Synthesis of a Water-Soluble Dicyanoanthracene as a Cap For β-Cyclodextrin

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Received October 1, 1993 (Revised Manuscript Received March 8, 1994)

Introduction

Cyclodextrins (CDs) are well-known host molecules which find extensive use in complexation and catalysis studies.[1] Their well-defined cavities, small size, and ease of functionalization make them ideal enzyme models.[2] A number of interesting catalysts have been synthesized from CDs.[3] Cyclodextrins also have been used to modify photochemical reactions;[4] however, only a few photochemically-active, derivatized CDs have been reported. Among the photoreactive groups attached to CDs are benzophenone, rose bengal, flavin, and porphyrin moieties (*cf.* Figure 1).[5-9] A flavin-β-CD host has provided for photooxidation of bound benzyl alcohols,[7] whereas photoreduction of benzoquinone has been demonstrated with porphyrin-β-CDs.[8,9]

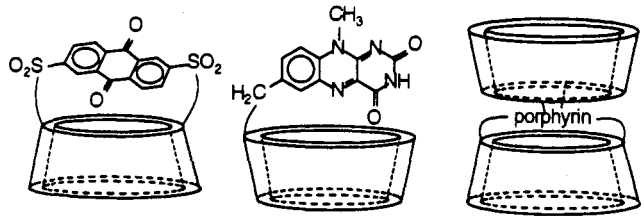

Figure 1. Photochemically-active β-CD derivatives.

We recently investigated anthraquinone-substituted β-CDs[10] with the hopes that they would be good hosts for photoinduced electron-transfer reactions. However, we found that the photoexcited anthraquinone moiety abstracts hydrogen from β-CD. We thought that 9,10-dicyanoanthracene (DCA), a well-known photooxidant,[11] would be more compatible with β-CD than an anthraquinone, since it abstracts hydrogen much less efficiently than a triplet carbonyl. Neither dicarboxylate or disulfonate derivatives of DCA are known, so we developed a synthesis for the C_2-symmetric 2,6-disulfonate for capping with β-CD.

Results and Discussion

The synthesis of 9,10-dicyanoanthracene-2,6-disulfonate (DCA-DS) follows standard methods (Scheme 1), but modifications of each step were necessary due to the presence of the two sulfonate groups. In the anthraquinone reduction, for example, ammonium carbonate was used instead of ammonium hydroxide. This change not only resulted in the complete conversion of the anthraquinone, but also allowed for a smaller excess of zinc to be used. The different counterion affects the reduction reaction, which proceeds by a series of electron-transfer/proton-transfer steps. Each protonation step is controlled by an equilibrium constant; since the sulfonates stabilize the anion forms, the equilibrium is shifted toward the reactants, thus hindering product formation. The less basic carbonate ion should somewhat counter this effect and shift the equilibrium toward the product side. Indeed, ammonium bicarbonate works just as well.

The bromination step was hampered by solubility problems. The reaction was unsuccessful in hot acetic acid where the anthracene disulfonic acid is only sparingly soluble. The disulfonic acid dissolves in aqueous acetic acid; however, in this solution it reacts with bromine to give only the anthraquinone *via* hydrolysis and oxidation of the initial bromine adduct. A 1:1 mixture of acetic acid and aqueous HBr proved most effective, and anthraquinone formation is reduced to 10-20%. Evidently, the added bromide aids the competition with water for anthracene-derived electrophiles.

The Rosenmund-von Braun cyanide substitution also suffered from solubility problems. In dimethylacetamide, benzyl cyanide, and diphenylacetonitrile the reaction often gave the anthraquinone, presumably from hydrolysis and oxidation. The reaction in diphenylacetonitrile at 330 °C was satisfactory only with rigorously dried materials. However, we found that DMSO, an atypical solvent for this reaction, was as good a reaction medium as diphenylacetonitrile. Surprisingly, the reaction in DMSO gives little anthraquinone. None of the solvents provided for complete conversion to the dinitrile. The crude dinitrile had to be reacted again with CuCN because recrystallization could not separate even small amounts of dibromide impurity. The water solubility of the dipotassium salt is 0.75 g/L.

