Solubilities of the Cyclodextrins in the Presence of Transition Metal Salts

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Abstract. The solubilities of α-, β-, and γ-cyclodextrin have been measured in the presence of the first row transition metals: Cr^{3+}, Mn^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}; chlorides, nitrates and sulphates (in this case Fe^{2+}), and, for companson, with $CaCl_2$, the corresponding Group IIa salt. Where possible the measurements are reported as a function of the activity of the salts. In general, for the transition metals the sulphates all show a linear decrease in solubility with increasing salt activity: for the nitrates the solubility increases and then reaches a limiting value; and for the chlorides a small decrease in solubility is observed at low activity followed by an increase in solubility at higher salt activity. Circular dichroism measurements confirm that there is no direct complexation at non-basic pH.

Key words: Cyclodextrins, solubility, metal ions.

1. Introduction

It has previously been shown that the solubilities of the cyclodextrins in aqueous solution can be strongly modified in the presence of co-solvents [1], co-solutes which modify the structure of water [2] and in particular metal salts [3, 4]. In the case of the Group II and Group III chlorides and nitrates large increases are observed; however, for Group I sulphate salts large decreases in solubility are observed.

In the case of the transition metals the formation of covalent complexes has been reported, under alkaline conditions, with Cu^{2+}, [5–8] Mn^{2+}, [8–10], Co^{2+} [7, 8], Ni^{2+} [7, 8], Cr^{2+}, [7, 8], and Fe^{2+} [7, 8] as well as with U(IV) and UO_2^{2+} [11] and also certain lanthanides [12]. The complexes have been studied by IR, Raman and visible spectroscopy [7, 9, 10], by electrochemistry and polarimetry [5, 6, 13], and by their magnetic properties [8], and it has been concluded that coordination takes place at the exterior of the cavity, forming binuclear systems. This has been shown for Cu and Pb alkoxide complexes and for the neutral $CaCl_2$ system by X-ray crystallography [14–16]. All these systems apparently dissociate under neutral or acid conditions.
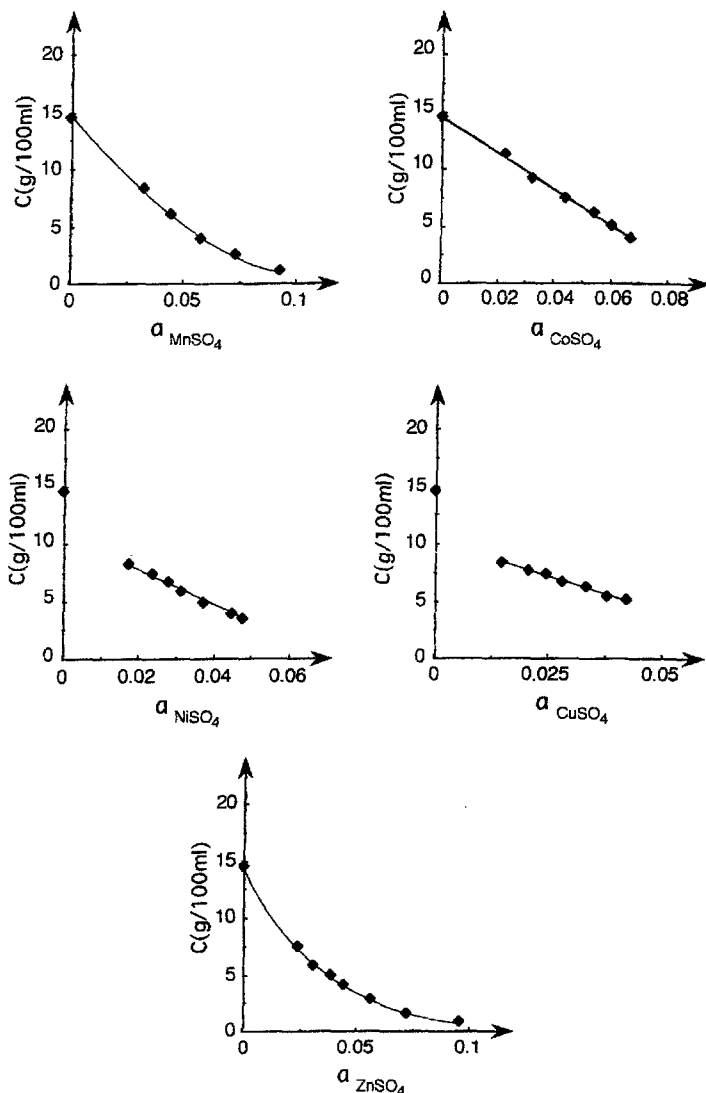

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Figure 1a. α-CD solubility as a function of divalent metal sulphate salt activity.

Basic data concerning the solubility of the cyclodextrins themselves are not available and here we wish to present a reasonably large but still not comprehensive study involving the first row transition metals, as well as treating the information in terms of the activity of the salts. All the experiments were carried out under the neutral or acid conditions generated by simple dissolution of the salts in water.
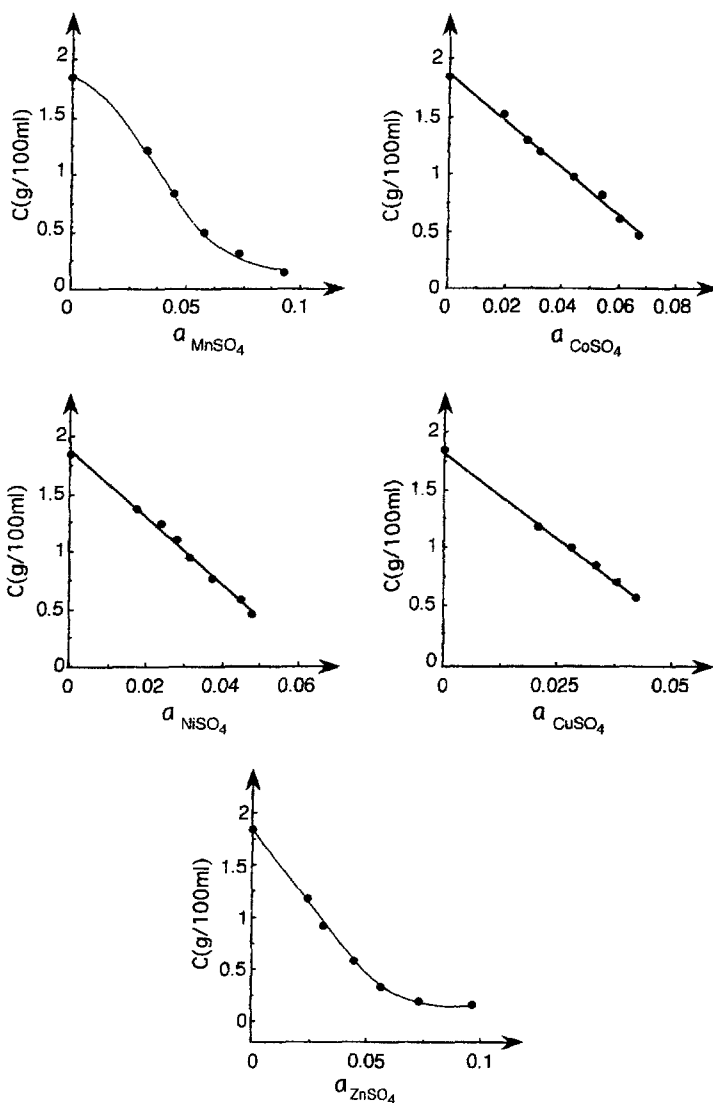
Figure 1b. β-CD solubility as a function of divalent metal sulphate salt activity.

