Cesium Fluoride Assisted Synthesis of Macrocyclic Polyethers with Aromatic Subunits

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Several features of the synthesis of crown ethers with aromatic subunits by reactions of dihydroxyaromatic or bis(hydroxyaromatic) compounds with cesium fluoride and polyethylene glycol tosylates are explored. The method is utilized to prepare several new crown ethers and to synthesize known crown compounds in improved yields.

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The first cesium-assisted syntheses of crown ethers with aromatic subunits were reported independently by Kellogg [1] and Reinhoudt [2]. Cyclization of catechol with polyethylene glycol dibromides and cesium carbonate [1] or with polyethylene glycol ditosylates and cesium fluoride [2] produced benzocrowns with 15- to 27- membered rings in 44-78% yields. It has also been shown that catechols substituted with acetyl, formyl, hydroxymethyl, and carboethoxy groups at the 4 position may be efficiently cyclized using the polyethylene glycol ditosylate and cesium fluoride combination [2,3]. Although good yields of crown ethers with aromatic subunits were also obtained by this latter method when the dihydroxy component was 1,2-bis(*o*-hydroxyphenoxy)ethane and 1,5-bis(*o*-hydroxyphenyl)-3-oxopentane [4,5], available literature data suggests that cyclization yields will be much lower for other bis(hydroxyaromatic) compounds [2,6].

To better define the scope and limitations for the cyclization of dihydroxyaromatic and bis(hydroxyaromatic) compounds with polyethylene glycol ditosylates and cesium fluoride, an investigation was undertaken with the objectives of determining: (a) if small ring 12-crown-4 compounds can be formed; (b) if 3-substituted catechol compounds can be cyclized; (c) what other types of dihydroxyaromatic or bis(hydroxyaromatic) components can be accommodated; and (d) if compounds with functional groups on the polyether rings themselves can be prepared.

Results and Discussion.

The general procedure involved stirring a mixture of the dihydroxyaromatic or bis(hydroxyaromatic) compound with five equivalents of cesium fluoride in dry acetonitrile under nitrogen for one hour followed by addition of the polyethylene glycol ditosylate dissolved in acetonitrile and heating at 65° for 1-3 days. Results are recorded in Table 1.

The feasibility of forming 12-crown-4 compounds was explored first. Although the preparation of one benzo-12-crown-4 derivative by this method has been reported [3], yield data, from which the reaction efficiency could be assessed, are not given. In this study reactions of catechol and 2,3-dihydroxynaphthalene with triethylene glycol ditosylate and cesium fluoride produced benzo-12-crown-4 (I) and 2,3-naphtho-12-crown-4 (II) in yields of 29 and 25%, respectively. The yield of I obtained by this method

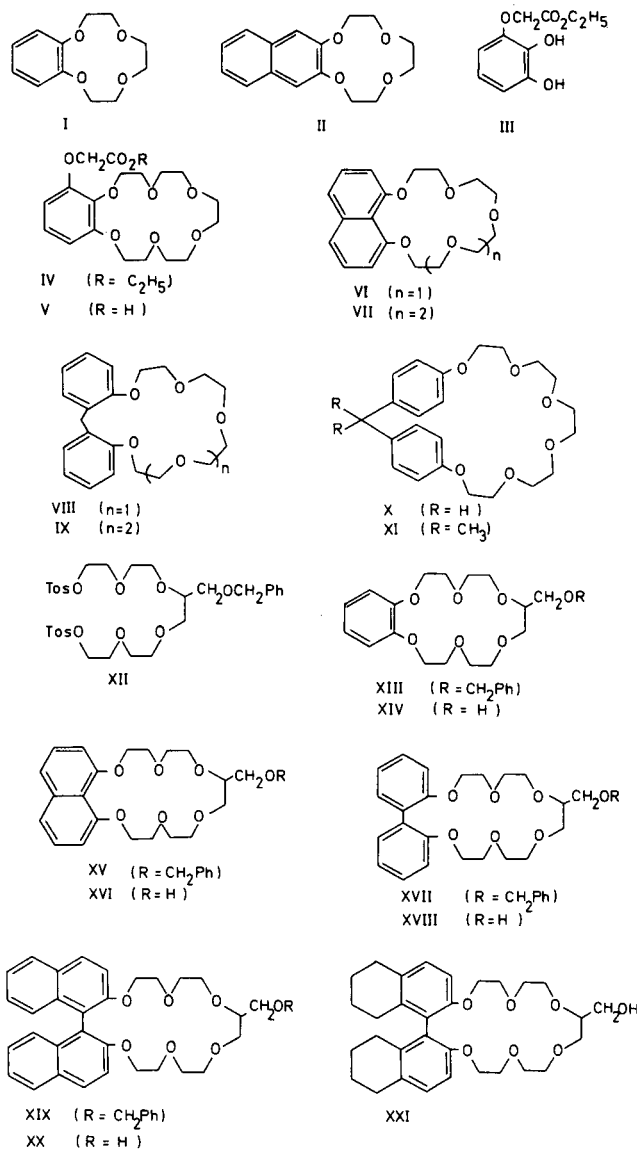

Table 1

Yields, Reaction Conditions, Analytical Data and Properties of Synthesized Crown Ethers

