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Molecular Design of Crown Ethers. 1. Effects of Methylene Chain Length: 15- to 17-Crown-5 and 18- to 22-Crown-6

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The ring-enlarged crown ethers, 16- and 17-crown-5 and 19- to 22-crown-6, were synthesized and their cation-binding abilities were evaluated by solvent extraction of aqueous alkali metal picrates. The cation-binding abilities of less symmetrical crown ethers, **3a–e** and **4a,b**, were generally lower than those of the common symmetrical crown ethers 15-crown-5 (**5a**) and 18-crown-6 (**5b**), for which the less symmetrical arrangement of the donor oxygen atoms must be responsible. Compared with 18-crown-6 (**5b**), the ring-extended crown ethers, **3d**, **3e**, and **4b**, showed a significant shift in cation selectivity, probably due to the enlarged cavity size. The thermodynamic parameters for the extraction of sodium and potassium picrates with **3a**, **3c**, and **5a,b** were calculated from the change of the extraction equilibrium constants (K_{ex}) between 10–25 °C. The stability of the cation–crown ether complexes was shown to be governed in general by the enthalpy change. However, a significant contribution of the entropy factor was found in unfavorable size combinations of K^+ with **3a** and Na^+ with **3c**.

A variety of functionalized crown ethers have been synthesized to control the complexation phenomena with cations.[1] It has been believed[2] that the cation-binding ability, and the cation selectivity as well, of a crown ether depend upon the following factors: (1) relationship between the cavity size of the crown ether and the cation diameter, (2) number of donor atoms including additional binding sites, (3) character of donor atoms, (4) spatial arrangement of binding sites, (5) conformational flexibility or rigidity of a crown ether, (6) lipophilicity of the crown ether and the cation, and (7) solvent employed.

Of these factors, we have been interested in the effects of changing the spatial arrangement of donor atoms by introducing extra methylene groups into a crown ether to give a less symmetrical crown ether. Although a variety of ring-enlarged crown ethers have been reported, they mostly contain rigid aromatic rings. No systematic study has been done to assess the effect of extra methylene groups on the cation-binding abilities of crown ethers.[3]

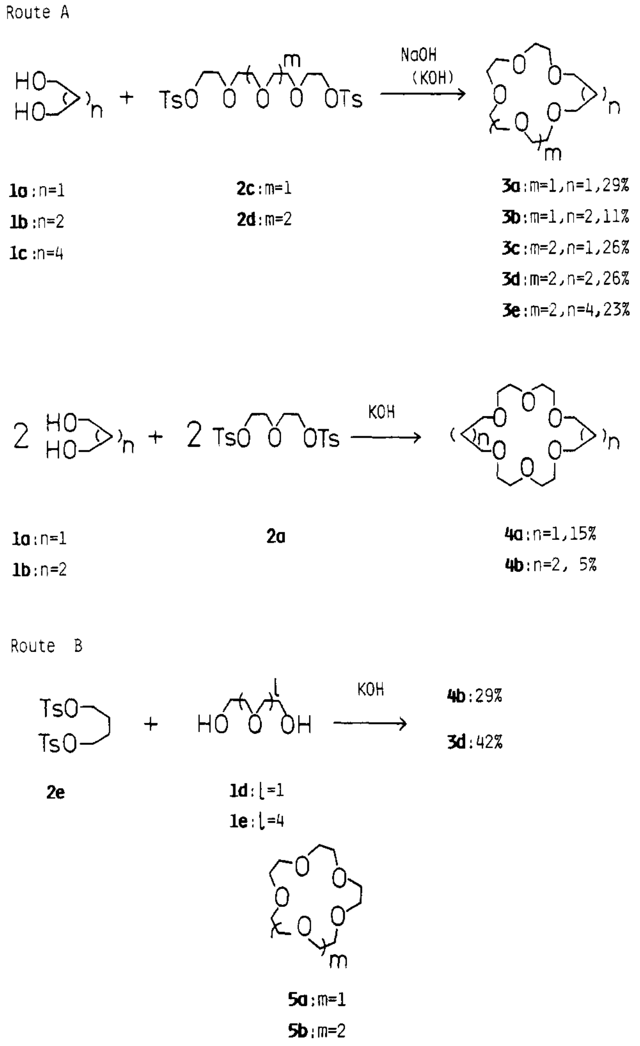
We have reported the syntheses of 13-crown-4, 16-crown-5, and 19-crown-6 derivatives[4] and found that the introduction of an extra methylene group into a symmetrical 3*m*-crown-*m* (*m* = 4–6) has drastic and different effects on its cation-binding ability; 13-crown-4 derivatives showed extremely low cation-binding ability even for Na^+, while 16-crown-5 derivatives showed much higher Na^+/K^+ selectivity than the parent 15-crown-5.

We now report the facile syntheses of a variety of less symmetrical crown ethers carrying extended methylene chains between two adjacent oxygen atoms of a crown ether, i.e., 16- to 17-crown-5 and 19- to 22-crown-6, and discuss their cation-binding ability and the thermodynamic parameters for the extraction equilibrium in view of the size–fit concept and conformational effects.

