Molecular Design of Crown Ethers. 6.[1] Substitution Effect in 16-Crown-5

Yoshihisa Inoue,*,[2a] Kazuhito Wada,[2b] Yu Liu,[2b,3] Mikio Ouchi,[2b] Akira Tai,[2a] and
Tadao Hakushi[2b]

*Basic Research Laboratory and Department of Applied Chemistry, Himeji Institute of Technology, 2167 Shosha,
Himeji, Hyogo 671-22, Japan*

A number of 14-, 15-, and/or 16-substituted 16-crown-5 derivatives were synthesized for systematic analysis of the effect of substitution in these crown ethers. The cation-binding ability of substituted 16-crown-5 rings was evaluated by the solvent extraction technique and found to be a critical function of the position, number, type, and stereochemistry of the substituent(s) introduced. Both 15- and 14/16-substituted 16-crown-5 exhibited gradually decreased extractabilities with increasing substitution, although the profiles of change in extractability were distinctly different between 15- and 14/16-substitution. The substitution-induced decrease of extractability is attributed to the limited access of counteranion and/or to the lack of conformational adjustments necessary to make a structure suitable for complex formation. The bridging substitutions at 14- and 16-positions dramatically enhanced the extractabilities for all cations without lowering the original relative cation selectivity. This may arise from the favorable entropic contribution of the conformational freezing by bridging substitution.
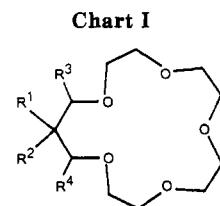
A good deal of effort has been devoted to the synthesis and complexation of a wide variety of functionalized crown ethers. Thus the recent investigations have related the cation-binding ability and selectivity to the crown ether's cavity size, electron density, softness, spatial arrangement, additional binding site, and other major factors governing cation–ligand complexation.[4] Curiously, little attention has been paid to the effect of ring substitution which accompanies the introduction of a functional group into the parent crown ether. Apart from the evident electronic effect in ring-substituted benzo crown ethers,[5] the direct influence of simple alkylation in a crown ether upon its cation-binding ability/selectivity has not been investigated systematically.

Our previous study on the 16-crown-5 lariats[1b] demonstrated that, though the ligating side arm introduced does enhance the cation-binding abilities for the size-matched cations specifically, the introduction of two methyl groups at the 15-position of the parent 16-crown-5 leads to a significant general decrease in its cation-binding ability for all cations examined. This result, as well as the diversity of possible derivatizations of 16-crown-5, prompted us to investigate systematically the substitution effect upon cation binding and selectivity. In the present work, we synthesized a series of 14-, 15-, and/or 16-substituted 16-crown-5 derivatives and evaluated their cation-binding abilities and relative cation selectivities by solvent-extraction technique.

Results and Discussion

Synthesis. All 16-crown-5 derivatives synthesized are illustrated in Chart I.

The parent 16-crown-5 and simple mono- or dimethyl derivatives, i.e. 1–3 and 11–13, were synthesized by reac-

Chart I

	R¹	R²	R³	R⁴
1	H	H	H	H
2	CH₃	H	H	H
3	CH₃	CH₃	H	H
4	CH₃OCH₂	CH₃OCH₂	H	H
5	n-C₈H₁₇OCH₂	n-C₈H₁₇OCH₂	H	H
6	CH₂OCH(Ph)OCH₂		H	H
7	CH₂OC(CH₃)₂OCH₂		H	H
8	CH₂OCH₂		H	H
9	CH₂O		H	H
10	=CH₂		H	H
11	H	H	CH₃	H
12	H	H	CH₃ (trans)	CH₃
13	H	H	CH₃ (cis)	CH₃
14	H	H	CH₂=CH₂	
15	H	H	CH₂CH₂	

tions of the respective diols with tetraethylene glycol ditosylate **16** in 31–48% yield according to the method reported previously.[1]

The key intermediate bis(hydroxymethyl)-16-crown-5, **17**, was prepared by hydrogenolysis over Pd/C of the spiro-16-crown-5 **6** synthesized from monobenzalpentaerythritol **18** and ditosylate **16**[6] (Scheme I). The alkylation of diol **17** with methyl iodide or octyl bromide gave the corresponding bis(alkoxymethyl)-16-crown-5 **4** and **5**, while the ketalization with dimethoxypropane afforded the 16-crown-5 isopropylidene ketal **7**. Treatment of diol **17** with tosyl chloride in the presence of NaOH in THF gave 16-crown-5 oxetane, **8**.

