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# Inorganic salt modulation of the aqueous solubility of $\beta$ -cyclodextrin

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The effect of mono-, di- and trivalent metal salts on the maximum aqueous solubility of  $\beta$ -cyclodextrin ( $\beta$ -CD) has been investigated. The results show the solubility to be highly dependent on the cation charge:  $M^+ < M^{2+} < M^{3+}$ . For chloride as the anion, the solubility increases down Group II for a given salt concentration:  $Mg^{2+} < Ca^{2+} < Sr^{2+} < Ba^{2+}$ . However for nitrate as the anion, solubility is largely cation-independent. The increased solubility allows medium-field NMR (200 MHz) to be used in the study of the  $\beta$ -CD–thymol inclusion complex.

## INTRODUCTION

The cyclodextrins are cyclic oligosaccharides possessing six, seven or eight  $\alpha$ -1,4-linked glucopyranose units and they are capable of forming inclusion complexes with a wide range of organic guest molecules. Their formation by enzymic catalysed cyclization of amylose has allowed their exploitation on a large scale and commercial applications are already being seen.<sup>1</sup>  $\beta$ -Cyclodextrin ( $\beta$ -CD) is the most widely available compound due in part to its abnormally low solubility ( $18.5 \text{ g l}^{-1}$ ). This low solubility in turn has considerable constraint on the utilization of  $\beta$ -CD and its inclusion compounds.

We have recently shown<sup>2</sup> that  $\beta$ -CD is present in aqueous solution as large aggregates and that the unfavourable interaction of these aggregates with the dynamic structure of water may give an explanation of the low solubility. In the same paper we have shown that the methylated cyclodextrins, which are present in solution as dimers for the 2,6-dimethyl compounds, and as monomers for the 2,3,6-trimethyl compounds, do not form the unfavourable aggregate water interactions and, in consequence, have greatly enhanced solubilities. Urea,<sup>3</sup> a structure altering solute, reduces these unfavourable interactions, and the solubility of  $\beta$ -CD increases in aqueous urea solutions. More recently we have clearly demonstrated that the

solubility of  $\beta$ -CD in water–co-solvent mixtures is related to the changes in bulk solvent properties and not to co-solvent– $\beta$ -CD interactions.<sup>4</sup> In view of the above, it seems likely that the solubility of  $\beta$ -CD in aqueous systems may be modified by changing the structural properties of the solvent, without direct  $\beta$ -CD–co-solute or co-solvent interactions.

The observation that concentrated  $CaCl_2$  solutions dramatically increase the solubility<sup>5</sup> has led us to investigate the effects of di- and trivalent metal salts on  $\beta$ -CD solubility.

In this paper we show that:

(1) co-dissolution of the Group II chlorides  $MgCl_2$ ,  $CaCl_2$ ,  $SrCl_2$ , and  $BaCl_2$ , and  $AlCl_3$ , at concentrations of up to 2 M, considerably increases the aqueous solubility of  $\beta$ -CD; this is in contrast to the previous study<sup>6</sup> on the Group I chlorides,  $LiCl$ ,  $NaCl$ , and  $KCl$  and the results we have obtained for  $NaCl$  at concentrations between 1.5 M and 2 M, where virtually no effect of co-solute is seen on the saturation solubility of  $\beta$ -CD.

(2) the Group II nitrates,  $Al(NO_3)_3$ ,  $La(NO_3)_3$  and  $Pr(NO_3)_3$  again dramatically increase the solubility of  $\beta$ -CD [the effect of  $Ba(NO_3)_3$  on the solubilization is limited by a salt saturation concentration of only 0.3 M]; the Group I nitrates  $NaNO_3$  and  $KNO_3$  are more effective at solubilization than their chloride analogues ( $\approx 36 \text{ mM}$  vs.  $16 \text{ mM}$ ).

(3) for the nitrates, the solubility enhancement is apparently only dependent on the metal charge; thus Group I < Group II < Al, La, Pr, but it remains constant within the group. The solubility of  $\beta$ -CD in Group II solutions is constant for a given concentration of any salt. For the chlorides, charge effects are also present for the solubility of  $\beta$ -CD, i.e. Group I < Group II < Group III. In addition, for a constant charge on the cation, the solubilization increases on descending the group, thus  $Mg < Ca < Sr < Ba$ .

