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Regioselectivity of the insertion reactions of some aromatic diazo compound complexes with cyclomaltoheptaose

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ABSTRACT

Pyrolysis of solid complexes of aromatic diazo compounds with cyclomaltoheptaose (β-cyclodextrin) yields ether derivatives via insertion of carbene into hydroxyl groups. The distribution of the 2-, 3-, and 6-*O*-isomers indicates that the regioselectivity is moderate. The guest geometry is not as important as its size in determining the ratios of regioisomers. The origins of the regioselectivity are discussed.

INTRODUCTION

The chemical modification of cyclomalto-oligosacchardes (cyclodextrins, CDs) is a popular approach for the construction of enzyme models[1]. Regiochemical control in the synthesis of CD derivatives is difficult, but is possible with βCD by way of sulfonates[2]. Thus, the reactions of tosyl chloride[2a], *m*-nitrophenyl *p*-toluenesulfonate[2b], and 2-naphthylsulfonyl chloride[2c] with βCD give the corresponding 6-, 2-, and 3-sulfonates. In the first reaction, the tosyl chloride is solvated and reacts with the most available hydroxyl groups, i.e., HO-6. The last two reactions proceed via an inclusion complex which restricts the reactive sulfur center to be near the face of the secondary hydroxyl groups (HO-2,3) of the glucose residues.

Since the complexation of a reactant with βCD in solution can give high regioselectivity, we wondered if reactions conducted in solid βCD complexes might also provide selectivity. The pyrolysis of several aromatic diazo compounds, $PhCHN_2$, $PhC(CH_3)N_2$, and Ph_2CN_2, complexed with βCD, results in the formation of mono-ether derivatives[3]. We have now investigated reactions of other complexes of βCD with aromatic diazo compounds in order to determine how the

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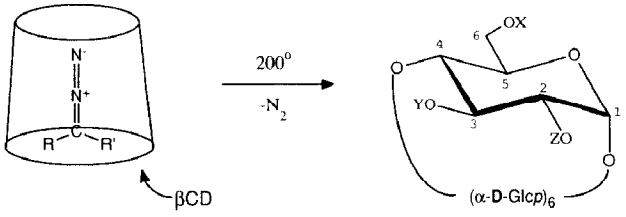
shape and size of the guest diazo compounds affects the selectivity of the insertion of carbene into the hydroxyl groups.

RESULTS

The solid complexes of the aromatic diazo compounds with βCD (see Experimental) were not stoichiometric. Complexation with an excess of βCD was carried out to ensure that the diazo compound–βCD ratio was < 1, in order to minimize side reactions, and the ratio varied from 0.6 to 0.9. Most of the diazo compounds partially decomposed during complexation, so that the inclusion complexes contained a mixture of guest species. The greatest decomposition occurred with 1-naphthyldiazomethane, and the diazo compound comprised only half of the guest composition. Azines were the main products of decomposition[4].



R = Ph, R′ = H
R = *o*-CF_3-Ph, R′ = H
R = *m*-CF_3-Ph, R′ = H
R = *p*-CF_3-Ph, R′ = H
R = 1-naphthyl, R′ = H
R = 2-naphthyl, R′ = H
R = Ph, R′ = CH_3
R = Ph, R′ = Ph
X = CHRR′, Y = Z = H
X = Z = H, Y = CHRR′
X = Y = H, Z = CHRR′

The dried complexes were pyrolyzed at 200° in order to induce loss of nitrogen from the diazo compounds. The reactions were complete within several minutes, as evidenced by the loss of the color of the diazo compounds, and they proceeded mildly even though the isolated diazo compounds will detonate under these conditions. Insertion products were separated from non-βCD derivatives by dissolving the product mixture in water and washing with ether. The aryl βCD ethers were separated from βCD by reverse-phase chromatography, the regioisomers were isolated (for the most part) by preparative HPLC, and their structures were determined by ^{13}C-NMR spectroscopy (Table I). The percentages of the isomers are shown in Table II.

