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Co-solvent Modulation of the Inclusion Selectivity of β-Cyclodextrin

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Abstract. The solubility of β-CD, which is increased to 87 gL^{-1} in 75% water – 25% isopropanol mixtures, does not behave in a linear fashion as a function of the water/isopropanol ratio. Application of this increased solubility to the formation of inclusion complexes between β-cyclodextrin and cineole : eugenol, cineole : pinene and eugenol : pinene shows strong solvent modulation of the inclusion selectivity. The proportion of guests complexed is in inverse ratio to the compatibility of the guests in the solvent mixture.

Key words. β-Cyclodextrin, inclusion selectivity, co-solvent, solubility.

1. Introduction

The cyclodextrins are well documented for their ability to form inclusion compounds with a large range of substrate molecules [1]. To aid the interaction between host and often highly hydrophobic guest molecules the use of water-miscible co-solvents has been widely used [2]. However, apart from ethanol [3], no reports on the solubility of β-cyclodextrin in aqueous co-solvent mixtures exist until recently (aside from a semi-theoretical treatment in which the precision of the measurement was rather inexact [4]). In the course of our investigation of the fundamental solution properties of cyclodextrins we have measured the solubilisation of β-cyclodextrin by a number of co-solvents [5]. The increase in solubility of β-CD from 18 gL^{-1} in H_2O to 87 gL^{-1} in 75% H_2O : 25% isopropanol and the nonlinearity of the general solubility curve for these solvent mixtures has lead us to investigate the inclusion selectivity for cineole, eugenol and pinene in β-cyclodextrin in the above mixtures. The results show a complex relation between the selectivity of inclusion (i.e. the relative proportion of each guest included) and the mole ratio of isopropanol–water. The selectivity is best treated in terms of the inverse of the relative solubility of the guests in the isopropanol–water mixtures.

2. Experimental

2.1. MATERIALS

Commercially available isopropanol (Merck, analytical grade) was used without further purification. β-Cyclodextrin was a gift from Roquette. Terpenes and

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DMSO-d_6 were purchased from Aldrich. Isopropanol-d_8 and D_2O were obtained from Sigma. NMR spectra were recorded on a Bruker AC200 spectrometer (200 MHz). Optical rotations were measured on a Zeiss polarimeter at the Na wavelength (550 nm).

2.2. METHODS

2.2.1. *β-Cyclodextrin Solubility in Water–Isopropanol Mixtures*

The solubility was measured as follows: β-cyclodextrin was added in excess to 50 mL of water–isopropanol mixture of composition varying from 100% (v/v) water to 100% (v/v) isopropanol. The solutions were stirred continuously for 72 h on a Bioblock 15 station magnetic stirrer at 25°C, in a thermostated bath. To verify equilibrium conditions a blank run of β-cyclodextrin in water at 1.8 g/100 mL was carried out. For solutions in which saturation concentration was not reached the experiment was repeated with an increased quantity of β-cyclodextrin.

The solutions were filtered and the concentration of the dissolved β-cyclodextrin was determined by optical rotation measurements in cells of 10 cm or 20 cm path length. To ensure reproductibility certain samples were repeated three times: the values obtained were always within the error limits of ±3%.

The specific rotation of β-cyclodextrin in water was calculated from measurement of the optical rotation of solutions of known concentration and was found to be 163, in agreement with the literature value [6]. The specific rotation of β-cyclodextrin in water–isopropanol mixtures was also calculated from the optical rotation of solutions of known concentration and was the same within the experimental limits.

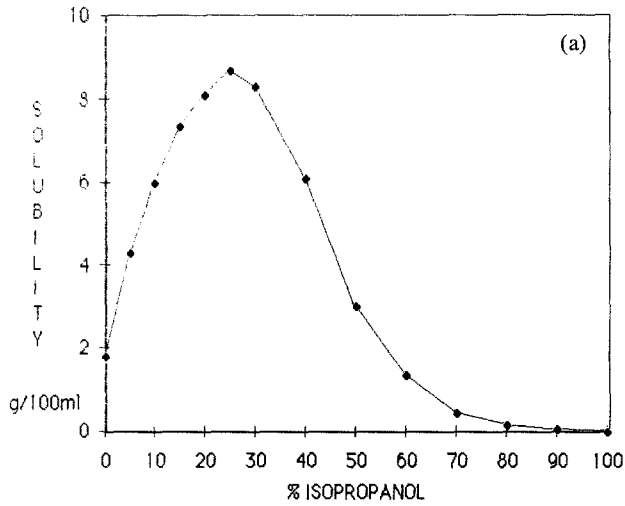
In a reference experiment it was shown that when quantities of β-cyclodextrin just below the calculated saturation value were added to the solutions, they were completely dissolved.

