JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 6, 651–659 (1993)

CLASSIFICATION OF THE SOLUBILITY BEHAVIOUR OF β-CYCLODEXTRIN IN AQUEOUS–CO-SOLVENT MIXTURES

ANTHONY W. COLEMAN, MARC MUNOZ AND ALEXIS K. CHATJIGAKIS
CNRS, Centre Pharmaceutique, Université de Paris-Sud, F-92296 Chatenay-Malabry, France
AND
PHILIPPE CARDOT
Laboratoire de Chimie Analytique, Centre Pharmaceutique, Université de Paris-Sud, F-92296 Chatenay-Malabry, France

The solubility behaviour of β-cyclodextrin in aqueous mixtures was studied by determining the interactions between the co-solvent and water. Three clear classes of co-solvent are evident. In the first, including ethanol, tetrahydrofuran and acetone, there is formation of clathrate hydrates by the co-solvent. In these systems the solubilization is a maximum at the mole fraction corresponding to the minimum in the partial excess molar volume. The second class, including such solvents as dimethyl sulphoxide and pyridine, forms strong molecular complexes with water, and here a valley and a plateau region occur in the solubility values. In the third class, including formamide and urea, a steady increase in the solubility is observed. For these highly polar solvents no maxima are observed in intrinsic solvent properties such as the partial excess molar volume.

INTRODUCTION

β-Cyclodextrin(β-CD), a cyclic oligosaccharide having seven α-1,4-linked glucopyranose units, has been widely applied for the inclusion and transport of hydrophobic substrates within its cavity.[1] However, its utility is limited by a low intrinsic solubility, 20 g L^{-1}, coupled with a decrease in solubility on complexation. Numerous workers have studied the effects of co-solutes[2–5] or co-solvents[6–10] on the solubility of β-CD. We have extended this work to cover a wide range of solvents and the full range of mole fractions from 0 to 100%. As a result of this more comprehensive study, three separate classes of solvent may be defined in terms of the solubility of β-CD in aqueous mixtures. A detailed model of the solubility behaviour requires an understanding of the exact structure of water and how this structure is modulated by co-solvents.[11] An exact model not being currently available, however, the solubility behaviour may be empirically linked to intrinsic solvent properties, such as the partial excess molar volume, which effectively measure this modulation of the 'normal' structure of water by the co-solvent. This allows a 'predictive' approach to the solubilization to be used for those solvents for which properties dependent on the modulation of the water structure have been measured (in general, the necessary information may be found in Ref. 12).

The three classes show the following characteristics: type A, a maximum in the solubilization for solvents forming clathrate hydrate systems; Type B, two regions separated by a sharp break (a valley and plateau system) for solvents forming strong molecular complexes with water; and type C, a simple increase in solubility for very polar solvents. The last type of behaviour may also be extended to ionic co-solutes in terms of their activity constants.[13]

EXPERIMENTAL

The procedure utilized has been described in detail elsewhere.[9] In general, solutions of the aqueous mixtures are prepared to a set volume, to which β-CD is added. The solutions are then stirred in a thermostated bath (20 ± 0·5 °C) for 48 h to allow maximum dissolution to occur. For those systems in which solid β-CD remains, it is assumed that saturation has been reached, and the solutions are filtered and the concentrations determined from measurement of the optical rotation, using a Perkin-Elmer Model 241C polarimeter. For solutions in which the β-CD is completely dissolved, a further quantity of solid β-CD is added and the experiment is repeated until saturation occurs.

The validity of the use of optical rotation to determine the concentration is confirmed by dissolution of

0894–3230/93/120651–09$09.50

Received 15 January 1993
Revised 17 August 1993

known quantities of β-CD in the various solvent mixtures and subsequent measurement of the optical rotation. Plots of concentration versus α_D for all solvent mixtures are linear and give values the same as that in water, 163 °C $dm^2 g^{-1}$.[14] Validation of the solubility is obtained by taking quantities of β-CD slightly above and below the experimentally determined values and carrying out the solubility measurement. In 95% of cases confirmation was observed and for the remainder lower solubilities were observed; repetition of the basic experiment twice gave solubilities consistent with the validation experiments in all cases.