Methylene-16-crown-5 (**10**) was synthesized from 2-(chloromethyl)-3-chloropropene and tetraethylene glycol according to the method reported.[7] Epoxidation of **10** with *m*-chloroperbenzoic acid gave 16-crown-5 oxirane (**9**).

(1) (a) Part 5: Inoue, Y.; Wada, K.; Ouchi, M.; Tai, A.; Hakushi, T. *Chem. Lett.* **1988,** 1005. (b) Part 4: Ouchi, M.; Inoue, Y.; Wada, K.; Iketani, S.; Hakushi, T.; Weber, E. *J. Org. Chem.* **1987,** *52,* 2420.

(2) (a) Basic Research Laboratory. (b) Department of Applied Chemistry.

(3) On the leave from Lanzhou Institute of Chemical Physics, Lanzhou, China.

(4) De Jong, F.; Reinhoudt, D. N. *Stability and Reactivity of Crown Ether Complexes*; Academic: London, 1981; pp 3–26 and the references cited therein.

(5) Ungaro, R.; El Haj, B.; Smid, J. *J. Am. Chem. Soc.* **1976,** *98,* 5198. Pannel, L. H.; Yee, W.; Lewandos, G. S.; Hambrick, D. C. *Ibid.* **1977,** *99,* 1457. Moore, S. S.; Tarnovski, T. L.; Newcomb, M.; Cram, D. J. *Ibid.* **1977,** *99,* 6398.

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

(7) Tomoi, M.; Abe, O.; Ikeda, M.; Kihara, K.; Kakiuchi, H. *Tetrahedron Lett.* **1978,** 3031.

Scheme I
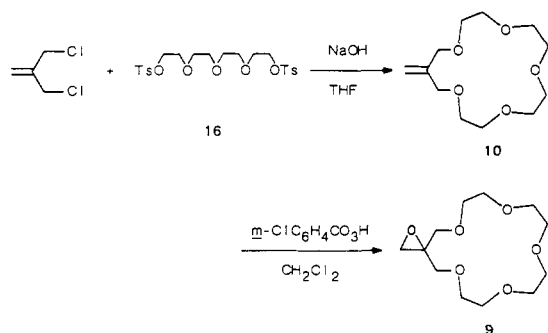
The reaction of cis-cyclopentenediol (19)[8] with ditosylate 16 afforded the cyclopentene-fused 16-crown-5 14, which was hydrogenated over Pd/C to give cyclopentane-fused 16-crown-5 15.
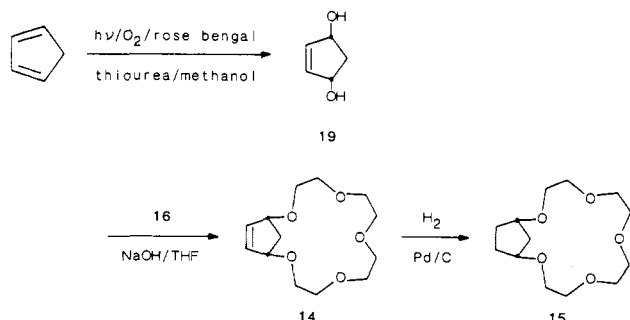
Solvent Extraction. The solvent extraction technique has been employed as a convenient method for evaluating cation-binding ability of crown ethers, and, as far as monovalent cations are concerned, affords the quantitative binding constants compatible with those obtained in the homogeneous-phase complexation.[9] The solvent extractions of aqueous alkali, alkaline earth, and some heavy-metal picrates were performed with the substituted 16-crown-5 derivatives 1–15 in dichloromethane under our standard conditions, in which common 3m-crown-m ethers show moderate extractabilities.[1] The results are shown in Table I. It is obvious that the extractability is affected drastically by several factors including the position, number, type, and stereochemistry of the substituent(s) introduced, which will be discussed separately.

15-Substituted 16-Crown-5. It is noted that the cation-binding ability of 15-substituted 16-crown-5 is insensitive to the type of substituent introduced at C15, as far as the substitution leads to the same structural category like cyclic, spiro, or small-ring spiro structure. Thus, the 15,15-disubstituted crown ethers 3–5 afford very close extractabilities for each cation, regardless of the chain length of substitutents. Similarly, the spiro[5.15]-16-crown-5 6 and 7 with different substituents on the dioxane ring also give practically identical extractabilities.