Compound Number	Yield (%)	Mp °C	Reaction Time (days)	Formula	IR, cm^{-1} (neat or deposit)	NMR, δ (deuteriochloroform)	Analysis Calcd.	Found
I	29 [a]	46-47 [a]	3	[a]	[a]	[a]		[a]
II	25	102-103	3	$C_{16}H_{18}O_4$	1126 (C-O)	3.3-4.4 (m, 12H) 7.1-7.85 (m, 6H)	C 68.92 [b] H 6.69	69.25 6.57
IV	25	oil	3	$C_{20}H_{30}O_9$	1759, 1736 (C=O) 1122 (C-O)	1.25 (t, 3H) 3.35-4.55 (m, 22H), 4.65 (s, 2H) 6.35-7.15 (m, 3H)	C 57.96 H 7.29	57.79 7.39
V	91	oil	[c]		2250-3690 (COOH) 1747 (C=O) 1120 (C-O)	3.35-4.5 (m, 20H) 4.63 (s, 2H) 6.4-7.1 (m, 3H) 9.88 (br s, 1H)	C 55.95 H 6.78	55.99 6.54
VI	63 [d]	110-112 [d]	2	[d]	1089-1145 (C-O)	3.4-4.35 (m, 16H) 6.6-6.9 (m, 2H) 7.1-7.45 (m, 4H)		[d]
VII	53 [e]	oil	2	[e]	1089-1145 (C-O)	3.5-4.4 (m, 20H) 6.65-7.0 (m, 2H) 7.2-7.5 (m, 14H)		[e]
VIII	49	93-95	2	$C_{21}H_{26}O_5$	1109 (C-O)	3.4-4.3 (m, 18H) 6.6-7.4 (m, 8H)	C 70.37 H 7.31	70.49 7.30
IX	45	61.5-63.5	2	$C_{23}H_{30}O_6$	1116 (C-O)	3.4-4.2 (m, 22H) 6.55-7.3 (m, 8H)	C 68.64 H 7.51	68.77 7.64
X	51	67-68	3	$C_{23}H_{30}O_6$	1116 (C-O)	3.3-4.25 (m, 22H) 6.6-7.35 (m, 8H)	C 68.64 H 7.51	68.56 7.27
XV	50	oil	2	$C_{28}H_{34}O_7$	1084-1141 (C-O)	3.1-4.3 (m, 21H) 4.40 (s, 2H) 6.55-7.45 (m, 11H)	C 69.69 H 7.10	69.76 7.16
XVI	80	oil	3	$C_{21}H_{28}O_7$	3345 (O-H), 1074-1140 (C-O)	2.57 (br s, 1H) 3.2-4.5 (m, 21H) 6.65-7.5 (m, 6H)	C 64.27 H 7.19	64.34 7.40
XVII	58	oil	2	$C_{30}H_{36}O_7$	1116 (C-O)	3.15-4.35 (m, 21H) 4.50 (s, 2H) 6.65-7.55 (m, 13H)	C 70.85 H 7.13	71.07 7.23
XVIII	83	oil	3	$C_{23}H_{30}O_7$	3458 (O-H), 1053-1145 (C-O)	2.75-4.3 (m, 22H) 6.65-7.5 (m, 8H)	C 66.01 H 7.23	65.99 7.13
XIX	53	oil	2	$C_{38}H_{40}O_7$	1090-1140 (C-O)	3.0-4.45 (m, 21H) 4.50 (s, 2H) 6.8-8.15 (m, 17H)	C 74.98 H 6.62	75.11 6.90
XX	46	oil	3	$C_{31}H_{34}O_7$	3450 (O-H) 1050-1145 (C-O)	2.85-4.5 (m, 22H) 6.8-8.2 (m, 12H)	C 71.18 [b] H 6.65	71.23 6.90
XXI	72	oil	7	$C_{31}H_{42}O_7$	3450 (O-H) 1091-1132 (C-O)	1.5-2.05 (m, 9H) 2.05-2.5 (m, 4H) 2.6-3.0 (m, 4H) 3.3-4.2 (m, 21H) 6.85 (ABq, 4H)	C 70.68 H 8.04	70.51 8.09

[a] Reference 7 reports 4% yield, mp 44-45.5°; Reference 8 reports 30% yield. [b] For a 0.25 hydrate. [c] See experimental. [d] Reference 9 reports 28% yield, mp 112-115°. [e] Reference 10 reports 7% yield.

equals the highest yield reported for alternative synthetic routes [7,8]. Thus even though the yields of 12-crown-4 compounds are lower than those reported for benzo-15-crown-5 and larger ring benzocrowns [2], the method remains viable.

