ketones by a standard procedure.[23]

General Procedure for the Reaction of Silyl Enol Ethers with *p*-NPSP. The silyl enol ether (1.65 mmol) was dissolved in a mixture of ethyl acetate (30 mL) and water (0.6 ml), and *p*-NPSP (0.60 g, 1.5 mmol) was added as a solid. The mixture was stirred vigorously at room temperature. The peroxide dissolved, the reaction took on a yellow color, and the active oxygen was monitored by quenching a small amount in 10% potassium iodide/acetic acid (1:1). After all the peroxide was consumed, the reaction was extracted with 2.5 M hydrochloric acid (2 × 20 mL) and water (2 × 20 mL), dried ($MgSO_4$), and evaporated to give a pale oil that solidified. Products **2**, **6**, **8**, **10**, **12**, and **14** were prepared by this method. The crude products generally showed no detectable impurities in the ^1H NMR spectra, and TLC analyses likewise showed only the α-nosyl ketone. Occasionally trace amounts of the parent ketone were detected in the product. Crystallization from ethyl acetate/hexane gave analytically pure materials. These products were identified by comparison to authentic samples.[8]

2,4-Dimethyl-2-[(*p*-nitrophenyl)sulfonoxy]-3-pentanone (16). To a solution of 2,4-dimethyl-3-(trimethylsiloxy)-2-pentene (**15**; 0.28 g, 1.5 mmol) in ethyl acetate (30 ml) was added *p*-NPSP (0.60 g, 1.5 mmol). The pale yellow mixture was stirred at room temperature for 20 h, at which time iodometry showed that all the peroxide was consumed. Workup as above yielded 0.36 g (77%) of a clear oil that showed only one component by TLC. Recrystallization from ethyl acetate/hexane gave **16** as a white solid: mp 84.5–85.5 °C; IR ν 3120 (aromatic CH), 2980–2880 (aliphatic CH), 1725 (C=O), 1610 (aromatic C=C), 1540 (NO_2), 1360, 1190 (SO_3) cm^{-1}; ^1H NMR δ 1.15 (d, J = 7 Hz, 6 H, $CH(CH_3)_2$, 1.72 (s, 6 H, CH_3), 3.2 (h, J = 7 Hz, 1 H, CH), 8.25 (AA′BB′, 4 H, aromatic H). Anal. Calcd for $C_{13}H_{17}NO_4S$: C, 49.67; H, 5.43; N, 4.46; S, 10.20. Found: C, 49.57; H, 5.53; N, 4.26; S, 10.01.

3-[(*p*-Nitrophenyl)sulfonoxy]norbornanone (18). To a solution of 2-(trimethylsiloxy)norbornene (**17**; 0.60 g, 3.3 mmol) in ethyl acetate (60 ml) was added *p*-NPSP (1.2 g, 3 mmol). The mixture was stirred at room temperature 24 h and worked up as above to give 0.87 g (95%) of a tan solid that had only one component by TLC. Recrystallization from ethyl acetate/hexane gave pure **18** as pale yellow crystals: mp 137.5–139 °C; IR ν 3105 (aromatic CH), 2950–2880 (aliphatic CH), 1760 (C=O), 1605 (aromatic C=C), 1532 (NO_2), 1360, 1185 (SO_3) cm^{-1}; ^1H NMR δ 1.4–2.6 (m, 6 H), 2.6 (br s, 1 H), 2.82 (br s, 1 H), 4.18 (d, J = 3 Hz, 1 H, C*H*ONs), 8.25 (AA′BB′, aromatic H). Anal. Calcd for $C_{13}H_{13}NO_6S$: C, 50.15; H, 4.21; N, 4.50. Found: C, 50.20; H, 4.09; N, 4.33.

The stereochemistry of **18** is probably exo as evidenced by the coupling constant J = 3 Hz of the methine proton at δ 4.18. The analogous exo triflate has J = 2.8 Hz whereas the endo isomer has J = 5 Hz.[24]

General Procedure for the Reaction of Enamines with *p*-NPSP. A solution of the enamine (1.1–1.2 equiv) in ethyl acetate (50 mL) was cooled in dry ice. Methanol (1 mL) and then *p*-NPSP (0.6 g, 1.5 mmol) were added. The mixture was stirred vigorously, it became homogeneous, and then some precipitate formed. The reaction was monitored for active oxygen with potassium iodide/acetic acid. When the active oxygen was gone, the reaction was extracted with 2.5 M hydrochloric acid (2 × 20 mL) and water (2 × 20 mL), dried ($MgSO_4$), and evaporated to yield the solid α-nosyl ketone. Usually no byproducts were observed by ^1H NMR or TLC. Occasionally, traces of the parent ketone could be detected; however, the crude product is sufficiently pure for most purposes.