2.2.2. *Terpene Relative Solubilities in Water–Isopropanol Mixtures*

Equimolar terpene mixtures were added in excess to 2 mL of D_2O–isopropanol-d_8 mixtures of composition varying from 100% (v/v) D_2O to 50% D_2O–50% isopropanol-d_8. The solutions were stirred for 24 h. The relative solubility of terpenes was measured by integration of the ^1H NMR spectra of the solution. Values have a ±5% uncertainty.

2.2.3. *Inclusion Selectivity Measurements*

β-Cyclodextrin (2.5 g: 2.2×10^{-3} mole/1) was added to 50 mL of water–isopropanol mixtures of composition varying from 100% (v/v) water to 50% water–50% isopropanol. Equimolar terpene mixtures (2.2×10^{-3} mole of each) were added to the solutions under stirring and were maintained at 40°C for 1 h. The precipitated complexes thus obtained were filtered, washed with water and diethyl ether and dried under reduced pressure. The relative selectivity of the complexation of terpenes by β-cyclodextrin was measured by integration of the ^1H NMR spectra of the precipitated compounds in DMSO-d_6. Values have a ±5% uncertainty.



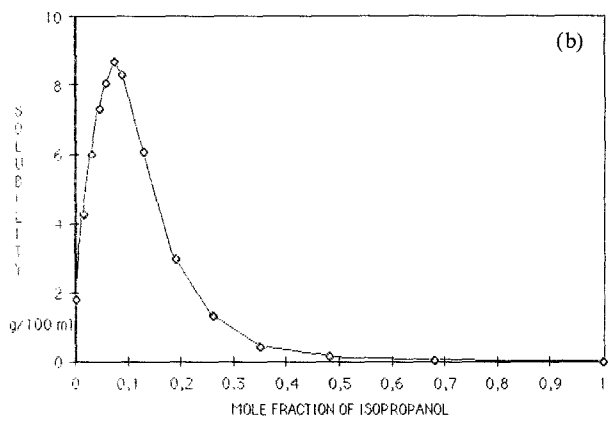


Fig. 1. (a) Solubility of β-CD in water/iso-propanol mixtures (v/v). (b) Solubility of β-CD in water/isopropanol mixtures (mole fraction).

3. Results and Discussion

The β-CD solubility versus component percentage for the isopropanol–water mixture is given in Figure 1 (1a for % volume, 1b for % mole fraction). Concerning solubility curves: whilst, for a given solvent, % v/v values are easier to use, for comparison between solvents % mole fractions are essential. The curve shows a rapid increase in solubility to a maximum at 25% (v/v) isopropanol (10% mole fraction), a region of almost constant solubility of 85 gL^{-1} to a 70 : 30 ratio and a decrease of solubility to almost zero at 90% isopropanol. Given that β-CD exists in aqueous solution as large (2000 Å) aggregates [7], we are unwilling to propose an

explanation for this effect until full measurements of aggregation in the solvent mixture become available. A similar curve has been previously observed for the solubility of β-cyclodextrin in water–ethanol mixtures and the effects have been ascribed to an interaction between the alcohol and cyclodextrin [3]. However, we do not agree with this conclusion, as a large number of solution properties (excess partial molar volume, ultrasonic absorption, dielectric relaxation) show very similar changes as a function of solvent–water proportion, all increasing to a maximum value at 10% mole fraction of ethanol [8], exactly as is observed for the solubility. Similar effects are observed for isopropanol [8], where again many solvent properties show variations with a maximum at 10% mole fraction, this corresponds to a 25% volume fraction, in agreement with the observed proportion for maximum solubility of β-CD. It might be stated that these values are simply coincidental; however, for other solvents solubility properties may be shown to depend on variations in the solvent mixtures properties [5]. Thus in our opinion the solubility properties of β-cyclodextrin are related to inherent solvent properties and not to interaction between co-solvent and the cyclodextrin.