The identification of the regioisomers was based on the $\Delta\delta$ values for the ^{13}C resonances of the glucose moiety on the formation of an ether[5]. Thus, the resonance of the carbons relative to the position of the alkoxy group should be shifted (ppm) as follows: α, 8.6 downfield; β, 2.8 upfield; γ, 0.4 downfield; δ, 0.3 upfield. The C-6 derivatives showed two shifted ^{13}C resonances between 72 and 65 ppm for C-6 (downfield) and C-5 (upfield). The differentiation of the C-2 and C-3 isomers was more difficult. The downfield shift of the resonances of the substituted carbon in each isomer was masked by overlap of the C-4 resonance at ~ 82

TABLE I

Substitutent-induced ^{13}C-NMR chemical shift differences [a]

Regio-isomer	$\Delta\delta$	Substituent								
		$PhCH_2-$	*o*-CF_3-$PhCH_2-$	*m*-CF_3-$PhCH_2-$	*p*-CF_3-$PhCH_2-$	1-Naph-CH_2-	2-Naph-CH_2-	PhMe-CH- [b]	PhMe-CH- [b]	Ph_2CH-
2-*O*-	ΔC_1	+1.5	[c]	+1.9	+1.9	+1.8	+1.6	[c]	[c]	[c]
	ΔC_2	−9.1	[c]	−9.2	−9.1	−9.1	−9.2	[c]	[c]	[c]
	ΔC_4	+1.3	[c]	+1.4	+1.5	+2.2	+2.0	[c]	[c]	[c]
3-*O*-	ΔC_1	+0.7	+0.7	+0.7	+0.7	+1.1	+0.7	+0.9	+0.5	+1.2
	ΔC_4	+3.4	+2.9	+3.0	+3.0	+3.3	+5.5	+3.5	+3.0	+3.0
6-*O*-	ΔC_1	−0.5	−0.5	−0.4	−0.4	−0.4	−0.5	−0.6	−0.2	−0.4
	ΔC_4	−0.7	−0.8	−0.8	−0.6	−0.6	−0.7	−0.7	−1.0	−1.2
	ΔC_5	+1.6	+1.6	+1.7	+1.6	+1.5	+1.6	+1.6	+1.5	+1.6
	ΔC_6	−8.9	−9.7	−9.3	−9.2	−9.1	−9.1	−7.4	−7.5	−8.2

[a] A minus sign indicates a downfield shift. [b] Diastereomers. [c] Information not available.

ppm. Thus, the upfield shifts of the resonances of the β-carbons were used to differentiate the regioisomers. The C-2 derivatives were those which have C-1 resonances shifted upfield by 1.5–1.9 ppm, and the C-3 derivatives were those which have C-4 resonances shifted upfield by > 2.8 ppm. The elucidation of the chemical shift patterns was possible only if all three regioisomers were available. For example, in both of the 2-*O*-naphthyl derivatives the $\Delta\delta$C-4 (γ) value is greater than the $\Delta\delta$C-1 (β) value, whereas the opposite would be expected, and previous assignments[3] have been changed in light of these data. With $PhC(Me)N_2$ the products assigned as C-2 and C-3 derivatives are now assigned as diastereomeric C-3 derivatives, since each shows a large shift of the C-4 resonance. Likewise, with Ph_2CN_2, the product assigned as a C-2 derivative is now assigned as a C-3 derivative.

The yields of the insertion products were relatively low: typically, 30% of the crude product and 5% after the isomers had been separated. The yields of the various regioisomers (Table II) showed certain trends. Aryldiazomethanes with a

TABLE II

Distribution of insertion products [a]

Diazo compound	3-*O*	2-*O*	6-*O*
$PhCHN_2$	76 [b]		24
$PhMeCN_2$	23/18 [c]	[d]	34/25 [c]
Ph_2CN_2	36	[d]	64
o-CF_3PhCHN_2	60	8	32
m-CF_3PhCHN_2	59	21	20
p-CF_3PhCHN_2	62	17	21
1-$NaphCHN_2$	45	44	11
2-$NaphCHN_2$	37	27	36

[a] Relative mass percent. [b] 3- and 2-isomers are not separable. [c] Diastereomers. [d] None isolated.

small aryl group (phenyl) gave mainly the C-3 isomers, whereas with larger aryl groups (naphthyl) the selectivity for C-3 diminished. Disubstituted diazo compounds showed selectivity for insertion into HO-6 and against insertion into HO-2.

