Thermochimica Acta, 221 (1993) 183–193
Elsevier Science Publishers B.V., Amsterdam

The thermodynamics of the binding of benzene to β-cyclodextrin in aqueous solution

Isabel Gómez-Orellana [a,*] and Dan Hallén [b]

[a] *Department of Applied Physics, Faculty of Physics, University of Santiago de Compostela, E-15706, Santiago (Spain)*
[b] *Division of Thermochemistry, Chemical Center, University of Lund, P.O. Box 124, S-221 00, Lund (Sweden)*

(Received 19 August 1992; accepted 7 September 1992)

Abstract

The apparent enthalpies, entropies and Gibbs energies for the binding of benzene to β-cyclodextrin in aqueous solution have been determined at 291.15, 298.15 and 308.15 K by microcalorimetry. The calorimetric data are consistent with a binding model that assumes formation of both 1:1 and 2:1 (benzene:β-cyclodextrin) adducts. The apparent change in heat capacity for the 1:1 binding, calculated from the temperature derivative of the enthalpy changes, indicates that the hydrophobic effect is the driving force for formation and stability of this complex.

INTRODUCTION

Cyclodextrins are well-known cyclic oligosaccharides formed of α(1–4) linkages of D(+)-glucopyranose units. Cyclodextrin molecules have a truncated cone shape, with the primary and secondary hydroxyl groups located at the edges of both bases, which results in a hydrophobic cavity and a hydrophillic exterior [1]. Their ability to form inclusion complexes with a large variety of substances has made them very useful as model compounds for the study of ligand binding processes. They have also found important applications as separation and catalysis agents, and in the pharmaceutical, food, cosmetic and agricultural industries [2].

Van der Waals forces, hydrophobic effects, liberation of high-energy water molecules from the cyclodextrin cavity and hydrogen bonding, are considered the driving forces of complexation. The relative contribution of each of these interaction forces depends on the chemical and structural properties of the ligand, and on the cyclodextrin and ligand sizes [3].

Several features support the idea that hydrophobic effects may play an

* Corresponding author.

important role in the formation of these complexes: (a) it has been found that complexes with the same ligand are weaker in non-aqueous solvents than in water [4–7]; (b) highly hydrophilic substances are not, or only very weakly, complexed by cyclodextrins, although non-polar or partially apolar ligands form stable complexes in aqueous solution [8]; (c) the ligand binding is enhanced by capping one side of the cyclodextrin cavity, as a way of increasing the apolar nature of the cavity [9, 10]; (d) a large decrease in heat capacity has been observed for formation of these inclusion complexes in aqueous solution [11].

Many determinations of the thermodynamic properties for formation of cyclodextrin complexes with a large number of different ligands have been carried out in order to understand the nature of the binding forces [12–16]. In most of these studies, polar derivatives of aromatic and aliphatic hydrocarbons have been used as ligands; this has complicated the interpretation of the results, because several different interaction forces are involved simultaneously in the binding. There are relatively few thermodynamic studies of cyclodextrin complex formation with unsubstituted hydrocarbons [17–20], and all have been performed using non-calorimetric methods. But because of the difficulty in estimating values of enthalpy and heat capacity changes with sufficient precision using non-calorimetric measurements [21], it is convenient to determine these parameters by calorimetry.

In this work we have used flow microcalorimetry to determine the apparent enthalpy, entropy, Gibbs energy and heat capacity for the interaction of benzene with β-cyclodextrin in aqueous solution, in order to contribute to the understanding of the role of hydrophobic effects on the formation and stability of cyclodextrin inclusion complexes.

EXPERIMENTAL

β-Cyclodextrin (supplied by Merck) was used without further purification. The water content of the solid samples was determined from the difference in weight of samples stored at 298.15 K in a desiccator over a saturated solution of $Ca(NO_3)_2$, before and after drying at 353.15 K and reduced pressure; it was observed that β-cyclodextrin contains 14.4% water; therefore the molecular weight was considered to be 1326 g mol^{-1}.

