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2-HYDROXY-3-TRIMETHYLAMMONIOPROPYL DERIVATIVES OF CYCLOMALTOHEPTAOSE AS PHASE-TRANSFER CATALYSTS

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ABSTRACT

Cyclomaltoheptaose (β-cyclodextrin, **1**) can act as a phase-transfer catalyst owing to its ability to form host–guest complexes. Reaction of **1** with 2,3-epoxypropyltrimethylammonium chloride (**2**) gave mainly 2-*O*-(2-hydroxy-3-trimethylammoniopropyl) derivatives (**3**) with degrees of substitution (d.s.) depending on the ratio of reagents. Model nucleophilic substitution reactions were catalyzed more effectively by **3** than by **1** because of the proximity of the reactive site and the guest molecule. The decrease in catalytic effect with increasing d.s. of **3** indicated formation of the complex to be the limiting step.

INTRODUCTION

The ability of cyclomalto-hexaose (αCD), -heptaose (βCD), and -octaose (γCD) to form inclusion compounds[1–3] has prompted many investigations of the applicability of these compounds for drug or cosmetic encapsulation[4] and in chromatography[5].

The formation of host–guest complexes can improve the solubility of organic compounds in aqueous phases. Catalytic amounts of βCD can promote reverse-phase transfer reactions in liquid–liquid two-phase systems involving water-soluble nuceophilic[6], oxidizing[7–9], and reducing agents[10]. However, the catalytic efficiency of quaternary ammonium salts is higher since reactions take place in the organic phase. Of particular interest is the effect of the shape and chirality of the cavity of βCD, which lead to regioselectivity[11–13] and enantioselectivity[7,14]. For this purpose, βCD is generally used as an auxiliary, *i.e.*, in a more or less stoichiometric ratio in order to improve the selectivity.

βCD derivatives, in which a catalytic site is appended to the cavity, have attracted considerable attention for the design of artificial enzymes[2,3,15] since they can effect marked acceleration of reaction rates and selectivity. The aim of our

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work was to apply this concept to organic syntheses, using readily available βCD derivatives as catalysts.

We now report on derivatives of βCD that carry substituents with a quaternary ammonium moiety. The attachment of such groups could promote the attack of anions on the guest molecule, thereby enhancing the rate of reaction.

RESULTS AND DISCUSSION

The binding and catalytic properties of mono- or di-substituted ammonio derivatives of βCD have been investigated as models for enzyme action[16–18]. These compounds were obtained by nucleophilic displacement of mono- or di-sulphonated derivatives of βCD, but their purification was tedious and the overall yields were low. In order to increase solubility in water, cationic derivatives of βCD with a high degree of substitution (d.s.) were prepared by reacting[19] an epoxyammonium reagent with the alkali-activated βCD.

This little used route is now exemplified by the reaction between βCD (**1**) and 2,3-epoxypropyltrimethylammonium chloride (**2**) to afford *O*-(2-hydroxy-3-trimethylammoniopropyl) derivatives (**3**). Data on the preparation and the characterization of the products are summarized in Table I.

The molar ratio **2**:**1** was varied from 0.5 to 14 and gave values of d.s. from 1.1 to 4.6. When a large excess of **2** was used (*e.g.*, **3c–3f** in Table I), the crude products were ultrafiltered to ensure a complete removal of small molecules and

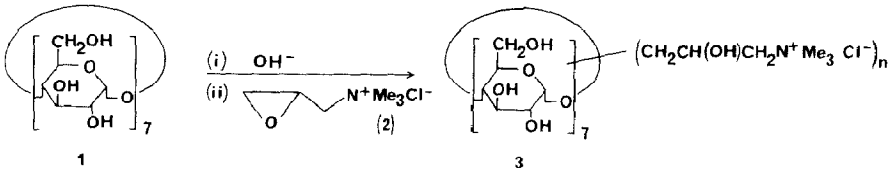

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TABLE I

DATA ON THE SYNTHESIS AND CHARACTERIZATION OF THE *O*-(2-HYDROXY-3-TRIMETHYLAMMONIOPROPYL)-βCD DERIVATIVES **3**

Structure	*Molar ratios* **1**:HO^-:**2**	*D.s.*	*Average d.s. (number of glucose residues substituted)*	$[\alpha]_D^{25}$ *(degrees)*
3a	1:1:0.5	0.16	1.1	—
3b	1:1:1	0.19	1.3	+130
3c	1:1:7	0.40	2.8	+120
3d	1:2:7	0.47	3.3	+116
3e	1:2:14	0.56[a]	3.9	—
3f	1:14:14	0.68	4.8	+98

[a]Ref. 18, 1.15.