In view of the above, we consider the technique used to be reliable and accurate, giving solubilities accurate to ±0·01 g per 100 ml.

RESULTS

The complete solubility data for β-CD in all the solvents used are given in Table 1.

The solubility curves for β-CD in ethylene glycol dimethyl ether (**1**), dimethylformamide (**2**) and formamide (**3**) aqueous mixtures are presented in Figures 1, 2 and 3, respectively. It is apparent that the behaviour in each solvent system is different.

In **1**, the solubility rapidly increases from the basal (100% aqueous) value of 1·8 per g 100 ml to reach a maximum of 3.8 g per 100 ml at 2% mole fraction **1**, followed by a decrease to give an effective zero solubility at 100% **1**. For concentrations of **1** above 5% the observed solubility is lower than the basal value.

In **2** the observed solubility remains constant at the basal value until 30% mole fraction **2**, there is then an increase to 5 g per 100 ml at 35%; between 35 and 40% mole fraction **2** the solubility increases dramatically to 26 g per 100 ml. After this increase there is a plateau region of constant solubility to 90% mole fraction, followed by small decline to a 100% mole fraction solubility of 24 g per 100 ml.

For **3**, the most polar of these solvents, the solubility increases linearly to a value of 7 g per 100 ml at 40% mole fraction **3**, there is then a second linear increase with a steeper slope until the maximum solubility of 40 g per 100 ml^{-1} is observed at 100% mole fraction **3**.

Comparison with our previous results using other solvent systems[9,10] plus the observed values for urea–water mixtures[3] allow a more general classification to be obtained: class A solvents are methanol, ethanol, propan-1-ol, propan-2-ol, tetrahydrofuran, acetonitrile, ethylene glycol dimethyl ether, acetone and dioxane; class B solvents are dimethyl sulphoxide (DMSO, pyridine and dimethylformamide (DMF); and class C solvents or solutes are formamide, urea and ionic salts.[13]

The maximum solubilities of β-CD in the mixtures and the co-solvent mole fractions for which maximum solubilization occurs are given in Table 2.

In class A solvents there is a maximum in the solubilization effect, which is solvent dependent but generally at low mole fractions of co-solvent. In class B solvents a valley–plateau system is observed with a break point occurring at *ca* 33% mole fraction for both DMSO and

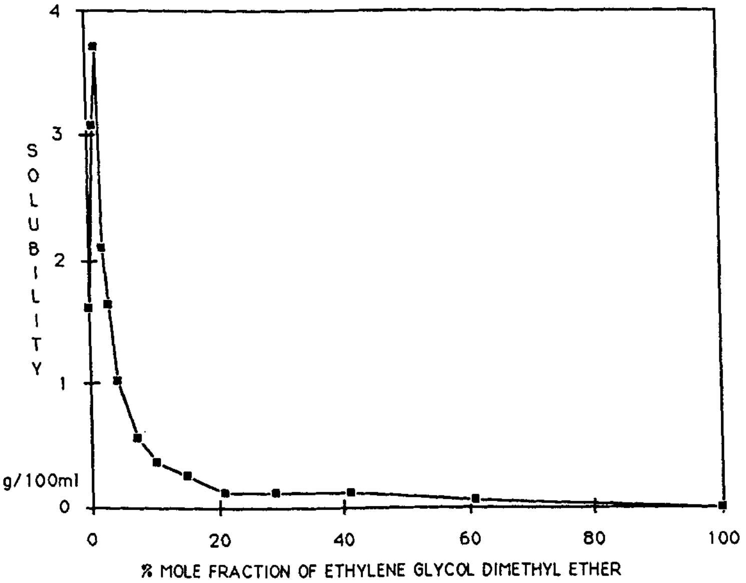

Figure 1A. Solubility curve for β-CD as a function of concentration of ethylene glycol dimethyl ether