On the other hand, the number of substituent at C15 affects the cation-binding ability considerably. In Figure 1, the extractabilities for selected cations are plotted as a function of the degree and type of substitution. Although the extractabilities decrease in general with increasing substitution at C15, the change is not monotonic. The first methylation at C15 has only a small effect upon extractability, whereas the second substitution diminishes the extractabilities dramatically. Since the substitution at 15-position does not appear to alter the electron density
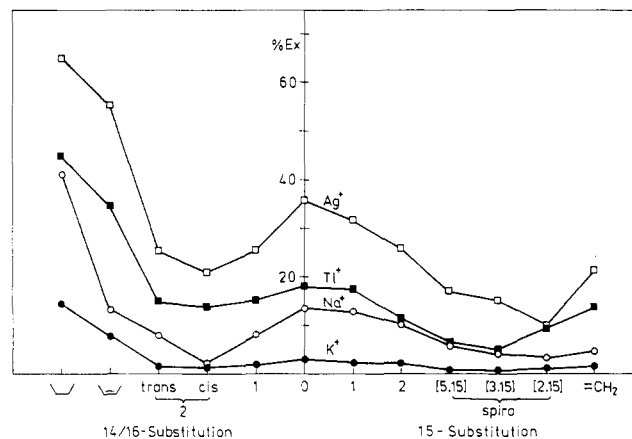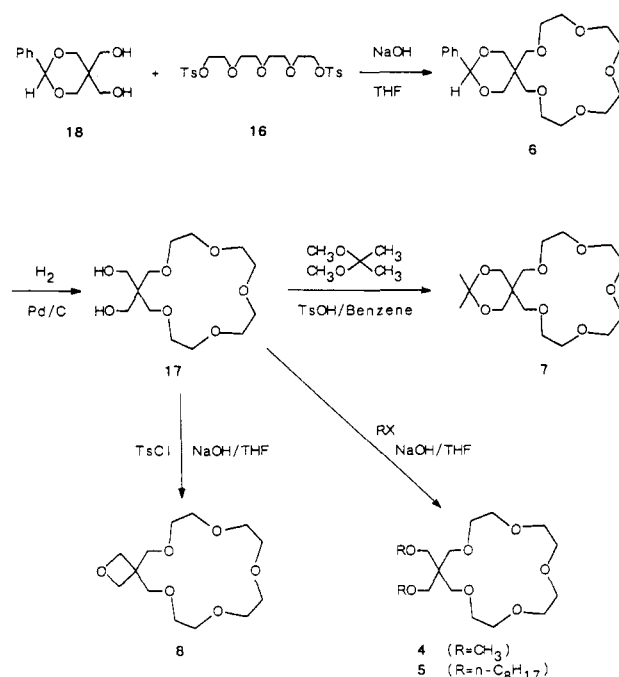

Figure 1. Percent extractabilities (% Ex) for selected cations as a function of number and structure of substituent at 15- (right-hand-side plots) and 14/16-position (left-hand-side plots) of 16-crown-5; unless depicted otherwise, the substituent(s) introduced are straight-chain, mostly methyl.

of the donor oxygens, the decrease in extractability must originate from the conformational reason.

Upon examination with CPK molecular models, the introduction of methyl group(s) at the axial and/or equatorial position of C15 does not appear to cause steric repulsion with the adjacent methylene groups or make significant change in conformation. Therefore the substitution effect upon extractability may be interpreted in terms of the steric hindrance of the axial substituent introduced at C15 rather than the unfavorable conformation compelled by the introduction of substituent(s). As metal ion is extracted into the organic phase in the form of contact ion-pair complex accompanying lipophilic picrate anion(s),[10] the access of counteranion to the complexed cation is a crucial factor determining complex stability, or extractability. In this context, 15-methyl-16-crown-5 2, in the complexation with metal picrate, is able to avoid the steric hindrance against the coordinating picrate through

(8) Kaneko, C.; Sugimoto, A.; Tanaka, S. *Synth. Commun.* **1974**, 876.
(9) Inoue, Y.; Ouchi, M.; Hakushi, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 525.

(10) Inoue, Y.; Fujiwara, C.; Wada, K.; Tai, A.; Hakushi, T. *J. Chem. Soc., Chem. Commun.* **1987**, 393.

