } C_1 + D_{22} \text{ grad } C_2 \tag{10b}$$

where the D_{II} terms are the main diffusion coefficients accounting for the diffusion of each solute under its own concentration gradient, while the D_{IJ} terms are the cross-diffusion coefficients accounting for the diffusion of solute I under the concentration gradient of solute J.

In general, cross-terms cannot be ignored. They may indeed be of the same order of magnitude as the main ones and even greater [10,11]. In dilute solutions, however, they become negligible and approach zero as C_1 and C_2 approach zero.

However, when an association equilibrium is present between the solute species, an appreciable effect has to be expected on the cross terms, even in dilute solution [12–14].

In the presence of a third species, the complex between solute 1 and solute 2, eqns. (10), should be replaced by

$$-J_1^\star = D_{11}^\star \text{ grad } C_1^\star + D_{12}^\star \text{ grad } C_2^\star + D_{13}^\star \text{ grad } C_3^\star \tag{11a}$$

$$-J_2^\star = D_{21}^\star \text{ grad } C_1^\star + D_{22}^\star \text{ grad } C_2^\star + D_{23} \text{ grad } C_3^\star \tag{11b}$$

$$-J_3^\star = D_{31}^\star \text{ grad } C_1^\star + D_{32}^\star \text{ grad } C_2^\star + D_{33}^\star \text{ grad } C_3^\star \tag{11c}$$

where the cross-term diffusion coefficients $D_{IJ}^\star$ give the interactions of the solute species caused only by the diffusion process. They are independent of the chemical reaction.

In terms of the constituent species

$$J_1 = J_1^\star + J_3^\star, \qquad J_2 = J_2^\star + J_3^\star \tag{12}$$

$$C_1 = C_1^\star + C_3^\star, \qquad C_2 = C_2^\star + C_3^\star \tag{13}$$

and the binding constant, in terms of molarity, is

$$K_C = C_3^\star/(C_1^\star C_2^\star) \tag{14}$$

The molar binding constant (eqn. (14)) is related to the molal binding constant by the expression

$$K_C = K_B\left(1000 + \sum_s m_s M_s\right)/1000d \tag{15}$$

where d is the solution density and M_s is the molecular weight of species s (s being CD and L).

In dilute solution, eqn. (15) reduces to

$$K_C = K_B/d \tag{15a}$$

In aqueous solutions, K_C and K_B differ by a few per cent.

Assuming that, in dilute solution, all cross-terms, $D_{IJ}^\star (i \neq j)$, are negligible in eqns. (11), by inserting eqns. (11)–(14) in eqns. (10), one obtains, after some rearrangement

$$D_{11} = \tfrac{1}{2}\left\{(D_{11}^\star + D_{33}^\star) + (D_{11}^\star - D_{33}^\star)[1 - K_C(C_2 - C_1)]R\right\} \tag{16a}$$

$$D_{12} = \tfrac{1}{2}\left\{(D_{33}^\star - D_{11}^\star) + (D_{11}^\star - D_{33}^\star)[1 + K_C(C_2 - C_1)]R\right\} \tag{16b}$$

$$D_{21} = \tfrac{1}{2}\left\{(D_{33}^\star - D_{22}^\star) + (D_{22}^\star - D_{33}^\star)[1 - K_C(C_2 - C_1)]R\right\} \tag{16c}$$

$$D_{22} = \tfrac{1}{2}\left\{(D_{22}^\star + D_{33}^\star) + (D_{22}^\star - D_{33}^\star)[1 + K_C(C_2 - C_1)]R\right\} \tag{16d}$$

where

$$R = \left\{[1 + K_C(C_2 - C_1)]^2 + 4K_C C_1\right\}^{-\frac{1}{2}} \tag{17}$$

In order to compute K_C from eqns. (16) and (17), the diffusion coefficients of the binary systems CD–water (D_1) and L–water (D_L) were used for $D_{11}^\star$ and $D_{22}^\star$; $D_{33}^\star$ and K_C were chosen as the values giving the best agreement with the experimental D_{IJ} data.