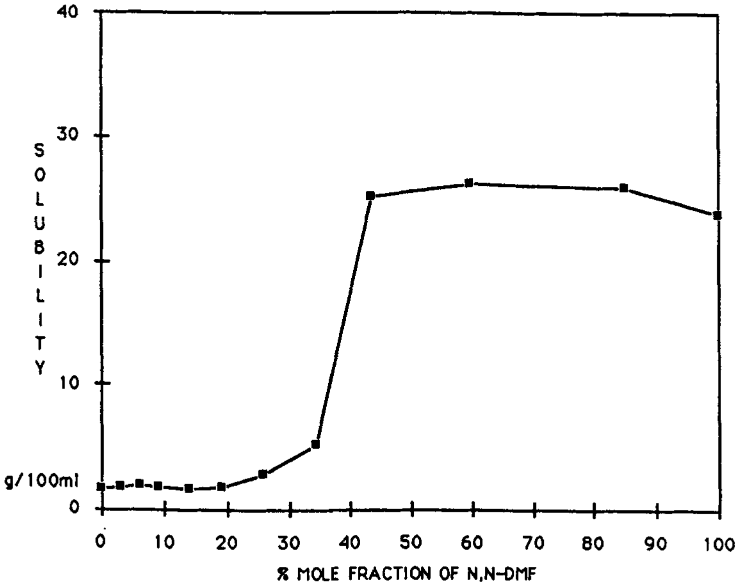

Figure 2. Solubility curve for β-CD as a function of concentration of dimethylformamide