As we have noted above, co-solvents, and in particular aliphatic alcohols [2], have frequently been used in the study of cyclodextrin inclusion compounds.

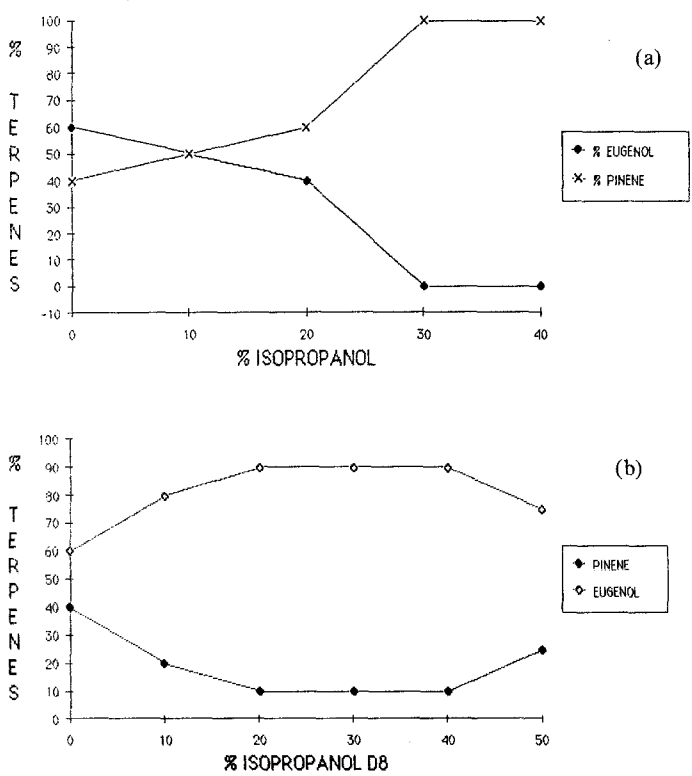


Fig. 2. (a) Co-solvent modulation of inclusion selectivity for eugenol : pinene–β-CD inclusion complexes. (b) Relative solubilities of eugenol and pinene in isopropanol–water mixtures.

Unfortunately, little data exist on the co-solvent concentration dependent inclusion behaviour or guest selectivity processes [9]. We have carried out a series of experiments on the relative selectivity of inclusion for eugenol, pinene and cineole: common constituents of essential oils. The curves for the relative selectivity are presented in Figures 2a, 3a, and 4a for the mixtures eugenol : pinene, cineole : eugenol and cineole : pinene, respectively. These curves are based on the isolated precipitated inclusion compounds obtained from the interaction of equimolar quantities of the guests with one equivalent of β-CD in aqueous solutions at 40°C during 1 h, and are measured from ^{1}H NMR spectra of the material. We emphasize that the conclusions drawn will be relevant only for inclusion compounds obtained under the same conditions [10]. In Figures 2b, 3b and 4b we present the relative solubility for the above mixtures as a function of isopropanol/water proportion, the absolute values have not been measured and for the purpose of comparison the relative values are probably more relevant.

It may be concluded from these figures that, at present, no generalisation concerning relative inclusion selectivity should be made. Comparison with the relative solubility measurements suggests that a higher relative solubility in the isopropanol–water mixture leads to a lower proportion of the component present

