A Built-in Route Leading to a Self-inclusion Complex of $6^A,6^B$-(Bis-*O*-*p*-allyloxyphenyl)hexakis(2,3-di-*O*-methyl)-α-cyclodextrin

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Hexakis(2,3-di-*O*-methyl)-α-cyclodextrin was treated with 2,4-dimethoxybenzene-1,5-disulfonyl chloride to give $6^A,6^B$-di-*O*-sulfonated product **5** in only a 3.0% yield. When treated with sodium *p*-allyloxyphenoxide, **5** gave $6^A,6^B$-(bis-*O*-*p*-allyloxyphenyl)hexakis(2,3-di-*O*-methyl)-α-cyclodextrin (**6**) in a 57% yield. A careful ^{1}H nmr analysis of **6** shows that one of the allyloxphenyl groups is in the α-cyclodextrin cavity. This is the first intramolecular complex formed from a modified α-cyclodextrin. Molecular modeling was used to explain the experimental facts. A novel *built-in* route leading to a self-inclusion α-cyclodextrin complex is proposed for this reaction.

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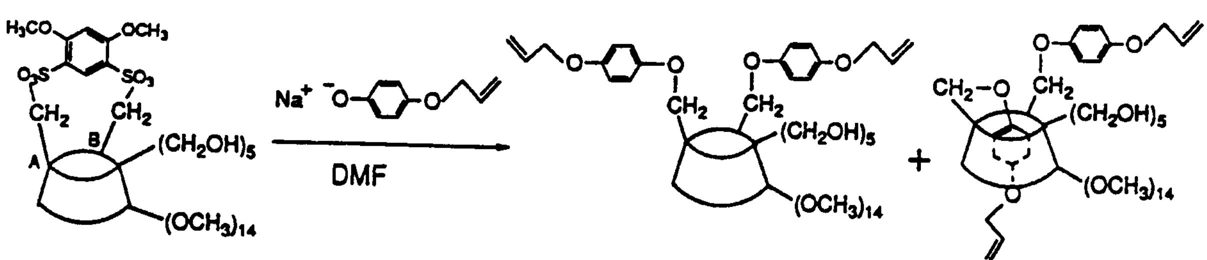
Cyclodextrins are cyclic oligosaccharides obtained from starch by enzymatic degradation [1]. The three best characterized forms are α, β, and γ-cyclodextrins consisting of 6, 7, and 8 D-glucose units, respectively. Cyclodextrins are very popular building blocks for supramolecular structures [2,3], and their derivatives are widely used in analytical chemistry [4], especially for the purpose of chiral discrimination [5]. There are numerous studies of the intermolecular complexes of the cyclodextrins. In some cases, a modified cyclodextrin to which an aromatic moiety is attached through a flexible arm can include its aromatic moiety to form an intramolecular complex. Several intramolecular complexes formed by modified β-cyclodextrin have been reported [6,7]. In a recent paper [8], we reported that when $6^A,6^B$-bis-*O*-(2',4'-dimethoxybenzene-1',5'-disulfonyl)heptakis(2,3-di-*O*-methyl)-β-cyclodextrin (**1**) was treated with sodium *p*-allyloxyphenoxide in *N*,*N*-dimethylformamide, two products were formed. One, compound **2**, has the two *p*-allyloxyphenyl arms directed away from the cyclodextrin cavity and the other, **3**, has one of the *p*-allyloxyphenyl groups through the cavity to form a self-inclusion complex (Scheme 1). Detailed 1D and 2D nmr spectroscopic studies were carried out to characterize the structures of **2** and **3**. We decided to prepare $6^A,6^B$-bis-*O*-(2',4'-dimethoxybenzene-1',5'-disulfonyl)hex- akis(2,3-di-*O*-methyl)-α-cyclodextrin (**5**) (Scheme 2) to see if it would also produce a self-inclusion complex upon reaction with the *p*-allyloxyphenoxide ion. Interestingly, when **5** was treated with sodium *p*-allyloxyphenoxide only the intramolecular self-inclusion complex was produced.