Table I. Solvent Extraction of Aqueous Metal Picrates with 14-, 15-, and/or 16-Substituted 16-Crown-5[a]

ligand	% extractability[b]									
	Na+	K+	Rb+	Cs+	Ag+	Tl+	Mg²⁺	Ca²⁺	Sr²⁺	Ba²⁺
1[c]	13.5	3.0	2.1	0.9	35.7	18.1	0.3	0.8	5.7	15.4
2	13.0	2.4	2.0	1.0	31.6	17.6	1.7	1.0	4.9	12.5
3[c]	10.2	2.2	2.2	1.6	25.9	11.4	1.2	1.1	1.9	3.9
4[c]	9.8	2.7	2.5	2.1	24.7	11.1	1.6	1.6	3.1	9.3
5[d]	10.6	1.9	1.7	1.0	27.1	12.5	1.7	1.5	2.0	6.8
6	5.6	0.8	0.8	0.5	17.0	6.4	0.5	0.4	0.9	2.0
7	4.8	0.7	0.7	0.4	16.6	5.6	0.4	0.3	0.9	1.7
8	4.0	0.6	e	e	15.1	5.1	e	e	0.9	2.6
9	3.2	1.0	0.8	0.5	9.9	9.3	0.4	0.3	0.9	4.4
10	4.7	1.5	1.3	0.6	21.1	13.5	0.5	0.3	2.6	8.1
11	8.0	1.9	1.3	0.8	25.5	15.3	0.5	0.5	3.7	8.9
12 + 13[f]	5.1	1.4	1.0	0.5	23.4	14.4	0.3	0.3	3.6	8.2
12	7.9	1.5	1.3	0.8	25.2	13.8	0.3	0.4	4.6	9.9
13[g]	2.3	1.3	0.7	0.2	21.0	15.0	0.3	0.2	2.6	6.5
14	13.1	7.6	6.8	6.2	55.3	34.6	0.6	0.8	2.0	14.2
15	41.0	14.5	12.7	6.2	65.0	45.0	1.1	2.0	9.0	28.0

[a] Temperature 25.0 ± 0.1 °C; aqueous phase (10 mL), [picrate] = 3.0 mM; organic phase (CH_2Cl_2, 10 mL), [ligand] = 3.0 mM. [b] Defined as percent picrate extracted into the organic phase. Average of two or three independent runs: error <0.7. [c] Reference 1b. [d] Reference 14. [e] Not determined. [f] A 1:1 mixture. [g] Calculated from the extractabilities for 12 + 13 and 12.

adopting an equatorial methyl conformation. However, owing to the dual substitution at C15, this avoiding mechanism no longer functions in 15,15-disubstituted 16-crown-5 3–5 and spiro-16-crown-5 6–9, thus affording much decreased extractabilities.

The spiro substitution, though regarded formally as a sort of dual substitution, has yet a larger diminishing effect, which depends to some extent on the size of spiro ring. As can be seen from Figure 1, spiro[5.15]- and spiro[3.15]-16-crown-5 6–8 give such extractabilities that are similar with each other but much lower than those for nonspiro analogues 3–5. These lowered extractabilities arise presumably from the rotational fixation of the alkyl groups attached directly to C15, since the examination with CPK models indicates that the introduction of a spirodioxane (chair form) into 16-crown-5 does not greatly change the original conformation as is the case with the dimethyl analogue. In the nonspiro analogue 3, the axial methyl may rotate, minimizing steric hindrance against the bulky counteranion picrate, whereas the spirodioxane with a fixed methylene group causes greater repulsion with the counteranion.

Interestingly, spiro[2.15]-16-crown-5 9 exhibits a recovery in extractability for the larger cations but a further decrease for the size-fitted cations Na+ and Ag+; see Table I and Figure 1. Consequently, the cation selectivities for Na+/K+ and Ag+/Tl+ decrease substantially, which is indicated evidently by the nonparallel changes of their extractabilities in Figure 1. The increased bond angle of C14–C15–C16 up to 115°, which is compelled by the introduction of an oxirane ring at C15, and the subsequent enlargement of cavity size may be responsible for the altered cation selectivities.

A similar situation is encountered upon introducing *exo*-methylene at C15 of 16-crown-5. In methylene-16-crown-5, 10, the methylene group at C15 enlarges the ring size likewise, but, lacking axial substituent, reduces the upward steric hindrance to a great extent, facilitating closer approach of the counteranion and stabilizing contact ion-pair complex extracted. As a result, the extractabilities are recovered considerably with all cations, while the cation selectivities are not greatly improved due to the enlarged cavity size.

