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COMPLEXATION OF AROMATIC COMPOUNDS WITH, AND THEIR RELEASE FROM, CYCLOMALTOHEPTAOSE-CONTAINING POLYMERS, HYDROXYETHYLCYCLOMALTOHEPTAOSE, AND CYCLOMALTOHEPTAOSE

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ABSTRACT

The complexation of phenol with cyclomaltoheptaose (β-cyclodextrin), hydroxyethylcyclomaltoheptaose, and cyclomaltoheptaose-containing polymers has been studied. The results of a comparative study of the complexation of a series of aromatic compounds in the cyclodextrin-containing polymer provide a basis for a method for standardizing the performance of these polymers in non-chromatographic separations.

INTRODUCTION

Cyclomalto-oligosaccharides (cyclodextrins, CDs) are valuable because of their ability to form complexes with a wide variety of molecules and to release them therefrom. This utility is found also in chemically or enzymically modified CDs and CD-containing polymers. We now report on the comparative binding and release of guest molecules from different forms of CD and also propose a method for standardizing the complexing ability of CD-containing polymers.

EXPERIMENTAL

Cyclomaltoheptaose (βCD), hydroxyethyl-βCD, and CD-containing polymers (CD-P) were obtained from American Maize-Products Co. and used without further purification. The average d.s. of the hydroxyethyl-βCD was 1.50 (9–10 2-hydroxyethyl groups per βCD molecule). The polymer beads were swollen in deionized water and only those in the size range of 40–60 mesh were used. Standard analysis of the polymer was adapted from established methods[1]. Characteristics of the resin are shown in Table I.

All reagents were analytical or chromatographic grade or better. Adsorption

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TABLE I

CHARACTERISTICS OF THE βCD-CONTAINING POLYMER

Solids	11.16%[a]
Bead size (425–250 μm)	40–60 mesh[b]
Hydrated volume	0.88 g/mL
Content of βCD	50.57%[c]
Void volume	0.23 mL/g

[a]Vacuum-oven solids. [b]ASTM E-11 Specifications. [c]Modification of method in ref. 1.

of substances on CD-P was determined by calculating the reduction of u.v. absorbance in the eluate. U.v. spectra were measured with a Beckman Model DU-7 spectrophotometer fitted with a flow-through cell.

Method for determining breakthrough capacity. — (*1*) Swollen wet beads [70.1 g; 7.82 g on a dry (W_d) basis] were packed by gravity in a glass column (1.5 × 60.0 cm). (*2*) Elution with deionized water was carried out at a standard flow rate of 5.0 mL/min. (*3*) The void volume (V_0) of the polymer was determined by eluting a blue dextran (0.1%) solution (0.5 mL). (*4*) All solutions for polymer analysis, except where indicated by a solubility limit, were 0.1M in deionized water. (*5*) Elution of the test solution was begun at the standard flow rate. The volume (in mL) which passes through the column before the test material appears (inflection point as absorbance increases) in the eluate is called the breakthrough volume (V_B). (*6*) The breakthrough capacity (C_B) is defined as $C_B = [(V_B - V_0)/W_d] \times 0.1$. The dimensions of C_B are mM/g of resin (dry basis).

Complexes of phenol with βCD were placed in a Micro Filtration System, Model UHP #43, ultrafiltration cell which was fitted with an Amicon YCO5 membrane. The phenol released into the filtrate was assayed by using a Beckman Model DU-65 spectrophotometer at 266 nm. The ultrafiltration cell was stirred constantly under nitrogen at 50 p.s.i. Initially, the cell contained 50 mL of the solution of the complex, and 25 mL of filtrate was collected and assayed for phenol. Water or the appropriate alcoholic solution was added to the cell to restore the volume to 50 mL. The filtration and replacement steps were repeated several times. The amounts of hydroxyethyl-βCD and phenol were the same as previously used, and the 1-propanol concentration was either 0.066% or 5.0%.

RESULTS AND DISCUSSION

CDs are effective agents for complexation[1] and the complexes have been used to reduce or increase the solubility of, and control the release of, included guests. The release of guests involves, first, solubilization of the complex, and the amount released depends on the balance of affinities of the guest for the solvent or the cavity of the CD. One approach for controlling the solubility of CD complexes and expanding their utility is to incorporate CDs in polymers. CD-Ps have long been known[2] and their industrial uses for pharmaceuticals have been summarized[3].

A broad array of CD-Ps has been described which differ considerably in their chemical and physical properties. There are copolymers that have different concentrations of CDs and different cross-linking agents[4], or block polymers with CDs added to polymer chains[5,6]. Some polymers are formed as solid blocks which are subsequently ground[7], and others are synthesized as spherical beads[2].

