Acknowledgment. We are grateful to a referee and Dr. Cheves Walling for valuable comments.

References and Notes

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(3) See: Liu, K.-T.; Tong, Y.-C. *J. Org. Chem.* **1978,** *43,* 2717. Mazur, Y.; Keinan, E. *Ibid.* **1978,** *43,* 1020, and references cited therein.
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(7) In this experiment, 5 mL of 0.5 M 1-bromooctane in toluene was reacted with 0.5 g of **1** for 48 h at 90 °C and yielded **1.14** mmol of cyanooctane as determined by GLC. Further heating for 24 h did not change the yield significantly.
(8) Analyses were carried out on a Hewlett-Packard 5830 flame ionization instrument using a 2 ft × 0.125 in QF 1(10%) on Chromosorb W column at 160°C.
(9) Values of k_0 at 70, 90 and 100 °C were 2.1×10^{-5}, 6.9×10^{-5}, and 24.3×10^{-5} L mol^{-1} s^{-1}, respectively, and gave $\Delta H^{\ddagger} = 18.4 \pm 1.8$ kcal mol^{-1} and $\Delta S^{\ddagger} = -26.2 \pm 5$ eu.
(10) In this experiment, 0.25 g of **1** was reacted with 25 mL of 0.2 M 1-bromooctane in toluene at 110 °C.
(11) The observed first-order rate constant was 1.9×10^{-5} s^{-1}. The concentration of NaCN in the organic phase was 4.8×10^{-4} M (determined by reaction of an aliquot with excess 1-bromooctane at 100 °C).
(12) In principle, two fundamentally different mechanisms for displacement at the alumina surface can be envisaged. In the first, A, a soluble organic halide undergoes direct attack by an impregnated cyanide ion. In the second, B, the halide is adsorbed prior to displacement. While the observed first-order dependence on 1-bromooctane is in agreement with A, it is also consistent with B if the organic halide is weakly adsorbed. To the extent that alumina may assist the departure of bromide ion from the reactant, the apparent reactivity of cyanide must be regarded as a maximum value.

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Symmetrical Triamino-per-*O*-methyl-α-cyclodextrin: Preparation and Characterization of Primary Trisubstituted α-Cyclodextrins

Sir:

Exploitation of the unique geometry of cyclodextrins for the construction of models of receptor binding and of enzyme catalysis has been severely limited by the dearth of well-characterized polysubstituted derivatives. Thus, while the efficient modification of *all* of the primary hydroxyl groups of α- and β-cyclodextrins has been described[1] and numerous monosubstituted compounds have been reported,[2] no derivatives of intermediate substitution number have been described for which the positions of substitution are established.[3] We report here the preparation and characterization of 6,6″,6‴,6⁗-triamino-6,6″,6‴,6⁗-trideoxy-6′,6‴,6⁗″,2,2′,2″,2‴,2⁗,2⁗″,2⁗″,3,3′,3″,3‴,3⁗,3⁗″,3⁗″-pentadeca-*O*-methyl-α-cyclodextrin (**1**) (= symmetrical triamino-per-*O*-methyl-α-CD), a trisubstituted α-cyclodextrin of known regiosubstitution that possesses a threefold axis of symmetry (Figure 1).

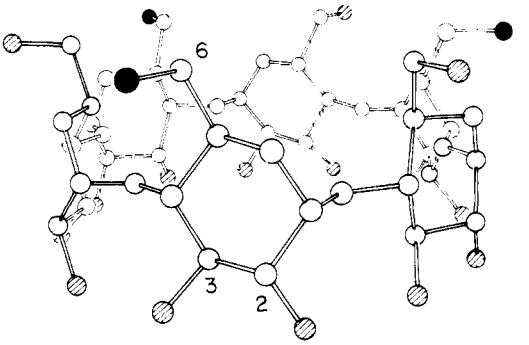
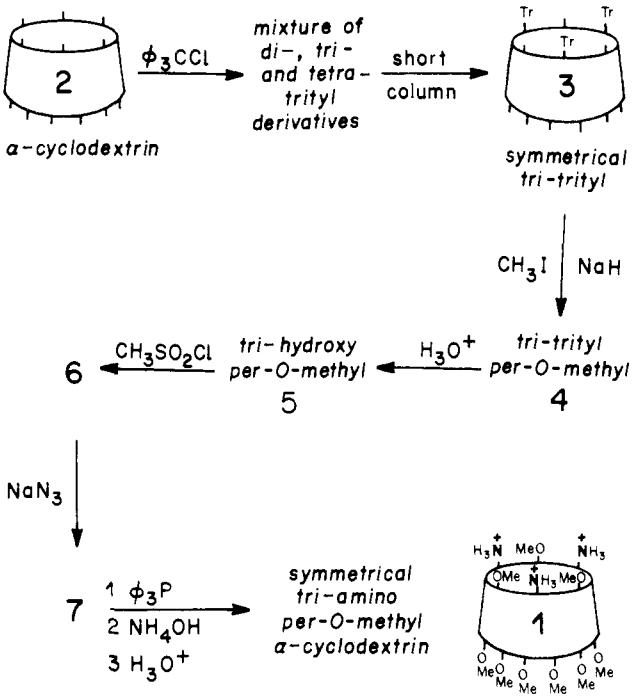