The capping of the difunctional dicyanoanthracene to β-CD was performed according to the method of Tabushi.[12] The disulfonyl chloride was generated with thionyl chloride and dimethylformamide, and it was allowed to react with dry β-CD in pyridine. Pure DCA-β-CD was isolated by reversed-phase liquid chromatography and HPLC. This extensive workup typically gave no more than a 1% overall yield. The capping reaction gives poor yields due to the electron-deficient nature of the aromatic system and

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Scheme 1. Synthesis of DCA-β-CD

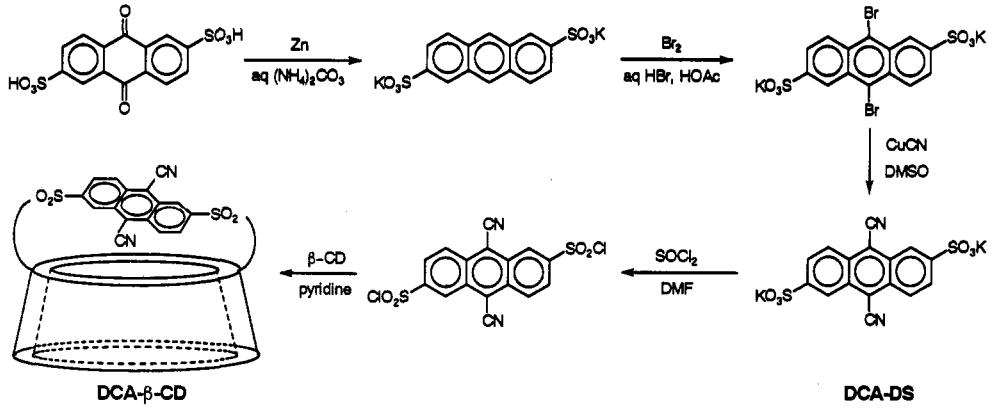

Table 1. Lowest Energy Conformers for A,D and A,C-Capped β-Cyclodextrin

					dihedral angles along cap (A–X)					
capping	type[a]	rel energy[b,c]			C5–C6	C6–O	O–SO_2	SO_2–O	O–C6	C6–C5
A,D	lid	0.0	0.3	4.4	89	−166	−167	173	−175	151
A,D	lid	1.2	0.0	0.4	99	−173	−170	−73	160	41
A,D	insert	4.3	1.8	9.0	−175	−156	72	−66	91	51
A,D	insert	5.2	5.7	2.5	167	−96	76	82	−97	172
A,D	lid	6.2	6.4	5.4	180	−171	90	77	−146	−163
A,D	lid	6.6	6.7	6.1	97	−76	165	−82	163	46
A,D	insert	7.2	19.9	0.0	−179	180	106	−84	172	41
A,C	h-lid	11.4	10.7	7.3	167	−164	83	44	57	42
A,C	r-lid	12.3	11.8	11.1	172	−152	83	−65	168	56
A,C	lid	16.8	12.7	13.1	158	−164	93	55	172	−64
A,C	lid	19.1	15.6	28.5	−46	176	−83	51	163	−68

[a] Key: insert, anthracene short axis parallel to C_7-axis of β-CD; lid, short axis perpendicular; h-lid, short axis between 45° and 90°; r-lid, anthracene lies over the "rim". [b] Dielectric constants: 1.5, 59, and −1, respectively. [c] In kcal/mol.

adventitious water.[13] In this reaction pyridine acts as a nucleophilic catalyst[14] in forming a sulfonylpyridinium intermediate which subsequently reacts with β-CD to form a sulfonate ester. Water will also react rapidly with the intermediate to regenerate a sulfonic acid. The sulfonate ester is also susceptible to nucleophilic attack by pyridine,[14] since the sulfonate leaving group possesses an electron-deficient aromatic group. However, the reaction could be left for days at room temperature without any diminution in yield, suggesting that this secondary process is not important. The regenerated disulfonic acid was recovered in the first fractions of the reversed-phase chromatography and recycled.