In considering the use of these materials in non-analytical chromatographic applications, it is important to develop a method for comparing different CD-Ps since standardized products are important for commercial application. The following standardized protocol is now proposed. Since many commercial separation systems operate continuously with multiple parallel cells for the selective removal of components from mixtures, the breakthrough capacity was selected as the key indicator. The breakthrough capacity is defined as the number of moles of test material to be adsorbed by a fixed mass of polymer (dry basis), in a column of fixed dimensions, and at a defined flow rate before the test material appears in the eluate. The void volume is subtracted from the volume of eluate before calculation.

Wiedenhof *et al.*[8] observed that phenol is tightly held in the CD-P, so that this compound was used as the standard test material. The related compounds benzoic acid, benzyl alcohol, benzylamine, cetylpyridinium chloride, and sodium benzoate were incorporated in order to determine the effects of functional groups on the adsorption process. Cetylpyridium chloride was also included since CD-P has been used[9] as a controlled release agent for this salt. Data on the chromatographic behavior of the test materials appear in Fig. 1 and Table II.

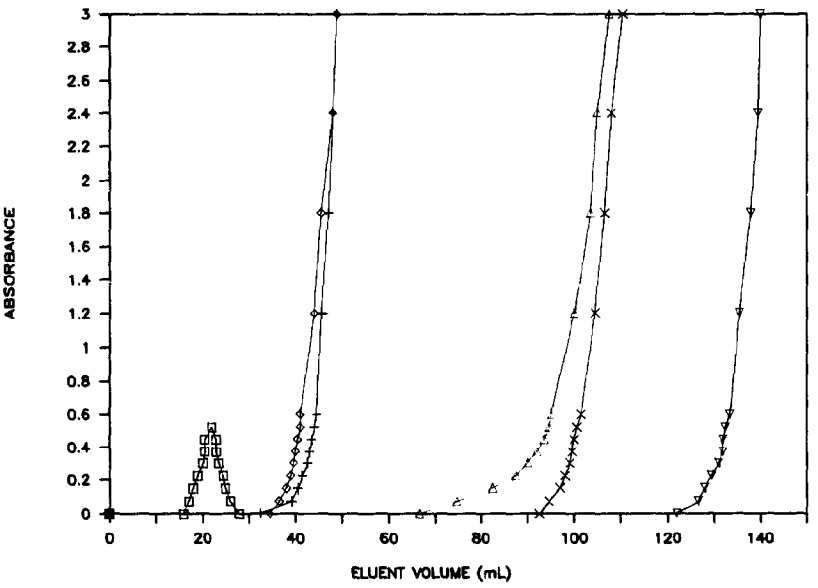

Fig. 1. Breakthrough points of βCD-P: +, sodium benzoate; ◇, cetylpyridinium chloride; △, benzylamine; ×, benzyl alcohol; ▽, phenol; □, blue dextran.

TABLE II

RATIO OF COMPOUNDS ADSORBED ON βCD-CONTAINING POLYMER

Compound (M)	*Wavelength measured (nm)*	C_B *(mmol of test substance/g of βCD-P dry basis)*	*Ratio to βCD in βCD-P (mmol/mmol of CD)*
Phenol (0.1)	270.0	1.355	3.041
Benzyl alcohol (0.1)	256.7	0.946	2.123
Benzylamine (0.1)	257.0	0.614	1.378
Cetylpyridinium chloride (0.1)	259.0	0.230	0.516
Benzoic acid (0.014)	227.8	0.225	0.505
Sodium benzoate (0.1)	224.0	0.211	0.474

These data indicate that phenol was the most strongly held of the compounds tested (3 moles of phenol adsorbed per mole of CD); benzyl alcohol was slightly less firmly held. The amines have reduced adsorption, and cetylpyridinium chloride, with its bulky side group, is less strongly held than benzylamine. Whereas cetylpyridinium chloride forms[9] a 2:3 complex with βCD, the ratio for βCD-P was 1:2. The carboxylic acids were the most weakly held.

The interaction of βCD and hydroxyethyl-βCD with phenol was studied. The soluble phenol complexes were placed in an ultrafiltration cell with a membrane having a reported mass cut-off of 500 Da, so that βCD and hydroxyethyl-βCD were