2. Experimental

2.1. MATERIALS

The cyclodextrins were a gift from Wacker S.A. (Lyon) and were used after recrystallization from water. The percentage of water was analysed (SCA, CNRS) and was found to be; α-CD = 12%, β-CD = 14%, γ-CD = 11%. All the salts were of analytical grade purchased from Aldrich and used as supplied. Water was Milipore Q grade.
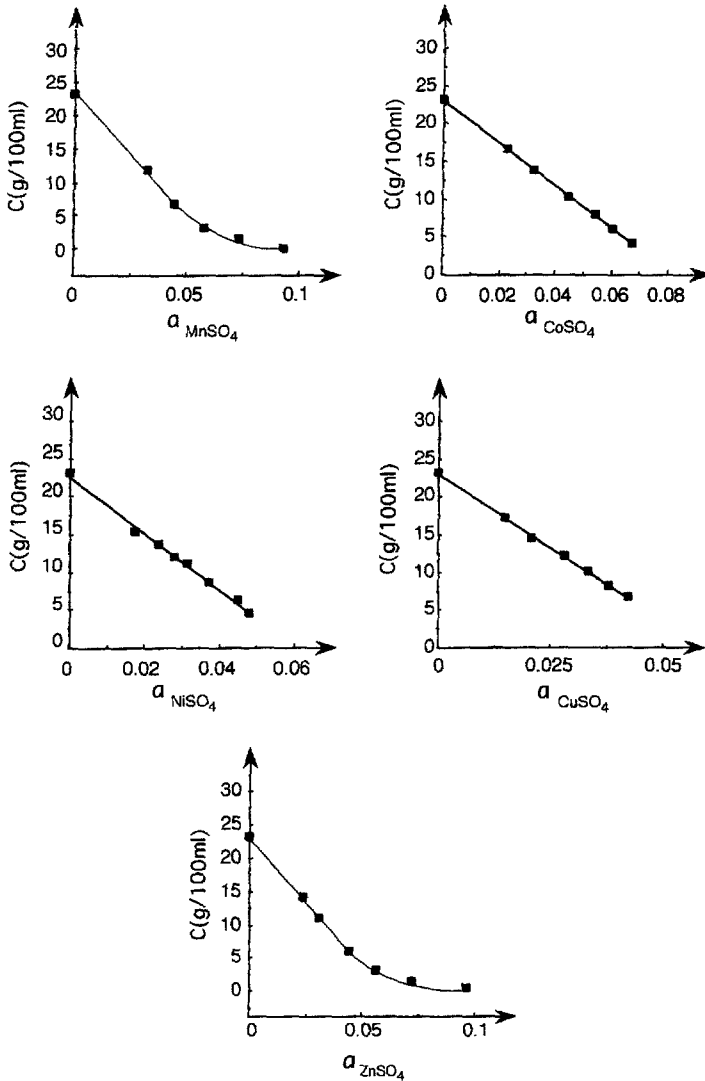
Figure 1c. γ-CD solubility as a function of divalent metal sulphate salt activity.

2.2. SOLUBILITY MEASUREMENTS

The solubility measurements were carried out as follows: the cyclodextrin was added in excess to solutions of known salt concentration in a range of 0 to 2.5 M. The solutions were shaken frequently until equilibrium was reached (at least 2 days); in cases where complete dissolution of the cyclodextrin ocurred a further quantity was added and the above cycle repeated [4]. No pH measurements or buffering were carried out.
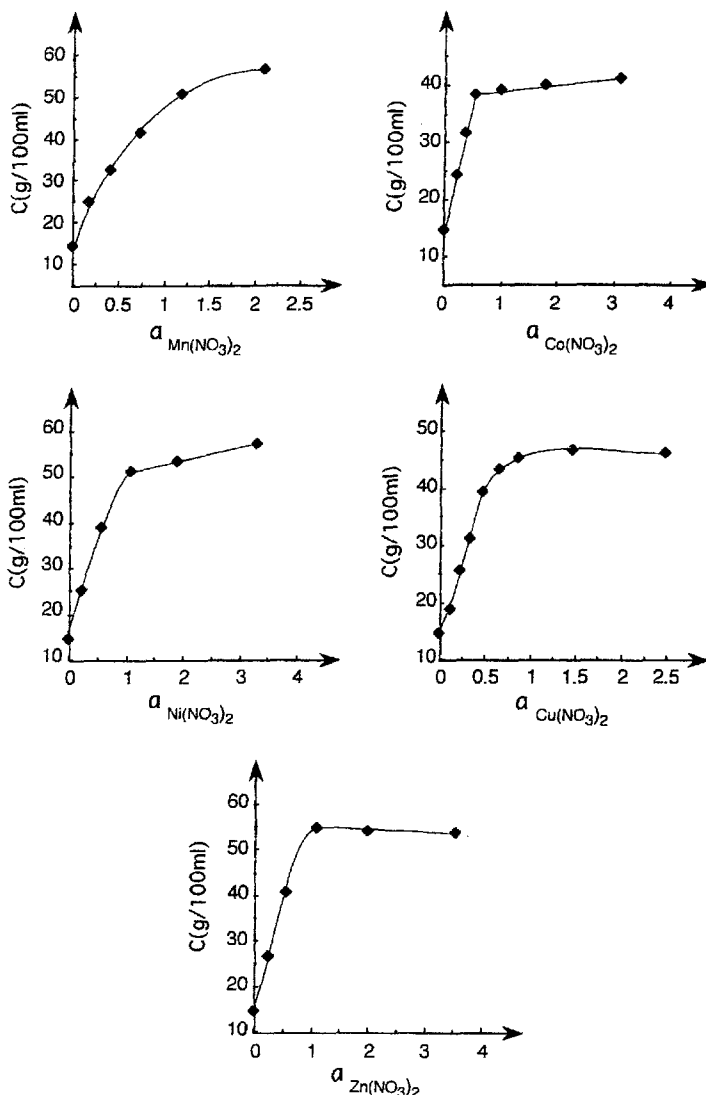
Figure 2a. α-CD solubility as a function of divalent metal nitrate salt activity.