Benzene, purity >99.5%, was supplied by Probus. Saturated solutions of benzene were prepared at 291.15, 298.15 and 308.15 K, by adding excess benzene to water and stirring the mixture for seven days in a glass bottle located inside a thermostated bath ($\pm$ 0.1°C). The benzene concentration in these solutions was calculated from the data reported by Franks et al. [22].

Experiments were performed at 291.15, 298.15 and 308.15 K, in the flow-mixing microcalorimetric vessel of a 2277 Thermal Activity Monitor

(ThermoMetric AB, Sweden). A peristaltic pump (Masterfex, Cole Parmer Instrument) was used for the flow of the β-cyclodextrin solution, and an HPLC pump (L-6200 Merck–Hitachi) for the flow of the benzene solution.

The benzene concentration in the microcalorimetric vessel was varied by changing the flow rate of the benzene solution from the HPLC pump within the range from 0.11 to 0.59 ml min^{-1}. The concentration of the β-CD solution ranged from 0.01 to 0.001 M and the flow rate was maintained constant at 0.31 ml min^{-1}, except for some measurements at 298.15 and 291.15 K where it was necessary to change it to prevent precipitation of the complex inside the microcalorimetric vessel, because the solubility of the benzene:β-CD adducts is lower at these temperatures.

The instrument was calibrated electrically, using a permanently installed heater positioned close to the mixing point of the vessel.

RESULTS AND DISCUSSION

To rationalize the enthalpy of mixing of aqueous solutions of benzene and β-cyclodextrin, we have compared three different binding models: 1:1, 1:2 and 2:1 (benzene:β-CD). In the calculations of the free concentrations of the reactants A and B, we have used the apparent equilibrium constants for the overall reactions β_i' defined as

$$iA + B \rightleftarrows BA_i \qquad \beta_i' = [BA_i]/[B][A]^i \qquad \Delta H_i^{\ominus\prime} \tag{1}$$

The total concentrations of A and B can be calculated from,

$$[A]_0 = [A]\left(1 + [B]\sum i\beta_i'[A]^{(i-1)}\right) \tag{2}$$

$$[B]_0 = [B]\left(1 + \sum \beta_i'[A]^i\right) \tag{3}$$

The overall equilibrium constants were selected rather than the step-wise constants K_i, in order to avoid linear dependences of the fitting parameters $\left(\beta_n = \prod^n K_i\right)$.

The thermal power measured when mixing a solution of A with a solution of B in a flow calorimeter using flow rates f_A and f_B is

$$P_{exp} = P_{compl} + P_{dil\ A} + P_{dil\ B} \tag{4}$$

The function to minimize is χ^2

$$\chi^2 = \sum (P_{compl} - P_{calc})^2 \tag{5}$$

where

$$P_{calc} = (f_A + f_B)\left(\sum \Delta H_i^{\ominus\prime}[BA_i]\right) \tag{6}$$

The regression involves non-linear parameters (equilibrium constants) and linear parameters (enthalpies). Normally both linear and non-linear parameters are optimized in a non-linear regression. However, in this work we have used the Marquard–Levenberg algorithm [23] for the gradient search on the equilibrium constants and an elimination of the linear parameters according to Lawton and Sylvestre [24]. From the Marquard–Levenberg algorithm, we obtained $[BA_i]$ and from linear regression we could calculate the enthalpies of complex formation in which the calculated concentrations of the formed complexes were treated as the dependent variables. In the cases where more than one equilibrium was assumed, we used the Newton–Raphson method to calculate the free concentrations of the reactants from the total concentrations of benzene and β-cyclodextrin, and the equilibrium constants obtained from the gradient search. The uncertainties of the fitting parameters were calculated from the diagonal of the error matrix.