DISCUSSION

Pyrolysis of the diazo compounds in the βCD cavity should produce the highly reactive aryl carbenes that are capable of undergoing various reactions, including insertion into C–H and O–H bonds. However, for βCD, only the latter reaction was observed. Most reactions gave all three regioisomers, indicative of a process with a small activation barrier. The yields of the βCD ethers isolated were low due to the several steps involved, especially the preparative HPLC, and to the competing guest–guest reactions which produce mainly azine[3]. On the other hand, selective mono-functionalization of CDs is notoriously inefficient.

The use of ^{13}C-NMR chemical-shift arguments for the assignment of structures to regioisomers has precedents in the literature. Thus, the three monosulfonates show shifts consistent with predicted values. For example, 2-*O*-tosyl-βCD shows[2b] upfield shifts of 3.8 and 3.7 ppm for the resonances of C-1 and C-3, respectively, and a smaller shift for that of C-4. This pattern ($\Delta\delta$C-1 ~ $\Delta\delta$C-3 > $\Delta\delta$C-4) is also seen for a 2-*O*-imidazolyl-βCD and for several 2-*O*-substituted βCDs[6,7]. On the other hand, 3-*O*-β-naphthylsulfonyl-βCD and -γCD, and also 3-*O*-tosyl-αCD, each have small (even zero) $\Delta\delta$C-1 values[2c,8,9]. Retention times on reverse-phase HPLC columns are also in accord with data in the literature; the elution sequence for the ether derivatives is C-3 ≪ C-2 < C-6, although, in some series, the last two are reversed. The same sequence is reported for the *O*-β-naphthylsulfonyl-γCDs and the *O*-tosyl-αCDs[8,9].

The results in Table II indicate that the influence of the size and shape of the guest diazo compound on the regiochemistry of the O–H insertion reaction is moderate at best. The larger proportion of C-3 ethers from diazo compounds with small aryl groups (e.g., phenyl) may reflect the electronic preference for insertion into HO-3. All of the carbenes studied are electrophilic; therefore, the initial step should be the electrophilic attack of the carbene on the hydroxyl *n*-orbital (carbene LUMO–*n*-orbital HOMO interaction)[10]. The most electron-rich oxygen should be the preferred site of reaction. The secondary hydroxyl groups (HO-2,3) should be more electron-rich than the primary hydroxyl groups (HO-6), and HO-3 should be better than HO-2 because of the pattern of hydrogen bonding. The dominant hydrogen bond in solution[11] is HO-3 · · · O-2 which leaves more negative charge on C-3 and at the expense of C-2. As a result, HO-2 is more acidic, a property which has been exploited in the selective synthesis of 2-*O*-substituted βCDs[7]. However, data from solid-state structural analysis tend to cloud this interpretation. In the solid state, βCD forms hydrogen-bonding loops which switch directions in a concerted operation above −171° ("flip-flop" hydrogen-bonding)[12]. How this property might affect the insertion reaction is not clear. With bigger

groups, the proportion of the C-2 isomer increases. Naphthyl groups align axially in CDs, where the naphthyl substituent is nearer to the secondary face of βCD due to steric requirements[13]. The enforced proximity (HO-2 is closer to the CD C_7-axis than HO-3) would favor reaction at HO-2 due to entropy effects.

The most interesting results occur with the two disubstituted diazo compounds where the selectivity for C-6 goes up, and the formation of the C-2 isomer is inhibited completely. Several factors may be involved. First, these carbenes should be more stable, and therefore more selective, which explains the greater preference for C-3 over C-2 substitution. The two groups may tend to "shield" the carbene especially as the C–C–C bond angle increases. The increased steric requirements discriminate against attack at HO-2 and HO-3, which are fixed in positions away from the center axis. On the other hand, HO-6 can move by rotation about the C-5–C-6 bond. Thus, the "channel alignment" effect will favor reaction at C-6 by impeding reaction at C-2 and C-3. These interpretations are speculative, but they serve as a basis for our continuing studies.