The concentration of the dissolved cyclodextrin was determined by optical rotatory measurements using a Schneider Electronic VT 300 instrument at the wavelength of 589 nm (sodium D line) in a cell with a 2 or 5 cm optical path.

Plots of rotation versus α-, β- and γ-cyclodextrin concentration were linear with slopes (specific rotation $[\alpha]_D$) respectively of 0.150, 0.162 and 0.177 grad dm^2/g, in good agreement with literature values [17].

In the presence of the salts studied the $[\alpha]_D$ values were found to be constant up to a salt concentration of 2.5 mol dm^{-3}, this value was checked by the dissolution
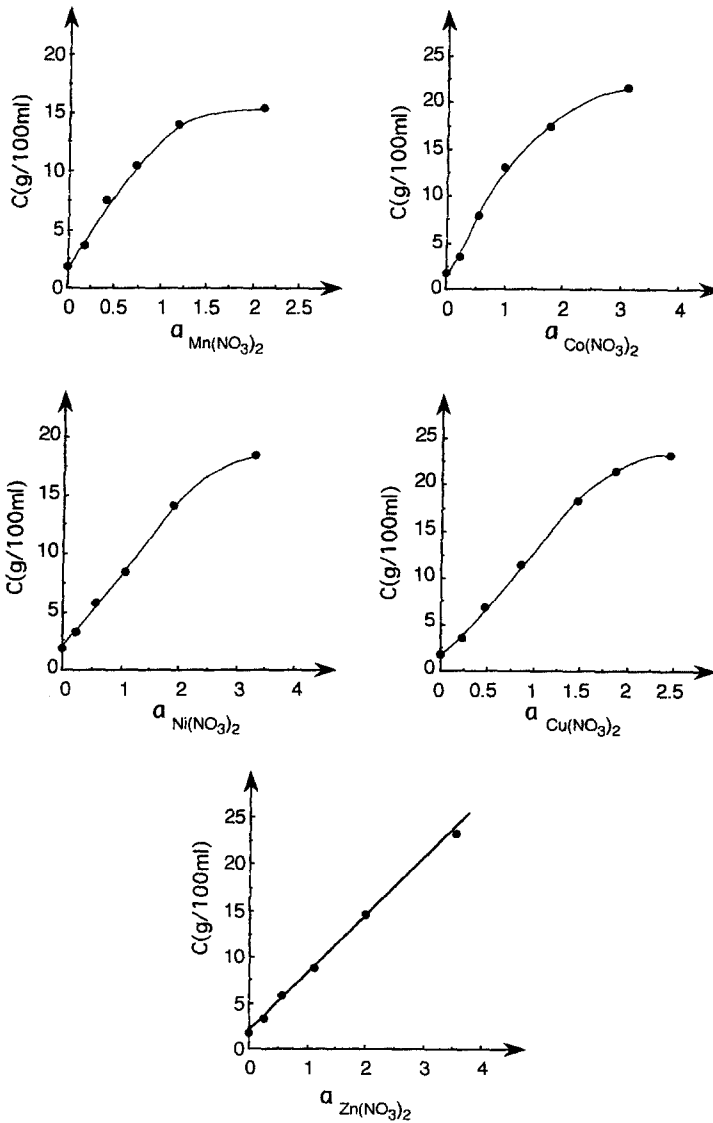
Figure 2b. β-CD solubility as a function of divalent metal nitrate salt activity.

of a known quantity of the cyclodextrin in a known concentration of salt. At least two randomly chosen values were measured for each metal salt. In all cases where the solubility curves diverge strongly from the apparent norm, measurements were rechecked at least four times. For these systems at least five known concentration values were measured to verify that no variation in the $[\alpha]_D$ value occurred. In no case was such a variation observed. The plot of observed optical rotation versus
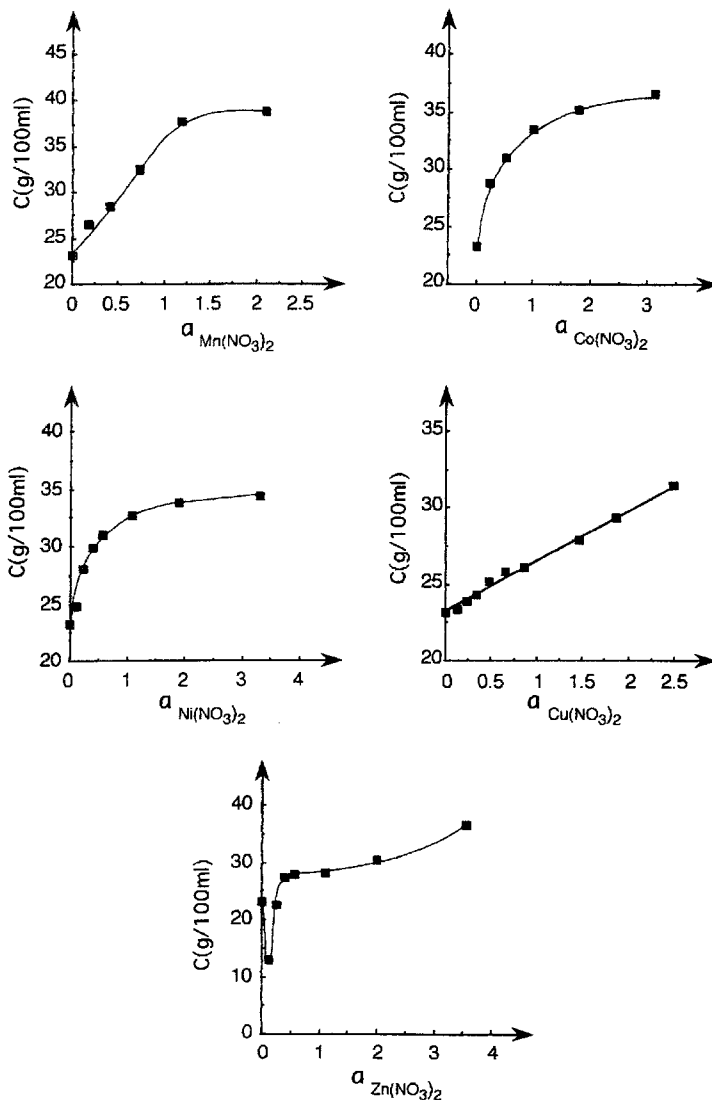
Figure 2c. γ-CD solubility as a function of divalent metal nitrate salt activity.