TABLE 2

Diffusion data for the systems L-phenylalanine–water [9] and α-cyclodextrin–L-phenylalanine–water at 25 °C [4]: cyclodextrin molarity: $C_1 = 0.02015$ for all solutions; C_2 is the L-phenylalanine molarity; and D_L is the diffusion coefficient of L-phenylalanine in the binary solution [9]

C_2 (mol l^{-1})	D_L		D_{11}	D_{12}	D_{21}	D_{22}
			($\times 10^6$ cm^2 sec^{-1})			
0.02503	6.973	a	3.276	−0.007	−0.411	6.287
		b	3.318	−0.006	−0.633	6.483
	6.705	c	3.318	−0.006	−0.592	6.248
0.05001	6.895	a	3.245	−0.002	−0.951	6.315
		b	3.257	−0.004	−1.110	6.541
	6.630	c	3.257	−0.004	−1.037	6.300
0.07491	6.821	a	3.177	+0.005	−1.220	6.298
		b	3.210	−0.003	−1.465	6.557
	6.559	c	3.210	−0.003	−1.394	6.379
0.1002	6.753	a	3.157	0.000	−1.630	6.332
		b	3.127	−0.002	−1.780	6.546
	6.493	c	3.127	−0.002	−1.617	6.305

a, Experimental data. b, Data computed through eqns. (16) using the following $D^\star$: $D^\star_{11} = 3.395 \times 10^{-6}$ cm^2 sec^{-1} from ref. 3; $D^\star_{22} = D_L$; $D^\star_{33} = 2.9 \times 10^{-6}$ cm^2 sec^{-1}; and $K_C = 10$ dm^3 mol^{-1} from ref. 4. c, Data computed correcting the D_L values for the viscosity of the 0.02015 M cyclodextrin solution: $\eta/\eta_0 = 1.04$, $D^\star_{22} = D_L/(\eta/\eta_0)$.

Table 2 sets out the experimental diffusion coefficients of the binary system L–water, those of the ternary system C–L–water, and the values computed with eqns. (16). The data are taken from refs. 3 and 4.

The phenylalanine diffusion coefficient measured in water (D_L) may be corrected for the viscosity effect due to the presence of CD, so one obtains $D^\star_{22} = D_L \eta_0/\eta$, where η/η_0 is the relative viscosity of the 0.02015 M CD solution. This correction greatly improves the agreement between the experimental and computed diffusion coefficients for the ternary system (see Table 2, lines c and footnote c).

CONCLUSION

The agreement between the calorimetric binding constant of phenylalanine to α-cyclodextrin, 13.6 kg mol^{-1}, with that obtained from diffusion data, 10 dm^3 mol^{-1}, is surprisingly good, especially since the unknown cross-terms, $D^\star_{IJ}$, were neglected in eqns. (16). This assumption, though reasonable, oversimplifies the mechanism of the transport process.

In our opinion, other systems with binding equilibria could usefully be studied so as to test the reliability of eqns. (16) in a broader set of experimental conditions.

ACKNOWLEDGEMENTS

This research was supported by the Italian Ministero della Pubblica Istruzione and by the Italian C.N.R.

REFERENCES

1 O. Huber and J. Szejtli, Proc. 4th Int. Symp on Cyclodextrins, Munich, April, 1988, Kluwer Acad. Press, Dordrecht, 1989.
2 G. Barone, G. Castronuovo, P. DelVecchio, V. Elia and M. Muscetta, J. Chem. Soc., Faraday Trans. 1, 82 (1986) 2089.
3 L. Paduano, R. Sartorio, V. Vitagliano and L. Costantino, J. Solution Chem., 19 (1990) 31.
4 L. Paduano, R. Sartorio, V. Vitagliano, J.G. Albright, D.G. Miller and J. Mitchell, submitted to J. Phys. Chem.
5 G. Barone, P. Cacace, G. Castronuovo and V. Elia, J. Chem. Soc., Faraday Trans. 1, 77 (1981) 1569.
6 V. Abate, G. Barone, G. Castronuovo, V. Elia and V. Savino, J. Chem. Soc., Faraday Trans. 1, 80 (1984) 759.
7 G. Barone, G. Castronuovo, V. Elia and M. Muscetta, J. Solution Chem., 15 (1986) 129.
8 M. Eftink and R. Biltonen, in A.E. Beezer (Ed.), Biological Microcalorimetry, Academic Press, London, 1980.
9 L. Paduano, R. Sartorio, V. Vitagliano and L. Costantino, submitted to J. Mol. Liquids.
10 V. Vitagliano, G. Borriello, C. DellaVolpe and O. Ortona, J. Solution Chem., 15 (1986) 811.
11 D.G. Miller, V. Vitagliano and R. Sartorio, J. Phys. Chem., 90 (1986) 1509.
12 J.G. Albright, Ph.D. Thesis, University of Wisconsin, 1963.
13 V. Vitagliano and R. Sartorio, J. Phys. Chem., 74 (1970) 2949.
14 H. Kim, J. Solution Chem., 3 (1974) 271.