Results and Discussion

Synthesis. Crown ethers **3a–e** and **4a,b** were synthesized in modest yields by reaction of α,ω-glycols with polyethylene glycol ditosylates in THF in the presence of NaOH or KOH (Scheme I, route A). Somewhat higher yields of **3d** and **4b** were obtained by the inverse reaction of α,ω-glycol ditosylates with the polyethylene glycols under the same conditions (Scheme I, route B).

Scheme I



The fact that route B gives better yields than route A may indicate that more stabilization, through the "template" effect, is achieved with the well-oriented intermediate in B than in A, which is assisted only by limited templation due to the extended methylene chain in the templating ligand (Scheme II).

Pentaglyme (**6b**) was synthesized in 46% yield by the reaction of ethylene glycol monomethyl ether with tri-

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(1) For a recent review, see: Gokel, G. W.; Korzeniowski, S. H. "Macrocyclic Polyether Syntheses"; Springer-Verlag: Berlin, 1982.

(2) For a detailed description of the concept, see: de Jong, F.; Reinhoubt, D. N. "Stability and Reactivity of Crown Ether Complexes"; Academic: London, 1981; p 5. Patai, S., Ed. "The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and Their Sulphur Analogues. Part 1"; Wiley: Chichester, 1980; p 92.

(3) A very low cation-binding ability of 20-crown-6 derivatives has been reported: Coxon, A. C.; Stoddart, J. F. *J. Chem. Soc., Perkin Trans. 1*, **1977**, 767.

(4) Ouchi, M.; Inoue, Y.; Sakamoto, H.; Yamahira, A.; Yoshinaga, M.; Hakushi, T. *J. Org. Chem.* **1983**, *48*, 3168.

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Scheme II

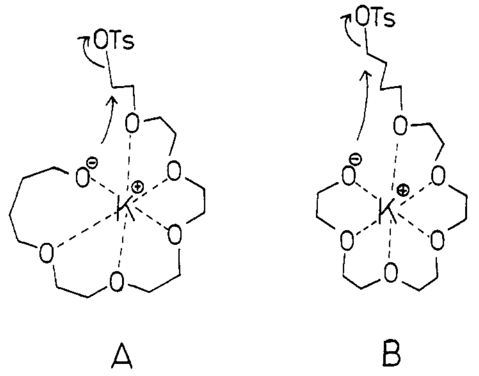

Table I. Extraction of Alkali Metal Picrates[a]

ligand	extractability, %[b]			
	Na^+	K^+	Rb^+	Cs^+
15-crown-5 (**5a**)	13.2	14.3	9.6	3.3
16-crown-5 (**3a**)	13.5	3.0	2.1	0.9
17-crown-5 (**3b**)	1.8	1.9	0.9	0.7
tetraglyme (**6a**)	0.1	0.1	0.1	0.1
18-crown-6 (**5b**)	6.3	69.0	57.6	36.7
19-crown-6 (**3c**)	2.5	22.4	17.0	7.4
asym-20-crown-6 (**3d**)	1.1	14.1	19.7	18.1
sym-20-crown-6 (**4a**)	2.1	2.6	1.8	0.9
asym-22-crown-6 (**3e**)	0.5	1.2	1.7	2.5
sym-22-crown-6 (**4b**)	0.5	0.6	1.0	1.8
pentaglyme (**6b**)	0.2	0.7	0.6	0.5

[a] Temperature 25.0 ± 0.1 °C; aqueous phase (10 mL): [picrate] = 3×10^{-3} M; organic phase (CH_2Cl_2, 10 mL): [ligand] = 3×10^{-3} M. [b] Defined as % picrate extracted into the organic phase. Average of two independent runs; error < 0.3%.

ethylene glycol ditosylate (**2b**) in THF in the presence of NaOH as a base.

Extraction Studies. The cation-binding ability of the crown ethers **3**–**5** and the glymes **6** was assessed by solvent extraction of aqueous solution of alkali metal picrates (Na^+, K^+, Rb^+, and Cs^+) at 25 °C with dichloromethane solutions of the crown ethers. The extractabilities are shown in Table I.

Under the conditions employed ([ligand]/[picrate] = 1), symmetrical 15-crown-5 (**5a**) and 18-crown-6 (**5b**) gave moderate extractabilities, and **5a** showed the highest extractabilities for Na^+ and K^+ and **5b** for K^+, in agreement with the generally accepted size–fit concept.[5] However, the ring-enlarged, less symmetrical crown ethers **3** and **4**, in general, showed lower extractabilities for all cations employed than the symmetrical **5a** and **5b**. Extractability decreased with increasing methylene chain length; e.g., extractability for K^+: **5a** > **3a** > **3b** and **5b** > **3c** > **3d**. A more drastic decrease in extractability was observed with the doubly enlarged crown ethers **4a** and **4b**, and the singly but even more enlarged **3e** as well.