CD concentration was linear and the slopes were identical to those observed for the pure cyclodextrins in the absence of co-solute.

3. Results

Full solubility data for α-, β- and γ-cyclodextrin in the presence of the Cl^-, $(NO_3)^-$ and $(SO_4)^{2-}$ salts of the first row transition metal salts Cr^{3+}, Mn^{2+}, Fe^{2+},[*] Co^{2+},

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[*] For the Fe^{3+} salt we used NO_3^- and Cl^-.

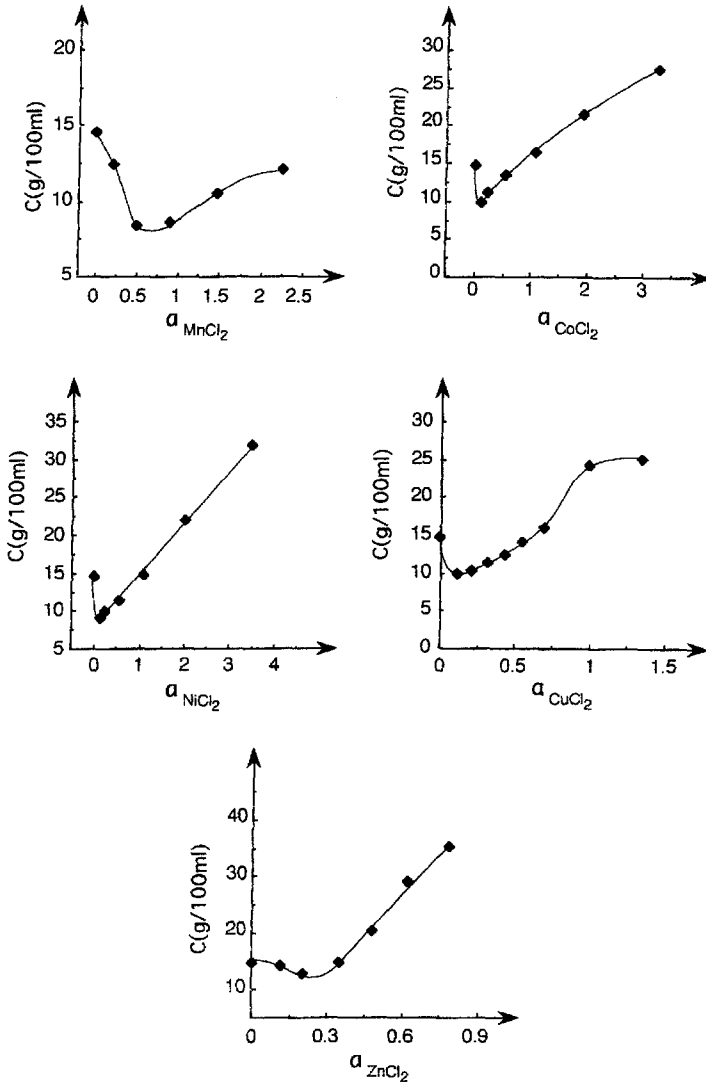*Figure 3a.* α-CD solubility as a function of divalent metal chloride salt activity.

Ni^{2+}, Cu^{2+} and Zn^{2+} are given as supplementary data. The solubilities are given in terms of molarity and, where available, activity [18]. For clarity the solubilities as a function of activity are presented graphically in Figures 1(a,b,c); 2(a,b,c), 3(a,b,c) and 4(a,b,c,d), showing respectively, sulphate, nitrate and chloride solubilities of divalent metals for $a = \alpha$-CD, $b = \beta$-CD and $c = \gamma$-CD. Figure 4a, b and c show the curves for trivalent salts of Cr^{3+} and Fe^{3+}, and the solubility plots for $Fe(SO_4)$ are given in Figure 4d. For comparison, the curves for $CaCl_2$ solubilisation of the cyclodextrins are shown in Figure 5.
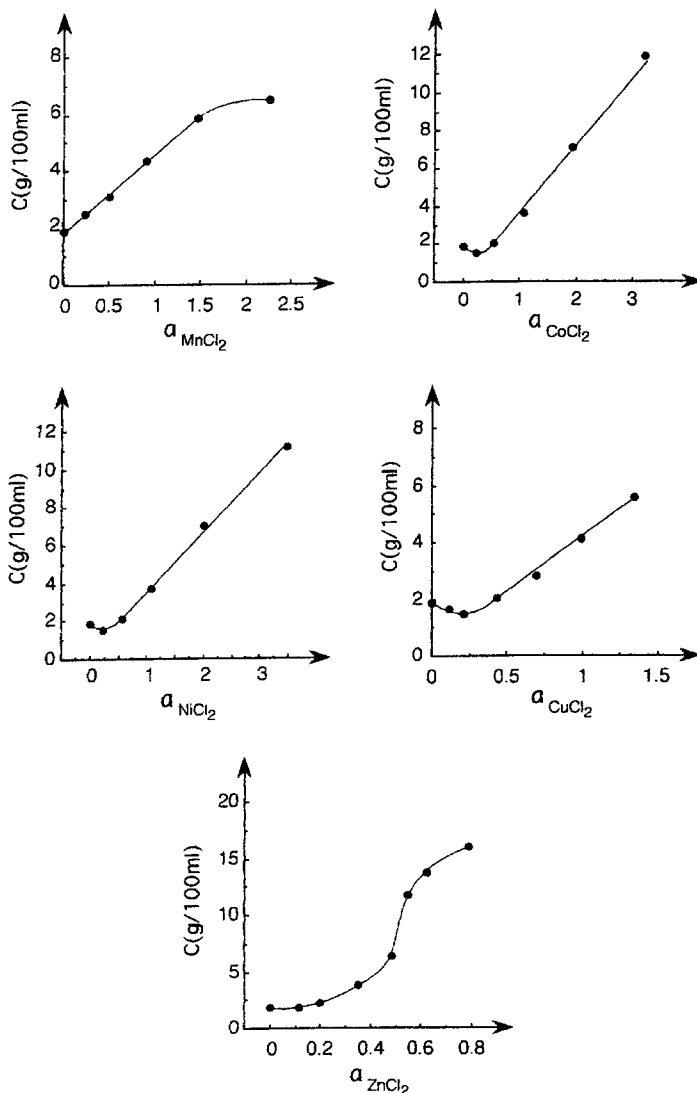
Figure 3b. β-CD solubility as a function of divalent metal chloride salt activity.