Hexakis(2,3-di-*O*-methyl)-α-cyclodextrin (**4**) was prepared as reported [9] (Scheme 2). The key intermediate, $6^A,6^B$-bis-*O*-(2',4'-dimethoxybenzene-1',5'-disulfonyl)-hexakis(2,3-di-*O*-methyl)-α-cyclodextrin (**5**) was prepared by treating **4** with 2,4-dimethoxybenzene-1,5-disulfonyl chloride [10] in dry pyridine at 40° for 4 hours. After purification by column chromatography, **5** was obtained in a yield of only 3.0%. $6^A,6^B$-Bissulfonate ester **5** was treated with sodium *p*-allyloxyphenoxide in *N*,*N*-dimethylformamide to yield $6^A,6^B$-(bis-*O*-*p*-allyloxyphenyl)hexakis(2,3-di-*O*-methyl)-α-cyclodextrin (**6**), the first intramolecular complex formed by a modified α-cyclodextrin.

Scheme 1

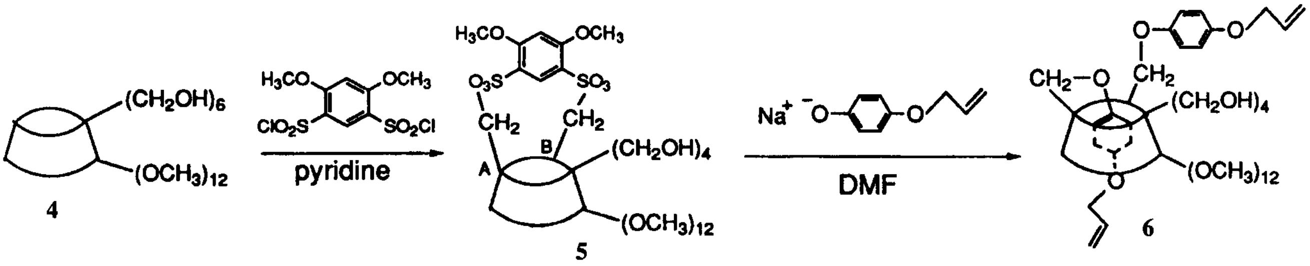
The Reaction of the $6^A,6^B$-Bissulfonate Ester of β-Cyclodextrin (**1**) with *p*-Allyloxyphenoxide Ion



1 **2** **3**

Scheme 2

Preparation of 6^A,6^B-(Bis-*O*-*p*-allyloxyphenyl)hexakis(2,3-di-*O*-methyl)-α-cyclodextrin (**6**)



The proposed structure of **6** is based on nmr spectral studies. Spectroscopy (^{1}H nmr) 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 within the cavity (H3 and H5) are susceptible to anisotropic shielding by the aromatic moiety, and thus an upfield shift will occur [11]. The aromatic proton resonances of the guest will also change upon inclusion. The ^{1}H nmr spectrum of **6** was so complicated at the cyclodextrin signals that each signal could not be assigned to individual protons. This result suggests that the nmr environment of the six glucose units are not equivalent, which is also indicated by the well-resolved anomeric proton signals (4.9-5.5 ppm). Part of the ^{1}H nmr spectrum of **6** along with spectra for the comparable

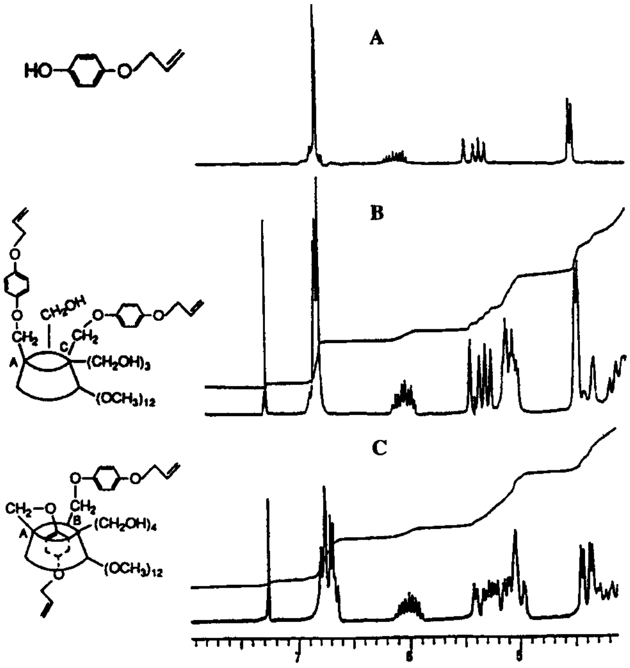


Figure 1. Partial ^{1}H nmr spectra of **A**, *p*-allyloxyphenol, **B**, 6^A,6^C-bis-*O*-(*p*-allyloxyphenyl)hexakis(2,3-di-*O*-methyl)-α-cyclodextrin (**7**) [9], and **C**, 6^A,6^B-bis-*O*-(*p*-allyloxyphenyl)hexakis(2,3-di-*O*-methyl)-α-cyclodextrin (**6**).