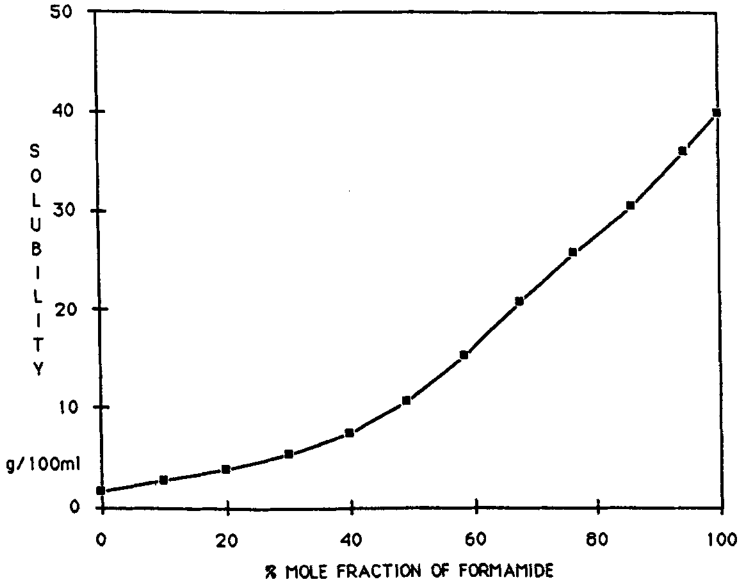

Figure 3. Solubility curve for β-CD as a function of concentration of formamide

Table 1. Complete solubility data for β-CD in various solvents

Solvent	Mole fraction	Solubility (g per 100 ml)	Solvent	Mole fraction	Solubility (g per 100 ml)	Solvent	Mole fraction	Solubility (g per 100 ml)
Acetone	0	1·6	Tetrahydrofuran	0	1·6	Methanol	0	1·61
	0·015	3·72		0·02	2·1		0·03	1·00
	0·03	4·66		0·05	2·2		0·07	0·71
	0·07	2·94		0·09	1·88		0·12	0·50
	0·09	1·69		0·13	1·3		0·17	0·40
	0·13	0·97		0·18	0·9		0·24	0·34
	0·19	0·41		0·25	0·5		0·31	0·26
	0·26	0·24		0·31	0·2		0·42	0·10
	0·35	0·19		0·47	0·15		0·55	0·05
	0·48	0·17		0·66	0·06		0·73	0·02
	0·68	1·12		1·00	0		1·00	0
	1·00	0						
Acetonitrile	0	1·6	DMSO	0	1·6	Propan-2-ol	0	1·6
	0·02	2·5		0·03	1·95		0·015	3·41
	0·04	3·3		0·06	2·10		0·03	4·81
	0·06	4·0		0·08	2·20		0·045	6·04
	0·08	4·08		0·14	2·75		0·06	7·04
	0·11	3·97		0·2	6·31		0·075	7·25
	0·13	3·04		0·27	16·2		0·09	6·9
	0·19	2·0		0·33	47·1		0·13	3·61
	0·26	0·98		0·4	76·5		0·19	2·31
	0·34	0·32		0·53	75·6		0·26	1·13
	0·44	0·16		0·69	74·6		0·35	0·41
	0·58	0·04		0·91	50·2		0·48	0·14
	0·75	0·02		1·00	50·1		0·68	0·04
	1·00	0					1·00	0
DMF	0	1·65	Ethylene glycol dimethyl ether	0	1·6	Ethanol	0	1·6
	0·03	1·82		0·07	3·08		0·03	1·82
	0·06	1·87		0·013	3·71		0·07	2·01
	0·09	1·72		0·02	2·1		0·12	2·2
	0·14	1·63		0·03	1·63		0·17	1·8
	0·19	1·81		0·04	1·01		0·24	1·3
	0·26	2·8		0·07	0·55		0·31	0·8
	0·344	5·2		0·1	0·36		0·42	0·29
	0·44	25·2		0·15	0·25		0·55	0·1
	0·60	26·2		0·21	0·12		0·73	0·05
	0·85	26		0·29	0·12		1·00	0
	100	23		0·41	0·12			0
				0·61	0·05			
				1·00	0			
Dioxane	0	1·6	Pyridine	0	1·6	Formamide	0	1·6
	0·02	2·26		0·1	8·00		0·05	2·8
	0·05	2·31		0·2	8·11		0·1	3·9
	0·08	2·20		0·3	7·5		0·23	7·4
	0·12	2·01		0·4	7·6		0·30	10·6
	0·17	1·49		0·5	21·3		0·39	15·3
	0·23	0·93		0·6	26·2		0·49	20·7
	0·33	0·58		0·7	35·0		0·596	25·9
	0·45	0·12		0·8	46·5		0·73	30·5
	0·67	0·08		0·9	60·1		0·889	36
	100	0·01		1·00	59·6		1·00	40·1

Table 2. Maximum solubility of β-CD in various solvents and mole fraction concentration for maximum solubilization

Class	Solvent	Mole fraction for maximum	$(g\ l^{-1})$
A	Methanol	0 (22)[1]	18·5
	Ethanol	10	22
	Propan-2-ol	8	70
	Acetonitrile	8	37
	Tetrahydrofuran	5	22
	Ethylene glycol dimethyl ether	2	38
	Acetone	7	47
	Dioxane	5	23
B	Dimethylformamide	40	365
	Dimethyl sulphoxide	40	770
	Pyridine	65	70
	Ethylene glycol	80[b]	29
C	Formamide	100	400

[a] Methanol shows an inflection in the solubility at 22% corresponding to A type.

[b] Ethylene glycol shows an initially decreasing solubility followed by a plateau-type behaviour.

DMF and at *ca* 50% mole fraction for pyridine. In class C systems there is a steady increase in solubility with increasing co-solvent or co-solute concentration.

DISCUSSION

In order to understand better the classification of solvent systems, Figures 4(a), 5(a) and 6(a) show the solubility plots for propan-2-ol, DMSO and DMF, and Figures 4(b), 5(b) and 6(b) show the equivalent plots of partial excess molar volumes, adapted from Franks.[15]

The correlation between the two types of measurement is striking, and general for all class A and B solvents. In class A solvents there appears to be a general curve for the decrease in the solubility of β-CD which is overlaid by a solvent-specific effect, the shape and size of which are apparently related to thermodynamic measures of solvent structure modulation such as the partial excess molar volume. In class C formamide shows a good correlation with such properties, but for ionic salts a similar inherent property, such as activity, is a better measure.