The F-test of the calculated results showed no significant differences in the different models at 291.15 K. At the other temperatures studied, a significant rejection of the 1:1 model could be made, but no statistical difference between the 1:2 or 2:1 models could be observed from the F-test. In order to have a tool with which to discriminate the models, we applied the van't Hoff equation to our models; the parameters from 298.15 K were used to calculate the $\beta_1'(T)$ over the temperature range studied

$$R \ln \beta_1'(T) = \frac{-\Delta G_1^{\ominus'}(\theta)}{\theta} + \Delta H_1^{\ominus'}(\theta)\left(\frac{1}{\theta} - \frac{1}{T}\right) + \Delta C_{p1}^{\ominus'}(\ln(T/\theta) + \theta/T - 1) \tag{7}$$

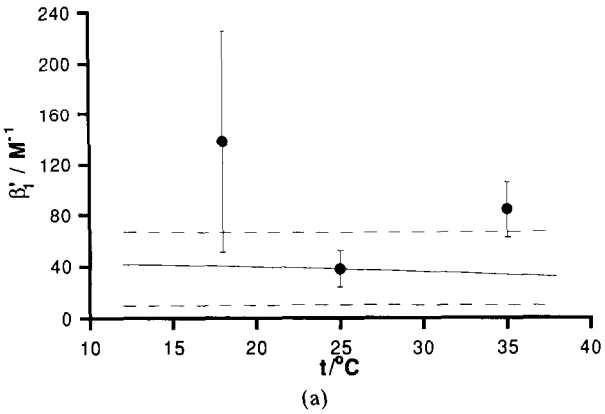
where $\theta = 298.15$ K.

In this comparison of the assumed models, the model in which two benzene molecules bind to a β-cyclodextrin molecule best reproduced the $\beta_1'(T)$. For both the other models, the van't Hoff calculations gave inconsistent results comparing the fitted values at 291.15 and 308.5 K (see Fig. 1(a)–(c):

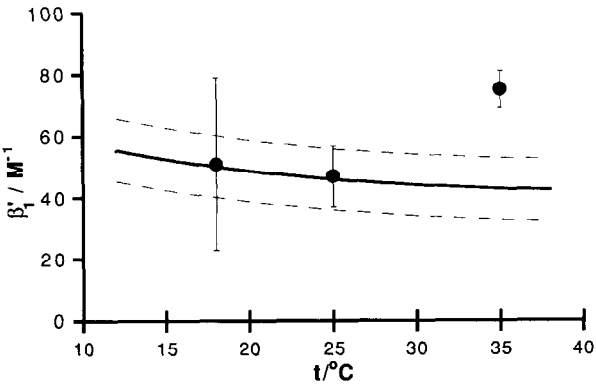
$$C_6H_6 + \beta\text{-CD} \rightleftarrows \beta\text{-CD}(C_6H_6) \qquad \beta_1' = \frac{[\beta\text{-CD}(C_6H_6)]}{[\beta\text{-CD}][C_6H_6]} \tag{8a}$$

$$2C_6H_6 + \beta\text{-CD} \rightleftarrows \beta\text{-CD}(C_6H_6)_2 \qquad \beta_2' = \frac{[\beta\text{-CD}(C_6H_6)_2]}{[\beta\text{-CD}][C_6H_6]^2} \tag{8b}$$

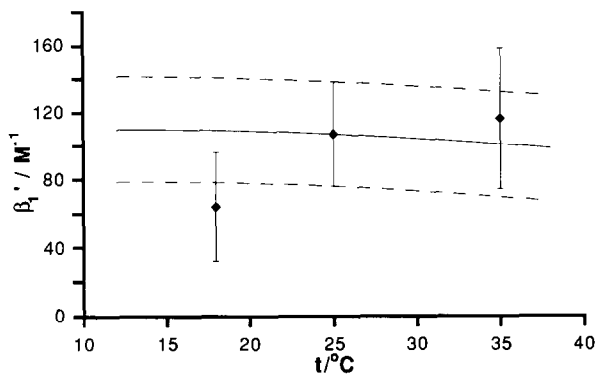
Both complexes are relatively weak, especially the second complex. Therefore, in order to have a well-defined minimum of the χ^2 function, one



(a)



(b)



(c)