3.1. SULPHATE SOLUBILITY CURVES

The $(SO_4)^{2-}$ anion is tetrahedral, with an effective diameter of 2 Å and is very weakly coordinating [19]. In view of this behaviour in solution, only the hydrated metal salt and the hydrated anions should be present.

The solubilities of α-, β- and γ-cyclodextrin show a linear decrease as a function of activity in the presence of Ni^{2+}, Cu^{2+} and Co^{2+} salts. For α-CD and $MnSO_4$, $ZnSO_4$ and $FeSO_4$ (Figure 4d) systems an initial sharp decrease in solubility is followed by this linear decrease (Figure 1a, b, c). The slopes are given in Table
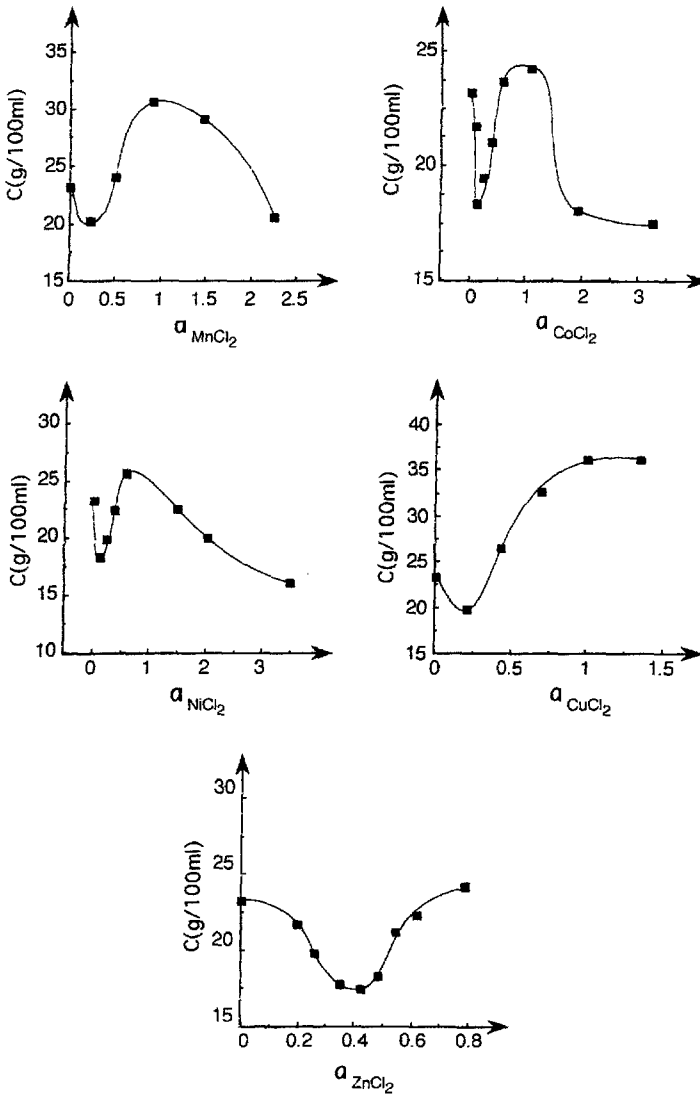
Figure 3c. γ-CD solubility as a function of divalent metal chloride salt activity.