(4) the solubilization effects of  $Sr(NO_3)_2$  may be used in  $^1H$ -NMR experiments to investigate the

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inclusion complexation of  $\beta$ -CD and thymol by use of medium-field (200 MHz) NMR.

## EXPERIMENTAL

### Materials

Commercial materials (Aldrich) were used without purification, the  $\beta$ -CD was a gift from Rhône-Poulenc.  $\beta$ -CD(OD)<sub>21</sub> was obtained by triple exchange of  $\beta$ -CD in excess D<sub>2</sub>O. <sup>1</sup>H-NMR spectra were recorded on a Bruker AC200P spectrometer (200 MHz) and optical rotations were measured on a Zeiss polarimeter at the sodium wavelength (589 nm).

### Solubility measurements

The solubility measurements were carried out as follows:  $\beta$ -CD was added in a slight excess to aqueous solutions (50 ml) of different salt concentrations (0–2.5 M) at 18–20°C. The solutions were stirred continuously for at least 48 h on a Bioblock 15 station magnetic stirrer at constant speed for all solutions. To verify equilibrium conditions a blank run of  $\beta$ -CD in water at 18 g l<sup>-1</sup> was carried out with each batch. Measurements were not carried out until a minimum of 12 h after complete dissolution of the control experiment. For solutions in which saturation concentration was not reached, the experiment was freshly repeated with an increased quantity of  $\beta$ -CD.

The concentration of the dissolved  $\beta$ -CD in the filtered solutions was determined by optical rotary measurements in 1 or 2 dm length cells. To insure reproducibility certain samples within each batch were repeated three times; the values obtained for these controls were always within the error limits of the experiments,  $\pm 1$  mM.

A plot of the optical rotation versus  $\beta$ -CD concentration between 0 and 41% w/v (0 and 0.31 M based on a hydration of 13.8%) was linear even in the presence of metal salts, with a slope of  $[\alpha]_D^{25} = 0.164$  grade dm<sup>2</sup> g<sup>-1</sup> in close agreement with the literature value of 0.163 grade dm<sup>2</sup> g<sup>-1</sup>.<sup>7</sup>

### <sup>1</sup>H-NMR studies of the $\beta$ -CD–thymol complex

Saturated solutions of (a) thymol– $\beta$ -CD in D<sub>2</sub>O, (b) thymol in 2 M Sr(NO<sub>3</sub>)<sub>2</sub>.D<sub>2</sub>O, (c) thymol– $\beta$ -CD in D<sub>2</sub>O, and (d) thymol– $\beta$ -CD in 2 M Sr(NO<sub>3</sub>)<sub>2</sub>.D<sub>2</sub>O, were prepared by stirring an excess of thymol and/or  $\beta$ -CD(OD)<sub>21</sub> with, as appropriate, D<sub>2</sub>O or 2 M Sr(NO<sub>3</sub>)<sub>2</sub>.D<sub>2</sub>O at 18°C over 72 h. The solutions were filtered using a 0.2 m syringe filter.

## RESULTS AND DISCUSSION

The maximum values for the solubility of  $\beta$ -CD in the presence of various metal salts are given in Table 1.

The values obtained for KCl and NaCl are slightly different from those of Buvari and Barcza,<sup>6</sup> but this discrepancy is within the error limits of the current experiment.

The results for the solubilization by the Group I, Group II and trivalent metal nitrates are given in Figures 1, 2, and 3, respectively. The Group I metal ions, Na<sup>+</sup> and K<sup>+</sup>, give rise to the least increase in solubility (35–38 mM), with a close to linear effect with concentration. For the Group II metal ions, Mg<sup>2+</sup>, Ca<sup>2+</sup>, Sr<sup>2+</sup> and Ba<sup>2+</sup>, [with the exception of Ba(NO<sub>3</sub>)<sub>2</sub> which has a saturation concentration of only 0.3 M] much greater increases in solubility occur, giving a maximum value of solubility of  $\beta$ -CD for the three metals of  $\sim 170$  mM. The effects are non-linear with concentration, and appear to be almost independent of the metal. For the lanthanide cations Pr<sup>3+</sup> and La<sup>2+</sup>, solubilization effects are greater, with saturation concentrations of 240 mM at 2 M and for La(NO<sub>3</sub>)<sub>3</sub> a maximum of 294 mM at 2.5 M metal concentration. The effects are more nearly linear and are almost completely independent of the nature of the M<sup>3+</sup> ion.