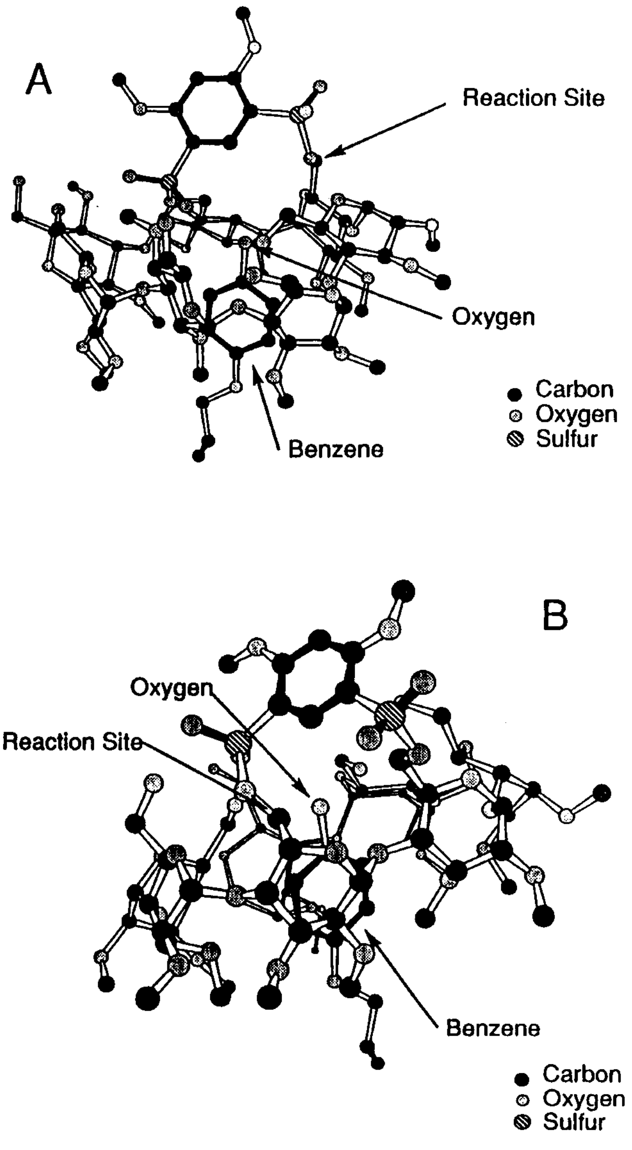


Figure 2. Computer-generated stereo views of **A**, the complex formed by β-cyclodextrin **1** with *p*-allyloxyphenoxide ion and **B**, the complexes formed by α-cyclodextrin **4** with *p*-allyloxyphenoxide ion. The hydrogen atoms are omitted.