Figure 1. Drawing of symmetrical triamino-per-*O*-methyl-α-cyclodextrin (**1**). The coordinates used for the cyclodextrin skeleton were based on crystal structure data summarized by Saenger.[11] The shaded circles represent methoxyl groups and the full circles represent ammonium groups.

Scheme I. Synthetic Route to Symmetrical Triamino-per-*O*-methyl-α-cyclodextrin (**1**)



Synthesis. The synthesis of **1** is outlined in Scheme I. Reaction of purified[4] α-cyclodextrin **2** with 3.3 equiv of trityl chloride in pyridine (55 °C, 24 h) gave a multitude of products.[5] Thin-layer chromatography (TLC) on silica gel (butanone-water-3-methylbutan-1-ol, 7:1:1) showed six major products, having R_f values of 0.37, 0.28, 0.26, 0.23, 0.20, and 0.14, and about 12 minor products. The desired symmetrically substituted 6,6″,6⁗″-tri-*O*-trityl-α-cyclodextrin **3** (R_f of 0.28) was isolated in 23% yield after "short column chromatography"[6] on silica gel eluting with butanone-water-3-methylbutan-1-ol, 100:10:1.[7] The product was identified by ^{1}H and ^{13}C NMR spectroscopy (vide infra).[8] Methylation of the 15 hydroxyl groups of **3** was accomplished using methyl iodide and *crystalline* sodium hydride in dimethylformamide (DMF).[1] Removal of the three trityl groups, by brief treatment of **4** in a two-phase system (concentrated hydrochloric acid-chloroform), gave **5**. Reaction of the three free hydroxyl groups with methanesulfonyl chloride in pyridine, followed by displacement of the sulfonate groups with sodium azide in DMF, gave the symmetrical triazido-per-*O*-methyl-α-cyclodextrin (**7**). Reduction of **7** with triphenylphosphine and ammonia in dioxane[9] gave the desired product **1**, isolated as its trihydrochloride salt. Each of the five reactions from **3** to **1** went in yields between 94 and 97%, and **1** was isolated in 19% overall yield from α-cyclodextrin **2**.

In a similar fashion, mono-6-amino-6-deoxy-6′,6″,6‴,6⁗,6⁗″,2,2′,2″,2‴,2⁗,2⁗″,2⁗″,3,3′,3″,3‴,3⁗,3⁗″,3⁗″-heptadeca-*O*-methyl-α-cyclodextrin hydrochloride (**8**) (= monoamino-per-*O*-methyl-α-CD) was prepared in 24% overall yield, beginning with the preparation of mono-6-*O*-trityl-α-cyclodextrin.[2a]

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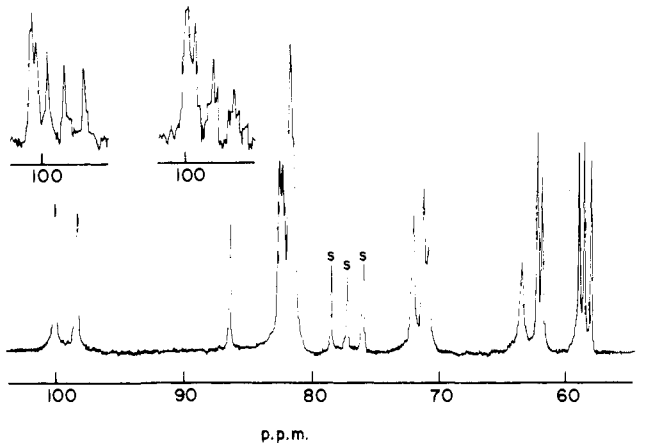

Figure 2. ^{13}C NMR spectrum of symmetrical tritrityl-per-*O*-methyl-α-cyclodextrin (**4**): solution in $CDCl_3$, chemical shifts from Me_4Si. The downfield trityl signals are not shown. Insets show the C-1 signals from the spectra of two isolated *un*symmetrical derivatives.

