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THERMOCHEMICAL STUDY OF CYCLODEXTRIN INCLUSION COMPLEXES

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ABSTRACT

Two different calorimeters (an LKB 2277 microcalorimeter in a flow–mix mode, and a DAK-1-1A differential microcalorimeter) were used to study the formation of cyclodextrin molecular complexes in water solutions. The dissociation constant values and changes of thermodynamic parameters (Gibbs energy, enthalpy and entropy) have been presented for 10 molecular inclusion complexes of α-, β- and γ-cyclodextrins.

INTRODUCTION

Calorimetry is a method for studying complex formation in solutions. It is used to investigate the inclusion complexes of cyclodextrins (CDs) as well. Takagi and Maeda [1] and Takeo and Kuge [2] used twin microcalorimeters for this purpose, which enable measurement of relatively weak interactions between CDs and guest molecules, e.g. aliphatic alcohols [3]. A thorough study of 4-nitrophenol complexes with α- and β-CDs has been carried out by Eftink and Harrison [4]. Zhang et al. used a microcalorimeter to investigate the inclusion of copper(II) with β-CD [5].

Our previous work in this field includes the results of thermochemical investigations using the flow–mix system [6]. In this paper, we present some new results obtained with an LKB 2277 microcalorimeter and show that batch-type microcalorimeters can equally be applied to investigate molecular complexes.

THEORY

On mixing the water solutions of cyclodextrin (C) and substrate (S) a 1 : 1 complex is formed:

$$C + S \rightleftharpoons CS \quad (1)$$

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The dissociation constant of the complex, K_d, is given by

$$K_d = \frac{[C][S]}{[CS]} \qquad (\text{M or mmol ml}^{-1}) \tag{2}$$

The initial (total) concentrations of components after mixing are $[C]_0$ and $[S]_0$. Using the material balances of components the following root equation can be obtained to find the complex concentration [CS] if the $[C]_0$, $[S]_0$ and K_d values are known:

$$[CS]^2 - ([C]_0 + [S]_0 + K_d)[CS] + [C]_0[S]_0 = 0 \tag{3}$$

Let us represent the heat effect of complexation by Q (mJ mol^{-1} or μJ mmol^{-1}). The problem is to calculate the K_d and Q values from experimental data. For the two types of calorimeters the data obtained are different. This problem will be briefly discussed below.

(A) Using a microcalorimeter in a flow–mix mode at a total flow rate q (ml s^{-1}), the steady concentrations of the complex CS and free components C and S can rapidly be obtained. Evidently, the heat flow observed by complexation can be expressed as follows:

$$N = q[CS]Q \qquad (\mu W) \tag{4}$$

and the quantity of heat formed in 1 ml is equal to

$$\frac{N}{q} = [CS]Q \qquad (\mu J\ ml^{-1} \text{ or } J\ m^{-3}) \tag{5}$$

From experimental data $N = f([C]_0, [S]_0$ and the K_d and Q values can be calculated by the non-linear regression method, minimising the sum of $(N_{calc} - N_{exptl})^2$ or $(N_{calc}/q - N_{exptl}/q)^2$, where N_{calc} and N_{exptl} are the calculated and experimental heat flow values respectively.

(B) Using a batch microcalorimeter the solutions of C and S are mixed to have a volume V (ml) of the mixture in which the complex concentration is [CS] (M or mmol ml^{-1}), and the total heat effect Q_{exptl} (μJ) corresponding to complex formation is measured. The quantity of heat for 1 ml of solution is Q_{exptl}/V (μJ ml^{-1}).

Therefore

$$\frac{Q_{exptl}}{V} = [CS]Q \qquad (\mu J\ ml^{-1} \text{ or } J\ m^{-3}) \tag{6}$$

To calculate the K_d and Q values from experimental data, the sum of $(Q_{calc} - Q_{exptl})^2$ or $(Q_{calc}/V - Q_{exptl}/V)^2$ has to be minimised, where Q_{calc} is the calculated heat effect.

It can be seen that eqns. (5) and (6) are analogous. Consequently, the experimental data obtained using different types of calorimeters can jointly be applied to computer analysis if necessary. Using almost the same concentrations of components in different calorimeters the N/q and Q_{exptl}/V values obtained are close, which guarantees the similar weight of experimental data in the calculations.

EXPERIMENTAL

Materials and apparatus

"Chinoin" dried cyclodextrins and chemically pure benzoic acid, benzyl alcohol, resorcinol (1,3-dihydroxybenzene), orcinol (1,3-dihydroxy-5-methylbenzene), and hydroquinone (1,4-dihydroxybenzene) were used in distilled water solutions.

An LKB microcalorimeter (bioactivity monitor) was used in the flow–mix mode at 30 °C. The solutions were pumped into a flow–mix cell by an LKB 2132 two-channel microperspex peristaltic pump at a total flow rate of about 20 ml h^{-1} (0.0056 ml s^{-1}), about 10 ml h^{-1} on each channel.