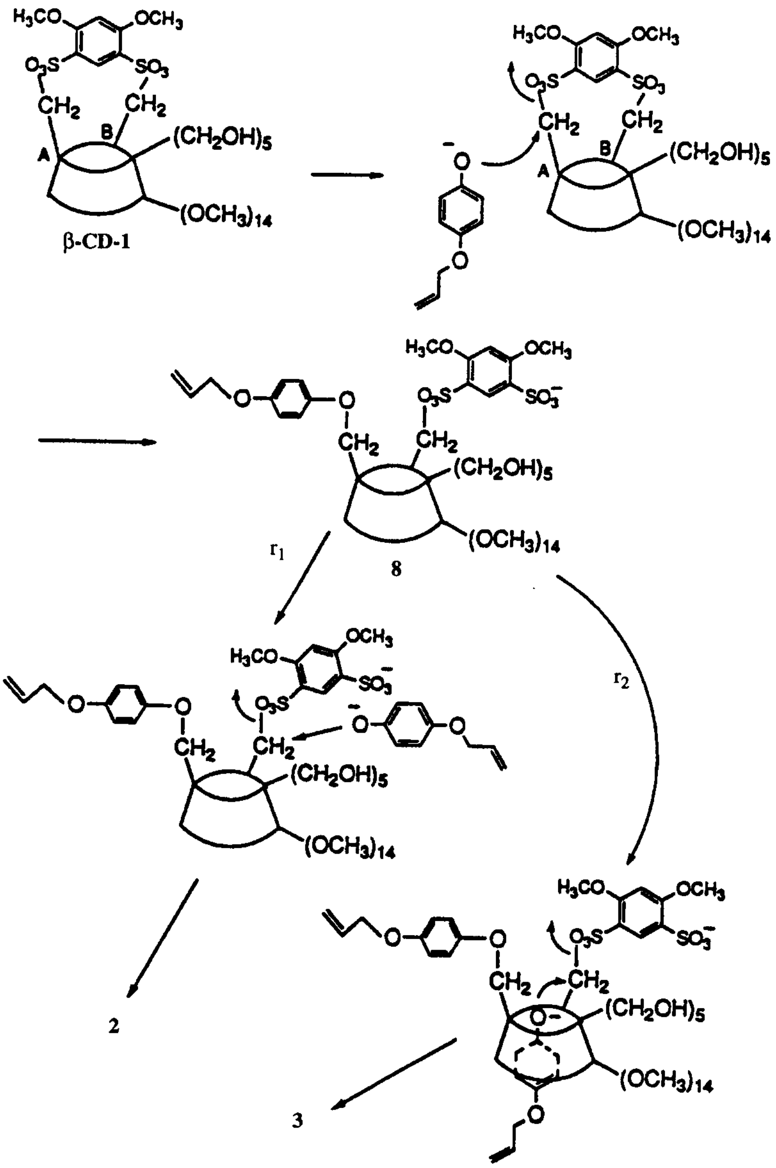


Figure 3. The proposed mechanism of reaction between the $6^A,6^B$-bissulfonate ester of β-cyclodextrin (1) with *p*-allyloxyphenoxide ion.

$6^A,6^C$-bis-*O*-(*p*-allyloxyphenyl)hexakis(2,3-di-*O*-methyl)-α-cyclodextrin (**7**) [9] and native *p*-allyloxyphenol are shown in Figure 1. The spectra of **6** and **7** differ mainly in the peaks at 6.6-6.9 ppm attributable to the aromatic hydrogen atoms of the two allyloxyphenyl 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 **7**) and 4.32-4.45 ppm (two doublets for **6**) attributable to the allyl protons. In fact, the signals of the allyl protons and aromatic protons of **6** split into two pairs, one of which moves upfield compared with that of **7** and native *p*-allyloxyphenol. From the characteristic resonances of phenyl and allyl protons, as we discussed before, for the similar $6^A,6^B$-bis-*O*-*p*-allyloxyphenyl substituted β-cyclodextrin derivatives **2** and **3** [8], we conclude that for $6^A,6^C$-bis-*O*-(*p*-allyloxyphenyl)hexakis(2,3-di-*O*-methyl)-α-cyclodextrin (**7**) [9], the two allyloxyphenyl substituents are in the same environment and both outside the α-cyclodextrin cavity. For compound **6**, one substituent is outside the cyclodextrin cavity while the other is inside the cavity.

Molecular modeling has been used to explain why **4** reacted with sodium *p*-allyloxyphenoxide to give only the intramolecular complex **6** and **1** gave two products [8]. The optimized structures of the complexes formed by compounds **1** and **4** with the *p*-allyloxyphenoxide ion (the allyloxyphenoxide ion is in the cyclodextrin cavity in each case) are shown in Figure 2. From these structures,