Preparation of 25. To a solution of boron trifluoride etherate (0.213 g, 1.5 mmol) and deoxybenzoin (0.294 g, 1.5 mmol) in dichloromethane was added *p*-NPSP (0.60 g, 1.5 mmol). The peroxide was not completely soluble at first; however, the mixture was stirred at room temperature for 3 h to give a homogeneous solution that was devoid of active oxygen. After storage at −20 °C overnight, the reaction was extracted with water (2 × 50 mL), saturated sodium chloride (50 mL), and water (50 mL). The organic layer was dried ($MgSO_4$) and evaporated to give a pale yellow oil (0.53 g, 89%) that had one principal component and a small amount of deoxybenzoin by TLC. Recrystallization from ethyl acetate/hexane gave pure **25**: mp 99–101 °C; IR ν 3077 (aromatic CH), 1668 (C=O), 1604 (aromatic C=C), 1530 (NO_2), 1360, 1190 (SO_3) cm^{-1}; ^1H NMR δ 6.84 (s, 1 H, methine CH), 7.3 (br m, 8 H, aromatic H), 7.85 (d, 2 H, aromatic H σ to C=O), 8.12 (AA′BB′, nosyl H). Anal. Calcd for $C_{20}H_{15}NO_6S$: C, 60.45; H, 3.77; N, 3.52. Found: C, 60.22; H, 3.70; N, 3.61.

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Registry No. 1, 6651-36-1; 2, 98990-62-6; 5, 17510-47-3; 6, 98990-63-7; 7, 13735-81-4; 8, 98990-64-8; 9, 37471-46-8; 10, 98990-64-8; 11, 38858-72-9; 12, 98990-65-9; 13, 1833-53-0; 14, 98990-66-0; 15, 55339-64-5; 16, 98990-67-1; 17, 57722-40-4; 18, 98990-68-2; 19, 670-80-4; 20, 13654-48-3; 21, 39655-41-9; 22, 31401-28-2; 23, 5024-92-0; 25, 87119-38-8; $PhCOCH_2Ph$, 451-40-1; bis[(*p*-nitrophenyl)sulfonyl] peroxide, 6209-72-9; bis[(*m*-trifluoromethyl)phenylsulfonyl] peroxide, 35673-10-0; boron trifluoride etherate, 109-63-7.

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Unsaturated Crown Ethers. 3.[1] Syntheses of Stilbeno Crown Ethers[2]

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A series of 6-, 9-, and 15-membered monostilbeno crown ethers (**3**) and 18-, 24-, and 30-membered distilbeno crown ethers (**4**), some of which are new compounds, were synthesized in the base-induced reactions of benzoin (**1**) with oligoethylene glycol ditosylates (**2a–d**) in homogeneous and heterogeneous solutions. The template effect is shown to be effective in controlling product yields and **4**/**3** ratios.

Except for the areno crown ethers with benzo and naphtho substituents, unsaturated crown ethers possessing C–C double, or triple, bond(s) on the crown ring have not been synthesized extensively.[3-7] Merz[4a] first prepared the

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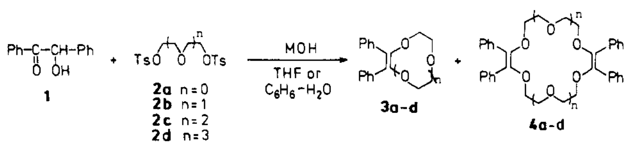
Scheme I



9- and 18-membered unsaturated crown ethers carrying stilbene chromophore(s) in the reaction of stilbenediol dianion, prepared from benzoin under the phase-transfer conditions, with diethylene glycol ditosylate. We have recently shown that this versatile synthetic method is applicable to the preparation of higher homologues.[2]

The unsaturated crown ethers are of much interest, since the double bond may affect the crown ether's complexation through its potential incorporation as a soft π donor and increased rigidity due to the fixed OC═CO linkage. The prochiral and UV-absorbing double bond also enables a wide variety of derivations including the partial[2,4c] and complete[2] hydrogenations, the photochemical isomerization to the (*E*) isomer or cyclization to phenanthro crown ethers[8] and the singlet oxygenation to chemiluminescent dioxetano crown ethers.[1]

In this paper, we report the extended and improved syntheses of 6-, 9-, and 15-membered monostilbeno crown ethers and 18-, 24-, and 30-membered distilbeno crown ethers, in which the mono/di ratios are controlled to some extent by utilizing the template effect[9] in homogeneous solutions.

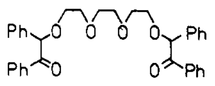
Results

The reactions of benzoin (1) with mono-, di-, tri-, and tetraethylene glycol ditosylates (**2a–d**) in the presence of a series of alkali metal hydroxides were performed in homogeneous solutions and comparatively in heterogeneous solutions under the phase-transfer conditions employed previously by Merz[4a] and us.[2] In most cases, the major course of the reaction was the cyclizations of 1/1 and/or 2/2 stoichiometries, giving rise to the mono- and/or distilbeno crown ethers **3** and **4** (Scheme I). The product yields under various reaction conditions were determined by liquid chromatography (LC) and listed in Table I.

The reactions of **1** with ethylene glycol ditosylate **2a** gave only the 1/1 product, 2,3-diphenyl-1,4-dioxene (**3a**), in all runs A1–6, and no peak corresponding to the 2/2 product, distilbeno-12-crown-4 (**4a**), was detected on LC. The reaction with sodium hydroxide under the phase-transfer conditions gave good yield of **3a** as had been reported.[10] By contrast, the reactions with lithium, sodium, and potassium hydroxides in the homogeneous solutions all led merely to poor yield in this particular case.