Figure 4 shows the data obtained for the Group II chlorides. As can be clearly seen, the solubility increases are dependent on both metal ion concentration and on the metal ion itself. Comparing  $\beta$ -CD solubility values at 1.4 M metal ion (the saturation concentration of BaCl<sub>2</sub>) it shows: MgCl<sub>2</sub>, 23 mM; CaCl<sub>2</sub>, 45 mM; SrCl<sub>2</sub>, 61 mM; and BaCl<sub>2</sub>, 89 mM. The effects are

**Table 1** Maximum  $\beta$ -cyclodextrin solubility in the presence of metal salts

Salt	Salt concentration (M)	Solubility of $\beta$ -CD (g/100 ml)	Solubility of $\beta$ -CD (mM)
NaCl	2.00	2.10	18.20
KCl	2.00	1.90	17.10
NaNO <sub>3</sub>	2.00	4.40	38.50
KNO <sub>3</sub>	2.00	4.00	35.60
AlCl <sub>3</sub>	2.00	25.20	221.60
Al(NO <sub>3</sub> ) <sub>3</sub>	1.60	21.20	187.10
MgCl <sub>2</sub>	2.19	7.80	68.70
CaCl <sub>2</sub>	2.00	12.90	113.20
SrCl <sub>2</sub>	2.00	15.20	133.80
BaCl <sub>2</sub>	1.39	10.10	89.40
Mg(NO <sub>3</sub> ) <sub>2</sub>	2.00	20.00	176.40
Ca(NO <sub>3</sub> ) <sub>2</sub>	2.00	19.40	171.30
Sr(NO <sub>3</sub> ) <sub>2</sub>	2.00	19.20	169.60
Ba(NO <sub>3</sub> ) <sub>2</sub>	0.30	3.60	31.90
La(NO <sub>3</sub> ) <sub>3</sub>	2.50	33.40	294.40
Pr(NO <sub>3</sub> ) <sub>3</sub>	2.25	31.10	274.40

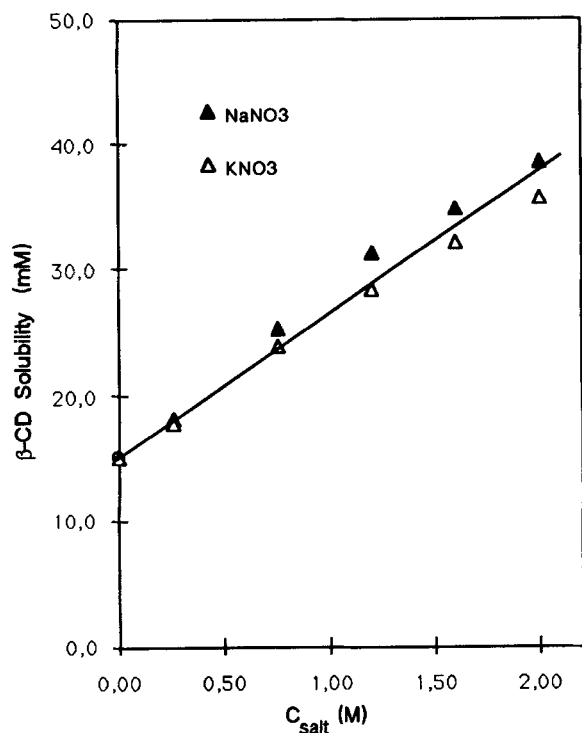


Figure 1 Solubility of  $\beta$ -cyclodextrin in the presence of Group I nitrates.  $C_{\text{salt}}$  = salt concentration.