EXPERIMENTAL

General methods.—The ^{1}H- and ^{13}C-NMR spectra were obtained on solutions in Me_2SO-d_6–D_2O with a GE QE-300 spectrometer. UV spectra were recorded on a Beckmann DU-70 spectrophotometer. Optical rotations were measured for solutions in aq 50% MeCN with a Perkin–Elmer 241 polarimeter. TLC was carried out on silica gel (Baker 60F-254) with detection by UV light and staining with vanillin (Fisher). Reverse-phase LC was done with Baker RP-18 silica gel. HPLC was performed on a Waters 600E system with a Whatman ODS-3 analytical column with detection at 254 nm, and a linear gradient of aq 15 → 25% MeCN for 30 min. Relative mol% compositions were calculated from peak areas, using the appropriate response-factor adjustments. Reported retention times are the averages of several chromatograms. Preparative HPLC was performed on a Waters 244 system equipped with a UV absorption detector (254 nm) and a Whatman Magnum 20 column packed with ODS or with ODS-3. Melting points were taken on a Thomas–Hoover capillary apparatus and are uncorrected. Combustion analysis was performed by Desert Analytics using a heated block technique. Commercially available βCD was used as obtained from Amaizo.

Diazo compounds[14].—Tosylhydrazones of *o*-, *m*, and *p*-trifluoromethylbenzaldehyde and of 1- and 2-naphthaldehydes were prepared by condensation of the carbonyl compounds with tosylhydrazine. The trifluoromethylphenyldiazomethanes were generated by vacuum pyrolysis of the sodium salts of the tosylhydrazones and condensed in an ice/acetone-cooled flask. The naphthyldiazomethanes were generated by pyrolysis of the sodium salts of the tosylhydrazones in ethylene glycol at 70°, then extracted into Et_2O, and the extracts were washed with water and aq 5% NaOH. Diazo compounds are toxic and potentially explosive, and appropriate safeguards should be employed with these materials.

Inclusion complexes.—Inclusion complexes were made by stirring an ethereal solution of the diazo compound with an aq solution of βCD (1:1.0–1.25 diazo/βCD; 0.04 M βCD) for several h under a stream of N_2. The precipitate was then collected and dried in vacuo overnight.

Pyrolyses.—The inclusion complexes were induced to react by heating them at 200° with manual stirring for several min (disappearance of the color of the diazo compound). The solid was allowed to cool, a solution in H_2O was washed several times with Et_2O, then concentrated in vacuo, and the residue was subjected to reverse-phase LC. Fractions containing the βCD ether derivatives were combined and concentrated in vacuo. The regioisomers were then isolated by HPLC.

O-*(2-Trifluoromethylbenzyl) derivatives of βCD.*—From diazo(2-trifluoromethylphenyl)methane (460 mg, 2.5 mmol) and βCD (3.45 g, 3.0 mmol) in H_2O (76 mL), 2.85 g of the complex (guest–βCD 0.55:1, 100 mol% of the diazo compound) was obtained. Pyrolysis afforded a (wet) water-soluble product (2.94 g) which gave a crude mixture (610 mg, 37%) of mono-ethers upon LC. Preparative HPLC gave the 3- (52.1 mg, R_t 14.4 min) and a mixture of the 2- (5.6 mg, R_t 21.2 min) and 6-isomer (15.6 mg, R_t 20.5 min) in a combined yield of 4%. The yield of the 2- and 6-isomers is estimated by the area ratio from the analytical chromatogram.

3-*O*-(2-trifluoromethylbenzyl)-βCD had $[\alpha]_D^{25}$ +131° (*c* 0.27). NMR data: ^{1}H, δ 7.81 (1 H, d, $J_{5,6}$ 7.4 Hz, Ar*H*-6), 7.68–7.61 (2 H, m, Ar*H*-3,5), 7.47 (1 H, dd, $J_{4,5}$ 7.0, $J_{3,4}$ 7.3 Hz, Ar*H*-4), 5.12 (1 H, d, J_{gem} 12.7 Hz, ArCH_2O), 5.01 (1 H, d, J_{gem} 12.7 Hz, ArCH_2O); ^{13}C, δ 137.7, 133.3, 130.3, 128.6, 128.5 (q, *J* 33.4 Hz, CF_3), 126.2, 123.4, 102.7, 102.6, 101.9, 82.5, 82.4, 82.2, 82.1, 81.8, 79.3, 74.0, 73.8, 73.1, 73.0, 72.9, 72.8, 72.6, 72.5, 70.6, 60.7.