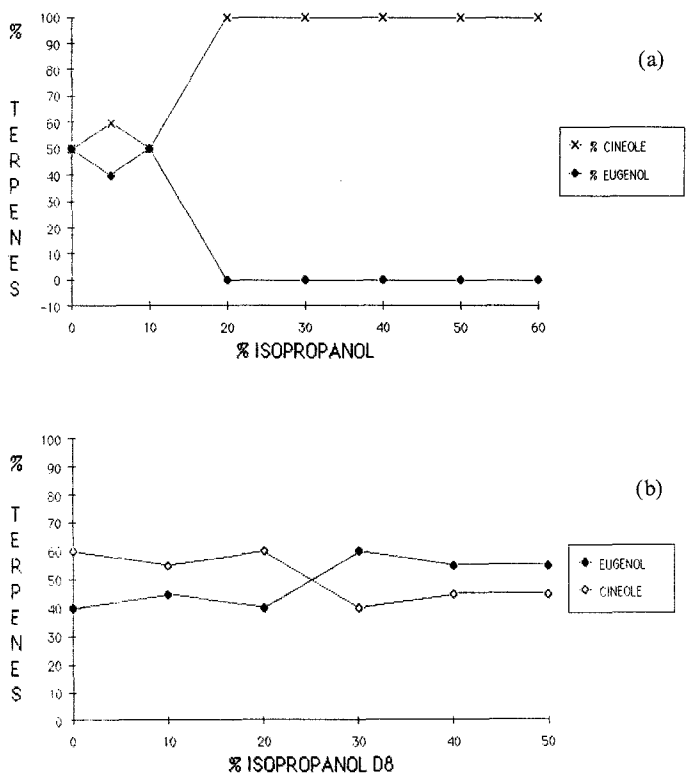


Fig. 3. (a) Co-solvent modulation of inclusion selectivity for cineole : eugenol–β-CD inclusion complexes. (b) Relative solubilities of cineole and eugenol in isopropanol–water mixtures.

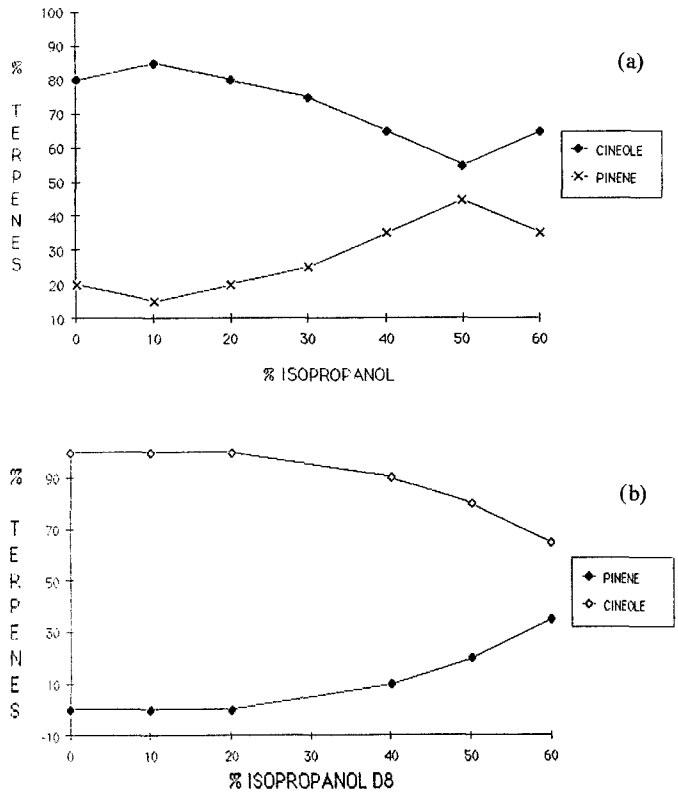


Fig. 4. (a) Co-solvent modulation of inclusion selectivity for cineole : pinene–β-CD inclusion complexes. (b) Relative solubilities of cineole and pinene in isopropanol–water mixtures.

in the inclusion compound, and thus higher compatibility with the bulk environment disfavours inclusion. For the cineole : eugenol and eugenol : pinene systems the most striking variations occur in the region of <30% isopropanol, i.e. within the zone in which the β-CD solubility is increasing to a maximum. For cineole : pinene (4a and 4b), the variations are more gradual, but there appears to be an extremely strong inverse relation between relative solubility and inclusion selectivity.

4. Conclusion

We have shown that the solubility of β-CD in isopropanol–water mixtures is strongly dependent on the composition of the mixture, and that there appears to be a strong relation between this and the bulk solvent properties. The inclusion selectivity of β-CD with regards to certain guest has been shown to be composition dependent and may be related to the relative guest solubilities in the mixtures.

Acknowledgements

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10. The results obtained in a continuing experiment show that there is a slow change in proportions found with time: at present we have results for a 30 day period: C. Donzé and A. W. Coleman, unpublished results.