Next cyclizations of dihydroxyaromatic compounds which contained an additional functional group were attempted. Failure to achieve cyclization of pyrogallol with pentaethylene glycol ditosylate presumably is attributable to insufficient solubility of the cesium salt formed from pyrogallol and cesium fluoride in acetonitrile. However, reaction of ethyl 2,3-dihydroxyphenoxyacetate (III) with pentaethylene glycol and cesium fluoride gave the 3-substituted benzo-18-crown-6 ester IV in 25% yield. The lower yield of IV compared with those reported for 4-substituted benzo-18-crown-6 compounds [2] may be readily rationalized in terms of steric hindrance to ring closure. Acid-catalyzed hydrolysis of IV produced an 89% yield of

the novel crown ether carboxyclic acid V.

Attention was then focused upon cyclizations which involved the diol components of 1,8-dihydroxynaphthalene, bis(2-hydroxyphenyl)methane, and bis(4-hydroxyphenyl)-methane. Crown ethers VI and VII have been prepared previously by reactions of 1,8-dihydroxynaphthalene with tetra- and pentaethylene glycol dichlorides in yields of 28% [9] and 7% [10], respectively. From reactions of this dihydroxyaromatic compound with cesium fluoride and tetra- and pentaethylene glycol ditosylates, much higher yields of VI (63%) and VII (53%) can be realized. Similarly, reactions of bis(2-hydroxyphenyl)methane with the appropriate polyethylene glycol ditosylates and cesium fluoride gave new crown ethers VIII and IX in yields of 49 and 45%, respectively. Surprisingly, the cesium fluoride-assisted cyclization of bis(4-hydroxyphenyl)methane and pentaethylene glycol ditosylate also produced a 51% yield of the paracyclophane-type crown ether X. Under the same conditions, the reaction of 2,2-bis(4-hydroxyphenyl)-propane with pentaethylene glycol ditosylate was sluggish and gave a complicated product mixture from which analytically pure XI could not be obtained. Examination of CPK models for the bis(hydroxyaromatic) reactant and crown ether XI reveals that the geminal methyl groups introduce additional rigidity which should hinder cyclization. The good yields of VI-X which were obtained establish the viability of the synthetic method for a variety of diol components.

In the final phase of this work, the cesium fluoride-assisted cyclization method was applied to the synthesis of crown ethers with aromatic subunits and functional groups attached directly to the polyether rings. As part of an earlier study [11], we observed that reaction of catechol with the benzyloxy-substituted pentaethylene glycol ditosylate XII and cesium fluoride gave a 70% yield of crown ether XIII from which the benzyl protecting group can be removed by catalytic hydrogenolysis [12] to produce hydroxymethyl-substituted crown ether XIV which is a versatile synthetic intermediate [13]. Reactions of 1,8-dihydroxynaphthalene, *o,o'*-biphenol, and 1,1'-bis-2-naphthol with ditosylate XII and cesium fluoride gave the corresponding (benzyloxy)methyl-substituted crown compounds XV, XVII and XIX in yields of 50,58, and 53%, respectively. Removal of the benzyl protecting groups from XV, XVII and XIX by catalytic hydrogenolysis with palladium on carbon gave hydroxymethyl group-functionalized crown compounds XVI, XVIII and XX in yields of 80, 83 and 46%, respectively (Table 1). Debenzylation of XIX required more forcing conditions than were employed for the deprotection of XV and XVII. This finding and the low yield of XX realized suggest that steric interactions of the binaphthyl unit hinders approach of the (benzyloxy)-methyl unit in XIX to the catalyst surface. Subsequently, XX was converted into the more lipophilic hydroxymethyl crown compound XXI (a mixture of isomers) in 72% yield by partial reduction of the binaphthyl unit with platinum oxide as the catalyst [14]. These results clearly establish the utility of cesium fluoride-assisted cyclizations for the synthesis of crown ethers with aromatic subunits and functional groups on the polyether rings.

