Self-Inclusion Complexes Derived from Cyclodextrins: Synthesis and Characterization of $6^A,6^B$-Bis-*O*-[*p*-(allyloxy)phenyl]-Substituted *β*-Cyclodextrins

Zhen Chen, Jerald S. Bradshaw,* Guoliang Yi, Dongjin Pyo,† Delbert R. Black, S. Scott Zimmerman, and Milton L. Lee

Department of Chemistry and Biochemistry, Brigham Young University, Provo, Utah 84602-5700

Weida Tong and Valerian T. D'Souza

Department of Chemistry, University of Missouri−St. Louis, St. Louis, Missouri 63121

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The syntheses, structures, and spectroscopic properties of $6^A,6^B$-bis-*O*-[*p*-(allyloxy)phenyl]-substituted *β*-cyclodextrins have been investigated. Selective activation of the $6^A,6^B$-hydroxy groups was carried out by treating heptakis(2,3-di-*O*-methyl)-*β*-cyclodextrin (**1**) with 2,4-dimethoxybenzene-1,5-disulfonyl chloride to give $6^A,6^B$-bissulfonate ester **2** in a yield of only 3%. This material was treated with sodium *p*-(allyloxy)phenoxide in DMF to form $6^A,6^B$-bis-*O*-[*p*-(allyloxy)phenyl]-heptakis(2,3-di-*O*-methyl)-*β*-cyclodextrin (**3**), which had two isomers. One (**3A**) has the two *p*-(allyloxy)phenyl arms directed away from the cyclodextrin cavity, and the other (**3B**) has one of the *p*-(allyloxy)-phenyl groups through the cavity to form a self-inclusion complex. When either **3A** or **3B** was treated with methyl iodide and sodium hydride, the resulting permethylated $6^A,6^B$-bis-*O*-[*p*-(allyloxy)-phenyl]heptakis(2,3-di-*O*-methyl)-$6^C,6^D,6^E,6^F,6^G$-penta-*O*-methyl-*β*-cyclodextrin (**4**) was composed of two isomers, in which **4B** is a self-inclusion complex. **3A** and **3B** also can be converted into a mixture of **3A** and **3B** in strong base but not when melted in the absence of base. **4A** and **4B** do not isomerize. Detailed 1D and 2D NMR spectroscopic studies were carried out to characterize the structures of these new compounds, and molecular mechanics techniques were used to explain the experimental facts.

Introduction

Cyclodextrins are obtained from starch by enzymatic degradation.[1] The three best characterized forms are α-, *β*-, and *γ*-cyclodextrins consisting of 6, 7, and 8 D-glucose units, respectively. Each of the glucose units are in the rigid C1 chair conformation and are linked by α-1,4 bonds. This geometry gives the cyclodextrin the shape of a hollow truncated cone with the wider side formed by the secondary 2- and 3-hydroxy groups and the narrower side by the primary 6-hydroxy groups. Figure 1 shows the structure of *β*-cyclodextrin. The inner surface of the cavity is lined by the hydrogen atoms (3-H and 5-H) and the glycosidic oxygen bridges and is thus relatively hydrophobic,[2] while the external face is hydrophilic since all hydroxy groups are located outside the cavity. Intramolecular hydrogen bonds between C(2)−OH and C(3)−OH of adjacent glucose units exist, and the C(3)−OH is the predominant proton donor.[3]

The most characteristic property of the cyclodextrins is their ability to form inclusion complexes with a wide range of guest molecules.[4] Due primarily to favorable hydrophobic and/or hydrogen-bonding interactions, guest molecules of appropriate size and shape can form inclusion complexes with the cyclodextrin. In recent years, the application of cyclodextrins in analytical chemistry has become an important part of cyclodextrin chemistry. A comprehensive review of the applications of cyclodextrins in spectrometric methods, in electrochemical analysis, as well as in chromatographic separations is given by Li and Purdy.[5] In addition, there have been numerous

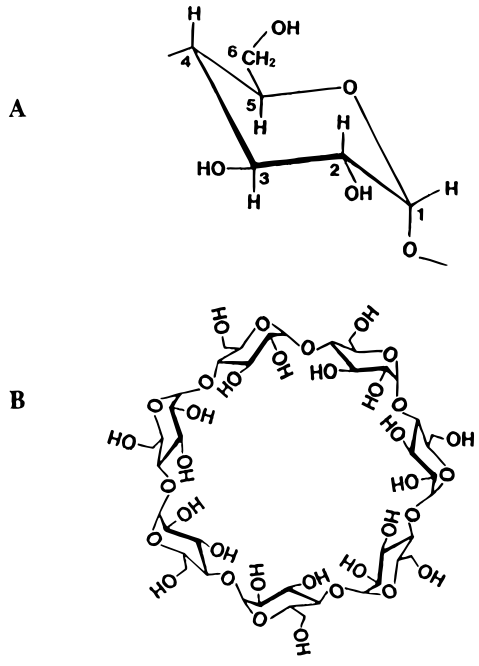

Figure 1. Structures of (A) the D-glucose unit and (B) *β*-cyclodextrin.

† Permanent address: Department of Chemistry, Kangweon National University, Chuncheon 200701, Korea.