Although their extractabilities were lower, the ring-enlarged crown ethers **3** and **4** showed significant changes in relative cation selectivity compared with the parent 3*m*-crown-*m* **5**. *asym*-20-Crown-6, **3d**, and *asym*- and *sym*-22-crown-6, **3e** and **4b**, prefer larger cations; the highest extractabilities were found for K^+ with **5b**, for Rb^+ with **3d**, and for Cs^+ with **3e** and **4b**.

Somewhat different properties were exhibited by (3*m* + 1)-crown-*m* **3a**. In contrast with the nonselective extractions of Na^+ and K^+ by 15-crown-5 (**5a**), 16-crown-5 (**3a**) showed fairly high relative selectivity for Na^+, which is attained by the significant decrease in extractabilities for the larger cations K^+, Rb^+, and Cs^+.

Table II. Estimated Cavity Sizes of 3, 4, and 5 by CPK Molecular Models and Cation Diameter

crown ether	cavity diameter, Å	cation	diameter, Å[a]
15-crown-5 (**5a**)	1.7	Na^+	1.90
16-crown-5 (**3a**)	1.8	K^+	2.66
17-crown-5 (**3b**)	2.0	Rb^+	2.96
18-crown-6 (**5b**)	2.6	Cs^+	3.38
19-crown-6 (**3c**)	2.7		
asym-20-crown-6 (**3d**)	3.3		
sym-20-crown-6 (**4a**)	3.0		
asym-22-crown-6 (**3e**)	3.4		
sym-22-crown-6 (**4b**)	3.9		

[a] Reference 6.

Table III. Extraction Equilibrium Constants (K_{ex})[a]

crown ether	$\log K_{ex}$[b]			
	Na^+	K^+	Rb^+	Cs^+
15-crown-5 (**5a**)[c]	4.52	4.40	4.29	3.74
16-crown-5 (**3a**)[c]	4.55	3.65	3.52	3.14
17-crown-5 (**3b**)	3.39	3.45	3.12	3.01
18-crown-6 (**5b**)	3.89	6.20	5.96	5.17
19-crown-6 (**3c**)	3.46	4.68	4.58	4.01
20-crown-6 (**3d**)	2.95	4.40	4.64	4.55

[a] Dichloromethane–water system; temperature 25.0 ± 0.1 °C. [b] Values for 1:1 crown ether–cation complexes. [c] Reference 4.

The low cation extractabilities of less symmetrical crown ethers **3** and **4** may be accounted for in terms of the molecular symmetry. Examination of CPK molecular models reveals that the less symmetrical arrangement of donor oxygen induced by extended methylene chains leads to an unfavorable conformation for complexation compared with the symmetrical 15-crown-5 (**5a**) and 18-crown-6 (**5b**). The models also show that the cavity sizes of **3** and **4** are greater than those of symmetrical **5a** and **5b** (Table II). This difference in cavity size may account for the selectivity of **3d** (cavity 3.3 Å) for Rb^+ and Cs^+ and of **3e** (cavity 3.4 Å) and **4b** (cavity 3.9 Å) for Cs^+, compared with the selectivity of **5b** (cavity 2.6 Å) for K^+, in accordance with the size–fit concept.[5] Models of the extensively enlarged *asym*-22-crown-6 (**3e**), *sym*-20-crown-6 (**4a**), and *sym*-22-crown-6 (**4b**), which have extremely low extractabilities, indicate conformations that are not favorable for ligand complexation.

Extraction studies were carried out to determine the extraction equilibrium constants (K_{ex}). The extraction equilibrium constant (K_{ex}) between an aqueous solution of alkali metal picrate and a dichloromethane solution of crown ether (CE) for an *n*:1 crown ether–cation complex can be obtained from eq 1. D_M represents the distribution

$$\log (D_M/[A^-]_{aq}) = n \log [CE]_{org} + \log K_{ex} \qquad (1)$$

ratio of a metal cation between the two phases ($D_M = [M(CE)nA]_{org}/[M^+]_{aq}$). The plot of $\log (D_M/[A^-]_{aq})$ as a function of $\log [CE]_{org}$ should give a straight line with a slope of n (n = 1 or 2) and $\log K_{ex}$ as an intercept. These plots for **3b**–**d** and **5b** gave straight lines with a slope of unity for all cations employed over the entire concentration range. The K_{ex} values thus obtained are given in Table III, along with those for 15-crown-5 (**5a**) and 16-crown-5 (**3a**).[4]

Then 15-crown-5 (**5a**) tends to form a 2:1 sandwich complex with K^+ and Rb^+ in the region where the [crown

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[5] For the earliest description of the concept, see: Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017.