Diethylene glycol ditosylate **2b** gave stilbeno 9-crown-3 (**3b**) and distilbeno 18-crown-6 (**4b**) in good combined yields in both homogeneous and heterogeneous phase reactions of **1**, runs B1–7. The **4**/**3** ratio however varied with the base used and the conditions applied. In homogeneous solution, the major product was the 2/2 product **4b**, and potassium, rather than sodium, hydroxide gave better yield. On the other hand, the results in the heterogeneous solution are puzzling. Although the reaction temperature and the phase-transfer catalyst used appear to affect little either the yield or the **4**/**3** ratio (runs B3–5 or B6, 7), the metal hydroxide employed has significant influence on the **4**/**3** ratio; sodium hydroxide gives the 1/1 product **3b** preferentially, while potassium hydroxide the 2/2 product **4b**. This result seems curious since it is presumed that the countercation brought into the organic phase is not metal ion but ammonium ion. However, it is revealed later that this is not the case and the stilbeno crown ether produced does function as a phase-transfer catalyst, taking a metal ion from aqueous phase to organic phase.

Triethylene glycol ditosylate **2c** gave distilbeno 24-crown-8 **4c** in relatively good yields in both homogeneous and heterogeneous solutions, runs C1–5. However, only a negligible peak that might be ascribable to stilbeno 12-crown-4 **3c** was detected on LC at the expected elution volume but could not be isolated. From the mechanistic point of view, it is interesting to note that, in addition to the cyclic 2/2 product **4c**, a small amount (0.9% yield) of triethylene glycol dibenzoin ether **5c** was isolated by column chromatography from the reaction mixture obtained in run C5.



5c

The reactions of **1** with tetraethylene glycol ditosylate (**2d**) were performed under a wide variety of conditions to give stilbeno 15-crown-5 (**3d**) and distilbeno 30-crown-10 (**4d**) in good yields. This combination of substrates is most widely investigated, since this system is appropriate to assess whether or not the template effect indeed works and controls the 2/2 and 1/1 product ratio, **4**/**3**.

The effects of reaction period and the countercation were first examined in THF by using the full set of alkali metal hydroxide, runs D1–12. With lithium hydroxide, the reaction was extremely slow and the yields were poor even after 60-h refluxing, although the 1/1 product **3d** was produced predominantly, runs D1,2. With sodium hydroxide, the maximum yield was obtained at the reaction time of 15 h and the shortened or prolonged reaction time resulted in the reduced yields, runs D3–5. The use of a 4.0, instead of a 2.5, molar excess of the base did not improve or diminish the product yields, indicating that the nearly stoichiometric amount of the base is enough to obtain the optimized yield, runs D4,6. As compared with sodium, potassium hydroxide gave much higher **4**/**3** ratios of 0.18–0.24, although the value varies somewhat with the reaction period, runs D7,8. With rubidium and cesium hydroxides, still increased **4**/**3** ratios of 0.23–0.33 were observed and the 5-h, rather than 15-h, refluxing gave better yields, runs D9–12. In summary, the **4**/**3** ratio increases from the lowest value of 0.02 for lithium up to 0.33 for cesium with increasing cation diameter.

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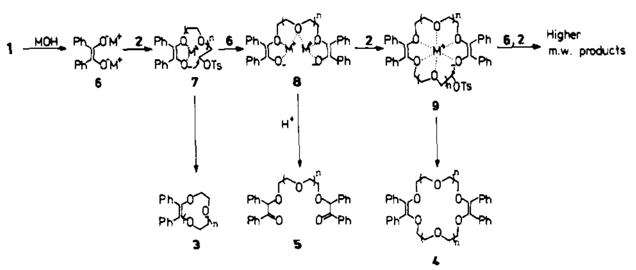
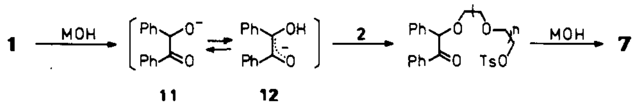
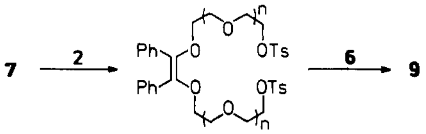
Scheme II



Scheme III



Scheme IV



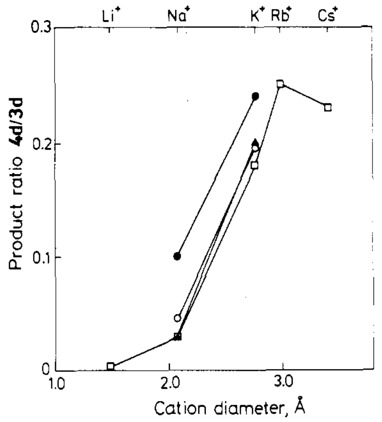


Figure 1. Product ratio **4d**/**3d** as a function of cation diameter upon alkali metal hydroxide induced reaction of benzoin (**1**) with tetraethylene glycol ditosylate (**2d**) in THF (□), 1,4-dioxane (▲), benzene/water with phase-transfer catalyst (○), and benzene/water without phase-transfer catalyst (●).