Fig. 1. The apparent equilibrium constant for the first binding step β_1' vs. temperature for (a) 1:1 model, (b) 1:2 model, and (c) the 2:1 model (benzene:β-cyclodextrin). The points are the constants obtained from the regression at the individual temperatures. The solid lines are the calculated values using $\beta_1'(\theta)$, $\Delta H_1^{\ominus\prime}(\theta)$, and $\Delta C_{p_1}^{\ominus\prime}(\theta)$, where $\theta = 298.15$ K. The dashed lines show the estimated errors of $\beta_1'(T)$.

needs to have data at relatively high concentrations (for a 1:1 complex, one of the reactants should be $1/K$–$1000/K$). For the second complex, this is impossible owing to the low solubilities of the reactants and complexes formed. This problem is independent of the experimental method or regression procedure used. Because of the large uncertainties in the second binding step, no van't Hoff treatment of the results was made in which $\beta_2'(T)$ was calculated. A result of the non-ideal situation concerning the concentration range used is that the parameters are highly correlated: this causes large covariances, and thus the error assignments on the fitted parameters are over-estimated (the Schwartz inequality).

Using vapor pressure measurements of aqueous solutions of benzene with β-CD, Tucker and Christian [20] have estimated the binding of benzene to β-XD. They have fitted their data to the 2:1 model. Their values of β_1 and β_2 at 25°C are similar to the values obtained in this work. However, the error assignments reported are small, although one would expect significant covariance contributions. Nevertheless, we used their reported values of equilibrium constants at 25°C to calculate the enthalpy parameters. From the regression, when fixing $\beta_1' = 169 \pm 1\ \mathrm{M}^{-1}$ and $\beta_2' = 2270 \pm 30\ \mathrm{M}^{-2}$, we obtain $\Delta H_1^{\ominus\prime} = -2.80 \pm 0.04\ \mathrm{kJ\ mol}^{-1}$ and $\Delta H_2^{\ominus\prime} = -10.73 \pm 0.43\ \mathrm{kJ\ mol}^{-1}$. The errors estimated on the enthalpies from this calculation are significantly smaller than in the case where we calculate all the parameters. This is due to the smaller covariance contribution to the errors on the parameters. The values should be compared to the values reported by Christian and Tucker ($\Delta H_1^{\ominus\prime} = -1.87 \pm 0.34\ \mathrm{kJ\ mol}^{-1}$ and $\Delta H_2^{\ominus} = -17 \pm 3\ \mathrm{kJ\ mol}^{-1}$). As can be seen, there are significant differences between the enthalpy values reported and those obtained in this work. The reasons for these differences may be as follows.

(i) Tucker and Christian measured the total pressure of the solution directly and converted the pressure data to benzene fugacities. The equilibrium constants are close to the thermodynamic equilibrium constants.

(ii) In the calorimetric determinations we assume that the enthalpy of dilution is zero for the complexes formed. The complexes are not formally at infinite dilution.

(iii) The enthalpy values calculated by Tucker and Christian were obtained from a regression using the van't Hoff equation. In order to calculate high-quality enthalpies and, in particular, high-quality heat capacities, one needs to have high precision data on equilibrium constants.

The calorimetric data and those calculated by the minimization program are reported in Tables 1–3.

Tables 4 and 5 show the values for the apparent thermodynamic properties determined for formation of 1:1 and 2:1 (benzene:β-cyclodextrin) complexes. The magnitude of the thermodynamic parameters

TABLE 1

Data from microcalorimetric measurements for the formation of β-CD–benzene complexes in the flow-mixing vessel at 291.15 K: the concentration of the saturated benzene solution was 0.0219 M