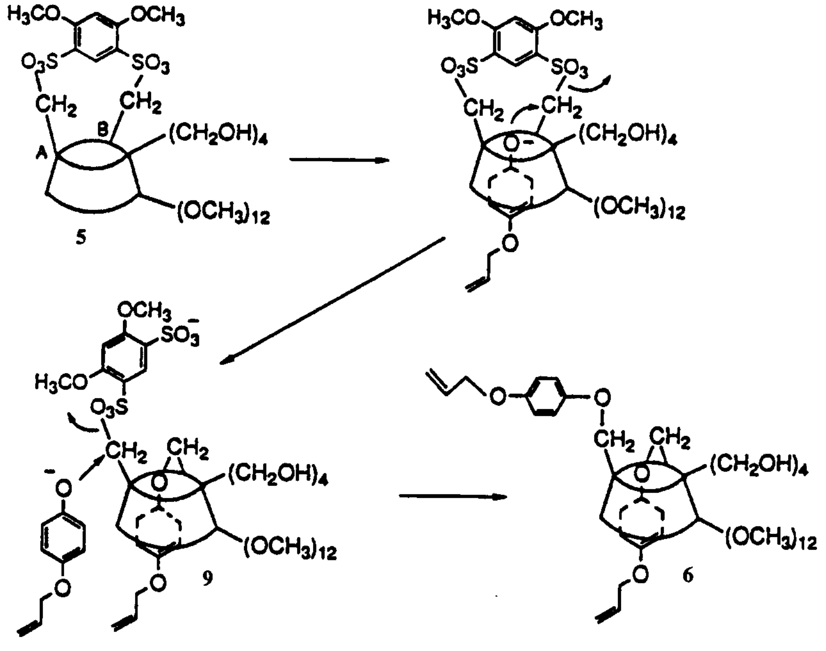


Figure 4. The proposed mechanism of reaction between the $6^A,6^B$-bissulfonate ester of α-cyclodextrin (**5**) with *p*-allyloxyphenoxide ion.

we can see that activated 6-CH_2 positions in β-cyclodextrin **1** are open to outside nucleophilic attack, and are relatively far from the phenoxide nucleophile inside the cavity. Thus, the first nucleophilic attack would happen from outside to form intermediate **8** (Figure 3). Molecular modeling was also performed to determine energies for the free *p*-allyloxyphenoxide ion and for various complexes of **1** and **8** with one *p*-allyloxyphenoxide ion. These results indicate that movement of the phenoxide ion from an infinite distance to inside the cyclodextrin cavity is more favorable for **8**, which already has one external *p*-allylphenyl group attached, than for **1**, by about 14 kcal/mol. From **8**, two different routes, r_1 and r_2, for the second attack exist. These two routes lead to the formation of **2** and **3**, respectively (Figure 3). Since r_2 is energetically more favorable, **3** was the major product. However, in the case of α-cyclodextrin, the activated 6-CH_2 positions are blocked by other 6-CH_2OH groups towards outside attack and are compressed to the inner cavity (Figure 2). The complex of **4** with the phenoxide has the phenoxide oxygen atom in position to attack one of the 6-CH_2 groups containing a sulfonate group as shown in Figure 2B. Thus, the first substitution happens inside the cavity to form intermediate **9** with the second substitution from the outside to produce **6** as the only product (Figure 4).

In a recent paper concerning the conformational behavior of perfunctionalized β-cyclodextrins, Lehn and coworkers [12] demonstrated that sterically hindered cyclodextrins bearing aromatic units of a size compatible with the cyclodextrin cavity and linked to the cyclodextrin core by ester groups, such as heptakis[6-*O*-(6'-methoxy-2'-naphthoyl)-2,3-di-*O*-benzyl]-β-cyclodextrin may exhibit conformational isomerism. The nature of this conformational isomerism is an equilibrium between a C_7 symmetrical form where all substituents in the 6-position are disposed on the outer side of the primary cyclodextrin rim and a C_1 symmetrical form where one of the 6-substituents is located inside the cyclodextrin cavity. The authors named the equilibrium a *self-satisfaction* or *auto-complexation* process, which is more entropically favorable than an intermolecular association. This model is suitable to other self-inclusion complexes [6,7] derived from cyclodextrins, but not to our compounds **3** and **6**. Our results demonstrate that, in addition to *auto-complexation* or *self-inclusion*, another model leading to self-inclusion exists. Our results show that self-inclusion complexes $6^A,6^B$-bis-*O*-(*p*-allyloxyphenyl)-substituted β- and α-cyclodextrins **3** and **6** are formed by nucleophilic attack from inside the cyclodextrin cavity. We call this a *built-in* inclusion process. Combined with the results from Lehn's group, we can conclude that for cyclodextrin derivatives which bear aromatic units of a size compatible with the cyclodextrin cavity, self-inclusion is not an unusual phenomena. It is important to consider this point when designing novel cyclodextrin-based molecular devices, especially if the intended process would be disrupted by self-inclusion.