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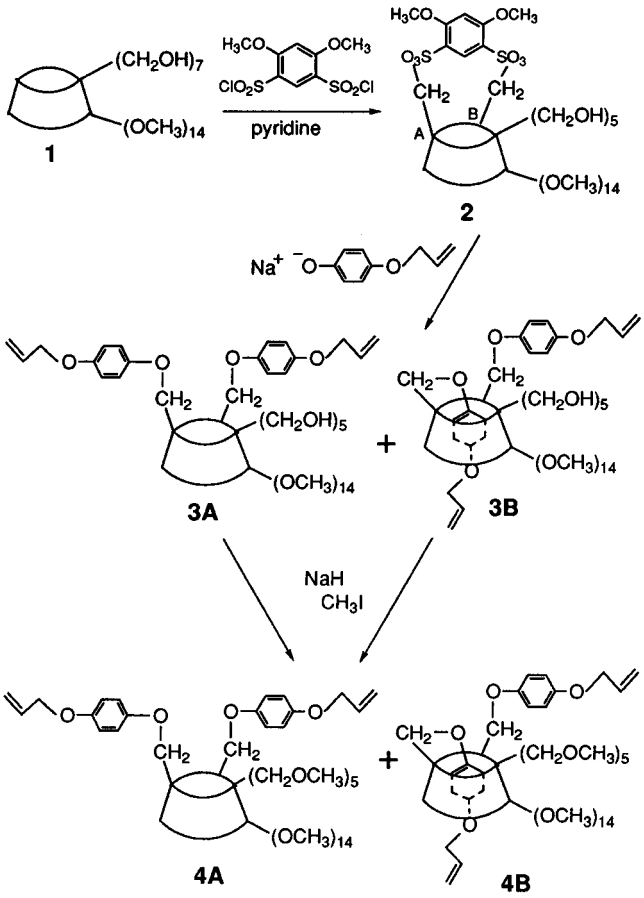
studies of the intermolecular complexes of the cyclodextrins using X-ray crystallography,[6] NMR spectroscopy,[7−9] and molecular mechanics.[10] Cyclodextrins have been commonly used as slow release dispensers for volatile or unstable biologically active compounds[11] and as biological catalysts and enzyme models.[12] In some cases, a modified cyclodextrin to which an aromatic moiety is attached can include its aromatic moiety to form an intramolecular complex. Several intramolecular complexes formed by monosubstituted β-cyclodextrins have been reported, such as 6-[*N*-(*N*′-formyl-L-phenylalanyl)deoxyamino]-β-cyclodextrin and its D isomeric form[13] and D- and L-mono-6-[(phenylalanyl)deoxyamino]-β-cyclodextrin.[14] Aromatic moieties of these compounds are included or partially included in the cyclodextrin cavities. Chemical shift changes of the phenyl proton resonances were used to support the postulated structures.[13] However, a satisfactory, complete picture explaining the observations could not be drawn because "the spectrum was so complicated that each signal could not be assigned to individual cyclodextrin protons."[13]

One aspect of research in our laboratories is the design and synthesis of novel cyclodextrin-based chiral stationary phases applied in capillary gas chromatography (GC) and supercritical fluid chromatography (SFC) for enantiomer separations. We have used two methods to prepare cyclodextrin phases that have defined structures. First, permethylated cyclodextrins containing one alkene substituent have been hydrosilylated onto a polysiloxane of known composition and molecular weight.[15−17] Second, we have prepared dialkene-substituted permethylated cyclodextrins where the alkene substituents are located in 6^A and 6^C or 6^A and 6^D positions on the cyclodextrin macroring. Superscripts A, B, and C designate glucose units A, B, and C in the cyclodextrin. Thus, 6^A,6^C indicates positions 6 on the first and third glucose units in the cyclodextrin ring. These dialkene-substituted cyclodextrins were hydrosilylated with a hexasiloxane containing an Si−H unit on each end to form cyclodextrin−hexasiloxane copolymeric stationary phases.[18,19] All of these phases provide excellent resolution of enantiomeric organic solutes.[20,21] In order to explore the dependence of chromatographic characteristics (chiral selectivity, efficiency, and resolution) of different cyclodextrin−oligosiloxane copolymeric phases on their structural features, we decided to prepare the 6^A,6^B-β-cyclodextrin−hexasiloxane copolymer and study its separation properties.[22] In the process of doing this research, we discovered some unexpected results, which are of significance to both supramolecular and analytical chemistry. This paper gives the synthetic details and structures of new 6^A,6^B-bis-*O*-[*p*-(allyloxy)phenyl]-substituted β-cyclodextrins.

Scheme 1. Preparation of Self-Inclusion Compounds 3B and 4B



Results and Discussion

2,4-Dimethoxybenzene-1,5-disulfonyl chloride is the best reagent for selectively activating the 6^A,6^B-dihydroxy groups of unsubstituted β-cyclodextrin as reported by Breslow and co-workers.[23] Heptakis(2,3-di-*O*-methyl)-β-cyclodextrin (**1**) was prepared as reported.[18] Treatment of **1** with 2,4-dimethoxybenzene-1,5-disulfonyl chloride[24] at 40 °C gave 6^A,6^B-bis-*O*-(2′,4′-dimethoxybenzene-1′,5′-disulfonyl)heptakis(2,3-di-*O*-methyl)-β-cyclodextrin (**2**) in a yield of only 3.5% (Scheme 1). About 40% of the starting material was recovered when the reaction mixture was separated by chromatography. 6^A,6^B-Bis-*O*-[*p*-(allyloxy)phenyl]heptakis(2,3-di-*O*-methyl)-β-cyclodextrin (**3**) was obtained by treating **2** with sodium *p*-(allyloxy)phenoxide in DMF at rt. Two products, **3A**