In order to evaluate the effects of solvent and temperature upon the **4**/**3** ratio, the same reaction was carried out in dioxane at 35–101 °C, runs D13–19. As to the temperature effect, no significant difference in the **4**/**3** ratio was observed within this temperature range in both sodium and potassium cases; the ratios for sodium and potassium hydroxides were 0.03–0.05 and 0.14–0.20, respectively. These ratios are also in good agreement with the corresponding values in THF; for the solvent effect, compare run D4 with D16 for sodium hydroxide and run D8 with D18 for potassium hydroxide. Thus, the **4**/**3** ratio is shown to be insensitive to the temperature and solvent changes as long as the reaction is conducted in the homogeneous solutions.

For comparison purpose, the reactions in benzene/water in the presence of a phase-transfer catalyst were repeated under a variety of conditions. First examined were the effects of the concentration and molar excess of the base used, runs D20–25. Both concentration and molar excess of the base dissolved in the aqueous phase were shown to be important factors, runs D20–23. The use of a 10% aqueous solution resulted in the total recovery of the starting materials, while the 33% solution containing the same amount of the base gave **3d** in a considerably improved yield under comparable conditions, runs D20,21. When the molar excess of base was increased from 2.5 to 12.5, the yields of **3d** and **4d** increased gradually up to 48 and 4.8%, respectively, runs D21–23. It is noted that, in contrast to the homogeneous phase reactions, a substantially large excess of base is needed to obtain satisfactory yields in the phase-transfer reactions. The structure and amount of ammonium salt had no significant influence on the yield, runs D25,26. For all phase-transfer runs with sodium hydroxide, the **4**/**3** ratios observed are in the range of 0.02–0.05, which interestingly coincide with those in the homogeneous phase reactions. The reactions with potassium hydroxide under the phase-transfer conditions also gave the **4**/**3** ratios very close to those obtained in the homogeneous solutions; compare runs D7,8,18 with D28–30. These unexpected results may be rationalized by assuming that, except for the initial stages of the reaction, the phase-transfer catalyst mainly working is not the ammonium salt added initially but the stilbeno crown ethers produced in the course of the reaction.[11] Indeed, the reactions in benzene/water and even in dry benzene without added ammonium salt did afford the stilbeno crown ethers in comparable or somewhat lower yields, indicating effectiveness of the crown ether as a phase-transfer catalyst, runs D27,28,32,33.

Discussion

The general reaction mechanism proposed for the formation of mono- and distilbeno crown ethers **3** and **4** is shown in Scheme II. The stilbenediol dianion **6** is postulated as the primary reactive species, and the scheme starts with this dianion, although the stepwise mechanism according to Merz, in which the stilbenediol monoanions **10** and/or **11** intervene as shown in Scheme III, may not be ruled out rigorously. In any case, the monoanion **7** produced may cyclize to afford monostilbeno crown ether **3** as the 1/1 product or react with another stilbenediol dianion **6** to generate the dianionic intermediate **8**. Again, the possible contribution of the alternative route from **7** to **9**, shown in Scheme IV, is not eliminated strictly, but we prefer the mechanism shown in Scheme II since the isolation of the 2/1 product **5c** is the direct evidence in support of the intervention of **8**. The dianionic intermediate **8** reacts with another ditosylate **2** to give **9**, which in turn either cyclizes to distilbeno crown ether **4** or further reacts successively with yet another **6** and **2**, giving rise to higher molecular weight products.

The product ratios, and yields as well, observed under various reaction conditions may be accounted for within the framework of this cascade mechanism shown in Scheme II. The template effect[9] in the intermediate anions **7** and **9** is obviously one of the dominant factors that determine the fate of the anions, although the steric effect is also another important factor. The presence of a cation of appropriate size facilitates the ligation of the oxyethylene chain, and the intermediate anion **7** or **9** forms a pseudocavity to accommodate the cation. Therefore, when there is a cation size fitted to the pseudocavity of **7**, the cyclization of **7** is accelerated to give the 1/1 product **3** predominantly, and the higher homologues including **4** are produced only in limited yields. If the cation available is too large for the cavity of **7**, the cyclization process to **3** is retarded more or less and further reactions, with **6** and **2**, instead become dominant to give the anion **9**, in which the template effect by the larger cation may operate as is

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[11] This possibility has been suggested by Gokel and Korzeniowki, see: Reference 3, p 42.