Within class A the alcohols show a maximum in the solubility at the mole fractions observed to give rise to maxima in the thermodynamic and other data which may be related to structural modulation.[11] In the case of methanol there is an inflection point in the decreasing solubility curve at 22% mole fraction, corresponding to the maximum mole fraction for changes in the thermodynamic functions. Identical effects have been observed for α- and γ-CDs by Okada *et al.*[16] but not correlated with solvent properties.

For solvents such as acetone, tetrahydrofuran and acetonitrile the available thermodynamic data are more sparse, but still correlates well. Tetrahydrofuran forms a stable clathrate of stoichiometry 15 H_2O : 1 THF,[17] giving a mole fraction of 5% and thus fitting with the observed maximum value for the solubilization. Acetone also forms a clathrate hydrate,[18] and measurements using infrared spectroscopy on the influence of acetone on the hydrogen bonding in water show a maximum effect at 25 °C for a mole fraction of 7%,[19] again in close agreement with the maximum solubilization. Acetonitrile is generally treated as causing a breakdown in the structure of water and does not appear to form a clathrate hydrate. The only evidence for a structural modification of water by this solvent comes from the modification of the absorption energy in the ultraviolet spectrum of dilute solutions of KI, regarded as a measure of the change in water–water interactions; the observed maximum effect occurs at a mole fraction of 8%,[20] again in agreement with the value for maximum solubilization of β-CD.

The classes may now be related to general types of interaction with water. Franks[15] has detained the class A solvents as part of the group of 'solvophobic solutes' which form clathrate hydrates with water. Such formation leads to a stabilized deformation of the structure of water until the point where all the water molecules are involved in cavity formation in the clathrate hydrate structure. As we have noted previously, there is an inherent incompatibilty between the dynamic hexagonal structure of water and the sevenfold symmetry of β-CD, hence this restructuring of water should lead to more favourable interactions with β-CD and hence an increased solubility.

At concentrations higher than that for the maximum in effect on partial excess molar volume, according to

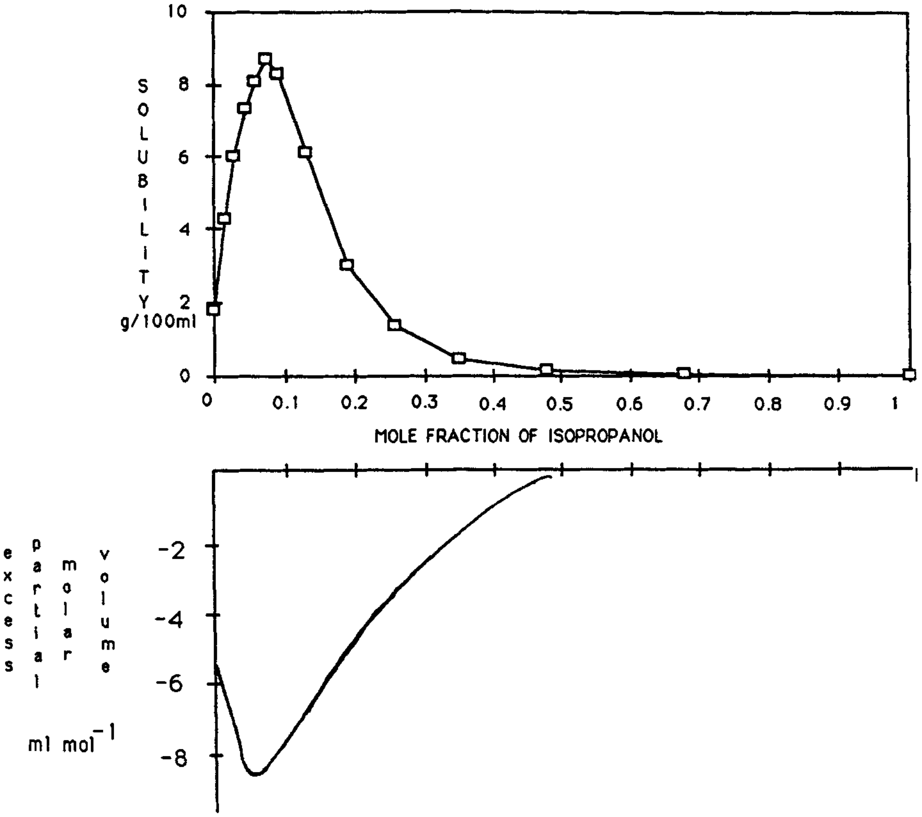

Figure 4. Solubility curve for β-CD as a function of concentration of propan-2-ol and the equivalent curve for the partial excess molar volume