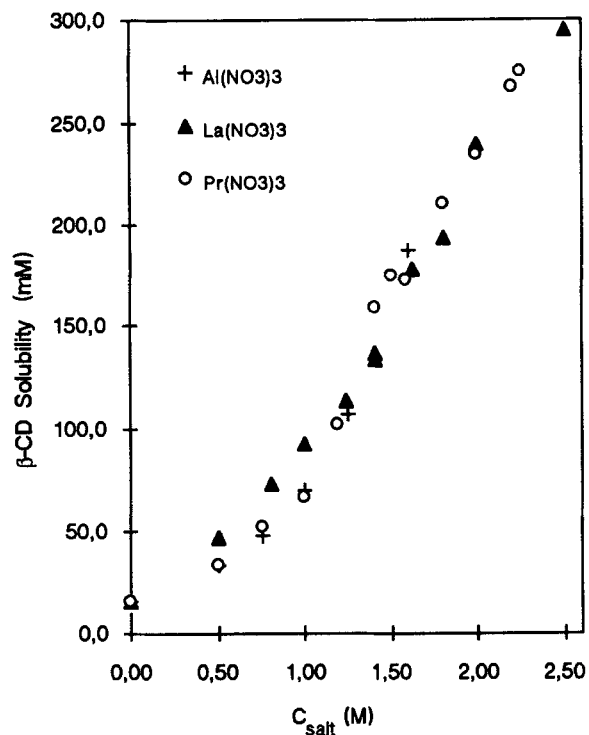


Figure 3 Solubility of  $\beta$ -cyclodextrin in the presence of trivalent cation nitrates.  $C_{\text{salt}}$  = salt concentration.

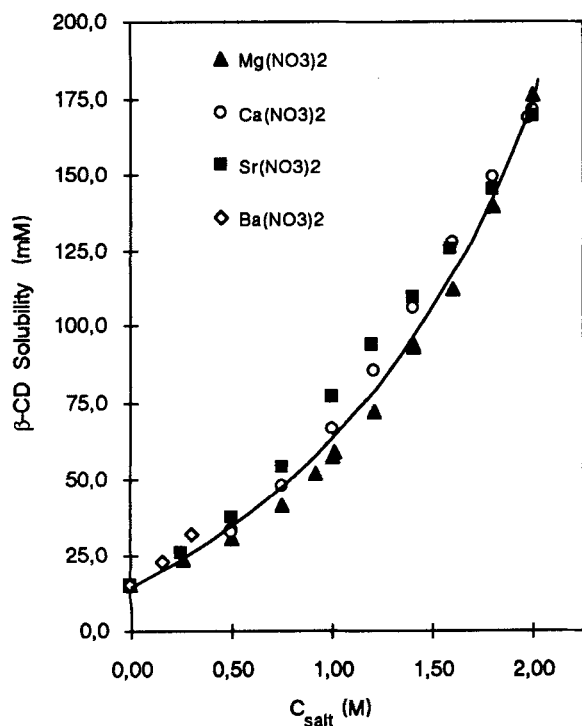


Figure 2 Solubility of  $\beta$ -cyclodextrin in the presence of Group II nitrates.  $C_{\text{salt}}$  = salt concentration.

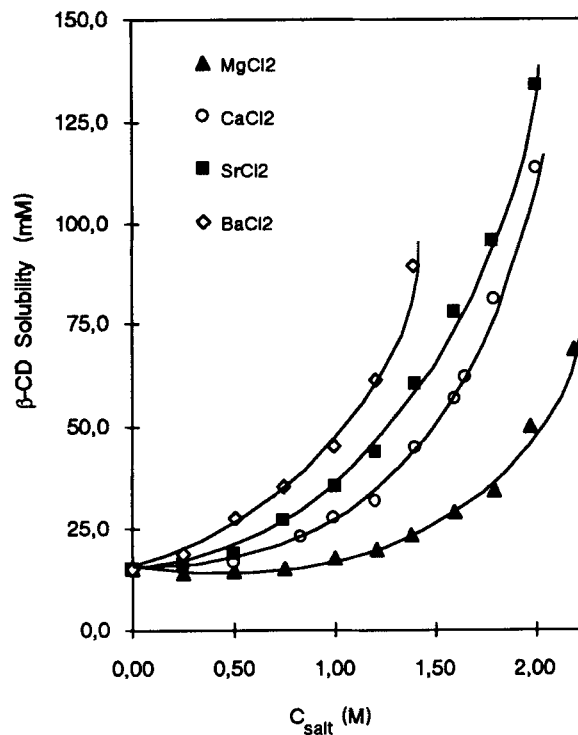


Figure 4 Solubility of  $\beta$ -cyclodextrin in the presence of Group II chlorides.  $C_{\text{salt}}$  = salt concentration.