Table IV. Thermodynamic Parameters in kcal/mol for Extraction Equilibrium at 25 °C

	Na+			K+		
crown ether	$-\Delta G°$	$-\Delta H°$	$T\Delta S°$	$-\Delta G°$	$-\Delta H°$	$T\Delta S°$
15-crown-5 (**5a**)	6.2	13.3	−7.1	6.0	8.4	−2.4
16-crown-5 (**3a**)	6.2	11.9	−5.7	5.0	11.5	−6.5
18-crown-6 (**5b**)	5.3	5.7	−0.4	8.4	20.5	−12.1
19-crown-6 (**3c**)	4.7	7.4	−2.7	6.4	14.1	−7.7

ether]/[picrate] ratio exceeds 1, while forming a 1:1 complex with them in the region where [crown ether]/[picrate] ratio is less than 1, and forms 1:1 complexes with Na^+ and Cs^+ over the entire concentration range.

The data indicate that **3b–d** and **5b** form 1:1 crown ether–cation complexes even in the presence of excess crown ether. As can be seen from Table III, the log K_{ex} values for 17-crown-5 (**3b**) are lower than those for 16-crown-5 (**3a**) and 15-crown-5 (**5a**), and those for 19-crown-6 (**3c**) and 20-crown-6 (**3d**) are also lower than those for 18-crown-6 (**5b**), which is consistent with the extractabilities shown in Table I.

The specific interaction of 16-crown-5 (**3a**) with Na^+ may be explained by cavity size and orientation of the donor atoms. Examination of a CPK molecular model shows that Na^+ (cation diameter, 1.90 Å)[6] is better accomodated in the cavity (1.8 Å) of 16-crown-5 (**3a**) than in the cavity (1.7 Å) of 15-crown-5 (**5a**). The five oxygen atoms are also directed inside because of the larger ring structure compared with that of 15-crown-5 (**5a**), which makes 1:1 complex formation with Na^+ favorable but 1:1 or 2:1 complex formation with larger cations (K^+, Rb^+, and Cs^+) unfavorable.

Thermodynamic Study. Extractions of sodium and potassium picrates were carried out at various temperatures (10, 15, 20, and 25 °C) with 15-crown-5 (**5a**), 16-crown-5 (**3a**), 18-crown-6 (**5b**), and 19-crown-6 (**3c**) according to a method reported in the literature.[7] Plots of log K_{ex} against the inverse of absolute temperature were linear, with log K_{ex} increasing with decreasing temperature. The enthalpy change, $\Delta H°$, was obtained from the slope, and the free energy and entropy changes, $\Delta G°$ and $T\Delta S°$, were calculated from the equations: $\Delta G° = -RT \ln K_{ex}$, $T\Delta S° = \Delta H° - \Delta G°$. The results are shown in Table IV.

The free energy changes for the symmetrical crown ethers are governed mostly by the enthalpy factor,[8] although an enthalpy gain tends to accompany a slightly increased negative contribution of the entropy factor. This is illustrated in Figure 1; a plot of $\Delta G°$ vs. $\Delta H°$ gives a good straight line ($r = 0.962$) for the complexes of the common symmetrical crown ethers **5** with Na^+ and K^+. As can be seen from Table IV, the results for the ring-enlarged crown ethers are more complicated, and the contribution of the entropy factor cannot be ignored in combinations of a crown ether and a cation in which the cavity size and the ionic diameter are mismatched. Thus the plots for 16-crown-5 with K^+ and 19-crown-6 with Na^+ show significant deviation from the line in Figure 1, while those for the size-fitted combination 16-crown-5 with Na^+ and 19-crown-6 with K^+ are on the line. This result clearly indicates that the less symmetrical crown ethers **3** have to change their conformations to a greater extent than the symmetrical crown ethers **5** in forming complexes with the unfavorable, less size-fitted cations. This is the reason why 16-crown-5 shows an anomalously high relative cation selectivity for Na^+ over K^+. We therefore conclude that changing the methylene chain length of a crown ether can be a simple but powerful tool to control the cation-binding ability and cation selectivity through the change in both cavity size and conformation.

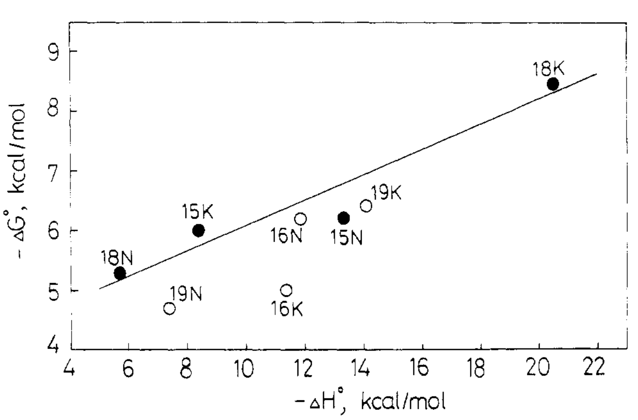

Figure 1. $\Delta G°$–$\Delta H°$ Relationship: Enthalpy-governed stability of cation complexes of common (●) and less symmetrical crown ethers (○); 15, 15-crown-5; 16, 16-crown-5; 18, 18-crown-6; 19, 19-crown-6; N, Na^+; K, K^+.