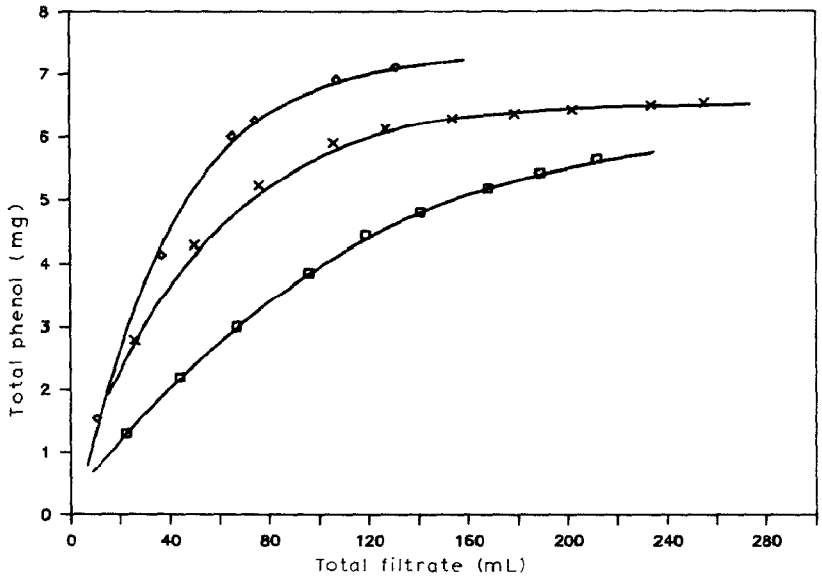

Fig. 2. Effect of concentration of βCD on the release of phenol in ultrafiltration: ◇, phenol (6.23 mg) in water (50 mL); □, plus 0.75 g of βCD (ratio 1:10); ×, plus 75 mg of βCD (ratio 1:1). Due to rounding of calculation of the amount of phenol, the cumulative effect results in an amount of phenol greater than actually used.

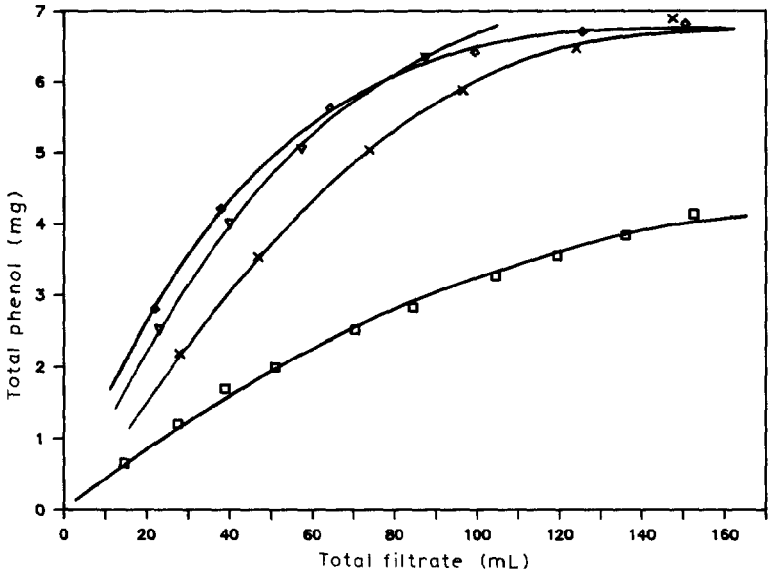

Fig. 3. Effect of concentration of hydroxyethyl-βCD on release of phenol in ultrafiltration: ◇, phenol (7.17 mg) in water (50 mL); plus hydroxyethyl-βCD: △, 0.1 g (1:1 ratio); ×, 1.0 g (10:1 ratio); □, 5.0 g (50:1 ratio).

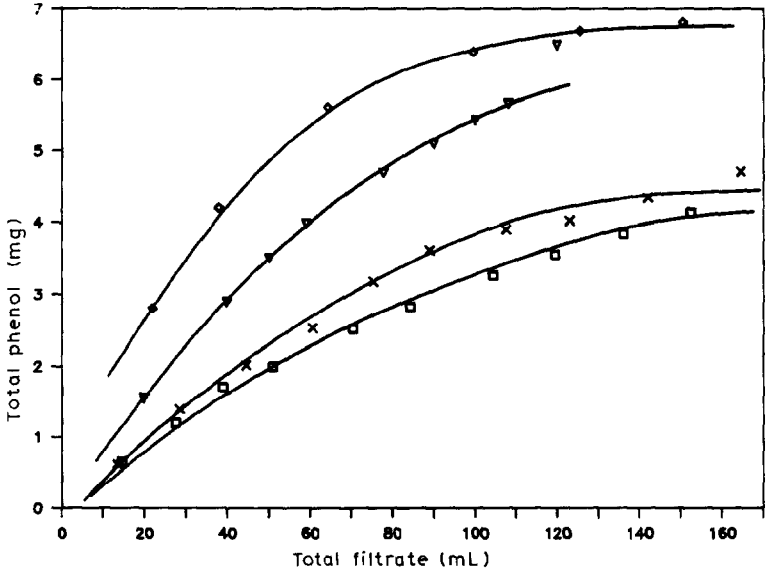

Fig. 4. Effect of 1-propanol on the release of phenol from a hydroxyethyl-βCD–phenol complex: □, phenol (7.17 mg) and hydroxyethyl-βCD (5.0 g) in water (50 mL); plus 1-propanol (%); ×, 0.66; ▽, 5.0; ◇, phenol only.