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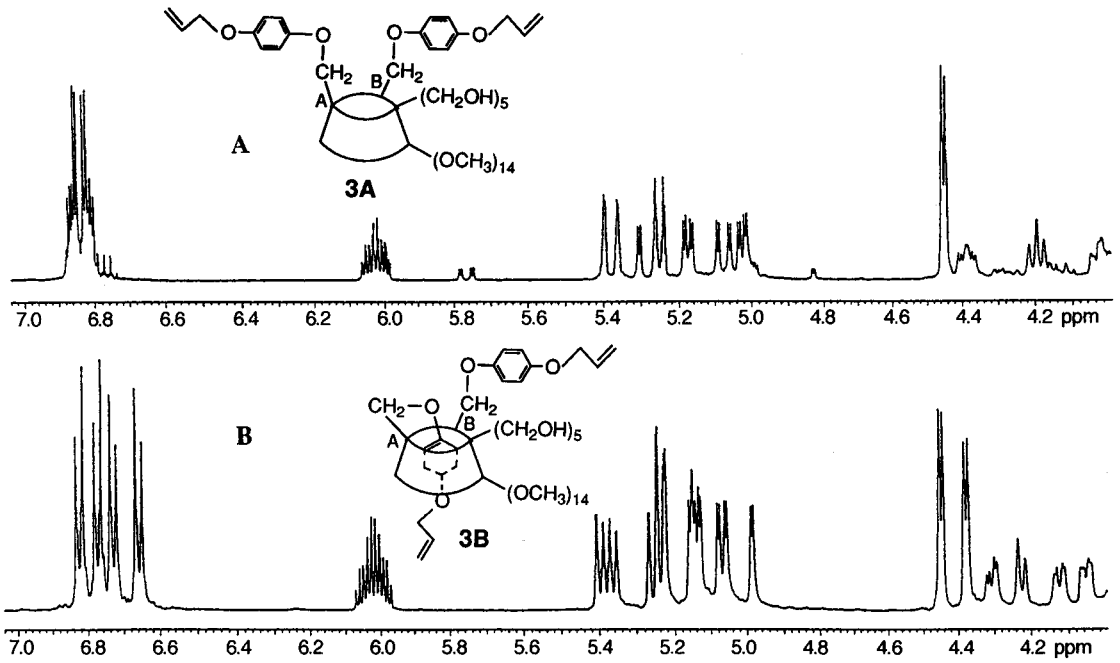

Figure 2. Partial ^{1}H NMR spectra of 6^A,6^B-bis-*O*-[*p*-(allyloxy)phenyl]heptakis(2,3-di-*O*-methyl)-β-cyclodextrins: (A) **3A** with two *p*-(allyloxy)phenyl substituents directed away from the cyclodextrin cavity; (B) **3B** with one *p*-(allyloxy)phenyl substituent in the cyclodextrin cavity.

and **3B**, were obtained in a ratio of **3A**:**3B** = 1:2 after careful separation by column chromatography. We believe that **3A** and **3B** are isomers with the structures shown in Scheme 1. **3A** has the structure with both (allyloxy)phenyl groups directed outside the cyclodextrin cavity, while **3B** has one (allyloxy)phenyl group in the cyclodextrin cavity to form an intramolecular complex. Although elemental and HRMS analyses show that **3A** and **3B** have the same composition, they exhibited very different physical and spectral properties. **3A** melted at 202 °C, while **3B** melted at 144 °C. The R_f value of **3A** is larger than that of **3B** when tested by thin-layer chromatography (TLC). This is because two (allyloxy)-phenyl groups outside the cyclodextrin hydrophobic cavity can decrease the polarity of the molecule to a greater extent than having only one outside (allyloxy)phenyl group.

The best evidence in support of the structures of **3A** and **3B** shown in Scheme 1 comes from ^{1}H NMR spectral studies. ^{1}H NMR spectroscopy is the most powerful tool for the study of inclusion complex formation between cyclodextrins and guest molecules. Generally, when the aromatic moiety of a guest molecule is included in the cyclodextrin cavity, protons located within the cavity (3-H and 5-H) are susceptible to anisotropic shielding by the aromatic moiety, and thus, an upfield shift will occur.[25] The aromatic proton resonances of the guest will also change upon inclusion. The ^{1}H NMR spectra of **3A** and **3B** are very complicated in the region of the cyclodextrin signals. This result suggests that the NMR environments of the seven glucose units are not equivalent and the cyclodextrin cavity shape is unsymmetrical, which is also indicated by the well-resolved anomeric proton signals at 4.9−5.3 ppm. Part of the ^{1}H NMR spectra of **3A** and **3B** are shown in Figure 2. The spectra of **3A** and **3B** differ mainly for the peaks at 6.6−6.9 ppm attributable to the aromatic hydrogen atoms of the two (allyloxy)phenyl substituents, the peaks at 4.9−5.5 ppm attributable to the anomeric cyclodextrin protons and the end vinyl protons of the allyl groups, the peaks at 4.44 ppm (one doublet for **3A**) and 4.36−4.46 ppm (two doublets for **3B**) attributable to the allyl protons. In fact, when the signals of the allyl groups of **3B** split into two pairs, one of them moves upfield compared with that of **3A** and native *p*-(allyloxy)phenol. Obviously, the two (allyloxy)phenyl substituents of **3B** are in different environments; one is outside the cyclodextrin cavity, whereas the other is inside. The signals for the aromatic protons of **3B** have separated into two sets of doublets typical of having two *p*-substituted benzene rings in different environments. One set of doublets at 6.71 ppm has moved upfield in comparison to the aromatic signals for **3A**. Indeed, Warner and co-workers[26] have shown that when epedrine is complexed with β-cyclodextrin, the aromatic proton resonances shift upfield with respect to their native chemical shifts. This is also in good agreement with the observations of Lehmann *et al.*,[27] who reported a remarkable shielding of the aromatic protons of D,L-1-phenylethanol and D,L-phenylalanine upon inclusion inside the β-cyclodextrin cavity.