[β-CD] [a] (mol l^{-1})	f_C [b] (ml min^{-1})	f_B [b] (ml min^{-1})	P_{compl} [c] (μW)	($P_{compl} - P_{calc}$) [d] (μW)
0.00100	0.28	0.11	2.84	−0.084
0.00100	0.37	0.23	4.67	−0.394
0.00100	0.37	0.35	5.23	−0.957
0.00100	0.58	0.11	3.51	−0.063
0.00300	0.28	0.11	7.83	−0.299
0.00300	0.37	0.23	13.87	−0.448
0.00300	0.37	0.35	17.33	−0.421
0.00300	0.76	0.11	9.28	−0.838
0.00500	0.28	0.11	12.42	−0.178
0.00500	0.37	0.23	22.45	−0.077
0.00500	0.37	0.35	28.98	0.669
0.00500	0.76	0.11	14.67	−0.611
0.00500	0.58	0.11	15.25	0.520
0.00800	0.28	0.11	18.56	0.369
0.00800	0.76	0.11	20.70	−0.695
0.00800	0.58	0.11	21.49	0.732
0.01000	0.76	0.11	24.03	−0.636
0.01000	0.58	0.11	25.2	1.188

[a] [β-CD] is the concentration of β-cyclodextrin solution before mixing. [b] f_C and f_B are the flow rates of β-cyclodextrin and benzene solutions respectively. [c] P_{compl} is the thermal power due to complexation. [d] ($P_{compl} - P_{cal}$) is the difference between experimental values and those calculated by regression.

associated with the formation of 1:1 complexes are characteristic of processes of transfer of non-polar compounds from aqueous to apolar medium, particularly the value for the apparent change in heat capacity, calculated from the variation of the enthalpy with temperature. These quantities are comparable with those reported for transfer of benzene from aqueous solution to pure liquid benzene at 298.15 K [25–26]. Differences in the values for the enthalpy changes may be explained because the formation of the complex involves the expulsion of high-enthalpy water molecules from the cyclodextrin cavity, which contributes to the decrease in the enthalpy of the system. The decrease in the heat capacity is larger for the formation of the complex than for the transfer process, which may be due to conformational changes and modifications in the solvation sphere of β-cyclodextrin after binding. No contribution to the change in heat capacity is expected from the expulsion of water molecules from the β-cyclodextrin cavity, as has been reported recently [27].

The value for the change in heat capacity for the 1:1 binding indicates

TABLE 2

Data from microcalorimetric measurements for the formation of β-CD–benzene complexes in the flow-mixing vessel at 298.15 K: the concentration of the saturated benzene solution was 0.0223 M [a]

[β-CD] (mol l^{-1})	f_C (ml min^{-1})	f_B (ml min^{-1})	P_{compl} (μW)	($P_{compl} - P_{calc}$) (μW)
0.00100	0.28	0.11	8.1	0.455
0.00100	0.28	0.23	10.81	−0.124
0.00100	0.28	0.35	11.9	−0.786
0.00100	0.28	0.47	12.22	−1.561
0.00300	0.28	0.11	22.1	0.774
0.00300	0.28	0.23	31.1	−0.298
0.00300	0.28	0.35	35.9	−0.988
0.00500	0.28	0.11	33.4	0.282
0.00500	0.28	0.23	48.8	−1.295
0.00500	0.28	0.35	58.0	−1.588
0.00500	0.56	0.11	39.2	−0.761
0.00500	0.75	0.11	44.0	1.880
0.00800	0.28	0.11	50.3	2.433
0.00800	0.28	0.23	76.6	1.480
0.00800	0.28	0.35	92.1	1.128
0.00800	0.56	0.11	54.9	−1.062
0.00800	0.75	0.11	58.6	0.234
0.01000	0.28	0.11	56.8	0.714
0.01000	0.28	0.23	89.97	−0.009
0.01000	0.56	0.11	62.3	−2.157
0.01000	0.75	0.11	66.5	−0.367

[a] See Table 1 footnotes for column headings.

that benzene penetrates inside the hydrophobic cavity of β-cyclodextrin, and that hydrophobic interactions are the forces responsible for the formation and stability of these complexes.

The enthalpy and entropy contributions to the process of binding benzene to β-cyclodextrin in aqueous solution are almost temperature-invariant, a feature that is common in related processes. This is illustrated in Fig. 3.

Because of the large uncertainties in the thermodynamic parameters for the second binding step, these numbers will not be discussed in detail.

ACKNOWLEDGEMENT

A grant from Vicerrectorado de Investigación de la Universidad de Santiago is gratefully acknowledged.