I normalised to 100% for zero salt concentrations; only for the sulphate salts are linear variations observed. Interestingly the metal ions of the extremes of the chosen series Cr^{3+} and Zn^{2+} show different behaviour. For Cr^{3+} with α-CD a rapid decrease is followed by a slower linear decrease up to $a = 0.0125$ with no further decrease (Figure 4a), whereas for β-CD and γ-CD there is a linear decrease to $a = 0.006$ for β-CD (Figure 4b) and to $a = 0.0125$ for γ-CD (Figure 4c) again with no further decrease in solubility.
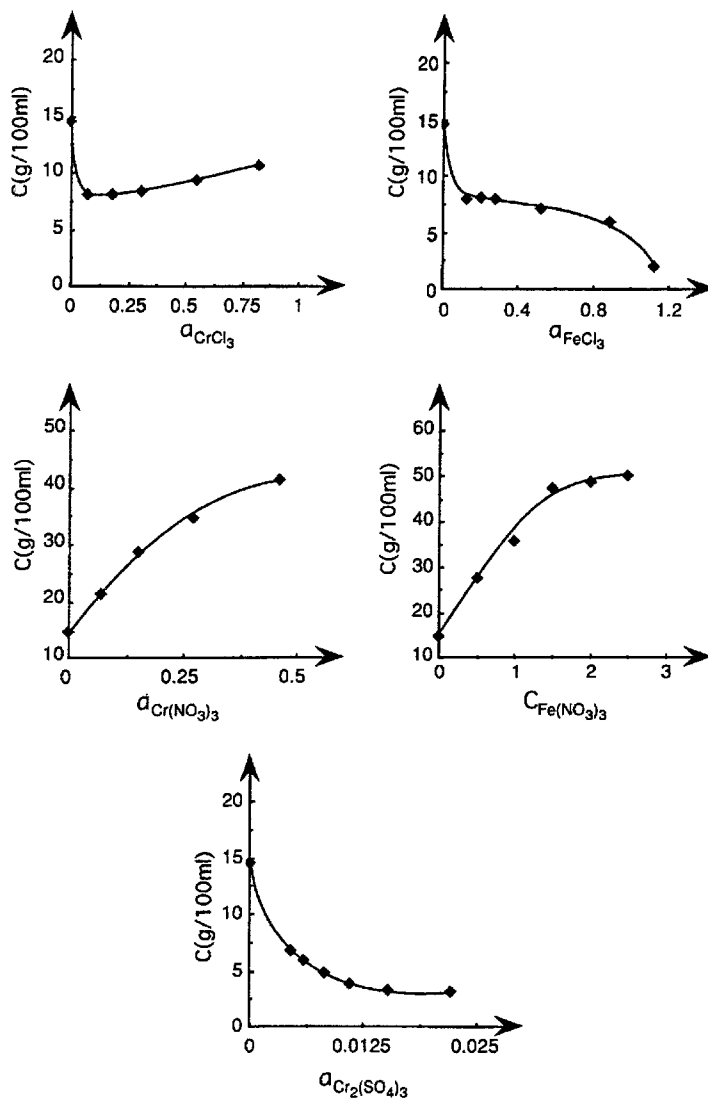
Figure 4a. α-CD solubility as a function of Cr^{3+} and $FeCl_3$ salt activity and $Fe(NO_3)_3$ concentration.

The solubility in the presence of $ZnSO_4$ shows an almost linear decrease to $a = 0.07$ for all CDs and then almost no further decrease (Figure 1a, b, c).

In general for β-CD there is only a slight variation for the divalent metal cations with a slope of the solubility curve around -25 and a slope of -43 for the trivalent Cr salt. For α-CD and γ-CD the observed slopes decrease towards the middle of the row with again much higher values for trivalent Cr.

The sulphates thus seemingly fit a relatively simple behaviour, with a strong charge sensitivity; this may be expected with sulphate being the largest anion and
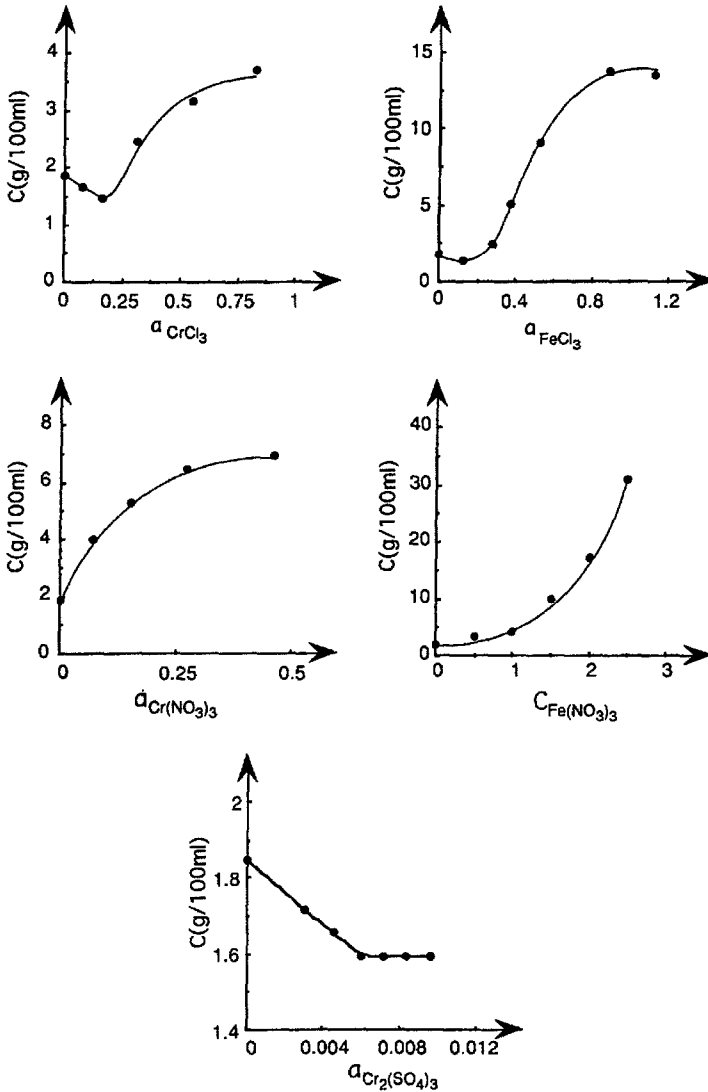
Figure 4b. β-CD solubility as a function of Cr^{3+} and $FeCl_3$ salt activity and $Fe(NO_3)_3$ concentration.