EXPERIMENTAL

Proton and carbon nmr spectra were recorded on a 200 MHz spectrometer. Pyridine was refluxed over calcium hydride powder overnight and then distilled before use. Hexakis(2,3-di-*O*-methyl)-α-cyclodextrin was prepared as reported [9].

$6^A,6^B$-Bis-*O*-(2',4'-dimethoxybenzene-1',5'-disulfonyl)hexakis(2,3-di-*O*-methyl)-α-cyclodextrin (**5**).

A solution of hexakis(2,3-di-*O*-methyl)-α-cyclodextrin (7.21 g, 6.32 mmoles) in 600 ml of dry pyridine was heated under nitrogen and 50 ml of the pyridine was distilled to remove traces of water. The solution was cooled to 40°, and 4,6-dimethoxybenzene-1,3-disulfonyl dichloride (2.11 g, 6.30 mmoles) was added in one portion. The mixture was stirred at 40° for 4 hours, then pyridine was removed under vacuum (0.2 mm, T <40°). The residue was partitioned between chloroform and water. The organic layer was separated, dried, and concentrated. The residue was subjected to column chromatography (silica gel, chloroform:methanol/15:1) to give 0.28 g (3.2%) of **5**, mp 172° dec; ^{1}H nmr (deuteriochloroform): 8.35 (s, 1H), 6.55 (s, 1H), 5.20-4.90 (m, 6H), 4.30-3.10 (m, 82H); ^{13}C nmr: 164.9, 163.8, 137.5, 116.8, 114.6, 100.4, 100.3, 100.0, 99.9, 99.8, 99.7, 83.3, 83.2, 83.1, 82.7, 82.6, 82.4, 82.2, 81.9, 81.8, 81.7, 81.6, 81.2, 73.3, 73.2, 73.0, 72.9, 70.8, 70.7, 70.6, 69.6, 69.5, 62.5, 62.4, 62.2, 62.1, 58.7, 58.5, 58.4, 58.3, 57.7, 57.6.

Anal. Calcd. For $C_{56}O_{36}H_{90}S_2 \cdot 4H_2O$: C, 45.59; H, 6.69. Found: C, 45.21; H, 6.56.

$6^A,6^B$-Bis-*O*-(*p*-allyloxyphenyl)hexakis(2,3-di-*O*-methyl)-α-cyclodextrin (**6**).

A solution of *p*-allyloxyphenol (225 mg, 1.5 mmoles) and 36 mg (1.5 mmoles) of sodium hydride in 10 ml of tetrahydrofuran was refluxed for 30 minutes. A solid formed after concentration and this was added to a solution of 0.21 g (0.15 mmole) of **5** dissolved in 10 ml of *N,N*-dimethylformamide. The above solution was stirred at ambient temperature overnight. After concentration, the residue was partitioned between 100 ml of chloroform and 10 ml of water. The crude product was subject to column chromatography (silica gel, chloroform:methanol/15:1) to give 0.12 g (57%) of **6**, mp 125-128°; ^{1}H nmr (deuteriochloroform): 6.90-6.60 (m, 8H), 6.10-5.90 (m, 2H), 5.45-4.90 (m, 14H), 4.50-3.0 (m, 76H); ^{13}C nmr: 153.5, 153.2, 153.0, 133.9, 118.0, 117.9, 116.0, 115.9, 115.8, 100.2, 99.9, 99.7, 99.3, 83.1, 82.97, 82.91, 82.8, 82.5, 82.4, 82.2, 82.0, 81.8, 81.2, 74.0, 73.5, 73.1, 72.8, 71.4, 69.8, 69.7, 69.6, 68.5, 63.4, 63.0, 62.34, 62.21, 61.9, 59.08, 59.02, 58.64, 58.5, 58.4, 58.3.

Anal. Calcd. for $C_{66}O_{32}H_{100}$: C, 56.40; H, 7.17. Found: C, 56.40; H, 6.93.

Computational Methodology.

For the optimized structures of the complexes formed by compounds **1** and **4** with the *p*-allyloxyphenoxide ion (the allyloxyphenoxide ion is in the cyclodextrin cavity in each case), CAChe version 3.7 was used for computer modeling. MM2 parameters were used for optimization.

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