^{13}C NMR spectroscopy can also be used to study the conformations of cyclodextrins and their derivatives. The ^{13}C resonances of the sugar moieties in **3A** and **3B** were assigned on the basis of the ^{13}C assignments for heptakis-(2,3-di-*O*-methyl)-β-cyclodextrin (**1**). The results of ^{13}C NMR spectral assignments for **3A** and **3B** are shown in Table 1 along with that of **1**[28] for comparison. Splitting of the ^{13}C NMR signals for **3A** and **3B** as compared to **1** are a result of unsymmetrical substitution. It is interest-

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Table 1. ^{13}C NMR Spectral Correlations for 1, 3A, and 3B[a]

	C-1	C-2, C-4	C-3	C-5	C-6, OCH_3	OCH_3
1	100.4	82.4, 83.1	81.4	73.7	62.1, 62.4	59.7
3A	99.38, 99.33	82.41, 82.32	80.95, 80.82	72.82	62.64, 62.34	59.42
	99.08, 99.03	82.12, 82.02	80.43, 80.68	72.46	62.27, 62.03	59.21
	98.97, 98.70	81.77, 81.72	79.31, 80.56	71.36	61.92, 61.80	58.99
	98.59	81.60	79.01	71.25	61.52, 68.38	58.88
3B	99.59	82.39, 82.21	80.79, 80.61	73.06	62.53, 62.46	59.44
	99.08	81.91, 81.74	79.97, 79.62	72.62	62.41, 62.05	59.25
	98.75		79.16	72.42	61.90, 61.78	59.00
	98.52			71.09	68.11, 67.83	58.78

[a] The numbering of carbon atoms in the cyclodextrin units is shown in Figure 1A.

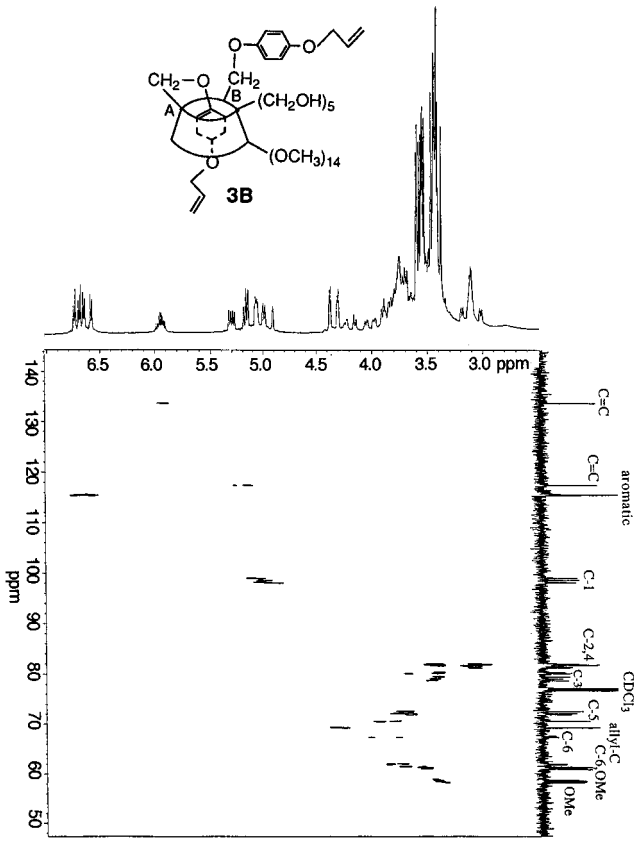

Figure 3. $^1H-^{13}C$ correlation spectrum of **3B**.

ing to note that, upon substitution, the C-6 ^{13}C NMR resonances of the two (allyloxy)phenyl-substituted sugar units in **3A** and **3B** change dramatically. For **3A**, one of the C-6 resonances moves from 62.1 to 68.38 ppm. For **3B**, the low-field C-6 resonance splits into two peaks at 68.11 and 67.83 ppm. In addition, the allyl carbon resonance of **3A** has one signal at 69.89 ppm, but for **3B**, the allyl carbon resonance splits into two signals at 69.82 and 69.61 ppm. These very different spectra indicate that the conformations of the two substituents in **3B** are different.

In order to assign the ^1H NMR spectral peaks of our new compounds, we obtained a two-dimensional $^1H-^{13}C$ correlation spectrum (HETCOR) for **3B**. This experiment yields responses that connect carbon peaks in one dimension to proton peaks in the other. The results are shown in Figure 3. From Figure 3, one can see that the small proton signals between 3.7 and 3.9 ppm are caused by protons on C-5 of the cyclodextrin and those around 4.0 ppm are on C-6. The partial two-dimensional $^1H-^1H$ correlation spectrum (ROESY) of **3B** is shown in Figure 4. Signals H_a and H_b are shifted upfield, which is caused by the benzene ring inside the cyclodextrin cavity. The key features of the spectrum are the crosspeak observed between H_a of the benzene and connecting 6-H of cyclodextrin and the crosspeak between H_a and 5-H of cyclodextrin. These correlations clearly suggest that the aromatic protons are in close proximity to 5-H (3-H signals are overlapped by those from $-OCH_3$ and cannot be distinguished) and strongly indicate that **3B** has the structure shown in Figure 4.