14/16-Substituted 16-Crown-5. The profile of change in extractability caused by methylation at the 14- and/or 16-position is depicted in Figure 1. In sharp contrast to the less affecting monoalkylation at C15, the first me-

thylation at C14 diminishes drastically the extractabilities for all cations examined; the drop is much greater for the size matched Na+ and Ag+ than for larger cations.

In the 14- and/or 16-substituted 16-crown-5, the alkylation occurs at position(s) immediately adjacent to the donor oxygen. This would significantly alter its electron density. Then we first evaluated the change in electron density of the donor oxygens by means of the molecular orbital calculation on simpler model compounds.[11] The MNDO calculations were performed with 2,6-dioxaheptane and 3-methyl-2,6-dioxaheptane as models for the parent 16-crown-5 1 and its 14-methyl derivative 11. Upon full optimization, the oxygen atoms in 2,6-dioxaheptane possess a net atomic charge of −0.346, while the net charges of oxygens at the 2- and 6-positions of 3-methyl-2,6-dioxaheptane increase only slightly to −0.350 and −0.347, respectively. Thus the influence of methylation upon oxygen's electron density turns out to be trivial, and therefore the decreased extractabilities of 14/16-substituted 16-crown-5 should not be ascribed to the change in electron density.

CPK model examination indicated that the 14/16-substitution causes steric repulsion with the adjacent methylenes giving rise to the substantial conformational change, while both axial and equatorial methylation do not appear to interfere with the approach of coordinating picrate. Thus the accompanying conformational change around the substituted carbon is considered to be responsible for the decreased extractabilities.

The importance of substitution-induced conformational change is further demonstrated by the second methylation at C16. The stereochemistry of the second substituent introduced at C16 turned out to be critical in determining extractability. Thus the cis and trans isomers of 14,16-dimethyl-16-crown-5 exhibit completely different extraction behavior. The cis isomer 13 further diminishes the extractabilities for most cations, while the trans isomer 12 affords extractabilities that are comparable with those for monomethylated 11; see Figure 1.

For *cis*-14,16-dimethyl-16-crown-5, 13, there are two possible conformers, but the ax,ax-conformer is highly unlikely because of its higher steric hindrance. We consequently discuss the conformational difference between *eq,eq-cis*-13ee and *eq,ax-trans*-12. Judging from the CPK

(11) The MNDO program (QCPE no. 353) running on a Fujitsu S-3500 computer was used.

molecular models, the two geometrical isomers of 14,16-dimethyl-16-crown-5 apparently show higher steric hindrance than their lower homologues or isomer, i.e. unsubstituted, monomethyl-, or 15,15-dimethyl-16-crown-5. As is the case with 14-methyl-16-crown-5, 11, the second equatorial methylation at C16, giving *eq,eq-cis*-13ee, alters direction of the lone pairs of O1, which may be responsible in part for the lowered extractabilities. Additionally, the O1–O13 distance of *eq,eq-cis*-13ee increases slightly and is considered to be unfavorable for complexation. By contrast the second methylation at the axial position, yielding trans isomer 12, does not appear to change the O1–O13 distance. The axial methyl rather locks the otherwise facile flip-flop motion of the trimethylene group of 16-crown-5, which may entropically facilitate the complex formation with cation.

The effect of partial structural freezing is clearly demonstrated in the extraction with 14,16-vinylene- and 14,16-ethylene-16-crown-5, 14 and 15, two substituents of which are fixed in the axial positions. As shown in Figure 1, both bridged 16-crown-5 derivatives, 15 in particular, give anomalously high extractabilities for all cations examined. These enhanced extractabilities may be interpreted in the framework of structural freezing by the axial bridge, which prohibits the flip-flop motion and firmly fixes two adjacent oxygens in the position appropriate for complexation. The lower extractabilities for cyclopentene-fused 14 than cyclopentane-fused 15 may be ascribed to its elongated O1–O13 distance as compared with that of 15.

Conclusion

The cation-binding ability of substituted 16-crown-5 is a critical function of the position, number, type, and stereochemistry of the substituent(s) introduced. In general, both 15- and 14/16-substituted 16-crown-5 exhibit decreased extractabilities with increasing extent of substitution, although the profiles of change are distinctly different between 15- and 14/16-substitution.

The CPK model examination indicates that some of the substituted crown ethers possess limited access for the approaching counteranion and the others lack conformational adjustments necessary to make a structure suitable for complex formation, which are jointly responsible for the decreased extractabilities for most substituted crown ethers.