also a non-coordinating anion. Here, as with Group Ia and IIa salts and urea, the effects can be expected to arise from the destructuring and structuring effects of the salts on the liquid structure of water [20]. The behaviour may also be particularly influenced by anionic inclusion in all the cases. Such behaviour might be expected to override smaller specific metal effects. This would be reinforced by the expected lack of metal-anion association in the case of the sulphate anion.
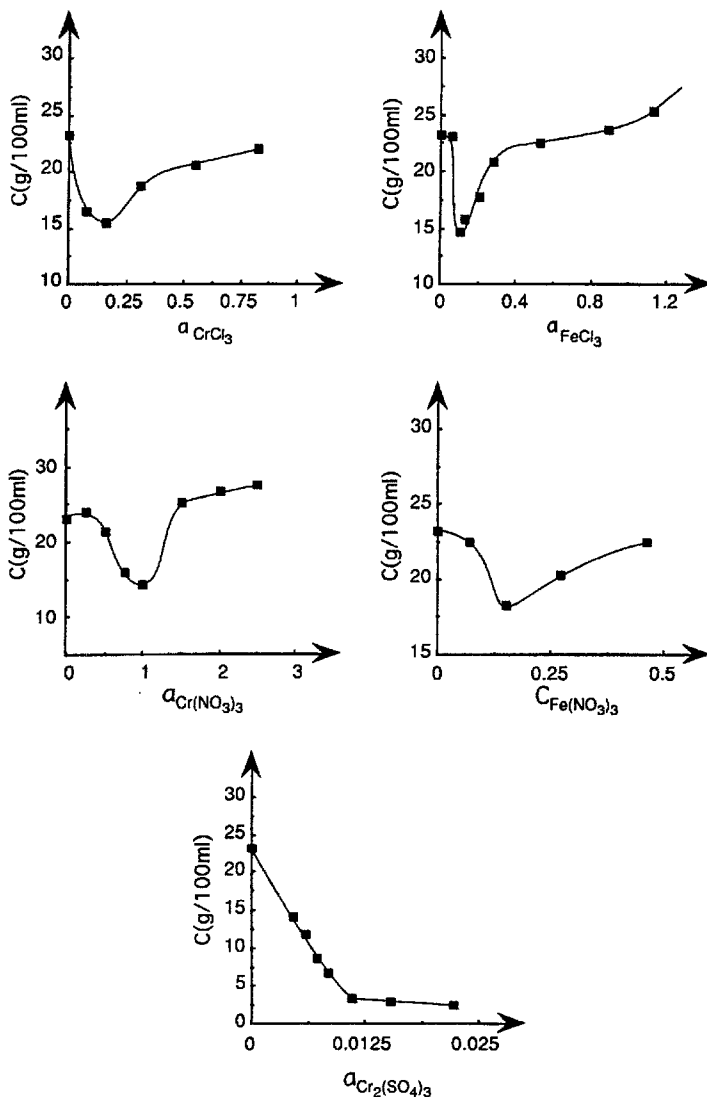
Figure 4c. γ-CD solubility as a function of Cr^{3+} and $FeCl_3$ salt activity and $Fe(NO_3)_3$ concentration.

3.2. NITRATE SOLUBILITY CURVES

The nitrate anion is trigonal planar with a diameter of 1.5 Å, it is weakly coordinating through the oxygen atoms and in solution some aquo-nitrato metal complexes may exist [19]. The presence of such complexes may be expected to lead to breaks in the solubility curves when complexes may be included and also to metal and/or CD specific variations.
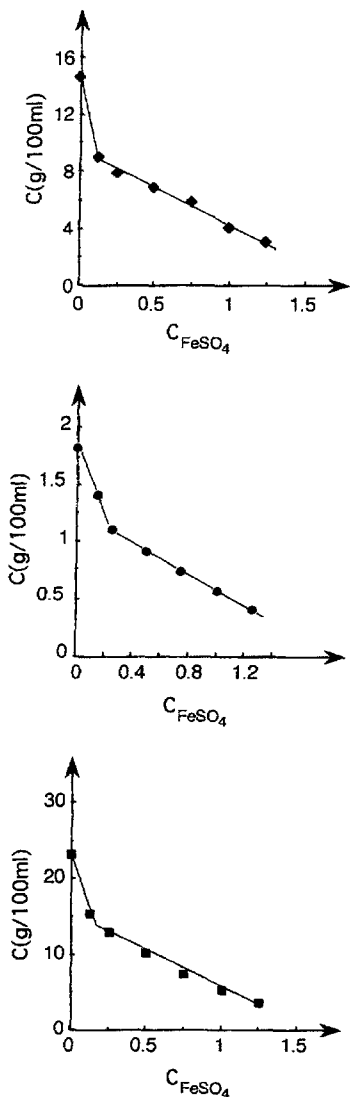
Figure 4d. CD solubility as a function of Fe(SO₄) concentration. (◆), (●) and (■) are respectively the symbols for α-CD, β-CD and γ-CD.

The curves as shown in Figure 2(a, b, c) take the general form of an increase in the solubility followed by a plateau, this being particularly emphasized for the α-CD systems. For β-CD there are two exceptions namely Fe(NO₃)₃ which shows an exponential increase with increasing salt concentration (Figure 4b) and Zn(NO₃)₂ (Figure 2b) for which there is an apparent linear increase in the solubility as a function of salt activity. This might be expected if inclusion of the metal-nitrato complexes occurs. The greatest perturbations are observed for γ-CD which possesses the largest cavity and therefore the largest capacity for including such
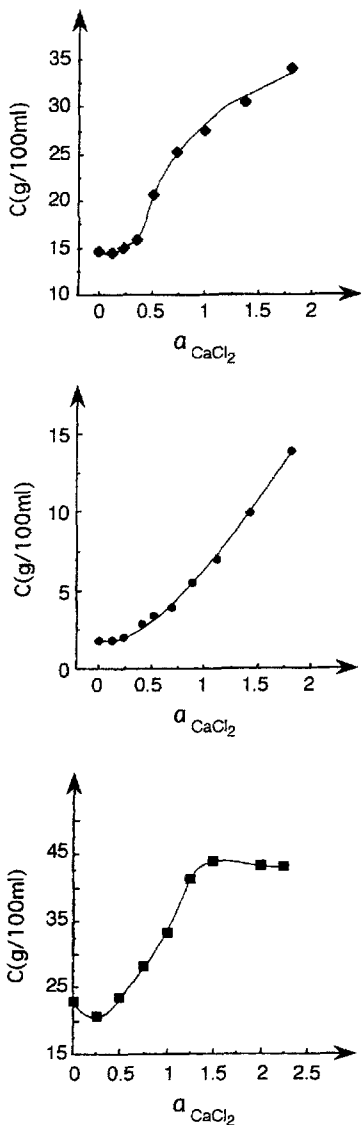
Figure 5. CD solubility as a function of calcium chloride activity. (♦), (●) and (■) are respectively the symbols for α-CD, β-CD and γ-CD.

complexes. The two M^{3+} systems, $Cr(NO_3)_3$ and $Fe(NO_3)_3$ both show distinct solubility minima, at $a = 0.175$ and $c = 1$ respectively (Figure 4c). Interestingly, for $Zn(NO_3)_2$, while the solubility curve is generally that of an increase and a plateau, there is a sharp decrease in solubility at very low activity $a = 0.1$ (Figure 2c).