The reaction of $6^A,6^B$-bissulfonate ester with sodium *p*-(allyloxy)phenoxide is different from that of $6^A,6^C$- and $6^A,6^D$-bissulfonate esters. When treated with sodium *p*-(allyloxy)phenoxide in DMF, both $6^A,6^C$-bis-*O*-[*p*,*p*′-methylenebis(benzenesulfonyl)]heptakis(2,3-di-*O*-methyl)-β-cyclodextrin and $6^A,6^D$-bis-*O*-(*p*,*p*-biphenyldisulfonyl)-heptakis(2,3-di-*O*-methyl)-β-cyclodextrin give only one product.[18,19] Part of the ^1H NMR spectra for $6^A,6^C$- and $6^A,6^D$-bis-*O*-[*p*-(allyloxy)phenyl]heptakis(2,3-di-*O*-methyl)-β-cyclodextrin isomers are shown in Figure 5. It is instructive to note that the partial ^1H NMR spectrum of the $6^A,6^D$-isomer[19] is nearly the same as that of **3A**, indicating that the (allyloxy)phenyl groups of those two compounds are in the same conformational environments. On the other hand, the ^1H NMR spectrum of the $6^A,6^C$-isomer is much more complex. We now believe that the $6^A,6^C$-product is a mixture of two isomers, one isomer with both (allyloxy)phenyl groups outside the cyclodextrin cavity and the other with one (allyloxy)phenyl group inside the cavity. Unfortunately, the supposed two isomers of the $6^A,6^C$ product could not be separated.[18]

When either **3A** or **3B** was treated with methyl iodide and sodium hydride, the resulting permethylated **4** was composed of two isomers (Scheme 1). In each case, **4A** was the main product. The ^1H NMR spectra for **4A** (mp 100 °C) and **4B** (mp 95 °C) were similar to those of **3A** and **3B**, respectively. We believe that **4A** has the two *p*-(allyloxy)phenyl groups outside the cavity and **4B** has one inside and one outside the cavity as shown. All four compounds, **3A**, **3B**, **4A**, and **4B**, are stable at high temperatures. However, when stirred in base solution, pure **3A** or pure **3B** isomerized to a mixture of **3A** and **3B**, but **4A** and **4B** do not (this result was confirmed by TLC). A molecular modeling study of these systems suggests that, when deprotonated, the individual glucose units of cyclodextrin can rotate about their glycosidic oxygen atoms. When the rotating glycose unit contains the *p*-(allyloxy)phenyl substituent, this rotation would cause **3A** or **3B** to convert to the other isomer. This conclusion resulted from the observation that, during molecular dynamics (MD) simulations, **3B** converted to **3A** due to rotations of a *p*-(allyloxy)phenyl glucose unit. Such a rotation presumably could also cause **3A** to convert back to **3B**, but we did not carry out the MD simulations long enough to observe this conversion. Calculations of the total energy of the system as a glucose

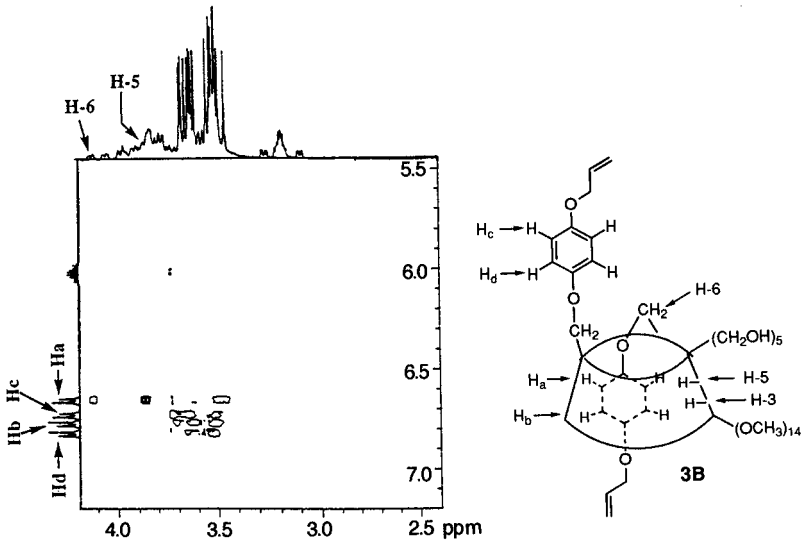

Figure 4. Partial $^1H-^1H$ correlation spectrum of **3B**.