Table I. Reactions of Benzoin (1) with Oligoethylene Glycol Ditosylates (2a–d) in Tetrahydrofuran or 1,4-Dioxane and in Benzene–Water with and without Phase-Transfer Catalyst

no.	tosylate	solv	temp, °C	base (molar ex)	phase-transfer catalyst	reactn time, h	yield,^{a} % 3	yield,^{a} % 4	product ratio:^{b} 4/3
A1	**2a**	THF	67	LiOH (2.5)	none	60	13	*c*	*d*
2				NaOH (2.5)	none	15	15	*c*	*d*
3						30	14	*c*	*d*
4				KOH (2.5)	none	15	20	*c*	*d*
5		C_6H_6/H_2O	76	NaOH^{e} (12.5)	(TBA)Br^{f}	15	78 (66)^{g}	*c*	*d*
6				KOH^{e} (8.9)	(TBA)Br^{f}	15	42	*c*	*d*
B1	**2b**	THF	67	NaOH (2.5)	none	15	1.9	6.7	1.8
2				KOH (2.5)	none	15	5.7	28 (25)^{g}	2.5
3		C_6H_6/H_2O	60	NaOH^{e} (12.5)	(TBA)Br^{f}	15	(19)^{g}	(5.6)^{g}	(0.15)
4			76	NaOH^{e} (12.5)	(TBA)Br^{f}	15	(20)^{g}	(7.1)^{g}	(0.18)
5					(HDT)Br^{h}	15	28 (24)^{g}	14 (9)^{g}	0.25
6				KOH^{e} (8.9)	(TBA)Br^{f}	15	(9)^{g}	(24)^{g}	(1.3)
7					(HDT)Br^{h}	15	16 (9)^{g}	24 (23)^{g}	0.75
C1	**2c**	THF	67	LiOH (2.5)	none	15	*c*	*c*	
2				NaOH (2.5)	none	15	*c*	20	*i*
3				KOH (2.5)	none	15	*c*	36	*i*
4		C_6H_6/H_2O	76	NaOH^{e} (12.5)	(HDT)Br^{h}	15	*c*	34 (33)^{g}	*i*
5				KOH^{e} (8.9)	(HDT)Br^{h}	15	*c*	24 (21)^{g}	*i*
D1	**2d**	THF	67	LiOH (2.5)	none	15	7.9	*c*	*d*
2						60	14	*c*	*d*
3				NaOH (2.5)	none	5	47	3.0	0.03
4						15	59^{j} (57)^{g}	3.6^{j}	0.03
5						25	35	1.8	0.03
6				(4.0)	none	15	55	3.6	0.03
7				KOH (2.5)	none	5	33	12	0.18
8						15	45	22	0.24
9				RbOH (2.5)	none	5	28^{j}	14^{j}	0.25
10						15	19	12	0.32
11				CsOH (2.5)	none	5	24	11	0.23
12						15	20	13	0.33
13		dioxane	35	NaOH (2.5)	none	30	37	3.7	0.05
14				KOH (2.5)	none	15	52	15	0.14
15						30	37	13	0.18
16			50	KOH (2.5)	none	15	41	15	0.18
17			67	NaOH (2.5)	none	15	45	2.5	0.03
18				KOH (2.5)	none	15	35	14	0.20
19			101	KOH (2.5)	none	4	37	12	0.16
20		C_6H_6/H_2O	76	NaOH^{k} (2.5)	(TBA)Br^{f}	15	*c*	*c*	
21				NaOH^{e} (2.5)	(TBA)Br^{f}	15	22	*c*	*d*
22				(5.0)	(TBA)Br^{f}	15	45	3.6	0.04
23				(12.5)	(TBA)Br^{f}	15	48	4.8	0.05
24						30	38	3.0	0.04
25					(TBA)Br (×4)^{l}	15	41	1.5	0.02
26					(HDT)Br^{h}	15	43	3.6	0.04
27				(8.9)	none	15	27	5.4	0.10
28				(12.5)	none	60	28	5.4	0.10
29				KOH^{e} (8.9)	(TBA)Br^{f}	15	18	7.0	0.19
30						45	20	6.4	0.16
31					(HDT)Br^{h}	15	15	5.9	0.20
32						42	(16)^{g}	(14)^{g}	(0.43)
33					none	60	18	8.7	0.24
34		C_6H_6	72	KOH^{m} (8.9)	none	60	8.8	1.8	0.10

[a] Yield determined by HPLC, unless noted otherwise. [b] Molar ratio. [c] Yield less than 0.5%. [d] Less than 0.02. [e] A 33% aqueous solution used. [f] Tetrabutylammonium bromide (0.016 molar equiv of 1). [g] Isolated yield by column chromatography. [h] Hexadecyltrimethylammonium bromide (0.016 molar equiv of 1). [i] Very large (≫10). [j] Average of two independent runs, error ± 2%. [k] A 10% aqueous solution used. [l] Tetrabutylammonium bromide (0.064 molar equiv of 1). [m] Finely ground powder.

the case with 7, if the sizes of cation and cavity match. The cation diameters reported[12] and the cavity sizes of 9- to 30-membered crown ethers estimated by CPK space-filling molecular models are shown in Table II.