Anal. Calcd for $C_{50}H_{75}F_3O_{35} \cdot H_2O$: C, 45.80; H, 5.92; F, 4.35. Found: C, 45.46; H, 5.68; F, 4.33.

6-*O*-(2-Trifluoromethylbenzyl)-βCD. NMR data: ^{1}H, δ 7.75–7.65 (3 H, m, Ar*H*-3,5,6), 7.50 (1 H, dd, $J_{4,5}$ 7.4, $J_{3,4}$ 7.5 Hz, Ar*H*-4), 4.68 (1 H, d, J_{gem} 13.6 Hz, ArCH_2O); ^{13}C, δ 137.1, 132.8, 129.1, 128.0 (q, *J* 34.0 Hz, CF_3), 127.9, 125.6, 122.7, 102.6, 102.1, 101.9, 82.5, 81.7, 81.5, 73.4, 73.2, 73.1, 72.6, 72.5, 72.3, 72.2, 70.6, 69.8, 68.3, 60.0, 59.9.

Anal. Calcd for $C_{50}H_{75}F_3O_{35}$: C, 46.44; H, 5.85; F, 4.41. Found: C, 46.47; H, 5.82; F, 4.46.

O-*(3-Trifluoromethylbenzyl) derivatives of βCD.*—From diazo(3-trifluoromethylphenyl)methane (0.95 g, 5.1 mmol) and βCD (10.86 g, 9.6 mmol), 4.91 g of the solid complex (guest–βCD 0.7:1, 85 mol% of the diazo compound) was obtained. Pyrolysis gave water-soluble products (2.81 g) which gave a crude mixture (502.4 mg, 17%) of mono-ethers upon LC. Preparative HPLC gave the 3- (102.3 mg, R_t 15.8 min), 2- (35.8 mg, R_t 30.1 min), and 6-isomer (36.4 mg, R_t 29.1 min) in a combined yield of 6%.

3-*O*-(3-Trifluoromethylbenzyl)-βCD had $[\alpha]_D^{25}$129° (*c* 0.24). NMR data: ^{1}H, δ 7.67–7.82 (4 H, m, Ar*H*), 5.12 (1 H, d, J_{gem} 11.6, ArCH_2O), 5.00 (1 H, d, J_{gem} 11.6 Hz, ArCH_2O); ^{13}C, δ 139.5, 134.5, 130.6, 130.3 (q, *J* 31.8 Hz, CF_3), 126.7, 125.8,

123.5, 103.5, 103.2, 103.0, 102.3, 82.6, 82.5, 82.4, 79.4, 74.3, 74.2, 73.8, 73.6, 73.4, 73.1, 73.0, 61.0, 60.7.

Anal. Calcd for $C_{50}H_{75}F_3O_{35}$: C, 46.44; H, 5.85; F, 4.41. Found: C, 46.42; H, 6.05; F, 4.72.

2-*O*-(3-Trifluoromethylbenzyl)-βCD had $[\alpha]_D^{25}+118°$ (*c* 0.24). NMR data: ^1H, δ 7.79 (1 H, s, Ar*H*-2), 7.58–7.73 (3 H, m, Ar*H*), 4.96 (2 H, ArCH_2O); ^{13}C, δ 139.8, 132.4, 130.1 (q, *J* 32.1 Hz, CF_3), 130.0, 125.1, 124.9, 123.0, 102.5, 102.3, 100.6, 82.7, 82.0, 80.6, 73.5, 72.9, 72.8, 72.7, 72.6, 72.3, 60.4, 60.3.

Anal. Found: C, 46.67; H, 6.13; F, 4.60.