Table Ia. Slopes of the solubility measurements
for sulphate salts: α-CD.

Cation	Activity	Slope	r^*
Cr^{3+}	0–0.0045	−1697	0.999
	0.0045–0.0111	−456	0.995
	0.0111–0.0222	0.00	
Mn^{2+}	0.00–0.06	−183	0.999
	0.06–0.10	−81.2	0.995
Fe^{2+}	0.00–0.125	−26.8	0.99
(conc)	0.125–1.25	−5.13	0.99
Co^{2+}	0.00–0.067	−157.2	0.999
Ni^{2+}	0.00–0.0173	−363.5	0.999
	0.0173–0.048	−161	0.99
Cu^{2+}	0.00–0.025	−419.5	0.999
	0.025–0.042	−119	0.995
Zn^{2+}	0.00–0.04	−255	0.99
	0.04–0.096	−72	0.97

* Goodness of fit.

Table Ib. Slopes of the solubility measurements
for sulphate salts: β-CD.

Cation	Activity	Slope	r^*
Cr^{3+}	0–0.006	−42.3	0.999
	0.006–0.0222	0	
Mn^{2+}	0.00–0.06	−23.4	0.999
	0.06–0.093	−9.7	0.992
Fe^{2+}	0.00–0.125	−2.92	0.98
(conc)	0.125–1.25	−0.70	0.99
Co^{2+}	0.00–0.067	−20.6	0.998
Ni^{2+}	0.00–0.048	−29.17	0.997
Cu^{2+}	0.00–0.042	−29.50	0.999
Zn^{2+}	0.00–0.056	−27.7	0.99
	0.04–0.096	−3.91	0.99

* Goodness of fit.

3.3. CHLORIDE SOLUBILITY CURVES

The chloride anion has an anionic radius of 1.8 Å, and it should be noted that it
is readily hydrated [19]. Halo-metal complexes are well known, and in particular
for the Zn^{2+} at high ionic strengths the $(ZnCl_4)^{2-}$ anion is one of the predominant
species present in a complex equilibrium system [21].

Table Ic. Slopes of the solubility measurements for sulphate salts: γ-CD.

Cation	Activity	Slope	r^*
Cr^{3+}	0–0.0111	−1826	0.99
	0.0111–0.0222	0.00	
Mn^{2+}	0.00–0.06	−350.6	0.998
	0.06–0.093	−89.80	0.99
Fe^{2+}	0.00–0.125	−62.7	0.99
(conc)	0.125–1.25	−10.35	0.999
Co^{2+}	0.00–0.067	−281.6	0.999
Ni^{2+}	0.00–0.048	−374.24	0.998
Cu^{2+}	0.00–0.042	−388.5	0.999
Zn^{2+}	0.00–0.044	−387	0.999
	0.056–0.1	−60.40	0.97

* Goodness of fit.

In general, for the divalent cations with α-, β- and γ-cyclodextrin there is a small but significant decrease in cyclodextrin solubility at low salt activity. For both α-CD and β-CD at higher salt activities the solubility then strongly increases. This type of behaviour has been previously observed for the β-CD Group IIa and lanthanide systems [4]. However, for γ-CD more complex behaviour is observed (Figure 3c); only for $CuCl_2$ is the typical solubility curve observed. That of $ZnCl_2$ is similar, but does not regain the initial solubility even at high activity values. With the other divalent cations $MnCl_2$, $CoCl_2$ and $NiCl_2$, after an initial decrease the solubility increases to a maximum before decreasing again at high salt activity. For the trivalent cations the situation is reversed with β-CD and γ-CD now generally showing an initial decrease in solubility followed by an increase which apparently reaches a plateau at high activity. For α-CD with $CrCl_3$ (Figure 4a) there is a small increase in solubility after a sharp initial decrease, and for $FeCl_3$ the solubility decreases, flattens out as a plateau and then for activity >0.8 decreases apparently to an effective zero solubility.

The apparent solubility changes could be simply due to metal-anion complexation leading to a change in $[\alpha]_D$ of the cyclodextrins. This was checked by measurement of the optical rotation at known CD and salt concentrations. In all cases the observed values were the same as those calculated from the cyclodextrin concentration in pure water [17]. In order to check for metal ion complexation, circular dichroism spectra were recorded for each metal salt in the presence of all three cyclodextrins. In no case were any effects observed. However, great care must be taken with such results as absorption effects require considerable dilution of the solutions, which will of course dissociate weak complexes. A large number of crystals were obtained on leaving the saturated solutions to evaporate slowly; in general for low metal salt concentration the crystals were the pure cyclodextrins

with only slight variations in the hydration levels being observed [22]. Although some cases of specific interaction may exist (γ-CD/ZnCl$_2$, γ-CD/CaCl$_2$) as yet no high resolution X-ray structures are available [23].

4. Conclusion

For the sulphate complexes it may be proposed that the solubility is affected generally by anion interaction with cyclodextrin; here formation of [anion–CD] complexes may lead to a decrease in solubility. For the chloride systems the solubility is probably best treated at low concentrations in terms of how the anion perturbs the water structure, destabilising interaction between the CD clusters present in solution [24] and the aqueous medium and leading to a lower solubility. At higher concentrations either anion or cation complexation at the hydroxyl groups may electrostatically influence the apparently delicate structures present in solution and lead to a higher solubility of around 40–50 g/100 mL for γ-CD, 20–25 g/100 mL for β-CD and 35–40 g/100 mL for α-CD, suggesting a strong anion effect, which is then modulated by the cation present. However, in all the systems apparent specific interactions may lead to strong deviations from these so-called typical curves; this is the case for γ-CD with most of the chlorides and with Zn(NO$_3$)$_2$ and for α-CD with the trivalent chlorides. There are no apparent correlations between solubility curve or absolute effects on the solubility values and metal-hydration life times [25]. This suggests that simple metal ion perturbation of the water structure is not the determinant effect in the solubilisation of the cyclodextrins.

Given this information* we are now systematically undertaking crystallisation experiments with these non-typical systems to determine the nature of the solid-state CD–salt interactions, and studies are being undertaken on the thermodynamics of CD–metal interactions in solution.

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* As stated by one reviewer: 'However, the work raises more questions than answers'.

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