TABLE 3

Data from microcalorimetric measurements for the formation of β-CD–benzene complexes in the flow-mixing vessel at 308.15 K: the concentration of the saturated benzene solution was 0.0233 M [a]

[β-CD] (mol l^{-1})	f_C (ml min^{-1})	f_B (ml min^{-1})	P_{compl} (μW)	($P_{compl} - P^{calc}$) (μW)
0.00130	0.31	0.11	19.2	0.634
0.00130	0.31	0.23	27.1	1.051
0.00130	0.31	0.35	31.5	1.598
0.00130	0.31	0.47	32.8	0.530
0.00130	0.31	0.59	34.5	0.622
0.00500	0.31	0.11	64.8	2.160
0.00500	0.31	0.23	94.2	1.431
0.00500	0.31	0.35	111.3	2.319
0.00500	0.31	0.47	119.8	0.699
0.00500	0.31	0.59	127.2	1.175
0.00850	0.31	0.11	96.5	1.858
0.00850	0.31	0.35	179.1	3.134
0.00850	0.31	0.47	196.0	1.385
0.01300	0.31	0.23	202.7	−1.799
0.01300	0.31	0.35	249.3	−2.498
0.01300	0.31	0.47	281.5	−1.214
0.01300	0.31	0.59	302.6	−1.754

[a] See Table 1 footnotes for column headings.

TABLE 4

Apparent thermodynamic properties for the formation of 1:1 β-cyclodextrin:benzene complex in aqueous solution

T (K)	β_1' (l mol^{-1})	$\Delta G_1^{\ominus\prime}$ (kJ mol^{-1})	$\Delta H_1^{\ominus\prime}$ (kJ mol^{-1})	$\Delta S_1^{\ominus\prime}$ (J K^{-1} mol^{-1})	$-T\Delta S_1^{\ominus\prime}$ (kJ mol^{-1})	$\Delta C_{p_1}^{\ominus\prime}$ (J K^{-1} mol^{-1})
291.15	64 ± 32	−10.1 ± 0.9	−1.74 ± 0.58	28.6 ± 3.7	8.3 ± 1.1	
298.15	107 ± 31	−11.6 ± 0.8	−3.52 ± 0.58	27.0 ± 3.3	8.1 ± 1.0	−268 ± 12
308.15	116 ± 38	−12.2 ± 1.0	−6.30 ± 1.30	19.1 ± 5.1	5.9 ± 1.6	

TABLE 5

Apparent thermodynamic properties for the formation of 2:1 benzene:β-cyclodextrin complex in aqueous solution obtained from non-linear regressions for the individual temperatures

T (K)	β_2' (l^2 mol^{-2})	$\Delta H_2^{\ominus\prime}$ (kJ mol^{-1})
291.15	1400 ± 4500	−4 ± 11
298.15	1000 ± 3000	−14 ± 36
308.15	7500 ± 1700	−7 ± 1

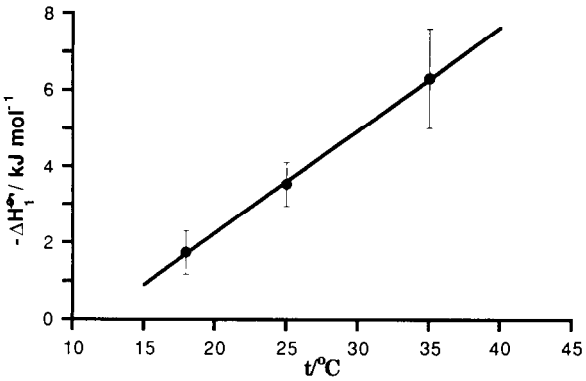


Fig. 2. The apparent enthalpy of binding one benzene to β-cyclodextrin $\Delta H_1^{\ominus'}$ vs. temperature.