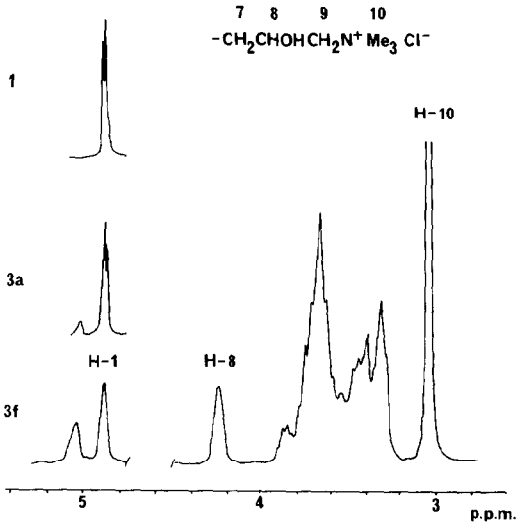

Fig. 1. 300-MHz ^{1}H-n.m.r. spectrum of **3f** in D_2O and a comparison of the H-1 resonances of βCD (**1**), **3a** (d.s. 0.16), and **3f** (d.s. 0.66).

salts. The derivatives **3a–f**, isolated by precipitation in acetone in yields of 40–60%, were soluble in water and methanol.

Substitution in the cavity of the βCD is evidenced in ^{1}H-n.m.r. spectra of **3** by the presence of resonances at 3.04 and 4.24 p.p.m. assigned to H-10 and H-8 of the hydroxypropylammonium moiety (Fig. 1). The d.s. was determined by comparing the integrated areas of the resonances for H-1, H-8, and H-10. These d.s. values were confirmed by argentimetric titrations of chloride anions and the elemental analyses. The data in Table I for **3e–3f** show that a maximum of about five glucose residues reacted in spite of a large excess of **2**. This result, which is markedly lower than that reported[19], probably reflects the purification achieved by ultrafiltration.

Since hydroxide ions are used as catalyst, the reaction of **1** with **2** should involve the secondary hydroxyl groups because of their higher acidity[20]. Also, HO-2 is usually (pK_a 12.1) more reactive than HO-3. The ^{13}C-n.m.r. data (Table II) are consistent with mainly 2-substitution of βCD as indicated by the chemical shift (9.0 p.p.m.) of the C-2 resonance and the β-shift (−2.5 p.p.m.) of the C-1 resonance. These data accord with those reported[21] for the methylation of βCD. There were no significant shifts in the resonances of C-3 and C-6 when the d.s. was <0.5. The regioselectivity of the reaction diminished when a large excess of base was employed (**3f**) and some 6-substitution occurred as demonstrated by the signals at 72.1 and 73.2 p.p.m., due to C-6 (shifted by 9.3 p.p.m.) and C-5 (β-shift of −1.3 p.p.m.), respectively.

In spite of the fact that there are two resonances for H-1 (4.87 and 5.03 p.p.m., Fig. 1), the downfield signal, present in the spectra of substituted

TABLE II

^{13}C-N.M.R. DATA (P.P.M., EXTERNAL Me_4Si) FOR βCD (**1**) AND THE 2-HYDROXY-3-TRIMETHYLAMMONIOPROPYL DERIVATIVES **3** IN D_2O

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-7*	*C-8*	*C-9*	*C-10*
1	104.3	74.3	75.5	83.6	74.5	62.8	—	—	—	—
3	104.2	74.2	75.5	83.6	74.5	62.8	70.4	73.9	67.6	56.7
	101.7	83.2			73.2[a]	72.1[a]				

[a]Only in **3f**.

derivatives, was only ~60% of the intensity of that predicted from the d.s. Consequently, the high-field absorption is a combination of resonances of unsubstituted and substituted units. In addition, the difference of chemical shifts decreased when the spectra were recorded at temperatures up to 70°; but coalescence did not occur. These data indicate the existence of two different conformations of the hydroxypropylammonium moiety, the interchange of which is slow on the n.m.r. time-scale.

By the use of an appropriate ratio of **1** and **2**, reaction can be limited to about one glucose residue (**3a**). Purification on a column of carboxymethylcellulose[16] then gave a monosubstituted derivative. Thus, selective mono-2-substitution of **1** may be achievable generally by the use of reagents bearing both an epoxy group and other desired functionality.

The activity of the derivatives **3** as phase-transfer catalysts was examined using the standard nucleophilic substitution reaction

$$R\text{–}Br + I^- \rightarrow R\text{–}I + Br^-,$$

where R = C_8H_{17} and $Ph(CH_2)_3$. The reaction involving 3-phenylpropyl bromide was investigated because of the better fit in the cavity of βCD of compounds that carry a phenyl group. The tests were performed in the absence of solvent, using the lipophilic reagents as the organic phase. The conversion into the iodide product was determined by g.l.c. with a standard deviation of 1.5%.