The regioisomer distribution in the capped product was elucidated by reacting it with *tert*-butylbenzenethiolate to generate the bis(*tert*-butylphenyl)sulfenyl derivatives which are separable by HPLC.[12] Area integration indicated a 76:24 mixture of A,D- and A,C-isomers.[15] No separation of *A,D*- and *A,C*-DCA-β-CD was achieved even with analytical HPLC, but this result is not unusual with capped β-CD regioisomers.[16] Spectral data and combustion analysis of the mixture were consistent with the capped structure. The aromatic portion of the proton NMR showed one major isomer. The spectrum of the major isomer consisted of two singlets and four doublets, thus indicating that the DCA is no longer in a symmetrical environment. The carbon NMR also showed at least double the number of resonances for a symmetrical DCA derivative, although in this case the signals due to the A,D- and A,C-regioisomers could not be unambiguously assigned. Two resonances from another isomer were evident in the aromatic region of the proton spectrum. One of these signals was a singlet, thus identifying it as H-1 or H-5 of the DCA moiety. Area integration of this signal and the downfield H-1 or H-5 signal of the major isomer indicated that the ratio of these isomers was 73:27, which is consistent with the HPLC results. Greater shielding of the aromatic protons of the A,C-isomer is expected because the DCA group lies over the "rim" of the β-CD (*vide infra*).

Molecular modeling was carried out to provide insight into the structures of the A,D- and A,C-capped CDs. The conformational energy surface was probed by permuting the torsional minima of the bonds along the cap to generate as many distinct, viable structures as possible. The dielectric term was varied to determine the sensitivity of the calculations to solvation effects. The relative energies and torsional angles of the most viable structures are shown in Table 1, and the structure of the lowest energy conformation is shown below (Figure 2).

Molecular mechanics calculations suggest both lidtype and inserted-type structures are energically feasible for the A,D-isomer, whereas the A,C-isomer is mainly lidtype. The relative energies of the conformers are very dependent on the dielectric term, suggesting that solvent effects are important in the solution structure. Indeed, the hydrophobic effect should favor an inserted structure to minimize the hydrophobic surface area. The conformational barriers were not investigated. The calculations show that the A,C-regioisomer is significantly higher in energy than the A,D-isomer. This result is in accord with

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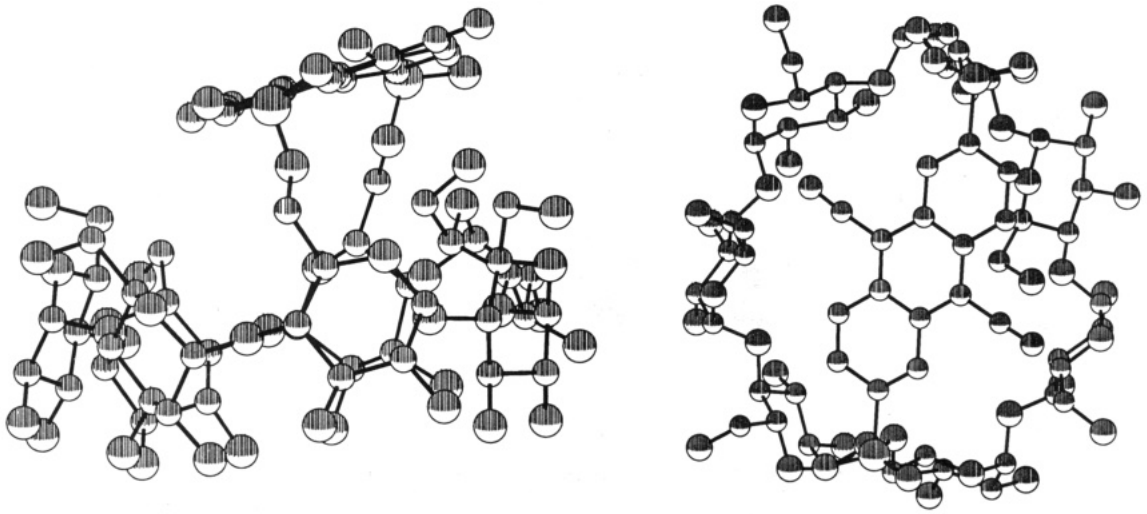

side view *top view*

Figure 2. Lowest energy conformation of DCA–β-CD.