Franks water is 'squeezed' out of the clathrate and relaxes to its normal structure.[15] This, coupled with a low basal solubility of β-CD in the organic solvents, leads to a rapid decrease in the observed solubility.

In contrast, the class C solvents belong to the group of relatively well behaved systems in their interactions with water. Here the strong polar forces lead to a gradual reorganization of the structure of water about the solvent molecule; this reorganization may be treated in terms of structure making or structure breaking,[11] each of which implies a different restructuring of water; urea and the other systems discussed here are structure breakers. This effect reduces as a function of co-solvent the hexagonal dynamic water structure and hence the expected increase in solubility is observed.

The class B solvents present a very different problem; here the systems are typified by the formation of strong molecular complexes between the co-solvent and water. The stoichiometry of these complexes is determined by the hydrogen bond-forming capacity of the molecule; pyridine bonds to only one water molecule but DMSO and DMF bond to two. Hence the break points in the behaviour would be expected to arise at mole fractions of 50%, 33% and 33% respectively, as is observed. For these solvents the physical and solvation properties are best treated in terms of free solvent and a molecular complex; in the respective zones in which one solvent is present in excess the system behaves as if this solvent were pure, hence the plateau. The lack of variation in the solubility implies that sufficient free solvent is available to solvate the cyclodextrin outside the zone of change between valley and plateau; this is reasonable as in the case of water the low solubility of β-CD would involve small quantities of water even if large hydration numbers are postulated (probably around 25 molecules in the first hydration sphere), and in the case of the second solvent the higher solubility is probably compensated for by a much lower solvation and also the maxima in the solubilities occur at mole fractions (about 5–8% above the stoichiometry of the solvent–water complex) that leave significant quantities of free solvent. Similarly, in the ^{1}H NMR spectra of the system for mixtures of DMSO and water, the resonances for β-CD behave in the valley and plateau regions as those