By contrast, the bridging substitutions dramatically enhance the extractabilities for all cations without lowering the original relative cation selectivity. This marked enhancement must have an entropic origin arising from the conformational fixing of a part of donor oxygens into an arrangement suitable for complexation. The conformational freezing may be applied to the other flexible cyclic and acyclic systems as a tool for enhancing cation-binding ability.

Experimental Section

General Methods. Infrared spectra were obtained on a JASCO A-100 grating spectrophotometer. Melting points were measured with a Yanaco micro melting point apparatus and are uncorrected. Mass spectra were obtained at 70 eV on a Hitachi RM-50GC or RMU-6E instrument. ^{1}H NMR spectra were recorded on a JEOL PMX-60 (60 MHz) spectrometer in CDCl$_3$ solution containing tetramethylsilane as an internal standard. Electronic spectra are recorded on a Shimadzu UV-300 spectrophotometer.

Materials. Tetrahydrofuran (THF) and 1,4-dioxane were dried over CaCl$_2$ and then distilled from NaH or LiAlH$_4$. Benzene, methanol, and dichloromethane were fractionally distilled prior to use. The other commercially available reagents were used without further purification.

Metal picrates were prepared according to the method reported previously.[1b,12]

Synthesis. All crown ethers synthesized were viscous oils and were purified by distillation under a reduced pressure, unless noted otherwise. Spectral (IR, MS, ^{1}H NMR) and analytical data of all new compounds are given in the supplementary material.

Tetraethylene glycol ditosylate (16) was prepared in 90–95% from tetraethylene glycol and *p*-toluenesulfonyl chloride in the presence of NaOH in water/THF as reported previously.[1b]

16-Crown-5 (1), 15,15-dimethyl-16-crown-5 (3), 15,15-bis(methoxymethyl)-16-crown-5 (4), 4-phenyl-3,5,8,11,14,17,20-heptaoxaspiro[5.15]heneicosane (6), and 15-methylene-16-crown-5 (10) were synthesized as reported.[1b]

15-Methyl-16-crown-5 (2), 14-methyl-16-crown-5 (11), *trans*-(R,R)-14,16-dimethyl-16-crown-5 (12), and a 1:1 mixture of *trans*- and *cis*-14,16-dimethyl-16-crown-5 (12 + 13) were synthesized from the corresponding alcohol and 16 in 48, 45, 42, and 38% yields, respectively, under analogous reaction conditions reported previously (NaOH as a base in THF);[1b] 2, bp 107 °C (0.2 Torr); 11, bp 105–110 °C (0.35 Torr); 12, bp 108 °C (0.3 Torr); 12 + 13, bp 110–115 °C (0.1–0.15 Torr).

15,15-Bis(hydroxymethyl)-16-crown-5 (17) was prepared in 89% yield by hydrogenolysis of 6 over 10% Pd/C.[6] Alkylation[1b] of 17 (1.5 g) with octyl bromide (5.8 g) gave **15,15-bis[(octyloxy)methyl]-16-crown-5 (5)** (1.85 g, 70% yield); bp 205–210 °C (0.12 Torr).[13]

Treatment of 17 (3.0 g) with 2,2-dimethoxypropane (3.1 g) in benzene (100 mL) in the presence of *p*-toluenesulfonic acid (40 mg) gave **4,4-dimethyl-3,5,8,11,14,17,20-heptaoxaspiro[5.15]heneicosane (7)** (1.5 g, 50%); bp 120 °C (0.2 Torr).

Reaction of 17 (3.0 g) with *p*-toluenesulfonyl chloride (1.9 g) in 1,4-dioxane (50 mL) in the presence of NaOH (2.0 g) gave crude **3,6,9,12,15,18-hexaoxaspiro[3.15]nonadecane (8),**[14] a small portion of which was purified by preparative TLC to give the pure sample (200 mg) used for the solvent extraction.

2,5,8,11,14,17-Hexaoxaspiro[2.15]octadecane (9, bp 125 °C (0.25 Torr)) was prepared in 70% yield by epoxidation of 10 (2.5 g) with *m*-chloroperbenzoic acid (3.5 g) in dichloromethane (50 mL) at 0 °C.

cis-4-Cyclopentene-1,3-diol (19) was prepared by singlet oxygenation of 1,3-cyclopentadiene in the presence of thiourea.[8] Freshly distilled cyclopentadiene (10.0 g), rose bengal (500 mg), and thiourea (7.0 g) were dissolved in methanol (1 L), and the solution was irradiated for 3 h at 0 °C with continuous bubbling with oxygen gas, using a 300-W high-pressure mercury lamp (Eikosha Co.) fitted with a Pyrex sleeve. Workup procedure[8] gave 19 (8.6 g, 60%); bp 94–98 °C (0.3–0.4 Torr).