Tabushi's looper's walk mechanism for capping.[12] The distance between the reactive sulfur centers (11.1 Å) is too great for A,B and is unfavorable for A,C-capping. A similar A,D/A,C ratio (80:20) was found with anthraquinone-2,6-disulfonyl chloride.[10] The disparity between the calculated energy differences between the A,D- and A,C-isomers and the observed product distribution results from the fact that this difference is only partially developed in the S_N2 transitions states and that entropy and solvent effects are ignored. Since the A,D/A,C ratio generally decreases at lower temperature, $\Delta S^{\ddagger}$ is more favorable for A,C-capping.[12]

Conclusion

A water-soluble dicyanoanthracene derivative and a dicyanoanthracene-capped β-CD have been prepared. The isolated yield of DCA–β-CD is poor due to the strongly electron-deficient nature of the cap. A regioisomeric mixture results in spite of the fact that the distance between the reactive centers and elevated reaction temperature should greatly favor formation of the A,D-isomer. We are currently investigating DCA–β-CD as a host for photoinduced electron-transfer reactions.

Experimental Section[17]

Anthracene-2,6-disulfonic Acid.[18] Zinc metal was activated by washing twice with 3% aqueous HCl and once each with H_2O, EtOH, and Et_2O. The Zn was dried *in vacuo* before use. Anthraquinone-2,6-disulfonic acid (20.0 g, 48.5 mmol) was dissolved in 20% aqueous $(NH_4)_2CO_3$ (700 mL). Activated Zn (20.0 g, 305 mmol) was added, the reaction was warmed to 70 °C, and the liberated gases were vented to a water bubbler. After 3 h another portion of activated Zn (20.0 g, 305 mmol) was added, and heating was continued overnight. The reaction turned orange-gray. The hot solution was filtered to remove Zn and Zn salts. The filtrate was cooled in an ice bath while H_2SO_4 (80 mL) was added slowly, causing the anthracene to precipitate. The solid was isolated by filtration and washed with acetone. It was recrystallized from water (300 mL) and KCl (20 g) to give the anthracene as shiny plates (17.2 g, 41.5 mmol, 86%): mp > 400 °C, ^{1}H NMR (DMSO-d_6) δ 8.60 (s, 2H), 8.27 (s, 2H), 8.00 (d, J = 8.8 Hz, 2H), 7.68 (d, J = 8.8 Hz, 2H).

9,10-Dibromoanthracene-2,6-disulfonic Acid. Anthracene-2,6-disulfonic acid (10.0 g, 29.6 mmol) was slurried in a mixture of acetic acid (300 mL) and 48% aqueous HBr (300 mL). Bromine (31.0 g, 194 mmol) was added dropwise, and then the mixture was heated to 90 °C for 18 h under a water bubbler. Most of the solvent was removed by distillation. The residue was poured into ice–water, and the solid was collected and washed with water and acetone to give nearly pure dibromide (11.8 g). It was purified as the dipotassium salt by recrystallization from H_2O, EtOH, and KOH (900 mL, 450 mL, and 4 g, respectively) to give the dibromide as a yellow fluffy solid (11.3 g, 21.2 mmol, 72%): mp > 400 °C; ^{1}H NMR (DMSO-d_6) δ 8.78 (s, 2 H), 8.50 (d, J = 9.1 Hz, 2 H), 7.94 (d, J = 9.1 Hz, 2 H); ^{13}C NMR (DMSO-d_6/DCl) δ 146.4, 131.7, 131.2, 129.7, 126.8, 125.5, 124.7.