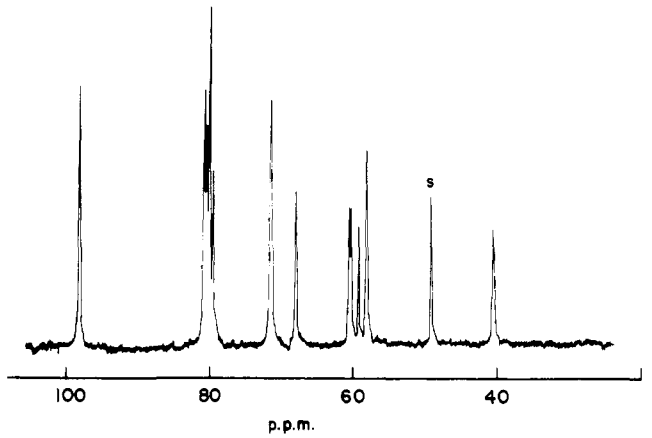

Figure 3. ^{13}C NMR spectrum of symmetrical triamino-per-*O*-methyl-α-cyclodextrin (**1**): solution in D_2O with internal methanol standard, chemical shifts from methanol referred to external Me_4Si.

Characterization. The characterization of compound **1** and of compounds **3**–**7** relied on their threefold rotational axis of symmetry, which is exhibited in their ^1H and ^{13}C NMR spectra.[10] Of the *four* possible primary trisubstituted isomers, only the desired isomer retains any rotational symmetry. For instance, the ^{13}C NMR spectrum of **3** (Figure 2) shows only *one* kind of trityl group and *two* kinds of α-glucose unit. Although the expected two pairs of signals for the 12 C-2 and C-3 atoms are not resolved (81.3 and 81.5 ppm), all other predicted signals are seen: C-1 at 100.2 and 98.5; C-4 at 82.4 and 82.2; C-5 at 71.8 and 70.9; and C-6 at 70.6 and 63.2 ppm. Remarkably, the threefold symmetry is exhibited even by the 15 *O*-methyl groups, 12 of which are on the secondary side of the cyclodextrin torus, away from the substitution site: C-2 OCH_3 at 61.9 and 61.5; C-3 OCH_3 at 58.2 and 57.6; and C-6 OCH_3 at 58.6 ppm. As expected, only one type of trityl group is observed, with the single quaternary carbon signal at 86.3 ppm (the four other singlets, for the ortho, meta, para, and ipso carbons, are downfield and are not shown in Figure 2). (In contrast, two of the *un*symmetrically substituted tri-*O*-trityl derivatives isolated from the tritylation reaction showed *three* different trityl groups plus a multiplicity (theoretically six) of α-glucose units. The number of spectroscopically distinct α-glucose units was most clearly seen in the C-1 signals of the ^{13}C NMR spectra (see insets in Figure 2).) The NMR spectra[10] for **1** and **3**–**7** all exhibit the expected symmetry, while those for unsymmetrical derivatives do not. In the ^{13}C NMR spectrum of **1** (Figure 3), the two C-1 signals are not resolved, but other signals (for C-3 through C-6) show the expected symmetry doubling. These results confirm that **1** is the desired isomer in high purity.[8]

The procedure outlined here provides access to a wide variety of cyclodextrin derivatives, and the rational synthesis of sophisticated model systems employing regiospecifically disposed functionality at the primary end of the cyclodextrin cavity and additional functionality at the secondary end, is now possible.

Acknowledgments. We are indebted to Teijin Ltd. (Tokyo) for gifts of cyclodextrins and to the National Science Foundation for support.

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(8) Chemical shifts are reported with reference to tetramethylsilane. Satisfactory elemental analyses were obtained for all compounds; infrared spectra and optical rotations were performed where appropriate. Each compound was examined critically on several TLC systems and found to be free from impurities (<1%).
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Symmetrical Triamino-per-*O*-methyl-α-cyclodextrin: A Host for Phosphate Esters Exploiting Both Hydrophobic and Electrostatic Interactions in Aqueous Solution

Sir:

With the aim of designing a host molecule that would catalyze a simple chemical reaction by specific stabilization of its transition state,[1] we have opted first to investigate the synthesis

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