retained. Fig. 2 shows a plot of the elution of phenol from the cell containing either phenol or phenol-βCD. Phenol passed through the membrane most rapidly when no βCD was present and most slowly from the solution containing the lowest ratio of phenol to βCD. Due to the solubility limitations of βCD, its concentration could not be increased further to slow the release of phenol into the filtrate. Hydroxyethyl-βCD was used to study the effect of further increases in CD concentration; βCD and hydroxyethyl-βCD have similar binding capacity[10]. The rate of migration of phenol decreased as the concentration of hydroxyethyl-βCD increased (Fig. 3). A 50:1 ratio, of hydroxyethyl-βCD to phenol produced the slowest release of phenol, and this ratio was used to study the effect of 1-propanol as a competitor with phenol for the cavity of the βCD. Fig. 4 shows that the effect of 1-propanol was related to its concentration.

Phenol forms soluble complexes with βCD and is distributed between the free and complexed state. The amount of phenol in the filtrate at a 1:1 ratio of phenol and βCD was close to that found using phenol alone, but decreased as the proportion of βCD was increased. Thus, the rate of release of the guest can be controlled by adjusting the relative concentration of βCD. Also, it is possible to control the release of guest by adding another compound (*e.g.*, 1-propanol) that competes with the guest for the cavity of the βCD.

The use of CD-Ps combines the processes of binding and release of guests because the cross-linking that occurs during polymerization stabilizes the CD, thereby enhancing binding with some substances (3 moles of phenol are bound per mole of CD in the polymer). However, it is not clear yet if this involves interaction with the cross-linked regions of the polymer outside the CD or if the rigidity of the polymer permits stacking of the phenol within the CD. The design of polymers for binding targeted guests may therefore require consideration of the nature of the cross-linking agent.

The study of the release of guests from CD complexes is limited by the solubility of the components of the systems. In order to obtain reliable measurement, the guest must be water-soluble. The complexation of phenol for βCD has been discussed[11] in terms of the ionic forms. Work is in progress aimed at understanding the relationship between the release, breakthrough, and the capacity of the CD-Ps.

SUMMARY

Data have been presented showing the differential binding ability of a series of compounds to a βCD-containig polymer. Phenol bound most strongly; benzyl alcohol, benzylamine, cetylpyridinium chloride, benzoic acid, and sodium benzoate bind in decreasing order. A method is also proposed for standardizing the behavior of cyclodextrin-containing polymers.

The release of phenol across an ultrafiltration membrane was dependent upon the CD concentration. As the CD or hydroxyethyl-CD concentration increased, phenol concentration in the filtrate decreased. 1-Propanol competes with

phenol for the cavity. The amount of phenol in the filtrate increased as the phenol concentration increased. Thus, the release of phenol could be controlled by regulating the CD concentration or by adding a substance which would compete for the CD cavity.

REFERENCES

1 J. SZEJTLI, *Cyclodextrin Technology*, Kluwer, Dordrecht, 1988.
2 N. WIEDENHOF, J. N. J. J. LAMMERS, AND C. L. VAN PANTHALEON VAN ECK, *Staerke*, 21 (1969) 119–123.
3 E. FENYVESI, *J. Incl. Phenom.*, 6 (1988) 537–545.
4 I. TABUSHI, N. SHIMIZU, AND K. YAMAMURA, U.S. Pat. 4,169,079; *Chem. Abstr.*, 91 (1979) 108650e.
5 J. SZEJTLI, E. FENYVESI, S. ZOLTAN, B. ZSADON, AND F. TUDOS, U.S. Pat. 4,274,985; *Chem. Abstr.*, 92 (1980) 181902p.
6 J. SZEJTLI, B. ZSADON, E. FENYVESI, O. HORVATH, AND F. TUDOS, U.S. Pat. 4,357,468; *Chem. Abstr.*, 97 (1982) 8052s.
7 J. SOLMS AND R. H. EGLI, *Helv. Chim. Acta*, 48 (1965) 1225–1228.
8 N. WIEDENHOF, *Staerke*, 21 (1969) 163–166.
9 R. B. FRIEDMAN, A. R. HEDGES, AND G. A. REED, *Proc. Int. Symp. Contrd. Rel. Bioact. Mater.*, 14 (1987) 311; U.S. Pat. 4,774,329; *Chem. Abstr.*, 110 (1988) 44969s.
10 F. A. MENARD, M. B. DEDHIYA, AND C. T. RHODES, *Drug Development and Industrial Pharmacy*, 14 (1988) 1529–1547.
11 A. BUVARI AND L. BARCZA, *J. Chem. Soc., Perkin Trans. 2*, (1988) 543–545.