Anal. Calcd for $C_{14}H_6Br_2K_2O_6S_2$: C, 29.38; H, 1.06; Br, 27.92; S 11.20. Found: C, 29.53; H, 0.95; Br, 27.72; S, 10.87.

9,10-Dicyanoanthracene-2,6-disulfonic Acid. 9,10-Dibromoanthracene-2,6-disulfonic acid, dipotassium salt (9.01 g, 15.7 mmol) was dried *in vacuo* at 100 °C overnight. It was combined with CuCN (18.00 g, 204 mmol) and anhydrous $CuSO_4$ (0.5 g), and the solids were covered with dimethyl sulfoxide (200 mL, distilled *in vacuo* from CaO). The mixture was heated to 170 °C under N_2 overnight. Most of the DMSO was removed by vacuum distillation. The residue was diluted in saturated aqueous KH_2PO_4, and the solid was collected by filtration. The solid was digested with 4 M HNO_3 (100 mL) (Danger! HCN may evolve). The oxidation of the copper complex occurred near 80 °C, sometimes very rapidly. The acid solution was diluted with 10% aqueous KH_2PO_4 to 500 mL, and the resulting solid was collected by filtration. The nitric acid digestion, dilution, and precipitation procedure was repeated. The recovered solid was dried *in vacuo* giving the dinitrile in 89% conversion (4.35 g, 9.67 mmol dinitrile, 1.23 mmol dibromide, 62% yield, 67% based on 100% conversion). Pure dinitrile was obtained by reacting the nearly converted material as above (using a 2:1 mass ratio of CuCN to anthracene). The dinitrile was recrystallized from water and aqueous KH_2PO_4: mp > 400 °C; ^{1}H NMR (DMSO-d_6) δ 8.62 (s, 2H), 8.43 (d, J = 9.0 Hz, 2H), 8.14 (d, J = 9.0 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 149.3, 131.6, 131.4, 128.9, 125.9, 121.2, 115.8, 111.3; UV (H_2O) log ε 6.3 (270 nm), 3.8 (382 nm).

Anal. Calcd for $C_{16}H_6K_2N_2O_6S_2$: C, 41.36; H, 1.30; N, 6.03; S, 13.80. Found: C, 41.65; H, 1.09; N, 5.80; S, 13.43.

$6^{A},6^{D(C)}$-(9,10-Dicyanoanthracene-2,6-disulfonyl)-β-cyclodextrin. 9,10-Dicyanoanthracene-2,6-disulfonic acid (2.58 g, 6.64

(17) For general experimental procedures see ref 10.
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mmol) was covered with $SOCl_2$ (50 mL), and the solution was heated to reflux under $CaCl_2$ drying for 1 h. DMF (1 mL) was added dropwise, and reflux was continued for another 45 min. Most of the $SOCl_2$ was removed by distillation. The residue was poured over ice, and the mixture was stirred vigorously. The resulting solid was collected by filtration, washed with H_2O, and dried *in vacuo* overnight. β-Cyclodextrin (4.80 g, 4.23 mmol) was added to pyridine (160 mL). The solution was heated under $CaCl_2$, and pyridine was distilled until the bp reached 114 °C (*ca.* 20 mL). The solution was cooled to 65 °C whereupon 9,10-dicyanoanthracene-2,6-disulfonyl chloride (1.76 g, 4.18 mmol) was added in one portion. The mixture was stirred at 60 °C for 3 h and then at room temperature for 2 days. The pyridine was removed by vacuum distillation (0.1 mm, $T < 50$ °C), and the residue was dried *in vacuo* for 1 h. The solid was ground under acetone and filtered three times; it was spread out and left to air-dry overnight giving a yellow powder (7.26 g). The powder was ground through a 200-mesh sieve, divided into four equal portions, and subjected to reversed-phase chromatography using a gradient elution (1–60% aq CH_3CN). Fractions containing the desired compound (R_f = 0.76, 5:4:3 *n*-BuOH, EtOH, H_2O) were concentrated *in vacuo*, affording the capped β-CD derivative (690 mg, 0.46 mmol, 11%). Final purification was accomplished through preparative HPLC using an CH_3CN–H_2O gradient elution (10% to 32%) giving the DCA–β-CD as a mixture of regioisomers (69.2 mg, 1.1% overall). A,D-isomer: ^{1}H NMR (DMSO-d_6, D_2O) δ 8.90 (s, 1H), 8.74 (s, 1H), 8.48 (m, 2H), 8.13 (m, 2H), 4.99 (s,1H), 4.91 (s, 1H), 4.89 (s, 1H), 4.87 (s, 1H), 4.77 (s, 1H), 4.63 (s, 1H), 4.49 (s, 1H) and β-CD resonances; ^{13}C NMR (major resonances, DMSO-d_6) δ 137.8, 133.0, 132.7, 131.3, 129.2, 128.9, 126.4, 126.3, 125.9, 125.3, 124.4, 121.1, 115.5, 115.2, 114.7, 113.9, 102.4, 102.0, 101.8, 101.6, 101.3, 82.4, 81.8, 81.6, 81.5, 81.4, 81.1, 73.6, 73.1, 72.9, 72.8, 72.7, 72.5, 72.3, 72.1, 71.6, 70.7, 68.7, 60.2, 60.1. The isomer ratio was determined from integration of the singlets at 8.90 (A,D) and 8.67 ppm (A,C).