Experimental Section

General Procedures. Infrared spectra were obtained on a JASCO A-100 grating spectrophotometer. Melting points were measured with YANACO Micro Melting Point apparatus and are uncorrected. Mass spectra were measured at 20 or 70 eV by using a Hitachi RM-50GC or RMU-6E instrument. ^1H NMR spectra were recorded on a JEOL PMX-60 spectrometer in chloroform-*d* or carbon tetrachloride solution containing 1 or 2% tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded on a JEOL FX-60 spectrometer in chloroform-*d* solution containing 1% tetramethylsilane as an internal standard. UV-VIS spectra were recorded on a Shimadzu UV-300 spectrophotometer. Gas chromatographic analyses were performed on a YANACO G-180 instrument using a 75-cm column of 3% SE-30 or 10% Apiezon grease L + 10% Carbowax 20M (4:1).

Synthesis. Solvent tetrahydrofuran (THF) was distilled from sodium hydride. Commercially available reagents were used in the following syntheses without further purification unless noted otherwise.

3,6,9,12-Tetraoxatetradecane-1,14-diol (Pentaethylene Glycol, 1e). Potassium hydroxide (113.4 g, 1.72 mol) and ethylene glycol (400 mL) were introduced into a 1-L three-necked flask equipped with a magnetic stirrer, reflux condenser, and dropping funnel. To the stirred mixture at 100 °C was added 1,8-dichloro-3,6-dioxaoctane (triethylene glycol dichloride) (160.8 g, 0.86 mol). Stirring was continued for 24 h at 100 °C, and the mixture was cooled and filtered. The precipitate was washed with acetone and the filtrate was distilled under water pump vacuum to remove acetone and ethylene glycol. The residue was distilled under reduced pressure to give 91.5 g (45%) of **1e**: bp 175 °C (0.6 Torr) [lit.[9] 173–174 °C (0.6 Torr)]; ^1H NMR (CCl_4) δ 3.53–3.66 (m, 20 H), 3.16 (s, 2 H, OH); ^{13}C NMR (neat), δ 73.8 (t), 71.6 (t), 62.4 (t); IR (neat) 3400, 2870, 1460, 1100 cm^{-1}.

Oligoethylene Glycol Ditosylates (2a–d). General Procedure. Sodium hydroxide (21.0 g, 0.53 mol) dissolved in water (100 mL) and the oligoethylene glycol (0.15 mol) in THF (100 mL) were mixed in a flask. To the stirred mixture at 0 °C was added *p*-toluenesulfonyl chloride (62.9 g, 0.33 mol) in THF (150 mL) dropwise over 2 h, and stirring was continued for an additional 2 h at that temperature. The mixture was then poured into 10% aqueous hydrochloric acid at 0 °C. The precipitated

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[6] Pauling, L. "The Nature of the Chemical Bond", 3rd ed; Cornell University Press: Ithaca, NY, 1960; Chapter 13.

[7] Sadakane, A.; Iwachido, T.; Toei, K. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 60. Kimura, K.; Tsuchida, T.; Maeda, T.; Shono, T. *Talanta* **1980**, *27*, 801. Takeda, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 931.

[8] Osa, T., Ed. "Host-Guest Chemistry"; Kyoritsu Shuppan: Tokyo, 1979; Chapter 2.

[9] Newcomb, M.; Moore, S. S.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6405.

ditosylate was filtered, washed with water and aqueous dilute sodium hydrogen carbonate, and then dried in vacuo. Recrystallization from methanol gave the ditosylate in 79–89% yield.

Oily ditosylates were isolated in a different manner. After the addition to aqueous hydrochloric acid, the mixture was extracted twice with benzene. The combined benzene extract was washed with two portions of water, aqueous dilute sodium hydrogen carbonate, and then with water. The benzene extract was dried over anhydrous calcium chloride and the solvent was evaporated to give the oily ditosylate. Purification by column chromatography over silica gel with dichloromethane eluent gave the oily ditosylate in 81–83% yield. The yields of ditosylates obtained by use of NaOH and water/THF[10] were higher (79–89%) than those obtained with pyridine as a base/solvent (56–75%),[11] and the products were purer.

Diethylene Glycol Ditosylate 2a: yield 79%; mp 87.0–87.5 °C (lit.[12] 86–87 °C, lit.[13] 88–89 °C); MS (70 eV), *m/e* 414 (M^+). The ^{1}H NMR spectrum was in agreement with published data.[13]

Triethylene Glycol Ditosylate 2b: yield 89%; mp 80.0–81.0 °C (lit.[13] 80.5–81.5 °C); MS (70 eV), *m/e* 458 (M^+).

Tetraethylene Glycol Ditosylate 2c: yield 83%; viscous oil; MS (70 eV), *m/e* 502 (M^+).