6-*O*-(3-Trifluoromethylbenzyl)-βCD had $[\alpha]_D^{25}+127°$ (*c* 0.19). NMR data: ^1H, δ 7.58–7.68 (4 H, m, Ar*H*), 4.64 (1 H, d, J_{gem} 12.6 Hz, ArCH_2O), 4.55 (1 H, d, J_{gem} 12.6 Hz, ArCH_2O); ^{13}C, δ 140.8, 132.3, 130.4, 130.1 (q, *J* 30.8 Hz, CF_3), 125.1, 124.6, 123.4, 103.2, 102.8, 102.6, 83.0, 82.3, 82.2, 82.1, 74.0, 73.9, 73.0, 72.9, 72.2, 71.4, 70.0, 60.8, 60.7.

Anal. Found: C, 46.63; H, 5.84; F, 4.54.

O-*(4-Trifluoromethylbenzyl) derivatives of βCD.*—From diazo(4-trifluoromethylphenyl)methane (0.90 g, 4.8 mmol) and βCD (10.86 g, 9.6 mmol), 6.72 g of the complex (guest–βCD 0.7:1, 100 mol% of the diazo compound) was obtained. Pyrolysis gave water-soluble products (3.54 g) which gave a crude mixture (1.48 g, 31%) of the mono-ethers upon LC. Preparative HPLC gave the 3- (125.9 mg, R_t 12.4 min), 2- (34.7 mg, R_t 24.8 min), and 6-isomer (41.7 mg, R_t 27.5 min) in a combined yield of 4%.

3-*O*-(4-Trifluoromethylbenzyl)-βCD had $[\alpha]_D^{25}+150°$ (*c* 0.17). NMR data: ^1H, δ 7.70 (2 H, d, $J_{2,3}$ 8.4 Hz, Ar*H*-3,5), 7.64 (2 H, d, $J_{2,3}$ 8.4 Hz, Ar*H*-2,6), 5.01 (1 H, d, J_{gem} 11.7 Hz, ArCH_2O), 4.94 (1 H, d, J_{gem} 11.7 Hz, ArCH_2O); ^{13}C, δ 143.4, 128.7, 128.0 (q, *J* 31.5 Hz, CF_3), 125.0, 122.7, 102.1, 101.9, 101.3, 81.7, 81.6, 81.3, 78.6, 73.3, 73.2, 72.7, 72.5, 72.2, 60.1.

Anal. Calcd for $C_{50}H_{75}F_3O_{35} \cdot H_2O$: C, 45.80; H, 5.92; F, 4.35. Found: C, 45.51; H, 5.93; F, 4.28.

2-*O*-(4-Trifluoromethylbenzyl)-βCD had $[\alpha]_D^{25}+189°$ (*c* 0.10). NMR data: ^1H, δ 7.72 (2 H, d, $J_{2,3}$ 8.1 Hz, Ar*H*-3,5), 7.62 (2 H, d, $J_{2,3}$ 8.1 Hz, Ar*H*-2,6), 5.01 (1 H, m, ArCH_2O); ^{13}C, δ 143.2, 129.1, 129.0 (q, *J* 32.0 Hz, CF_3), 125.9, 123.1, 102.6, 102.4, 100.7, 82.7, 82.2, 82.1, 82.0, 80.6, 73.6, 73.5, 73.2, 73.0, 72.7, 72.6, 72.5, 72.4, 72.3, 60.5, 60.4.

Anal. Calcd for $C_{50}H_{75}F_3O_{35} \cdot 3H_2O$: C, 44.58; H, 6.06; F, 4.23. Found: C, 44.68; H, 5.69; F, 4.55.

6-*O*-(4-Trifluoromethylbenzyl)-βCD had $[\alpha]_D^{25}+137°$ (*c* 0.22). NMR data: ^1H, δ 7.70 (2 H, d, $J_{2,3}$ 8.2 Hz, Ar*H*-3,5), 7.55 (2 H, d, $J_{2,3}$ 8.2 Hz, Ar*H*-2,6), 4.63 (1 H, d, J_{gem} 12.9 Hz, ArCH_2O), 4.56 (1 H, d, J_{gem} 12.9 Hz, ArCH_2O); ^{13}C, δ 143.8, 128.2 (q, *J* 32.4 Hz, CF_3), 128.0, 125.4, 122.8, 102.7, 102.2, 82.4, 82.0, 81.8, 73.4, 73.2, 72.5, 72.3, 71.6, 70.6, 69.4, 60.4, 60.3, 60.2, 60.1.