The results in Fig. 2 show that **3f** was a more efficient catalyst than **1** and, as expected, the reaction with 3-phenylpropyl bromide was faster with both catalysts. The catalysis of the reaction of octyl bromide as a function of d.s. is expressed in terms of pseudo-first-order rate constants (Table III). As the d.s. increases, there was a marked decrease in catalytic activity (**3a–3d**). Although **3d** (d.s. 3.2) was slightly less efficient than βCD (**1**), a higher reactivity was observed for **3f** (d.s. 4.6).

The halogen-exchange reactions catalyzed by the βCD derivatives **3** involve the initial formation of an inclusion complex which renders the alkyl bromide soluble in an aqueous phase. Nucleophilic attack of the iodide anion is followed by dissociation of the inclusion complex with release of the alkyl iodide, and regeneration of the starting catalyst by ion exchange promoted by the excess of iodide ion.

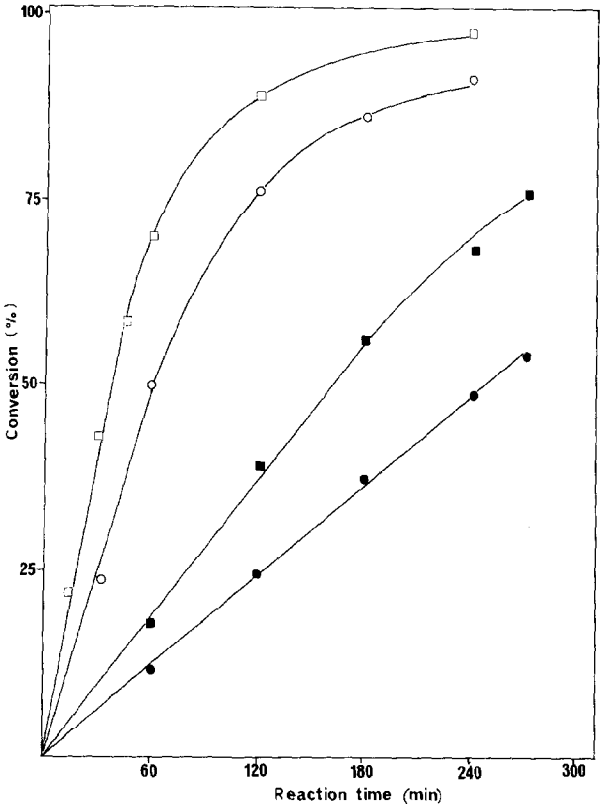

Fig. 2. Activity of βCD (**1**) and **3f** as phase-transfer catalysts in halogen exchange between sodium iodide and octyl bromide (●, **1**; ■, **3f**) and 3-phenylpropyl bromide (○, **1**; □, **3f**). Reaction conditions: 2 mol% of catalyst and 4.6 mmol of alkyl bromide in 3M NaI (5 mL) at 100° stirred at 1400 r.p.m.

The attachment of an ammonium-containing moiety to βCD should accelerate the second step by facilitating the approach of iodide ions to the guest. This view is supported by the higher reactivity for **3a** than for **1**. As βCD and the derivatives **3** are insoluble in organic solvents, the reaction takes place in the aqueous phase. Therefore, the catalytic activity of these compounds is much less than that of the tetrabutylammonium cation (Table III).

The results in Table III show that the rate of reaction is dependent on the d.s. As the d.s. increases, the electrostatic repulsion forces the ammonio sites to move away from the substrate inside the cavity with a consequent decrease of reactivity. Also, the presence of several quaternary ammonio substituents restricts the aperture of the βCD cavity and decreases the hydrophobicity. A decrease in the stability has been reported[16a] for an inclusion complex between a mono-6-trimethylammonio-βCD derivative and a bulky azo dye with two naphthalene rings.