The other apparatus used was a DAK-1-1A differential automatic microcalorimeter (U.S.S.R.), in which the total heat quantity liberated in the complexation process is measured by the integration of the compensation heat flow. A special construction of the reaction vessel was used where one of the solutions is placed on the bottom of a 8 cm^3 standard metal cylinder, the other in the inner Teflon tube, and the solutions are led into contact and mixed after the thermal stabilization of the system. This construction has been described in detail previously [7]. In each experiment, 3 ml of the CD solution and 2 ml of substrate solution were mixed.

RESULTS AND DISCUSSION

Experiments were carried out with an LKB 2277 microcalorimeter, mixing the cyclodextrin and substrate solutions in the flow–mix cell, using different molar ratios of components. The experimental design shown in Table 1 was used and can be recommended for study of molecular complexes.

TABLE 1

Design of experiments to study 1:1 molecular complexes between A and B

Concentration of A	Concentration of B			
	c	$2c$	$4c$	$8c$
c	(+)	(+)	+	+
$2c$	(+)	+	+	+
$4c$	+	+	+	+
$8c$	+	+	+	+

In this experimental design, a logarithmic scale of concentrations of components A and B is used and the molar ratio [A]/[B] varies over a wide range. Of course, 3×3 or 5×5 concentration matrixes can be used as well and it is not obligatory to use all concentrations pairs. The choice of concentration values depends on the sensitivity of the microcalorimeter and especially on the properties of the molecular complex formed.

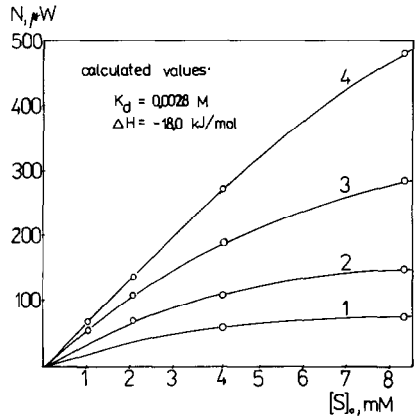

Fig. 1. The heat flow corresponding to the complex formation between β-CD and benzoic acid showing the dependence on benzoic acid concentration in solution. The concentrations of β-CD were as follows: curve 1, 1.03 mM; curve 2, 2.05 mM; curve 3, 4.10 mM; curve 4, 8.21 mM. The total flow rate was 0.00566 ml s^{-1}.

In Fig. 1 the heat flow values for β-CD + benzoic acid experiments are presented to demonstrate the advantage of this experimental design. In all runs, the heat flow values corresponding to complex formation were found by subtracting the dilution effects (which are usually relatively weak) from the total heat flow values observed. In our earlier publication, we presented data on CD complexes with benzoic acid [6]. In the present work, additional experiments with these systems were carried out and the values of the dissociation constant and thermodynamic parameters were corrected.

In experiments with a batch DAK-1-1A microcalorimeter about five to ten heat effect values were measured for each system using different concentrations of initial solutions. Weak dilution heat effects are difficult to measure with this calorimeter, and in some cases even impossible. At the concentrations of cyclodextrins used their dilution heat effects were insignificant, but some substrates had a considerable heat of dilution, e.g. orcinol, and in this case these effects were measured separately.

Some systems were studied with both of the microcalorimeters to compare the results and to prove the possibility of performing joint analysis of all data according to eqns. (5) and (6). As an example, in Table 2 the results for the system α-CD + resorcinol are given. In this table, the $Q^{\star}$ values are the heat effects for 1 ml of solution found by dividing the heat flow value by the total flow rate value in the flow–mix experiments, and by dividing the integral heat effect by the mixture volume in the case of the batch microcalorimeter.

As seen in Table 2, the results obtained with the two different calorimetric systems can be successfully compared. By minimising the sum of $(Q^{*}_{\mathrm{calc}} - Q^{*}_{\mathrm{exptl}})^2$, the dissociation constant value and the change of enthalpy in the

TABLE 2

Thermochemical study of α-CD complexes with resorcinol in water

Concentrations after mixing (M)		N (μW)	Q (J)	$Q^{\star}_{\text{exptl}}$ (J)	$Q^{\star}_{\text{calc}}$ (J)	Relative error (%)
0.01782	0.01688	187	–	0.03357	0.03380	0.7
0.01782	0.00844	99	–	0.01777	0.01821	2.5
0.01782	0.00422	52	–	0.00934	0.00946	1.4
0.00891	0.01688	101	–	0.01813	0.01831	1.0
0.00891	0.00844	57	–	0.01023	0.01001	−2.2
0.00446	0.01688	53	–	0.00952	0.00955	0.4
0.00446	0.00844	30	–	0.00539	0.00527	−2.2
0.00750	0.03624	–	0.1420	0.02831	0.02780	−1.8
0.00750	0.02716	–	0.1143	0.02278	0.02266	−0.5
0.00750	0.02416	–	0.0996	0.01985	0.02075	4.5
0.00750	0.01812	–	0.0869	0.01732	0.01654	−4.5
0.00750	0.00904	–	0.0492	0.00981	0.00910	−7.2

LKB 2277, 30 °C, total flow rate 0.00557 ml s^{-1}; DAK-1-1A, 25 °C, solution volume 5.017 ml.

formation of an 1 : 1 inclusion complex between α-CD and resorcinol have been calculated as 0.066 M and −11.0 kJ mol^{-1} respectively.