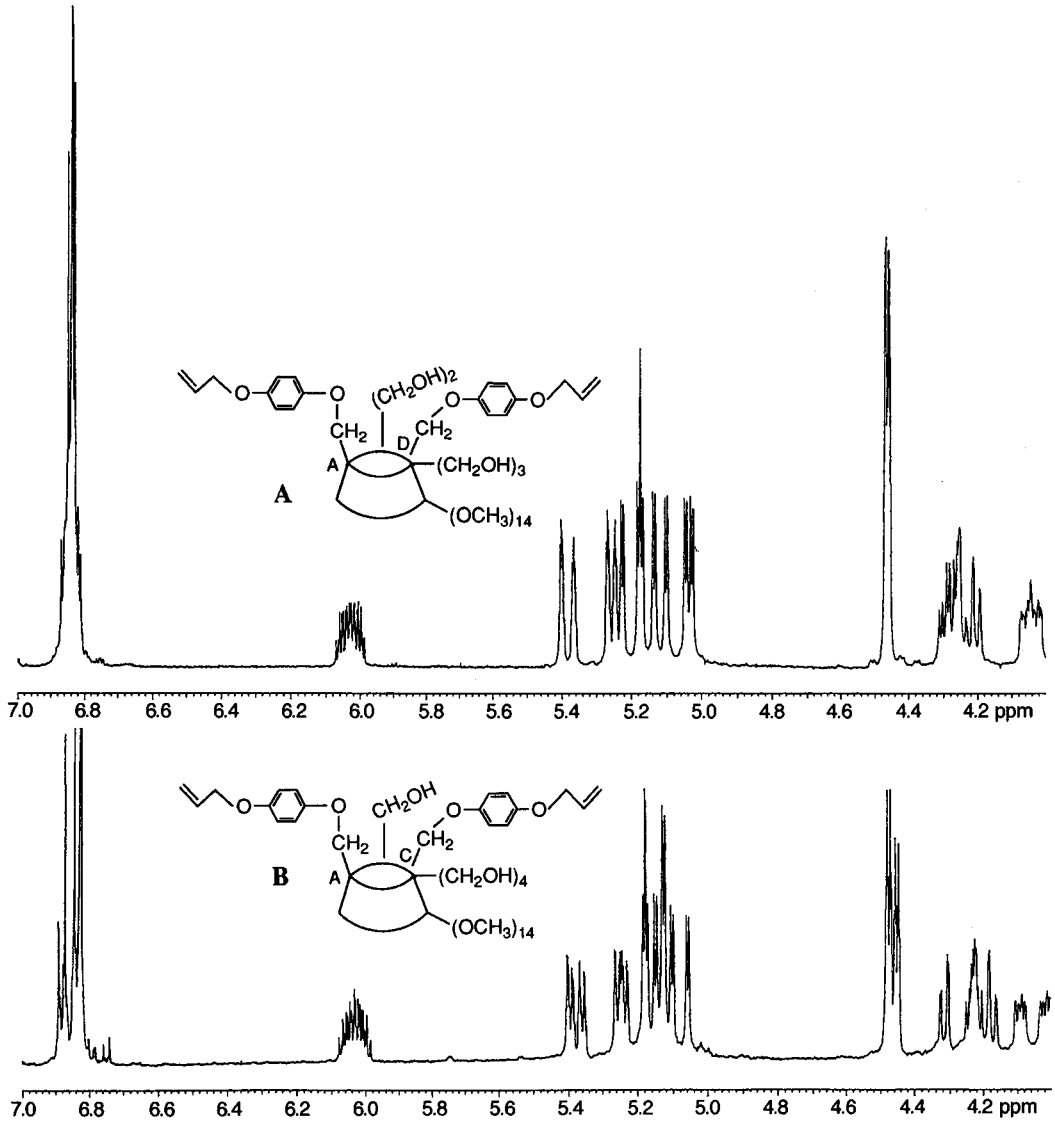

Figure 5. Partial ^1H NMR spectra of (A) $6^A,6^D$- and (B) $6^A,6^C$-bis-*O*-[*p*-(allyloxy)phenyl]heptakis(2,3-di-*O*-methyl)-β-cyclodextrin.[18,19]

unit rotates about its glycosidic oxygen atoms showed that the barrier to rotation is lower for the deprotonated molecules than for the protonated form. Further calculations showed that the methoxy-substituted (permethylated) molecules (like **4A** and **4B**) have higher barriers to rotation than the unsubstituted molecules (like **3A** and **3B**). Thus, addition of base (which causes deprotonation of the unsubstituted hydroxyl groups) could lead to

equilibration between the deprotonated forms of **3A** and **3B** but not between the permethylated **4A** and **4B**. (See "Computational methodology" in the Experimental Section for more details.)

Dialkene-substituted permethylated cyclodextrins **4A** and **4B** were treated with 1,1,3,3,5,5,7,7,9,9,11,11-dodecamethylhexasiloxane (with Si−H functions on each end) and enough 1-octene to control the molecular weight, using a platinum catalyst as reported for similar systems[19] to form two new copolymers.[22] The ^{1}H NMR spectra of these polymers showed that they were different from each other and that the polymer from **4B** probably had a benzene ring in the cyclodextrin cavity. Polyrotoxanes, in which many cyclodextrins are threaded on a single polymer chain and are trapped by capping the chain ends with bulky groups, have been reported.[29,30] To the best of our knowledge, the polymer from **4B** is the first polyrotoxane in which the cyclodextrin is part of the polymer chain. These polymers were coated on fused silica capillaries and evaluated as stationary phases in GC.[22] The polymer from **4A** separated both enantiomeric hydrocarbons and polar solutes, but the rotoxane polymer from **4B** separated only the polar solutes. This latter result strongly suggests that a benzene ring of the polymer is indeed in the cyclodextrin cavity. These chromatography results have recently been reported.[22]

Conclusions

We have synthesized and characterized a novel self-inclusion complex **3B**, which was derived from β-cyclodextrin. **4B**, the permethylated form of **3B**, is also believed to be a self-inclusion complex on the basis of its ^{1}H NMR spectrum, which is similar to that of **3B**, and the fact that a polysiloxane stationary phase produced from **4B** does not separate the enantiomers of chiral hydrocarbons.[22]

Experimental Section

Proton and carbon NMR spectra were recorded in $CDCl_3$ on 200 or 500 MHz spectrometers. TLC analysis was performed on aluminum-backed silica gel 60, 0.2-mm plates. Pyridine was purified by stirring over CaH_2 powder for 10 h followed by distillation. Heptakis(2,3-di-*O*-methyl)-β-cyclodextrin (**1**)[18] and 2,4-dimethoxybenzene-1,5-disulfonyl chloride[24] were prepared as reported.