The situation of this kind has been achieved in the syntheses of the 15- and 30-membered crown ethers **3d** and **4d**, in which the product ratio is drastically affected by the cation available in the organic phase. In Figure 1, the **4d**/**3d** ratios at the initial stages of the reactions in THF, dioxane, and benzene/water are plotted as functions of cation diameter. The **4**/**3** ratio increases with increasing cation diameter at least up to 3 Å and then levels off. This tendency roughly agrees with the cation selectivity of the

Table II. Estimated Cavity Size and Cation Diameter

crown ether	cavity diam,^{a} Å	cation	diam,^{b} Å
9-crown-3	0	Li^+	1.44
12-crown-4	1.2	Na^+	2.04
15-crown-5	1.7	K^+	2.76
18-crown-6	2.6	Rb^+	2.98
24-crown-8	2.0–4.9^{c}	Cs^+	3.40
30-crown-10	2.7–6.7^{c}		

[a] Estimated by CPK space-filling molecular model. [b] Reference 12. [c] For these crown ethers, the minimum and maximum values refer to the cavities for "encapsulating" complexation and for extended "formal" ring, respectively.

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[12] Shannon, R. D.; Prewitt, C. T. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1969**, *B25*, 925.

30-crown-10 **4d** assessed by the conventional solvent extraction technique; the percent extractabilities for sodium, potassium, rubidium, and cesium picrates were 8.0, 62.8, 47.4, and 25.7, respectively, under our "standard" extraction conditions employed widely.[13]

However, in the other combinations, i.e. **1** and **2a–c**, the situation is not so simple as the preceding discussion. The template effect is no longer almighty in rationalizing the **4**/**3** ratios in runs A–C, since the effective template effect that enhances cyclization of **7** to **3** will not work in these systems because of the mismatched pseudocavity for the cations used and also the diminished number of donor oxygens. The feasibility of the cyclization depends solely on the steric effect in **7**. As can be seen from Table I, the 6- and 9-membered stilbeno crown ethers **3a**,**b** are produced in fair to good yields in spite of the absence of size-fitted cation, whereas the 12-membered crown ethers **3c** and **4a**, as well, are not obtained in isolable yield. This suggests that the cyclization giving 12-membered polyoxyethylene ring is energetically unfavorable and the subsequent formations of the 2/2 or higher homologues are prefered. Similar observations have been reported in the syntheses of 3*m*-crown-*m*; in contrast to the good cyclization yields for 15- and 18-membered crown ethers, 12-crown-4 derivatives have been prepared in considerably lower yields.[3] This tendency is somewhat different from the strain energy trend of cycloalkanes, in which the highest strains are found in 9- and 10-membered rings.[14] Although this discrepancy between polyoxyethylene and all-carbon macrocycles may be rationalized by the more flexible COC linkages in the oxyethylene chains, the reason for the hindered cyclization to 12-membered stilbeno crown ethers in the present case is not necessarily clear.

Conclusion

A wide variety of mono- and distilbeno crown ethers can be prepared in the base-induced reactions of benzoin with the corresponding oligoethylene glycol ditosylates in homogeneous solution as well as in heterogeneous solution under Merz's phase-transfer conditions. The product yields and monostilbeno/distilbeno crown ether ratios can be controlled by selecting appropriate reaction conditions, mainly the solvent and cation used. The template effect in the intermediate anions plays the major role in determining product ratio even under the phase-transfer conditions, although the steric effect may not be neglected when the sizes of cation and cavity mismatch.

Experimental Section

Infrared spectra were recorded as KBr disks on a Jasco A-100 instrument. Melting points were measured with a Yanaco MP apparatus and are uncorrected. Mass spectra were measured at 70 eV on a Hitachi RMU-6E instrument. ^{1}H NMR spectra were recorded on a JEOL PMX-60 spectrometer in chloroform-*d* solution containing 1% tetramethylsilane (Me$_4$Si) as an internal standard. ^{13}C NMR spectra were recorded on a JEOL FX-60 spectrometer in chloroform-*d* solution with Me$_4$Si as an internal standard. UV spectra were recorded on a Shimadzu UV-300 spectrophotometer. Liquid chromatographic analyses were performed on a Yanaco L-4000W instrument equipped with a Yanaco M313 UV monitor, operated at 300 nm, and a Waters data module M730 using a 25-cm column of ODS-T with water/methanol (1/9) or water/THF (3/7) eluent at a flow rate of 1.0 mL/min. Under the conditions, the products **3** and **4** and the starting material **1** were separated satisfactorily one after another in each case. The response of detector was calibrated at 300 nm for **1**, **3a**, **3b**, **4b**, **4c**, **3d**, and **4d** by using the pure specimens isolated from the reaction mixture by column chromatography over silica gel.

Materials. Tetrahydrofuran (THF) and 1,4-dioxane were dried over calcium chloride and then distilled from sodium hydride. Benzene was distilled fractionally. Benzoin (**1**) was recrystallized from methanol. Other commercially available reagents were used as received. Oligoethylene glycol ditosylates (**2a–d**) were prepared in 80–90% yields according to the procedures reported previously.[13]