non-linear, but for  $\text{Ca}^{2+}$ ,  $\text{Sr}^{2+}$  and  $\text{Ba}^{2+}$ , it seems to be related and parallel, and for these metals there would appear to be a relationship between  $\beta$ -CD solubility and metal ion concentration.

In Figure 5 are given the data for  $\text{AlCl}_3$  and  $\text{Al}(\text{NO}_3)_3$ . Again considerable solubilization is observed [187 mM for  $\text{Al}(\text{NO}_3)_3$ , and 221 mM for  $\text{AlCl}_3$ ]. However the curve obtained for  $\text{AlCl}_3$  shows little effect until a concentration of 1.25 M after which point an extremely sharp rise in solubilization is observed. The  $^1\text{H}$  spectra of  $\beta$ -CD in high concentration solutions show no evidence of acid-catalysed ring opening, suggesting this effect does not arise from fragmentation of  $\beta$ -CD.

A comparison of effects along the second row chlorides,  $\text{NaCl}$ ,  $\text{MgCl}_2$  and  $\text{AlCl}_3$ , shows that for all three ions the solubility remains constant until a metal concentration of 1.25 M is reached (Fig 6), and that only above this concentration is solubilization observed for  $\text{MgCl}_2$  and  $\text{AlCl}_3$ .

As we have stated in the introduction, the solubility of  $\beta$ -CD in water-co-solvent mixtures has been shown to parallel exactly the changes in bulk solvent properties such as excess partial molar volume.<sup>4</sup> In the case of the current study recent X-ray crystallographic work on  $\text{CD}-\text{CaCl}_2$  complexes has shown that no inclusion of either anion or cation occurs; these are in fact present in a complex hydrated array,

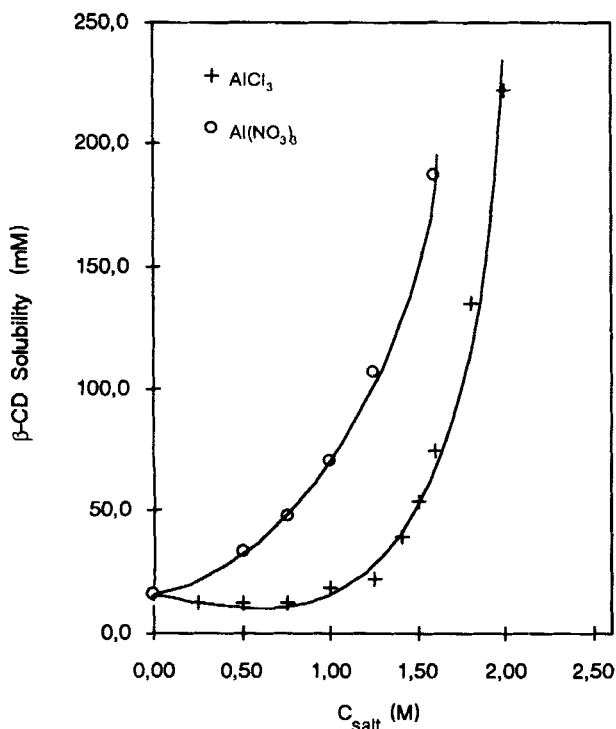


Figure 5 Solubility of  $\beta$ -cyclodextrin in the presence of aluminium salts.  $C_{\text{salt}}$  = salt concentration.