6^A,6^B-Bis-*O*-(2′,4′-dimethoxybenzene-1′,5′-disulfonyl)-heptakis(2,3-di-*O*-methyl)-β-cyclodextrin (2) (Scheme 1). To a stirred solution of **1** (10.65 g, 8 mmol) in 500 mL of dry pyridine was added a solution of 2,4-dimethoxybenzene-1,5-disulfonyl chloride (2.68 g, 8 mmol) in 100 mL of dry pyridine over 1 h at rt. The mixture was stirred at 40 °C for 3.6 h. Pyridine was removed by vacuum distillation (0.2 mm, rt). The residue was partitioned between $CHCl_3$ and water. The organic layer was separated, dried, and concentrated. Column chromatography on silica gel ($CHCl_3$:CH_3OH/15:1) of the crude product gave 0.45 g (3.5%) of **2**: mp 167−168 °C; $[\alpha]^{25}_D$ = 131.3° (*c* 1.12, $CHCl_3$); ^{1}H NMR δ 8.35 (s, 1 H), 6.58 (s, 1 H), 5.29−4.98 (m, 7 H), 4.50 (m, 4 H), 4.07 (s, 3 H), 4.04 (s, 3 H), 4.00−2.98 (m, 80 H), 2.60 (broad s, 5 H); ^{13}C NMR δ 164.8, 163.8, 128.6, 128.3, 128.2, 117.1,115.0, 100.3, 99.4, 99.2, 98.8, 98.7, 98.5, 82.6, 82.5, 82.3, 82.2, 82.0, 81.8, 81.6, 81.4, 81.3, 81.0, 80.9, 80.8, 80.7, 80.4, 79.5, 79.4, 79.2, 73.2, 73.1, 72.8, 72.7, 72.6, 72.4, 71.0, 69.6, 69.5, 62.4, 62.2, 62.0, 61.9, 61.6, 61.3, 59.7, 59.2, 58.9, 58.8, 58.7, 58.6. Anal. Calcd for $C_{64}H_{104}O_{41}S_2$: C, 48.24; H, 6.58. Found: C, 48.38; H, 6.41.

6^A,6^B-Bis-*O*-[*p*-(allyloxy)phenyl]heptakis(2,3-di-*O*-methyl)-β-cyclodextrin (3) (Scheme 1). A solution of **2** (1.00 g, 0.63 mmol) in 20 mL of DMF was stirred with sodium *p*-(allyloxy)phenoxide (0.93 g, 6.27 mmol) at rt for 24 h and concentrated under reduced pressure. The residue was partitioned between $CHCl_3$ and water. The organic layer was separated, dried, and concentrated. The crude product was subjected to column chromatography on silica gel ($CHCl_3$:CH_3OH/20:1) to give 0.18 g (18%) of **3A** and 0.39 g (39%) of **3B**. The properties of **3A** are as follows: mp 202−203 °C; $[\alpha]^{25}_D$ = 142.0° (*c* 1.11, $CHCl_3$); ^{1}H NMR δ 6.93−6.78 (m, 8 H), 6.03 (m, 2 H), 5.47−4.97 (m, 11 H), 4.47 (d, J = 5.15 Hz, 4 H), 4.38−3.36 (m, 77 H), 3.31−3.04 (m, 7 H), 2.82 (broad s, 5 H); ^{13}C NMR δ 134.0, 118.0, 116.2, 99.38, 99.33, 99.08, 99.03, 98.97, 98.70, 98.59, 82.41, 82.32, 82.12, 82.02, 81.77, 81.72, 81.60, 80.95, 80.82, 80.43, 80.68, 79.31, 80.56, 79.01, 72.82, 72.46, 71.36, 71.25, 69.89, 68.38, 62.64, 62.34, 62.27, 62.03, 61.92, 61.80, 61.52, 59.42, 59.21, 58.99, 58.88; HRMS (FAB) calcd for $C_{74}H_{114}O_{37}$ 1594.7039, found 1594.7076. Anal. Calcd for $C_{74}H_{114}O_{37}$: C, 55.70; H, 7.20. Found: C, 55.60; H, 7.29. The properties of **3B** are as follows: mp 144−146 °C; $[\alpha]^{25}_D$ = 142.1° (*c* 1.24, $CHCl_3$); ^{1}H NMR δ 6.83−6.57 (m, 8 H), 6.02 (m, 2 H), 5.46−4.90 (m, 11 H), 4.45 (d, J = 5.19 Hz, 2 H), 4.38 (d, J = 5.19 Hz, 2 H), 4.30−3.30 (m, 77 H), 3.30−3.00 (m, 7 H), 2.80 (broad s, 5 H); ^{13}C NMR δ 134.0, 117.9, 117.8, 116.0, 115.9, 99.59, 99.08, 98.75, 98.52, 82.39, 82.21, 81.91, 81.74, 80.79, 90.61, 79.97, 79.62, 79.16, 73.06, 72.62, 72.42, 71.09, 69.82, 69.61, 62.53, 62.46, 62.41, 62.05, 61.90, 61.78, 68.11, 67.83, 59.44, 59.25, 59.00, 58.78; HRMS (FAB) calcd for $C_{74}H_{114}O_{37}$ 1594.7039, found 1594.7031. Anal. Calcd for $C_{74}H_{114}O_{37}$: C, 55.70; H, 7.20. Found: C, 55.80, H, 7.21.

Stability of 3A and 3B. 3A and **3B** were each subjected to 250 °C in a sealed tube. The melting points of the cooled samples were the same as for the initial pure samples. When 10 mg of either **3A** or **3B** was reacted with 2,6-di-*tert*-butyl-4-pyridine in CH_2Cl_2 in a sealed tube at 80 °C for 2 h, or stirred with NaH in DMF at rt, each was converted into a mixture of **3A** and **3B**.