Synthesis. Reaction in Homogeneous Solution. To a 300-mL four-necked flask equipped with thermometer, nitrogen-inlet tube, reflux condenser, dropping funnel, and football-shaped magnetic stirrer were charged successively with stirring the solvent THF or dioxane (75 mL), benzoin (**1**; 0.01 mol), oligoethylene glycol ditosylate (**2**; 0.01 mol), and finely ground alkali hydroxide (0.025 or 0.04 mol). With nitrogen bubbling, the stirred mixture was heated to reflux or, in some cases, to a desired temperature by using a temperature-controlled water or oil bath (±0.1 °C). In typical runs that gave the products **3** and/or **4** in good yields, the solution jellified and turned deep green immediately after heating, with sodium or potassium hydroxide, or even upon mixing, with rubidium or cesium hydroxide, while lithium hydroxide gave yellow jelly after 30-min refluxing. On continued heating for 2–4 h, the solution became fluid and yellowish white in color. Nitrogen bubbling was then stopped, and heating was continued for the period shown in Table I. The resultant was cooled, poured into water, and extracted four times with benzene. The combined benzene extract was washed twice with water and dried over magnesium sulfate. Evaporation of the solvent gave the product as a pale yellow, viscous oil or white solid. The product yields were determined by LC under the conditions calibrated for each product.

Reaction under Phase-Transfer Conditions. A 10 or 33% aqueous solution of alkali metal hydroxide (0.025–0.125 mol) was added with stirring to a benzene solution (75 mL) of benzoin (**1**; 0.01 mol), ditosylate (**2**; 0.01 mol), and tetrabutyl- or hexadecyltrimethylammonium bromide (0.16 or 0.64 mmol) placed in a similarly equipped flask as above. The mixture was heated to reflux or to 60 °C with continued stirring and nitrogen bubbling. Roughly, the reaction proceeded in a manner similar to that in homogeneous solution. The subsequent workup and analysis procedures gave the products in the yields as shown in Table I.

Product. In order to isolate the pure specimens, some of the crude products obtained above were chromatographed over silica gel with hexane, hexane/benzene, and then benzene eluents. The isolated products were further purified by repeated sublimation or recrystalization until the melting points no longer changed.

Stilbeno 6-Crown-2 (2,3-Diphenyl-1,4-dioxene) (3a): mp 96.0–96.5 °C (sublimed) (lit.[10] mp 95 °C); m/z 238 (M$^+$); IR 1630, 1265, 770, 700 cm^{-1}; ^{1}H NMR δ 7.13 (s, 10 H), 4.27 (s, 4 H); ^{13}C NMR δ 136.4 (s), 136.1 (s), 130.1 (d), 129.0 (d), 128.6 (d), 66.1 (t); UV (hexane) $\lambda_{\max}$ (log ϵ) 311.5 nm (3.98), 245 (3.80).

Stilbeno 9-Crown-3 (3b): mp 84.0–84.5 °C (hexane) (lit.[4a] mp 78 °C); m/z 282 (M$^+$); IR 1640, 1260, 1250, 1130, 1075, 770, 710 cm^{-1}; ^{1}H NMR δ 7.13 (s, 10 H), 4.30 (t, 4 H), 3.97 (t, 4 H); ^{13}C NMR δ 142.0 (s), 137.8 (s), 131.1 (d), 129.0 (d), 128.5 (d), 73.2 (t), 72.0 (t); UV (cyclohexane) $\lambda_{\max}$ (log ϵ) 305 nm (4.01), 245 (sh, 3.87).

Stilbeno 15-Crown-5 (3d): mp 77.0–78.0 °C (hexane); m/z 370 (M$^+$); IR 1640, 1260, 1140, 775, 700 cm^{-1}; ^{1}H NMR δ 7.13 (s, 10 H), 3.81 (s, 8 H), 3.77 (s, 8 H); ^{13}C NMR δ 144.0 (s), 136.2 (s), 131.1 (d), 129.2 (d), 128.8 (d), 72.3 (t), 71.7 (t), 71.2 (t); UV (MeOH) $\lambda_{\max}$ (log ϵ) 295 nm (4.00), 242 (sh, 3.83), 220 (sh, 4.09). Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.17; H, 7.12.

Distilbeno 18-Crown-6 (4b): mp 174–176 °C (ethyl acetate/chloroform) (lit.[4a] 173–176 °C); m/z 564 (M$^+$); IR 1625, 1270, 1090, 790, 770, 720, 700 cm^{-1}; ^{1}H NMR δ 7.15 (s, 20 H), 3.96 (s, 16 H); ^{13}C NMR δ 143.6 (s), 136.3 (s), 131.1 (d), 129.0 (d), 128.7

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[13] Ouchi, M.; Inoue, Y.; Kanzaki, T.; Hakushi, T. *J. Org. Chem.* **1984**, *49*, 1408. Ouchi, M.; Inoue, Y.; Wada, K.; Hakushi, T. *Chem. Lett.* **1984**, 1137. Inoue, Y.; Ouchi, M.; Hakushi, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 525. E. Weber has indicated in a private communication that his group is going to employ the same equimolar extraction condition to assess cation binding ability of crown ethers. We propose that this condition is adopted widely for the facile assessment and that the results are accumulated for comparison.

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(d), 71.7 (t), 71.3 (t); UV (CH_2Cl_2) λ_{max} (log ϵ) 297 nm (4.34), 245 (sh, 4.24).