It is difficult to express the accuracy of the calculated K_d and Q (ΔH) values because the latter are always calculated together and the concavities of the dispersion minimum are usually quite flat. For LKB 2277, the relative errors of K_d and ΔH values can be estimated as ±10%.

On comparing the accuracy of the results obtained, as well as their reproducibility and sensitivity, the LKB 2277 microcalorimeter is better than the DAK-1-1A calorimeter. However, it can be concluded that two different types of calorimeters, the batch and the flow types, can be successfully used in molecular complex studies.

The results for the ten systems under study are given in Table 3. All the complexes presented are formed at a molar ratio of 1 : 1. In this table the corrected values of dissociation constants and excess thermodynamic functions for benzoic acid complexes with cyclodextrins are presented.

Relatively weak inclusion complexes are formed between benzyl alcohol and β-CD with a change in the free energy of about −8 kJ mol^{-1}. We have investigated the dependence of the formation of the β-CD–benzyl alcohol complex on the pH value of the solution as well, finding this to be insignificant [8].

Evidently, for the first time the formation of inclusion complexes between dihydroxybenzene derivatives and cyclodextrins has been studied.

As seen in Table 3, the hydroquinone complex with α-CD is quite unstable. The resorcinol derivatives form strong complexes with β-CD and they are bonded more weakly in the α-CD cavity. For benzoic acid com-

TABLE 3

Thermodynamic parameters and dissociation constants for the 1:1 complexes of α-, β- and γ-CD in water solutions at 25–30 °C

CD	Guest molecule	Calorimeter	Dissociation constant (M)	ΔG (kJ mol^{-1})	ΔH (kJ mol^{-1})	ΔS (J mol^{-1} K^{-1})
α	Resorcinol	LKB, 30 °C	0.060	−7.1	−10.2	−10.3
α	Resorcinol	DAK, 25 °C	0.061	−6.9	−10.7	−13.5
α	Resorcinol	LKB + DAK	0.066	−6.9	−11.0	−13.5
β	Resorcinol	LKB, 30 °C	0.010	−11.6	−18.2	−21.6
γ	Resorcinol	DAK, 25 °C	0.047	−7.7	−4.7	9.9
α	5-Methyl-resorcinol	LKB, 30 °C	0.065	−6.7	−13.7	−22.4
β	5-Methyl-resorcinol	LKB, 30 °C	0.011	−11.4	−20.8	−31.2
β	5-Methyl-resorcinol	DAK, 25 °C	0.021	−9.8	−21.2	−37.5
β	5-Methyl-resorcinol	LKB + DAK	0.014	−10.8	−19.3	−28.2
γ	5-Methyl-resorcinol	LKB, 30 °C	0.184	−4.3	−28.2	−78.9
α	Hydroquinone	DAK, 25 °C	0.120	−5.3	−16.2	−36.2
α	Benzoic acid	LKB, 30 °C	0.0017	−16.1	−38.2	−72.9
β	Benzoic acid	LKB, 30 °C	0.0028	−14.8	−18.0	−10.4
β	Benzyl alcohol	LKB, 30 °C	0.048	−7.7	−13.8	−20.3

plexes the reverse is true. We have used this phenomenon to develop a thermochemical method for determining α- and β-CD concentrations in their mixtures [9].

The structure of CD complexes remains unclear from the point of view of how the guest molecules are placed in CD cavities. It may be supposed that, in the case of benzene derivatives having one functional group only, the latter penetrates in the CD cavity, even if this group is quite hydrophilic. For the complexes of resorcinol and its derivatives, probably at least one of the hydroxyl groups resides in the cavity. Perhaps for such compounds different possibilities of binding can be realised if none of them has a clear energetic preference.

To study the geometry and structure of CD complexes, as well as their ^{1}H and ^{13}C NMR spectra [10], computer-projected images based on X-ray crystal structures may be used [11]. It seems that there is a direct correlation between the depth of substrate penetration into the cavity and the equilibrium constant (a reciprocal of the dissociation constant) of the complex.

Unfortunately, a thermochemical study allows no insight into the structure of inclusion complexes. Nevertheless, it is a powerful tool for a

systematic determination of the values of dissociation constant and thermodynamic parameters and can be recommended for wider use.

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