EXPERIMENTAL

Melting points were taken with a Fisher-Johns melting point apparatus and are uncorrected. The ir and nmr spectra were obtained with a Nicolet MX-S spectrophotometer and a Varian EM 360 spectrometer, respectively. Bis(2-hydroxyphenyl)methane, bis(4-hydroxyphenyl)methane, 2,3-dihydroxynaphthalene, *o,o'*-biphenol and 1,1'-bi-2-naphthol were obtained from Aldrich Chemical Company and were used directly. Catechol was obtained from Crown Zellerbach Corporation and was recrystallized from diethyl ether before use. The 1,8-dihydroxynaphthalene was obtained from Fluka Chemical Corporation. Reagent grade acetonitrile was dried over molecular sieves (5A) before use. Tri-, tetra- and pentaethylene glycol ditosylates [15,16], the ditosylate of 3,6,9,12-tetraoxa-7-(benzyloxymethyl)-1,14-tetradecanediol (XII) [11] and 2,3-dihydroxyphenoxyacetic acid [17] were prepared by literature procedures.

General Procedure for the Preparation of Crown Ethers.

A solution of the dihydroxyaromatic or bis(hydroxyaromatic) compound (3.0 mmoles) in dry acetonitrile (50 ml) was placed in a reaction flask which had been evacuated under vacuum and filled with nitrogen. Then, powdered anhydrous cesium fluoride (2.28 g, 15.0 mmoles) was added and the mixture was vigorously stirred at room temperature for 1 hour. To this suspension was added a solution of the appropriate ditosylate (3.0 mmoles) in 20 ml of acetonitrile and the mixture was heated with stirring at 65° for 24-72 hours under nitrogen. The solid material was filtered and washed with methylene chloride. The solvents were evaporated *in vacuo* and the crude product was purified by column chromatography on alumina with ethyl acetate-petroleum ether (bp 30-60°) as eluent.

General Procedure for the Preparation of Hydroxymethyl Crown Ethers.

To a solution of the (benzyloxy)methyl crown ether (1.5 mmole) in ethanol (20 ml) was added 10% Pd-C catalyst (100 mg/1 g) and a catalytic amount of *p*-toluenesulfonic acid. The mixture was shaken for 3 days under 50 psi pressure of hydrogen, at room temperature. The catalyst was filtered, the solvent was removed *in vacuo* and the residue was purified by column chromatography on alumina with ethyl acetate-methanol (25:1) as the eluent to give the pure hydroxymethyl crown ether. In the case of compound XIX hydrogenolysis was carried in dioxane at 55° for 3 days.

Preparation of Compound XXI.

Hydroxymethyl crown ether XXI was prepared by adapting a published procedure for the synthesis of a structurally-similar crown compound [14]. To a solution of hydroxymethyl crown ether XX (0.30 g, 0.6 mmole) in glacial acetic acid (20 ml) was added platinum(IV) oxide (0.02 g) and the mixture was shaken at room temperature under 50 psi pressure of hydrogen for 7 days. The catalyst was filtered and the filtrate was shaken with a mixture of 20 ml of methylene chloride and 40 ml of water. The organic layer was washed with water (3 × 20 ml) and 10% aqueous sodium bicarbonate (2 × 20 ml), dried over magnesium sulfate, and evaporated *in vacuo*. The crude product was purified by column chromatography on alumina with ethyl acetate-methanol (1:1) to give 0.22 g (72%) of XXI as a colorless oil. Spectral and elemental analysis data are given in Table 1.

Preparation of Compound III.

2,3-Dihydroxyphenoxyacetic acid [17] (12.8 g, 69.5 mmoles) was dissolved in a mixture of absolute ethanol (100 ml) and benzene (200 ml), and *p*-toluenesulfonic acid (1.0 g) was added. The mixture was refluxed overnight with the condensed vapors circulating continuously through a bed of anhydrous sodium sulfate. The solvent was evaporated *in vacuo* and the solid residue was filtered and washed with cold water and dried to give 12.4 g (80%) of III was white crystals, mp 152-154°; ir (mull): 3350, 3270 (O-H), 1737 (C=O), 1126 (C-O) cm^{-1}; nmr (hexadeuteriodimethyl sulfoxide): δ 1.25 (t, 3H), 4.20 (q, 2H), 4.70 (s, 2H), 6.25-6.7 (m, 3H), 7.98 (br s, 1H), 8.51 (br s, 1H).

Anal. Calcd. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.49; H, 5.83.

Preparation of Compound V.

Crown ester IV (0.50 g, 1.2 mmoles) was dissolved in 20 ml of a 1:1 (v/v) mixture of tetrahydrofuran and water and a small amount of Amberlite IR-120 (H^+ form) was added. The mixture was refluxed overnight and the catalyst was filtered. Tetrahydrofuran was removed *in vacuo* and the aqueous residue was extracted with chloroform (2 × 10 ml). The combined extracts were dried over chloroform (2 × 10 ml). The combined extracts were dried over magnesium sulfate to give 0.43 g (91%) of V as a colorless oil. Spectral and elemental analysis data are given in Table 1.

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