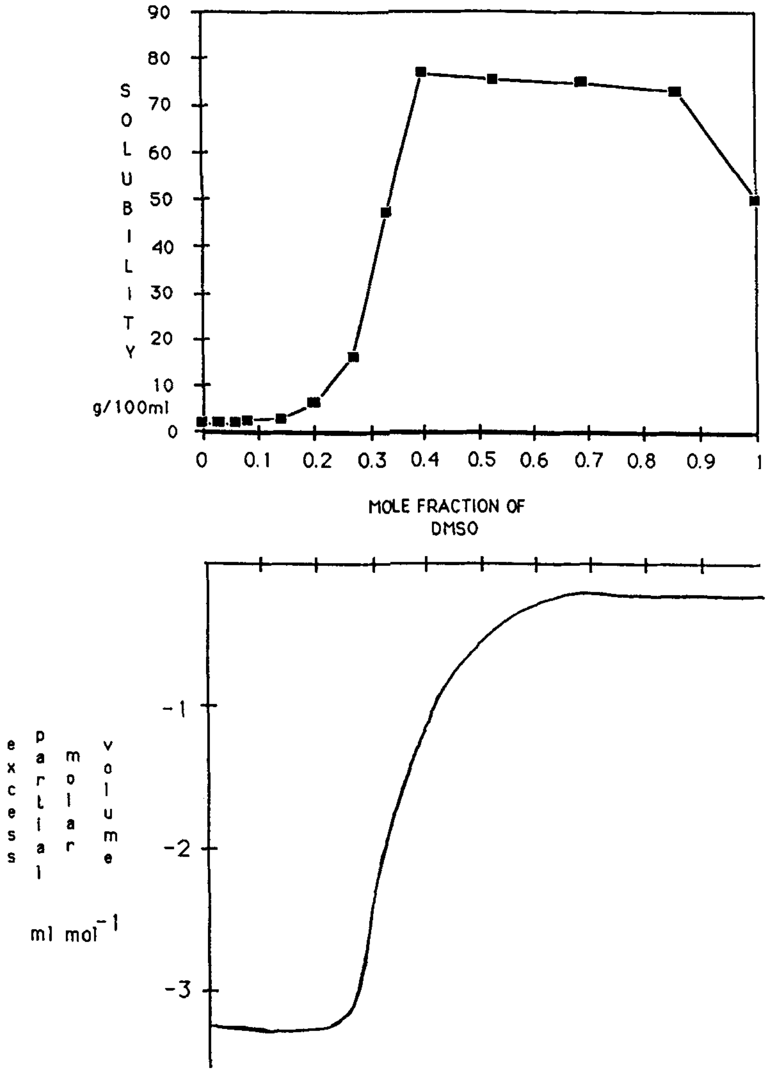

Figure 5. Solubility curve for β-CD as a function of concentration of dimethyl sulphoxide and the equivalent curve for the partial excess molar volume

observed in the pure solvents, and changes between the two types of spectra occur only in the region between 30 and 40% mole fraction, i.e. in the break-point zone. At very high mole fractions (>95%) the solubility behaviour becomes more complex with, for example, the formation of gels by anhydrous β-CD cyclodextrin in rigorously dried pyridine.[21]

Ethylene glycol is considered separately. From evidence in the literature,[22] it probably belongs to a fourth class of solvent combining the structural modulation properties of the mollo-Ltlcohols at low mole fractions, proposed by Nakanishi *et al.*[22] to be similar to that of methanol and hence in agreement with the observed solubility plot, with a large basal solubility of βCD.The large-scale reorganization of the water structure leads initially to a decrease in the solubility of β-CD, and above a mole fraction of about 25% there is an increase in the solubility which becomes almost constant above 50%. It is interesting that in general many of the partial molar properties of alcohols are very similar to those of pure alcohols for mole fractions >50%; hence ethylene glycol behaves in a manner paralleling that of the other alcohols but with the above mentioned difference in the solubility of β-CD in the pure solvent. We have chosen