Pentaethylene Glycol Ditosylate 2d: yield 81%; viscous oil; MS (70 eV), *m/e* 546 (M^+). The ^{1}H NMR spectrum was in agreement with published data.[14]

1,4-Butanediol ditosylate 2e was prepared in 67% yield (66.5 g) by the reaction of 1,4-butanediol (**1b**) (22.5 g, 0.25 mol) with *p*-toluenesulfonyl chloride (104.8 g, 0.55 mol) in pyridine according to the reported method.[15]

Crown Ethers. 1,4,7,10,13-Pentaoxacyclohexadecane (16-crown-5, 3a) was prepared by the reaction of 1,3-propanediol (**1a**) with tetraethylene glycol ditosylate (**2c**) in the presence of sodium hydroxide in THF.[4]

1,4,7,10,13-Pentaoxacycloheptadecane (17-Crown-5, 3b). Sodium hydroxide (6.0 g, 0.15 mol) and THF (300 mL) were introduced into a 1-L three-necked flask equipped with a magnetic stirrer, reflux condenser, dropping funnel, and nitrogen inlet tube. To the stirred suspension at 66 °C was added 1,4-butanediol (**1b**) (5.4 g, 0.06 mol) in THF (100 mL), and stirring was continued for 1 h at 66 °C with continuous bubbling of nitrogen. Tetraethylene glycol ditosylate (**2c**) (25.1 g, 0.05 mol) in THF (150 mL) was then added dropwise to the stirred mixture over 2 h, and stirring was continued for 24 h at 66 °C under a nitrogen atmosphere. The solvent was evaporated and the residue was extracted with chloroform. The chloroform extract was dried over magnesium sulfate and the solvent was evaporated. The subsequent distillation of the product under a reduced pressure gave 1.4 g (11%) of **3b**: bp 105–107 °C (0.13 Torr); MS (20 eV), *m/e* (relative intensity) 248 (M^+, 0.7), 89 (96), 73 (57), 71 (72), 45 (100). The ^{1}H NMR spectrum was in agreement with published data.[16]

1,4,7,10,13,16-Hexaoxacyclononadecane (19-crown-6, 3c) was prepared from 1,3-propanediol (**1a**) (3.8 g, 0.05 mol) and pentaethylene glycol ditosylate (**2d**) (21.8 g, 0.04 mol) in the presence of potassium hydroxide in THF according to the procedure described above. Distillation of the product gave 2.9 g (26%) of **3c**: bp 111–116 °C (0.09 Torr) [lit.[17] 115 °C (0.01 Torr)]; MS (20 eV), *m/e* 278 (M^+, 3), 89 (73), 45 (100). The ^{1}H NMR spectrum was in agreement with published data.[17]

1,4,7,10,13,16-Hexaoxacycloeicosane (20-crown-6, 3d) was prepared from **1b** (4.5 g, 0.05 mol) and **2d** (21.8 g, 0.04 mol) in the presence of potassium hydroxide in THF according to the procedure described above. Distillation of the product gave 1.4 g (12%) of **3d**. Likewise, reaction of pentaethylene glycol (**1e**) (9.5 g, 0.05 mol) and 1,4-butanediol ditosylate (**2e**) (15.9 g, 0.04 mol) gave 4.9 g (42%) of **3d**. The product obtained by both methods showed essentially identical spectra: bp 100–103 °C (0.28 Torr); MS (20 eV), *m/e* 292 (M^+, 0.9), 89 (95), 73 (62), 72 (64), 45 (100). Anal. Calcd for $C_{14}H_{28}O_6$: C, 57.51; H, 9.65. Found: C, 57.80; H, 9.84.

1,4,7,10,13,16-Hexaoxacyclodocosane (22-crown-6, 3e) was prepared from 1,6-hexanediol (**1c**) (5.9 g, 0.05 mol) and **2d** (21.8 g, 0.04 mol) in the presence of potassium hydroxide in THF according to the procedure described above. Distillation of the product gave 3.0 g (23%) of **3e**: bp 138–159 °C (0.39 Torr); MS (20 eV), *m/e* 320 (M^+, 2), 98 (62), 88 (85), 83 (71), 72 (58), 45 (100). Anal. Calcd for $C_{16}H_{32}O_6$: C, 59.97; H, 10.07. Found: C, 59.54; H, 10.20.

1,4,7,11,14,17-Hexaoxacycloeicosane (*sym*-20-crown-6, 4a) was prepared from **1a** (4.6 g, 0.06 mol) and diethylene glycol ditosylate (**2a**) (16.6 g, 0.04 mol) in the presence of potassium hydroxide in THF according to the procedure described above. Distillation of the product gave 0.85 g (15%) of **4a**: bp 100–110 °C (0.12–0.15 Torr); MS (20 eV), *m/e* 292 (M^+, 0.2), 103 (58), 59 (65), 45 (100). Anal. Calcd for $C_{14}H_{28}O_6$: C, 57.51; H, 9.65. Found: C, 57.72; H, 9.86.