Anal. Calcd for $C_{50}H_{75}F_3O_{35}$: C, 46.44; H, 5.85; F, 4.41. Found: C, 46.04; H, 5.78; F, 4.50.

O-*1-Naphthylmethyl derivatives of βCD.*—The diazo compound from 1-naphthaldehyde tosylhydrazone (3.00 g, 10.1 mmol) and βCD (6.65 g, 5.86 mmol) gave 6.28 g of the inclusion complex (guest–βCD 0.9:1, 44 mol% of the diazo compound). Pyrolysis gave water-soluble material (6.20 g), which gave a crude mixture (2.19 g, 89%) of mono-ethers upon LC. Preparative HPLC gave the 3- (138.2 mg, R_t 7.0 min), 2- (134.6 mg, R_t 24.6 min), and 6-isomer (33.0 mg, R_t 27.3 min) in a combined yield of 12%.

3-*O*-(1-Naphthylmethyl)-βCD had $[\alpha]_D^{25}+129°$ (*c* 0.24). NMR data: ^{1}H, δ 8.47 (1 H, $J_{7,8}$ 8.1 Hz, Ar*H*-8), 7.91 (2 H, m, Ar*H*-4,5), 7.76 (1 H, d, $J_{2,3}$ 6.9 Hz, Ar*H*-2), 7.69–7.53 (3 H, m, Ar*H*-3,6,7), 5.54 (1 H, d, J_{gem} 11.6 Hz, ArCH_2O), 5.26 (1 H, d, J_{gem} 11.6 Hz, ArCH_2O); ^{13}C, δ 134.1, 133.8, 132.6, 129.9, 129.0, 128.7, 127.0, 126.4, 126.3, 125.2, 102.6, 102.5, 102.4, 102.2, 101.4, 82.4, 82.2, 82.1, 81.9, 81.8, 81.6, 78.8, 78.3, 74.4, 74.1, 73.7, 73.6, 73.5, 73.3, 72.8, 72.7, 72.5, 71.0, 60.6, 60.4, 60.3, 59.9.

Anal. Calcd for $C_{53}H_{78}O_{35}$: C, 49.92; H, 6.17. Found: C, 50.19; H, 5.97.

2-*O*-(1-Naphthylmethyl)-βCD had $[\alpha]_D^{25}+162°$ (*c* 0.20). NMR data: ^{1}H, δ 8.31–8.22 (1 H, m, Ar*H*-8), 7.99–7.88 (2 H, m, Ar*H*-4,5), 7.63–7.46 (4 H, m, Ar*H*-2,3,6,7), 5.31 (1 H, d, J_{gem} 11.4 Hz, ArCH_2O), 5.13 (1 H, d, J_{gem} 11.4 Hz, ArCH_2O); ^{13}C, δ 134.1, 133.7, 132.2, 129.7, 129.3, 128.3, 127.3, 126.9, 126.3, 125.0, 102.8, 102.7, 102.5, 100.9, 82.8, 82.6, 82.3, 80.0, 73.8, 73.6, 72.9, 72.8, 72.6, 72.5, 72.4, 60.7.

Anal. Calcd for $C_{53}H_{78}O_{35}\cdot H_2O$: C, 49.23; H, 6.24. Found: C, 48.97; H, 6.29.

6-*O*-(1-Naphthylmethyl)-βCD had $[\alpha]_D^{25}+103°$ (*c* 0.23). NMR data: ^{1}H, δ 8.17–8.08 (1 H, m, Ar*H*-8), 7.99–7.89 (1 H, m, Ar*H*-5), 7.88 (1 H, d, $J_{3,4}$ 7.8 Hz, Ar*H*-4), 7.63–7.42 (4 H, m, Ar*H*-2,3,6,7), 5.01 (1 H, d, J_{gem} 11.4 Hz, ArCH_2O); ^{13}C, δ 134.6, 133.7, 131.7, 128.8, 128.7, 126.6, 126.4, 125.9, 124.6, 120.8, 102.4, 102.3, 82.6, 82.1, 82.0, 81.8, 73.6, 73.4, 72.7, 72.5, 71.1, 71.0, 69.4, 60.6, 60.5, 60.3.