2,5,8,11,14-Pentaoxabicyclo[13.2.1]octadec-16-ene (14,16-vinylene-16-crown-5, 14) was synthesized in 31% from 19 (11 g) and 16 (48 g) using the identical cyclization procedure as mentioned above; 14, bp 135 °C (0.4 Torr). Catalytic hydrogenation of 14 (2.0 g) over 5% Pd/C gave **2,5,8,11,14-pentaoxabicyclo[13.2.1]octadecane (14,16-ethylene-16-crown-5, 15)** (1.6 g, 80%); bp 120 °C (0.4 Torr).

Solvent Extraction. The general procedures employed were similar to those described in previous papers.[1b] The solvents, CH$_2$Cl$_2$ and H$_2$O, were saturated with each other prior to use in order to prevent volume changes of both phases during extraction. Equal volumes (10 mL) of a CH$_2$Cl$_2$ solution of the respective crown ether (3.0 mM) and of an aqueous solution of each metal picrate (3.0 mM) were introduced into a stoppered Erlenmeyer flask, and the mixture was shaken for 10 min in a Taiyo M100L incubator thermostated at 25.0 ± 0.1 °C. The equilibrated mixture was then allowed to stand for at least 2 h at that temperature in order to complete phase separation. The organic phase was separated by means of phase-separating filtration through a Toyo filter paper No. 2s. The concentration of metal picrates in the organic phase was determined as reported.[1b]

(12) Wong, K. H.; Ng, H. L. *J. Coord. Chem.* **1981**, *11*, 49.
(13) Ouchi, M. Ph.D. Dissertation, Himeji Institute of Technology, 1984.
(14) Krespan, C. G. U.S. Patent 1975, 3860611.

Synthesis of the Phenolic Derivatives of Highly Tumorigenic *trans*-7,8-Dihydroxy-7,8-dihydrobenzo[a]pyrene

Subodh Kumar,[*,1,2] Panna L. Kole, and Raj K. Sehgal

Great Lakes Laboratory, State University of New York College at Buffalo, 1300 Elmwood Avenue, Buffalo, New York 14222

Received March 14, 1989

Two isomeric phenolic derivatives of *trans*-7,8-dihydro-7,8-dihydroxybenzo[a]pyrene (**42**), 3,7,8-trihydroxy-*trans*-7,8-dihydrobenzo[a]pyrene (**40**), and 1,7,8-trihydroxy-*trans*-7,8-dihydrobenzo[a]pyrene (**41**), have been prepared in order to probe their relevance in the carcinogenesis of benzo[a]pyrene. Two methods have been developed for the synthesis of the key intermediates 3-acetoxy-9,10-dihydrobenzo[a]pyrene (**25**) and 1-acetoxy-9,10-dihydrobenzo[a]pyrene (**26**). In one method, known 1-methoxypyrene-6-carboxaldehyde (**5**) and 1-methoxypyrene-8-carboxaldehyde (**6**) were homologated, and the resulting 4-(methoxypyrene)butanoic acids **14** and **18** were cyclized with polyphosphoric acid (PPA) at 105 °C to produce 3-methoxy- and 1-methoxy-7,8,9,10-tetrahydrobenzo[a]pyren-7-one (**19** and **21**, respectively). The PPA cyclization at low temperature (90 °C) produced primarily the undesired seven-membered ring ketones **23** and **24**, respectively. Demethylation of methoxy ketones **19** and **21** followed by successive reduction, dehydration, and acetylation afforded the key intermediates **25** and **26**. The second method involves bromination of the trimethylsilyl cyanide derivative **27** of 7,8,9,10-tetrahydrobenzo[a]pyren-7-one followed by removal of the protecting group. 1-Bromo-7,8,9,10-tetrahydrobenzo[a]pyren-7-one (**28**) was obtained as a major and 3-bromo-7,8,9,10-tetrahydrobenzo[a]pyren-7-one (**29**) as a minor products of this synthesis. These bromo ketones **28** and **29** were, subsequently, used to synthesize the key intermediates **25** and **26**, respectively. Prevost reaction of the acetoxyalkenes **25** and **26** followed by selective dehydrogenation of the resulting tetrahydro triesters **36** and **37** with DDQ and base-catalyzed hydrolysis produced **40** and **41**, respectively.