1,4,7,12,15,18-Hexaoxacyclodocosane (*sym*-22-crown-6, 4b) was prepared from **1b** (5.4 g, 0.06 mol) and **2a** (16.6 g, 0.04 mol) in the presence of potassium hydroxide in THF according to the procedure described above. Distillation of the product gave 0.3 g (5%) of **4b**. Likewise, reaction of diethylene glycol (**1d**) (5.3 g, 0.05 mol) and **2e** (16.0 g, 0.04 mol) gave 1.9 g (29%) of **4b**. The products obtained by both methods showed essentially identical spectra: bp 135–145 °C (0.15 Torr); MS (70 eV), *m/e* 320 (M^+, 0.4), 161 (65), 117 (96), 114 (53), 73 (78), 71 (100). Anal. Calcd for $C_{16}H_{32}O_6$: C, 59.97; H, 10.07. Found: C, 59.80; H, 10.09.

2,5,8,11,14,17-Hexaoxaoctadecane (pentaglyme, 6b) was prepared from ethylene glycol monomethyl ether (5.3 g, 0.07 mol) and triethylene glycol ditosylate (**2b**) (13.8 g, 0.03 mol) in the presence of sodium hydroxide in THF according to the procedure described above. Distillation of the product gave 3.7 g (46%) of **6b**: bp 100–108 °C (0.27 Torr) [lit.[18] 120–123 °C (0.25 Torr)]; MS (20 eV), *m/e* 266 (M^+). Anal. Calcd for $C_{12}H_{26}O_6$: C, 54.12; H, 9.84. Found: C, 54.19; H, 10.11.

Alkali Metal Picrates. Picric acid (containing 12–15% water, Nakarai Chemical Co.) was recrystallized from water and dried in vacuo at room temperature in the dark. Sodium, potassium, rubidium, and cesium picrates were prepared from picric acid and the corresponding metal hydroxide according to the procedure described in the literature.[19] As they are heat and shock sensitive,[20] caution should be used in their synthesis; they should be handled with plastic spoons, as should picric acid. They are dried under reduced pressure at room temperature and stored in the dark.

Extraction. Commercially available tetraglyme (Nakarai Chemical Co.), 15-crown-5 (Nisso Co.), and 18-crown-6 (Nisso Co.) were used without further purification. Distilled dichloromethane and demineralized water were used. The solvents were saturated with each other before use in order to prevent volume changes of the phases during extraction. The extraction procedures were similar to those described by us[4] and by Kimura et al.[21] Equal volumes (10 mL) of a dichloromethane solution of a crown ether (3×10^{-3} M) and of an aqueous alkali metal picrate (3×10^{-3} M) were introduced into an Erlenmeyer flask, which was then stoppered and shaken for 10 min at 25.0 ± 0.1 °C using a TAIYO M100L incubator. This period of shaking was enough to establish equilibrium between the two phases, since shaking periods of 20 and 40 min gave the same results. The mixture was then allowed to stand for at least 2 h at that temperature in order to complete phase separation. After phase separation, 2 mL of the dichloromethane phase was withdrawn, to which 2 mL of acetonitrile was added. After further dilution, if necessary, with a 1:1 mixture

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(10) We are indebted to Dr. S. Yanagida, Osaka University, for his suggestion to use water as a solvent in the tosylate synthesis. Tosylates of other common alcohols, however, were prepared in lower yields in this method.

(11) Our results according to the procedures reported.[13]

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of dichloromethane and acetonitrile, the picrate concentration in the organic phase was determined from its absorption at 375 nm. The molar extinction coefficients at 375 nm for sodium, potassium, rubidium, and cesium picrates are 18600, 19000, 18800, and 18500 M^{-1} cm^{-1}, respectively.

In the experiments to determine extraction equilibrium constants (K_{ex}), dichloromethane solution of a crown ether of various concentrations (1×10^{-3} to 2×10^{-2} M) and aqueous alkali metal picrates (3×10^{-3} M) were brought to equilibrium at 25.0 ± 0.1 °C by the same procedure. With 15- and 16-crown-5 and 18- and 19-crown-6, the K_{ex} values were determined at several temperatures between 10 and 25 °C.

The free crown ether concentration in the organic phase, $[\mathrm{CE}]_{\mathrm{org}}$, was calculated by eq 2, described in our preceding paper.[4] $[\mathrm{CE}]_i$

$$[\mathrm{CE}]_{\mathrm{org}} = ([\mathrm{CE}]_i - n[\mathrm{M(CE)}_n\mathrm{A}_{\mathrm{org}}])/(1 + K_D) \qquad (2)$$

is the initial concentration of crown ether dissolved in the organic phase, and K_D is the distribution coefficient of crown ether between the two phases ($K_D = [\mathrm{CE}]_{\mathrm{aq}}/[\mathrm{CE}]_{\mathrm{org}}$).

In control experiments, detectable amounts of picrates were not extracted into the organic phase in the absence of crown ethers.