Distilbeno 24-Crown-8 (4c): mp 133.5–134.5 °C; m/z 652 (M^+); IR 1620, 1260, 1090, 770, 700 cm^{-1}; ^1H NMR δ 7.00 (s, 20 H), 3.83 (s, 24 H); ^{13}C NMR δ 143.6 (s), 136.5 (s), 131.0 (d), 129.0 (d), 128.6 (d), 72.0 (t), 71.8 (t), 71.3 (t); UV (MeCN) λ_{max} (log ϵ) 297 nm (4.29), 243 (sh, 4.13). Anal. Calcd for $C_{40}H_{44}O_8$: C, 73.60; H, 6.79. Found: C, 73.20; H, 6.80.

Distilbeno 30-Crown-10 (4d): mp 98.0–99.0 °C (hexane); m/z 740 (M^+); IR 1645, 1260, 1150, 1110, 775, 700 cm^{-1}; ^1H NMR δ 7.12 (s, 20 H), 3.83 (m, 16 H), 3.74 (s, 16 H); ^{13}C NMR δ 143.9 (s), 136.3 (s), 131.1 (d), 129.2 (d), 71.9 (t); UV (MeCN) λ_{max} (log ϵ) 298 nm (4.28), 243 (sh, 4.06), 220 (sh, 4.37). Anal. Calcd for $C_{44}H_{52}O_{10}$: C, 71.33; H, 7.08. Found: C, 71.05; H, 7.04.

Triethylene Glycol Dibenzoin Ether (5c): mp 128.5–129.5 °C; m/z 538 (M^+); IR 1690, 1165, 1100, 745, 695 cm^{-1}; ^{13}C NMR δ 137.5 (s), 134.2 (s), 130.3 (d), 129.6 (d), 128.8 (d), 86.5 (d), 71.7 (t), 70.3 (t).

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Registry No. 1, 119-53-9; **2a**, 6315-52-2; **2b**, 7460-82-4; **2c**, 19249-03-7; **2d**, 37860-51-8; **3a**, 4344-45-0; **3b**, 62698-60-6; **3d**, 82982-14-7; **4b**, 62726-46-9; **4c**, 77325-94-1; **4d**, 98976-66-0; **5c**, 98976-67-1.

A General Synthesis for Symmetrical Highly Branched Perfluoro Ethers: A New Class of Oxygen Carriers[1]

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Most highly branched perfluoro ethers, particularly those sterically crowded around the oxygen, are currently inaccessible synthetically by conventional synthetic techniques used in organofluorine chemistry. Such compounds are of unusual biomedical interest currently because they have been found[1] to be good oxygen carriers and quite surprisingly not to be retained in the liver. Previously linear ethers were thought by biomedical researchers to coordinate in some manner and definitely were found to be retained in the livers of mammals. Direct fluorination technology developed in our laboratories has succeeded with the synthesis of the novel compounds: bis(perfluoroisopropyl) ether, bis(perfluoroisobutyl) ether, bis(perfluoroisopentyl) ether, and bis(perfluoroneopentyl) ether.

Since the original discovery that animals could survive under liquid breathing conditions with oxygenated silicones and especially perfluoro chemicals by L. C. Clark, Jr.,[2] it was thought that ethers, presumably through some base-type interaction physiologically with liver tissue, were essentially retained in the liver in the same manner as perfluorinated amines,[2] making them undesirable for use as oxygen carriers in spite of some other advantages which they exhibit. We have previously theorized and then proven[3] that some types of highly branched fluorocarbons contain holes in their liquid phases which are conducive to higher oxygen solubility. Perfluoro ethers exhibit this property particularly because their bonds are extended by the carbon–oxygen distance.[4] Structures sought in this paper were selected particularly for large oxygen (O_2) holes in the liquid state. The branching, particularly in cases where there was steric crowding around the oxygen, was designed to prevent baselike or any other interaction with mammalian tissue. In addition, we have theorized[5] that the oxygen linkage acts essentially as a flexible hinge in the molecule to permit branched species to be transported across cellular membranes, more rapidly in cases where rigid perfluorocarbons of analogous structures would not bend to facilitate transport.

The direct fluorination technique is now becoming "well established"[6] and is in fact the most generally applicable synthesis of fluorocarbon structures. Here we see an excellent illustration of the advantages of direct fluorination synthetic techniques since the synthesis of some of these materials is impossible by conventional synthetic methods and others are difficult. In fact, none of the compounds in this paper have been reported previously perhaps due to these difficulties. Indeed it has been found[1] that 1-g samples of these ethers are not retained in the liver of mice (as observed by continuous gas chromatographic observation) and are removed from the body within a period of 2–5 days depending on the structure of the compounds.

It should be noted, however, that the first perfluoro ethers were prepared in the 1950s by J. H. Simons using the electrochemical fluorination method.[7] The synthesis of highly branched species not possible by the Simons method for kinetic reasons and often because they are not sufficiently soluble in anhydrous HF appear to be generally accessible through direct fluorination.

Experimental Section

Materials, Analysis, and Physical Measurements. Isopropyl ether was obtained from Aldrich Chemicals. Isobutyl ether was obtained from Tridom-Fluka Chemicals. Isopentyl ether was obtained from Pfaltz & Bauer Chemicals. Neopentyl ether was

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