Anal. Calcd for $C_{53}H_{78}O_{35}\cdot H_2O$: C, 49.23; H, 6.24. Found: C, 49.03; H, 6.09.

O-*2-Naphthylmethyl derivatives of βCD.*—The diazo compound from 2-naphthaldehyde tosylhydrazone (3.04 g, 10.3 mmol) and βCD (6.72 g, 5.92 mmol) gave 6.00 g of the inclusion complex (guest–βCD 0.6:1, 80 mol% of the diazo compound). Pyrolysis gave water-soluble material (5.68 g) which gave a crude mixture (680 mg, 23%) of mono-ethers upon LC. Preparative HPLC gave the 3- (48.0 mg, R_t 5.1 min), 6- (47.2 mg, R_t 22.5 min), and 2-isomer (36.0 mg, R_t 26.0 min) in a combined yield of 4%.

3-*O*-(2-Naphthylmethyl)-βCD had $[\alpha]_D^{25}+130°$ (*c* 0.24). NMR data: ^{1}H, δ 8.04–7.93 (4 H, m, Ar*H*-1,4,5,8), 7.72–7.63 (3 H, m, Ar*H*-3,6,7), 5.38 (1 H, d, J_{gem} 11.7 Hz, ArCH_2O), 4.98 (1 H, d, J_{gem} 11.7 Hz, ArCH_2O); ^{13}C, δ 134.4, 133.6, 133.2, 130.6, 129.9, 128.6, 128.5, 128.2, 127.2, 127.1, 103.2, 102.7, 102.6, 102.5, 101.9, 82.5, 82.2, 82.0, 78.3, 75.0, 74.4, 74.1, 73.9, 73.8, 73.7, 73.3, 73.2, 73.1, 73.0, 72.8, 72.7, 60.7, 60.6, 60.5, 59.8.

Anal. Calcd for $C_{53}H_{78}O_{35}$: C, 49.92; H, 6.17. Found: C, 50.14; H, 6.14.

2-*O*-(2-Naphthylmethyl)-βCD had $[\alpha]_D^{25}+137°$ (*c* 0.20). NMR data: ^{1}H, δ 7.95–7.87 (4 H, m, Ar*H*-1,4,5,8), 7.61–7.50 (3 H, m, Ar*H*-3,6,7), 5.00 (1 H, d, J_{gem} 12.1 Hz, ArCH_2O); ^{13}C, δ 135.9, 133.3, 133.2, 128.7, 128.5, 128.2, 127.5, 127.0, 126.9,

102.6, 102.5, 102.4, 101.0, 82.8, 82.2, 82.1, 82.0, 80.0, 74.0, 73.6, 73.5, 73.3, 72.8, 72.6, 72.5, 72.3, 60.5.

Anal. Calcd for $C_{53}H_{78}O_{35} \cdot 2H_2O$: C, 48.55; H, 6.30. Found: C, 48.80; H, 6.11.

6-*O*-(2-Naphthylmethyl)-βCD had $[\alpha]_D^{25}+167°$ (*c* 0.20). NMR data: ^1H, δ 8.00–7.82 (4 H, m, Ar*H*-1,4,5,8), 7.61–7.44 (3 H, m, Ar*H*-3,6,7), 4.70 (1 H, d, J_{gem} 12.0 Hz, ArCH_2O), 4.64 (1 H, d, J_{gem} 12.0 Hz, ArCH_2O); ^{13}C, δ 136.4, 132.9, 132.4, 127.8, 127.6, 126.2, 126.0, 125.8, 102.6, 102.0, 82.3, 81.8, 81.6, 73.1, 72.5, 72.4, 72.1, 71.8, 70.6, 69.1, 60.2, 60.0.

Anal. Calcd for $C_{53}H_{78}O_{35}$: C, 49.92; H, 6.17. Found: C, 49.59; H, 6.17.

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