6^A,6^B-Bis-*O*-[*p*-(allyloxy)phenyl]heptakis(2,3-di-*O*-methyl)-6^C,6^D,6^E,6^F,6^G-penta-*O*-methyl-β-cyclodextrin (4) (Scheme 1). A mixture of **3** (0.10 g, 0.063 mmol) and 23 mg (0.945 mmol) of NaH in 10 mL of dry DMF was stirred for 2 h at rt. Then 134 mg of CH_3I was added dropwise. The whole system was stirred overnight at rt. After concentration, the residue was partitioned between 100 mL of $CHCl_3$ and 10 mL of H_2O. The organic layer was washed succesively with 10 mL of a 1% aqueous solution of $Na_2S_2O_3$ and 10 mL of H_2O and then dried and concentrated. The crude product was purified by column chromatography on silica gel ($CHCl_3$:CH_3OH/80:1) to give **4A** (61 mg, 58%) and **4B** (23 mg, 22%). The properties of **4A** are as follows: mp 98−100 °C; $[\alpha]^{25}_D$ = 132.9° (*c* 1.23, $CHCl_3$); ^{1}H NMR δ 6.88−6.60 (m, 8 H), 6.00 (m, 2 H), 5.44−5.00 (m, 11 H), 4.45 (d, J = 5.19 Hz, 4 H), 4.27−3.00 (m, 99 H); ^{13}C NMR δ 153.4, 133.9, 118.0, 117.9, 116.0, 99.6, 99.5, 99.4, 99.3, 82.8, 82.3, 82.0, 80.9, 80.8, 80.7, 72.2, 71.9, 71.8, 71.6, 71.5, 71.4, 71.2, 69.9, 69.8, 69.6, 62.0, 61.8, 59.4, 59.3, 59.0, 58.9. Anal. Calcd for $C_{79}H_{124}O_{37}$: C, 56.96; H, 7.50. Found: C, 56.84; H, 7.65. The properties of **4B** are as follows: mp 95−96 °C; $[\alpha]^{25}_D$ = 133.1° (*c* 0.60, $CHCl_3$); ^{1}H NMR δ 6.91−6.60 (m, 8 H), 6.02 (m, 2 H), 5.46−4.98 (m, 11 H), 4.47 (d, J = 5.31 Hz, 2 H), 4.42−4.30 (m, 2 H), 4.30−3.10 (m, 99 H); ^{13}C δ NMR 153.4, 133.9, 117.9, 115.9, 99.7, 99.5, 99.3, 82.5, 82.3, 81.3, 80.7, 71.7, 71.5, 71.4, 71.0, 69.8, 69.7, 62.1, 62.0, 61.9, 61.8, 59.6, 59.5, 59.4, 59.3, 59.2, 59.1, 58.9, 58.8. Anal. Calcd for $C_{79}H_{124}O_{37}$: C, 56.96; H, 7.50. Found: C, 57.16; H, 7.68.

Computational Methodology. Molecular modeling calculations were performed using Biosym Insight II version 2.3 with the CVFF forcefield of Discover version 2.9 and executed on a Silicon Graphics Indigo workstation. The initial geometry of β-cyclodextrin was taken from the X-ray crystal structure.[31]

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Target compounds were constructed by connecting the proper residues with β-cyclodextrin and then minimizing the total conformational energy of the resulting structure using conjugate gradient methods. All complexes were created by moving the previously geometry-optimized substrate into the cavity of the cyclodextrin-based compounds. The global minimum conformation of complexes were searched by using molecular dynamics and minimized by conjugate gradient methods until the maximum derivative was less than 0.01 kcal/mol. Although it is impossible to prove that the global minimum of each complex was found, the search of conformation space was extensive, with all molecular geometries being allowed to vary during MD simulations and minimization. We have successfuly used similar methodologies on other cyclodextrin systems.[32]

Static measurements of cavity size and pendent arm length indicate that movement of arms into or out of the cavity by pivoting around their attachment point to the cyclodextrin ring is highly unlikely. However, during MD simulations at 1000 K, the conformation with *p*-(allyloxy)phenyl groups in the cavity converted to the conformation with the group outside the cavity by means of rotation of the glucose unit to which the *p*-(allyloxy)phenyl group was attached. This rotation of the glucose unit was systematically explored using a model system in which the *p*-(allyloxy)phenyl group was replaced by a phenoxy group. The phenoxy-substituted glucose unit was rotated in 10-degree increments around its glycosidic oxygens. At each increment, the rotation was constrained and the system partially relaxed through energy minimization. The resultant energies were used to calculate the approximate rotational energy barriers for rotating the phenoxy-substituted glucose unit. This technique was applied to three cyclodextrin systems: 6′-methoxy-substituted cyclodextrin, 6′-hydroxy-substituted cyclodextrin, and 6′-deprotonated hydroxy-substituted cyclodextrin. The barrier of rotation was lower in the deprotonated hydroxy-substituted system by 7.4 kcal/mol compared to the hydroxy-substituted system and by 6.2 kcal/mol compared to the methoxy-substituted system, suggesting a higher probablility of rotation in the deprotonated hydroxy-substituted system. This is readily understood by considering that rotation in the methoxy-substituted system is hindered by steric interference with the methoxy groups and that rotation in the hydroxy-substituted system is hindered by the hydroxy group participating in hydrogen bonding. The deprotonated system lacks both of these hindrances.

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