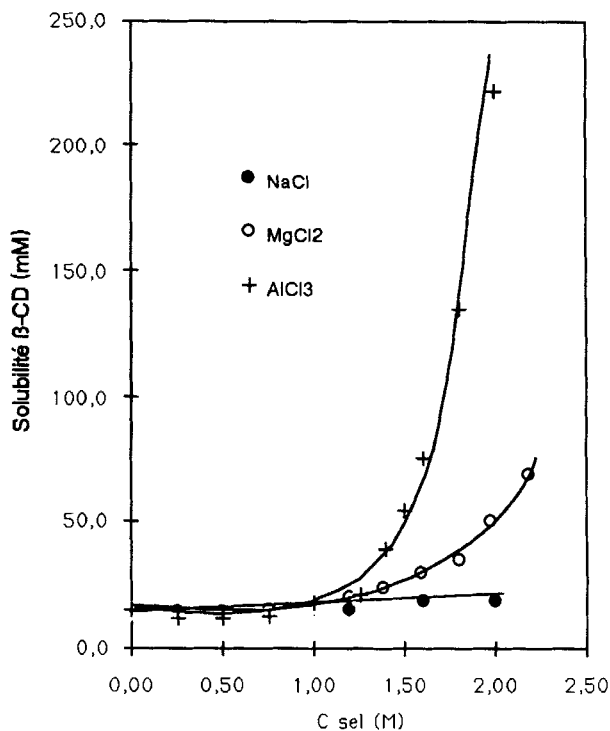


Figure 6 Solubility of  $\beta$ -cyclodextrin in the presence of second row chlorides.  $C_{\text{salt}}$  = salt concentration.

exterior to the CD molecule. At the high metal salt concentrations used, extensive ion pairing and clustering will strongly perturb the normal hexagonal dynamic water symmetry. In view of the above it is more than tempting to speculate that the solubility of  $\beta$ -CD in aqueous mixtures depends solely on the dynamic solvent structure, and this interacts with the heptagonal symmetry of  $\beta$ -CD aggregates. No evidence exists for specific co-solvent or co-solute interactions with  $\beta$ -CD, but some perturbation of the  $\beta$ -CD aggregate structure may occur.

We have employed this solubilization in the investigation of the  $^1\text{H}$ -NMR spectrum of the  $\beta$ -CD/thymol inclusion complex by comparison of the  $\text{D}_2\text{O}$  spectrum of thymol; aromatic proton chemical shifts  $a = 6.73$ ,  $b = 6.8$  and  $c = 7.18$  ppm with that obtained by an extraction of thymol by  $\beta$ -CD( $\text{OD}_{21}$ ) in  $\text{D}_2\text{O}$ .

This spectrum shows shifts of the aromatic protons to  $b = 6.7$ ,  $a = 6.73$  and  $c = 7.12$  ppm. Such changes

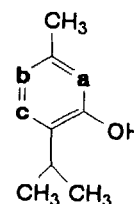


Figure 7a.

are typical for inclusion complexes,<sup>9,10</sup> however the integration shows a 2:1 thymol: $\beta$ -CD ratio. This is unlikely to be the correct stoichiometry of the  $\beta$ -CD/thymol complex and suggests that excess free thymol is present in solution and hence that displacement of signals arising from inclusion will be averaged with those of the free molecule. The spectrum of the extraction product in 2 M  $\text{Sr}(\text{NO}_3)_2 \cdot \text{D}_2\text{O}$  implies an empirical 1:1 stoichiometry in the complex, and the aromatic signals are now further displaced, being observed at  $b = 6.65$ ,  $a = 6.82$  and  $c = 7.10$ . Inclusion-induced shifts are thus  $a = 0.09$ ,  $b = -0.15$  and  $c = -0.08$  ppm. These preliminary results show that sufficient solubilization can occur to allow medium-field NMR to be used in observing inclusion behaviour, and that as a result of this solubilization, the inclusion equilibria may be displaced and remove peak averaging problems associated with extraction experiments in which the free guest has solubility similar to that of the inclusion complex.

## CONCLUSION

We have found that in contrast to monovalent cations, the di- and trivalent cations have dramatic effects on the solubility of  $\beta$ -CD in aqueous solutions. These effects are also influenced by the anion: for chloride

each cation has a discrete effect; however for nitrate the effects appear to be dependent on charge alone. These effects probably arise from the perturbation of the structure of water and lead to less unfavourable interactions with the  $\beta$ -CD aggregates.

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