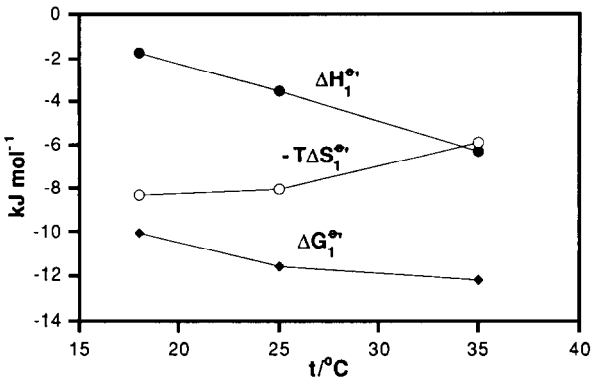


Fig. 3. The enthalpy and the entropy contribution to the apparent Gibbs energy at different temperatures.

REFERENCES

1 M.L. Bender and M. Komiyama, Cyclodextrin Chemistry, Springer Verlag, Berlin, 1978.
2 J. Szejtli, in J.L. Atwood, J.E.D. Davies and D.D. MacNicol (Eds.), Inclusion Compounds, Vol. 3, Academic Press, London, 1984.
3 J. Szejtli, Cyclodextrin Technology, Kluwer Academic Publishers, Dordrecht, 1988.
4 B. Siegel and R. Breslow, J. Am. Chem. Soc., 97 (1975) 6869.
5 A.F. Danil de Namor, R. Traboulssi and D.F.V. Lewis, J. Am. Chem. Soc., 112 (1990) 8442.
6 A.F. Danil de Namor, Pure Appl. Chem., 62 (1990) 2121.
7 A.M. Martre, G. Mousset, P. Pouillen and G. Dauphin, Bull. Soc. Chim. Fr., 3 (1988) 489.
8 T.L. Paál and J. Szejtli, Acta Chim. Acad. Sci. Hung., 106 (1981) 9.
9 I. Tabushi, K. Shimokawa, N. Shimizu, H. Shirakata and K. Fujita, J. Am. Chem. Soc., 98 (1976) 7855.
10 J. Emert and R. Breslow, J. Am. Chem. Soc., 97 (1975) 670.
11 M. Bastos, L.-E. Briggner, I. Shehatta and I. Wadsö, J. Chem. Thermodyn., 22 (1990) 1181.

12 M.R. Eftink and J.C. Harrison, Bioorg. Chem., 10 (1981) 388.
13 W.C. Cromwell, K. Bryström and M.R. Eftink, J. Phys. Chem., 89 (1985) 326.
14 G.L. Bertrand, J.R. Faulkner, S.M. Han and D.W. Armstrong, J. Phys. Chem., 93 (1989) 6863.
15 E.A. Lewis and L.D. Hansen, J. Chem. Soc. Perkin Trans. 2 (1973) 2081.
17 J.N.J.J. Lammers and A.J.G. van Dieman, Recl. Trav. Chim. Pays-Bas, 91 (1972) 843, 733.
18 A. Wishnia and S.J. Lappi, J. Mol. Biol., 82 (1974) 77.
19 M. Hoshino, M. Imamura, K. Ikehara and Y. Hama, J. Phys. Chem., 85 (1981) 1820.
20 E.E. Tucker and S.D. Christian, J. Am. Chem. Soc., 106 (1984) 1942.
21 H. Wiesinger and H.-J. Hinz, in H.J. Hinz (Ed.), Thermodynamic Data for Biochemistry and Biotechnology, Springer Verlag, Berlin, 1986.
22 F. Franks, M. Gent and H.H. Johnson, J. Chem. Soc. (1963) 2716.
23 P.H. Bevington, Data Reduction and Error Analysis in the Physical Sciences, McGraw-Hill, New York, 1969.
24 W.H. Lawton and E.A. Sylvestre, Technometrics, 13 (1971) 461.
25 P.L. Privalov and S.J. Gill, Pure Appl. Chem., 61 (1989) 1097.
26 D. Hallén, S.-O. Nilsson and I. Wadsö, J. Chem. Thermodyn., 21 (1989) 529.
27 L.-E. Briggner and I. Wadsö, J. Chem. Thermodyn., 22 (1990) 1067.