The derivative **3f** is substituted on both sides of the molecule and, because its activity is higher than the other derivatives **3**, it can be assumed that the presence

TABLE III

RATE CONSTANTS OF THE HALOGEN EXCHANGE[a] BETWEEN OCTYL BROMIDE AND IODIDE ANIONS CATALYZED BY THE 2-HYDROXY-3-TRIMETHYLAMMONIOPROPYL DERIVATIVES **3**

Catalyst	*D.s.*	*Pseudo-first-order rate constant* ($k \times 10^6/s^{-1}$)[b]	*Yield after 4 h* (%)
3a	0.16	48	60
3b	0.19	38	51
3d	0.46	27	42
3f	0.66	72	68
1	—	31	49
TBA[c]	—	278	95
None	—	5.7	10

[a]Reaction conditions: 2 mol% of catalyst and 9.3 mmol of octyl bromide in 10 mL of 3M KI at 100° stirred at 1400 r.p.m. [b]$k = k_{obs.} - k_{uncatalyzed}$. [c]TBA = Tetrabutylammonium hydrogensulfate.

of numerous ammonio groups allows it to react as well at the interface of the two phases as in the aqueous phase by formation of an inclusion complex. If the desired effect is orientation of a reaction by the formation of a host–guest system, then the catalyst **3a** is to be preferred to the more efficient derivative **3f**.

Transfer between the two phases associated with the formation of inclusion complexes appears to be the limiting step for reactions catalyzed by the derivatives **3**. The best compromise between an increase in the rate of reaction and the ability to form complexes involves the monosubstituted βCD. This conclusion is related to that of previous studies of enzyme models where the cavity of βCD plays the role of recognition site[15].

Studies are in progress on asymmetric syntheses with these derivatives as auxiliaries.

EXPERIMENTAL

General. — β-Cyclodextrin (**1**) was a generous gift from Roquette Freres (Lestrem, France). The following techniques were used for product analysis: F.t.-i.r. spectroscopy (Perkin–Elmer 1760), n.m.r. spectroscopy (Brüker Aspect 3000), g.l.c. (Varian 3700), and polarimetry (Perkin–Elmer 241MC).

Preparation of 2-hydroxy-3-trimethylammoniopropyl derivatives of cyclomaltoheptaose (βCD, **1**). — To a solution of **1** (2.27 g, 2 mmol) in aqueous NaOH (1.12 g in 2 mL; 28 mmol) was added dropwise an aqueous solution (15 mL) containing 2,3-epoxypropyltrimethylammonium chloride (4.24 g, 28 mmol). After storage overnight at 50°, the solution was neutralized with aqueous HCl and concentrated, a solution of the residue in methanol (30 mL) was filtered, and the product was precipitated by the addition of acetone. An aqueous solution of the product was ultrafiltered through Nuclepore (mol. wt. cut-off, 1,000) and the reprecipitation step was repeated, to give a white solid that was dried under vacuum

to give **3f** (1.84 g, 50%). D.s. 0.68 (elemental analysis), 0.67 (n.m.r.), and 0.66 (Ag^+ titration).

Anal. Calc. for $C_{70.8}H_{137.2}Cl_{4.8}N_{4.8}O_{39.8}$: C, 45.65; H, 7.42; Cl, 9.13; N, 3.60. Found: C, 45.50; H, 7.18; Cl, 9.16; N, 3.68.

The derivatives **3a–e** were prepared as described above, but with the ratios of **1** and **2** shown in Table I.

3a: D.s. 0.15 (n.m.r.) and 0.16 (Ag^+ titration).

3b: D.s. 0.19 (elemental analysis), 0.17 (n.m.r.), and 0.19 (Ag^+ titration).

Anal. Calc. for $C_{49.8}H_{88.2}Cl_{1.3}N_{1.3}O_{36.3}$: C, 44.90; H, 6.67; Cl, 3.46; N, 1.37. Found: C, 44.77; H, 6.62; Cl, 3.54; N, 1.29.

3c: D.s. 0.40 (elemental analysis), 0.39 (n.m.r.), and 0.36 (Ag^+ titration).

Anal. Calc. for $C_{58.8}H_{109.2}Cl_{2.8}N_{2.8}O_{37.8}$: C, 45.28; H, 7.06; Cl, 6.36; N, 2.51. Found: C, 44.91; H, 7.23; Cl, 6.33; N, 2.43.

3d: D.s. 0.47 (elemental analysis), 0.46 (n.m.r.), and 0.43 (Ag^+ titration).

Anal. Calc. for $C_{61.8}H_{116.2}Cl_{3.3}N_{3.3}O_{38.3}$: C, 45.39; H, 7.16; Cl, 7.15; N, 2.83. Found: C, 45.20; H, 7.24; Cl, 7.21; N, 2.88.

3e: D.s. 0.56 (n.m.r.), and 0.54 (Ag^+ titration).

Halogen exchange reactions. — A mixture of alkyl bromide (9.3 mmol), catalyst (0.185 mmol, 2 mol%), and 3M KI (10 mL) was stirred (1400 r.p.m.) at 100°. The reaction was monitored by g.l.c. (1% SE-30 on Chromosorb G) of a pentane extract.

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