Distribution of crown ethers was determined by the procedure in our preceding paper.[4] Equal volumes (10 mL) of dichloromethane solution of a crown ether (3×10^{-3} and 5×10^{-3} M) and demineralized water, which was saturated with distilled dichloromethane, were brought to equilibrium at 25.0 °C under the conditions used for extraction. The concentration of the crown ether in the organic phase was determined by gas chromatographic analysis using cyclododecane or bicyclohexyl as an internal standard. The average distribution coefficients, K_D, for 15-crown-5 (**5a**), 16-crown-5 (**3a**), 17-crown-5 (**3b**), 18-crown-6 (**5b**), 19-crown-6 (**3c**), and 20-crown-6 (**3d**) were determined in several runs to be 0.31, 0.18, 0.06, 0.10, 0.12, and 0.08, respectively. The value of K_D did not change significantly between 10 and 25 °C.

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Registry No. **1a**, 504-63-2; **1b**, 110-63-4; **1c**, 629-11-8; **1e**, 4792-15-8; **2a**, 7460-82-4; **2b**, 19249-03-7; **2c**, 37860-51-8; **2d**, 41024-91-3; **2e**, 4724-56-5; **3a**, 55471-28-8; **3b**, 62991-38-2; **3c**, 55471-27-7; **3d**, 62991-36-0; **3e**, 89144-63-8; **4a**, 54308-73-5; **4b**, 62708-71-8; **5a**, 33100-27-5; **5b**, 17455-13-9; **6a**, 143-24-8; **6b**, 1191-87-3; sodium picrate, 3324-58-1; potassium picrate, 573-83-1; rubidium picrate, 23296-29-9; cesium picrate, 3638-61-7; 1,8-dichloro-3,6-dioxaoctane, 112-26-5; ethylene glycol, 107-21-1; ethylene glycol monomethyl ether, 109-86-4.

Supplementary Material Available: ^{1}H NMR and ^{13}C NMR and IR spectra of glycol ditosylates and crown ethers (2 pages). Ordering information is given on any current masthead page.

Strained Aromatic Systems. Synthesis of Dicyclobuta[1,2:3,4]naphthalenes, Dicyclobuta[1,2:3,4]anthracene, and Tricyclobutabenzene

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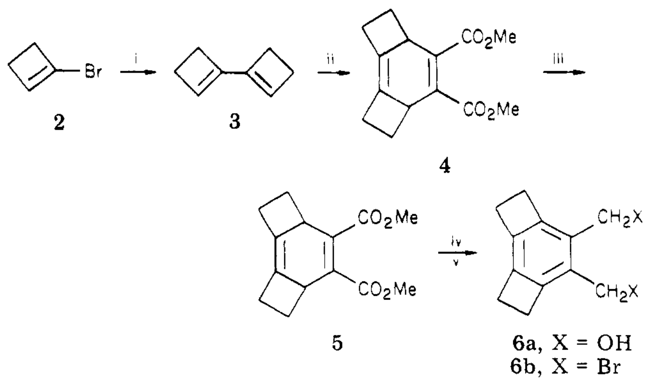
The syntheses of tricyclobuta[1,2:3,4:6,7]naphthalene (**1a**), dicyclobuta[1,2:3,4]cyclopenta[6,7]naphthalene (**1b**), and dicyclobuta[1,2:3,4]cyclohexa[6,7]naphthalene (**1c**) are described via a route involving annelation of the appropriate dilithiated 1,2-diester with 5,6-bis(bromomethyl)dicyclobutabenzene (**6b**). The ^{13}C NMR spectra of this series of annelated naphthalenes indicate a considerable change in hybridization at the C-5(8) atoms. A similar synthetic route to dicyclobuta[1,2:3,4]anthracene (**14**), presently the only known anthracene derivative annelated by two small rings on one phenyl ring, is described, and the ^{13}C NMR spectrum indicates a similar strain as for **1c**. An alternative preparation of tricyclobutabenzene (**21**) by a route involving pyrolysis of the sulfoxide derived from **6b** is outlined.

Benzene, naphthalene, and their higher homologues are more readily susceptible to out-of-plane rather than in-plane distortions.[1] Changes in the aromatic character of benzenoid systems are thus more likely to become manifest in compounds in which the aromatic rings have undergone bond angle and bond length distortion. Such systems might also exhibit the elusive Mills–Nixon effect.[2] We describe the synthesis of a series of dicyclobuta[1,2:3,4]-naphthalenes, which are annelated by a third carbocyclic ring in the 6,7-position, the preparation of dicyclobuta[1,2:3,4]anthracene, and an alternative route to tricyclobutabenzene and discuss some properties of these compounds.[3]

Results and Discussion

Tricyclobuta[1,2:3,4:6,7]naphthalene (1a), Dicyclobuta[1,2:3,4]cyclopenta[6,7]naphthalene (1b), and Dicyclobuta[1,2:3,4]cyclohexa[6,7]naphthalene (1c). We have recently introduced a method of annelation utilizing the reaction of dilithiated vicinal diesters and carboximides with benzylic α,ω-dihalides,[4] and we have employed this reaction in the synthesis of compounds **1a–c**.

Scheme I[a]



[a] i, Mg, $Cu_2(I)Cl_2$, ii, $MeO_2CC{\equiv}CCO_2Me$, Δ; iii, DDQ; iv, $LiAlH_4$, THF; v, PBr_3.

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