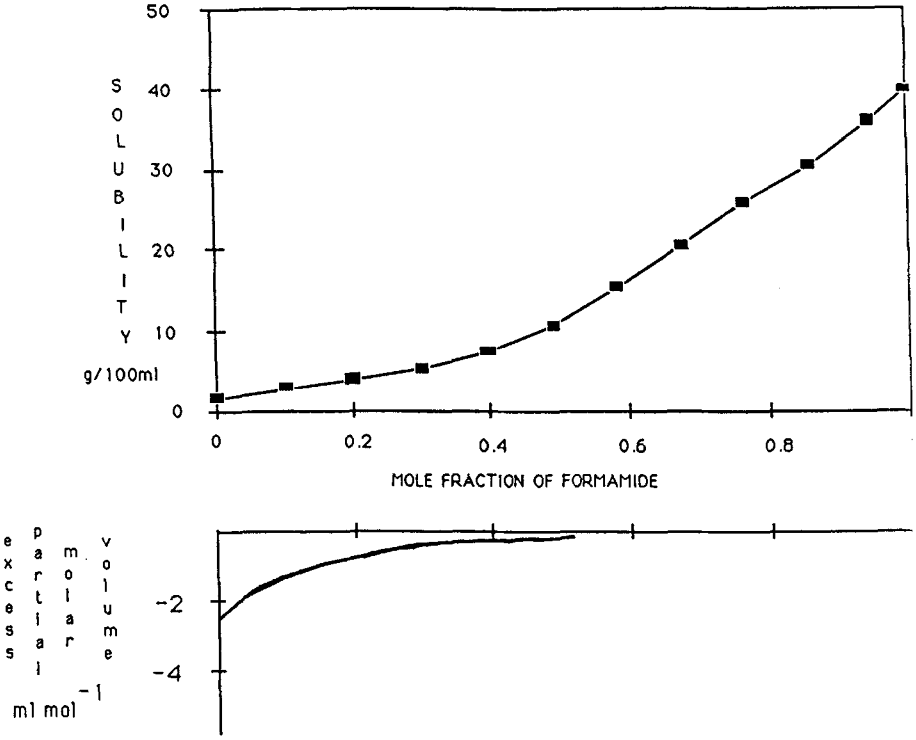

Figure 6. Solubility curve for β-CD as a function of concentration of formamide and the equivalent curve for the partial excess molar volume

not classify this solvent as it is the only example of this behaviour that we have so far encountered.

CONCLUSION

We have shown that the effect of co-solvent on the solubility of β-CD in aqueous mixtures may be related to the interaction of the co-solvent with water; and that this behaviour may be correlated with the intrinsic modulation of the water structure by the co-solvent.The use of this knowledge allows the prediction of the solubility of β-CD in solvents for which parameters such as partial excess molar volume have been determined.

REFERENCES

1. J. Szeijtli, *Cyclodextrins and Their Inclusion Complexes.* Akadémiai Kiadó, Budapest (1982).
2. A. Buvari and I. Barcza, *J. Inclus. Phenom. Mol. Recog. Chem.* **7**, 379 (1989).
3. D. Y. Pharr, Z. S. Fu, T. K. Smith and W. L. Hinze, *Anal. Chem.* **61**, 275–279 (1989).
4. A. W. Coleman and I. Nicolis, *J. Inclus. Phenom.* **13**, 139–143 (1992).
5. A. W. Coleman and I. Nicolis, *J. Supramol. Chem.* in press.
6. J. Zukowski, D. Sybilska and J. Jurczak, *Anal. Chem.* **57**, 2215–2219 (1985).
7. C. Donzé, A. Chatjigakis and A. W. Coleman, *J. Inclus. Phenom. Mol. Recog. Chem.* **13**, 155–161 (1992).
8. M. Taghvaei and G. H. Stewart, *Anal. Chem.* **63**, 1902–1904 (1991).
9. A. K. Chatjigakis, C. Donzé, A. W. Coleman and P. Cardot, *Anal. Chem.* **64**, 1902–1904 (1992).
10. A. W. Coleman, A. K. Chatjigakis and P. Cardot, *Pol. J. Chem.* **66**, 1 (1993).
11. F. Franks and J. E. Desnoyers, *Water Sci. Rev.* **1**, 171 (1985).
12. F. Franks, *Water a Comprehensive Treatise*, Vol. 2, and references cited therein. Plenum Press, London (1973).
13. I. Nicolis and A. W. Coleman, *J. Chem. Soc. Perkin Trans. 2* submitted for publication.
14. D. French, M. L. Levin, J. H. Pazur and E. Norberg, *J. Am. Chem. Soc.* **71**, 353 (1949).
15. F. Franks, *Water*, Royal Society of Chemistry, London, 1983.
16. Y. Okada, Y. Kubota, K. Koizuma, S. Hizukuri, T. Ohfjui and K. Ogata, *Chem. Pharm. Bull.* **36**, 2176 (1988).
17. S. R. Gough and D. W. Davidson, *Can. J. Chem.* **49**, 2691 (1971).

18. M. J. Fox, *Chem. Soc., Faraday Trans 1*, **68**, 1294 (1972).
19. A. S. Quist and H. S. Frank, *J. Phys. Chem.* **49**, 4660 (1968).
20. M. J. Wootten, *PhD Thesis*, University of Leicester (1969).
21. C. de Rango, A. W. Coleman, I. Nicolis, N. Keller, P. Charpin and F. Villain, *J. Am. Chem. Soc.* **113**, 5738 (1992).
22. K. Nakanishi, N. Kato and M. Maruyama, *J. Phys. Chem.* **71**, 814 (1967).