The burgeoning interest in studying the mechanism of carcinogenesis of polynuclear aromatic hydrocarbons (PAHs) stems from their ubiquitous occurrence in the environment and their carcinogenic properties.[3,4] It is now well recognized that PAHs are metabolized to highly reactive intermediates that are responsible for the cytotoxic, mutagenic, and carcinogenic effects of PAHs. Diol epoxide derivatives, especially bay-region diol epoxides, have been implicated as ultimate carcinogens of a number of PAHs.[5,6] However, the involvement of reactive intermediates other than diol epoxides in the carcinogenesis of PAHs has not been ruled out.[4] Therefore, it is indispensable that other reactive metabolites of PAHs, which are tentatively identified, be completely characterized and studied for their possible involvement in the metabolic activation of PAHs.

Recent studies[7] with PAHs have shown that these hydrocarbons can be metabolized to a new class of reactive intermediates which are tentatively characterized as the phenolic derivatives of diol epoxides. As reported for diol epoxides,[5,6] these derivatives are also capable of binding covalently to nuclear macromolecules and show mutagenic and cell transforming activities.[8-10] Since the covalent binding of phenolic diol epoxides of PAHs to nuclear macromolecules may also play a significant role in determining the susceptibilities of normal cells to be transformed to cancer cells, these phenolic diol epoxides and their precursors, phenolic dihydrodiols, are needed to study their biological relevance in PAH-induced carcinogenesis.

In the present study, we synthesized 1-hydroxy-*trans*-7,8-dihydro-7,8-dihydroxybenzo[a]pyrene and 3-hydroxy-*trans*-7,8-dihydro-7,8-dihydroxybenzo[a]pyrene, which are the suspected metabolites of the environmental carcinogen benzo[a]pyrene (BP, **1**)[11] and precursors to the highly reactive phenolic bay-region diol epoxides **2** and **3**. These phenolic diol epoxides have recently been tentatively characterized as the metabolites of *anti-trans*-7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-BP (**4**).[12,13] The

(1) This work was supported by Grant ESO4130 from the National Institute of Environmental Health Sciences, DHHS, awarded to S.K.
(2) Adjunct Associate Research Professor in the Deparment of Chemistry, SUNY College, Buffalo, NY.
(3) International Agency for Research on Cancer. *Polycyclic Aromatic Compounds, Part 1, Chemicals, Environmental and Experimental Data*, IARC, Lyon, 1983.
(4) Dipple, A.; Moschel, R. C.; Bigger, A. H. *Chemical Carcinogens*, 2nd ed.; Searle, C. E., Ed.; American Chemical Society Monograph 182; American Chemical Society: Washington, DC, 1984; pp 41–163.
(5) Harvey, R. G.; Geacintov, N. E. *Acc. Chem. Res.* **1988**, *21*, 66.
(6) Thakker, D. R.; Yagi, H.; Levin, W.; Wood, A. W.; Conney, A. H.; Jerina, D. M. *Bioactivation of Foreign Compounds*; Anders, M. W., Ed.; Academic Press: New York, 1985; pp 177–242.
(7) McKay, S.; Hulbert, P. B.; Grover, P. L. *Polycyclic Aromatic Hydrocarbon Carcinogenesis: Structure-Activity Relationships*; Yang, S. K., Silverman, B. D., Eds.; CRC Press, Ind.: Boca Raton, FL, 1988; Vol. II, pp 1–36.

(8) Glatt, H. R.; Seidel, A.; Bochnitschek, W.; Marquardt, H.; Marquardt, H.; Hodgson, R. M.; Grover, P. L.; Oesch, F. *Cancer Res.* **1986**, *46*, 4556.
(9) Phillips, D. H.; Glatt, H. R.; Seidel, A.; Bochnitschek, W.; Oesch, F.; Grover, P. L. *Carcinogenesis* **1986**, *7*, 1739.
(10) Glatt, H. R.; Seidel, A.; Ribeiro, O.; Kirkby, C.; Hirom, P.; Oesch, F. *Carcinogenesis* **1987**, *8* 1621.
(11) Ribeiro, O.; Kirby, C. A.; Hirom, P. C.; Millburn, P. *Carcinogenesis* **1985**, *6*, 1507.
(12) Graslund, A.; Waern, F.; Jernstrom, B. *Carcinogenesis* **1986**, *7*, 167.
(13) Dock, L.; Waern, F.; Martinez, M.; Grover, P. L.; Jernstrom, B. *Chem.-Biol. Interact.* **1986**, *58*, 301.