Anal. Calcd for $C_{58}H_{74}N_2O_{39}S_2$: C, 46.84; H, 5.01; N, 1.88; S, 4.31. Found: C, 47.14; H, 5.11; N, 1.64; S, 4.26.

Regioisomer Determination. To sodium 4-*tert*-butylbenzenethiolate (50 mg, 0.26 mmol) in DMF (2 mL, distilled from CaH_2) was added the HPLC-purified DCA–β-CD (18 mg, 0.012 mmol). The mixture was heated to 80 °C under N_2 overnight. The mixture was cooled and diluted with aqueous NaH_2PO_4 (0.5 g in 100 mL). The aqueous layer was washed with Et_2O (6 × 75 mL) and then basified with Na_3PO_4 (0.75 g). The solution was concentrated to 50 mL *in vacuo* and subjected to reversed-phase liquid chromatography as above. The later fractions (CH_3CN > 20%) were combined, concentrated, and collected by filtration from acetone. The solid was placed in a Soxhlet extractor and extracted with acetone overnight. The remaining solid was analyzed by analytical HPLC and compared with authentic *A,D*- and *A,C*-bis[(4-*tert*-butylphenyl)sulfenyl]-β-CD derivatives synthesized from benzophenone-capped β-CD.[12] The retention times for the A,D- and A,C-isomers were 9.6 and 10.8 min on the carbohydrate column (82/18 CH_3CN:H_2O, 2 mL/min) and 17.6 and 18.7 min on the ODS-3 column (linear gradient: 30/70 to 60/40 CH_3CN:H_2O, 30 min, 1 mL/min). Relative peak areas were determined and indicated a 76:24 ratio of A,D-/A,C-isomer.

Calculations. Molecular mechanics calculations were performed with MMX (Serena Software, 1989 version) as previously described.[10] The electrostatic energy was calculated from atomic charge/charge interactions. H-bonding was activated for the C3-OHs only, and all lone pairs were included. A planar π-calculation with full SCF was conducted for the DCA nucleus. The following constants were added to the parameter set:

torsion atoms	V1	V2	V3	angle atoms	kb	θ_o
0–6–18–0	0	0	1	3–7–20	0.10	120
20–6–18–0	0	0	0	20–7–20	0.25	120
20–7–18–0	0	15	0	18–7–20	0.10	120

Acknowledgment. This work was supported by the National Science Foundation (CHE-8920447). We thank American Maize Products for a gift of β-cyclodextrin.

Supplementary Material Available: ^{1}H NMR spectrum of DCA–β-CD (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.