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Synthesis and Conformational Studies of an Asymmetrical Dibenzo-16-crown-5 Carboxylic Acid

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Abstract. Asymmetrical *cis*-5,6-dimethyl-6-oxyacetoxy-(2,3)(9,10)-dibenzo-16-crown-5 was synthesized by a multi-step sequence and its stereochemistry determined by NOE experiments. Introduction of the 6-methyl group markedly reduces the stability constant for complexation of Na^+ and K^+ by the ionized form of the lariat ether carboxylic acid.

Key words: crown ether, NMR, complexation.

1. Introduction

Macrocyclic polyethers have long been known as specific metal ion extracting agents [1–3]. A lariat ether is a crown ether to which a side arm bearing one or more potential coordination sites is attached [4]. The metal ion complexation ability may be markedly enhanced by the introduction of a proton-ionizable group into the side arm [5]. Metal ion extraction by such chelating agents does not require concomitant transfer of an aqueous phase anion into the organic medium. This factor is of immense importance to potential applications in which hard aqueous phase anions (chloride, nitrate, and sulfate) would be involved.

Previously, we reported that attachment of an alkyl group to the central carbon of the three-carbon bridge of **1** gave *sym*-(R)dibenzo-16-crown-5-oxyacetic acids **2** and **3** which exhibited significant enhancement in the Na^+ selectivity [5, 6]. Examination of a CPK space-filling model for **2** and the solid-state structure of **3** reveals that the oxyacetic acid group is oriented over one face of the polyether ring when the alkyl group points away from the polar polyether portion of the molecule [7]. It is proposed that the enhanced Na^+ selectivity is due to a preorganized structure with intramolecular hydrogen bonding of the OH in the oxyacetic acid side arm with one of the polyether ring oxygens [8]. Subsequently, we probed the conformational rigidity of *sym*-(R)dibenzo-16-crown-5-oxyacetic acids in solution

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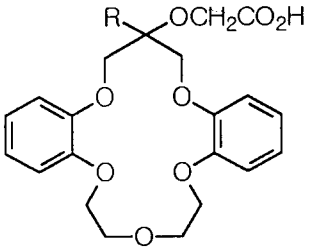
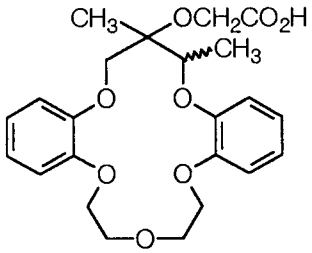
by NMR spectroscopy [8]. To further investigate the effects of the substituents upon the conformations of lariat ether carboxylic acids based on the dibenzo-16-crown-5 ring system, the synthesis of analog **4** with a second methyl group attached to a terminal carbon of the three-carbon bridge of **2** was proposed.



	R
1	H
2	CH_3
3	$C_{10}H_{21}$

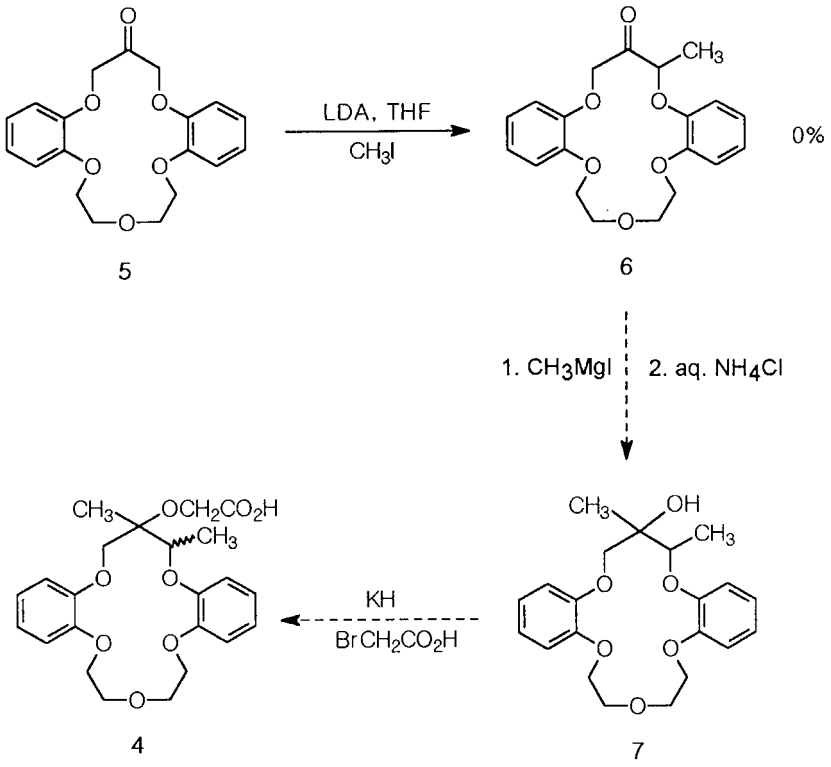


4a *cis*
4b *trans*

2. Results and Discussion

It was initially envisioned that crown ether carboxylic acid **4** which has two chiral carbons could be prepared from *sym*-(keto)dibenzo-16-crown-5 (**5**) in three steps as shown in Scheme 1. In a retro-synthetic analysis, compound **4** could be synthesized from lariat ether alcohol **7** by reaction with bromoacetic acid in the presence of base. Lariat ether alcohol **7** could be prepared by a Grignard reaction of crown ether ketone **6** with methylmagnesium iodide. The α-methyl ketone **6** would be prepared by alkylation of the crown ether ketone **5** using lithium diisopropylamide (LDA) at -78 °C. However, an attempted alkylation of crown ether ketone **5** with LDA and iodomethane was unsuccessful. Instead, the self-condensation (aldol) product **8** was isolated in 76% yield (Scheme 2). In further attempts to obtain the desired product **6**, the reaction temperature was varied. Addition of the iodomethane at -78 °C gave none of the desired product. At -45 °C, only aldol product **8** was evident. Addition of iodomethane at 0 °C provided only the self-condensation product as well. The structure of **8** was confirmed by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy, mass spectrometry, and elemental analysis (see experimental section). Upon careful search of the literature, we found a report of the related aldol product **11** (Scheme 2) which was formed as a by-product when 9-ketobenzo-13-crown-4 was treated with *t*-BuLi in the preparation of tertiary alcohol **10** [9]. In light of this unanticipated problem with the first step of the synthetic strategy, an alternative route to the desired lariat ether carboxylic acid **4** was developed.

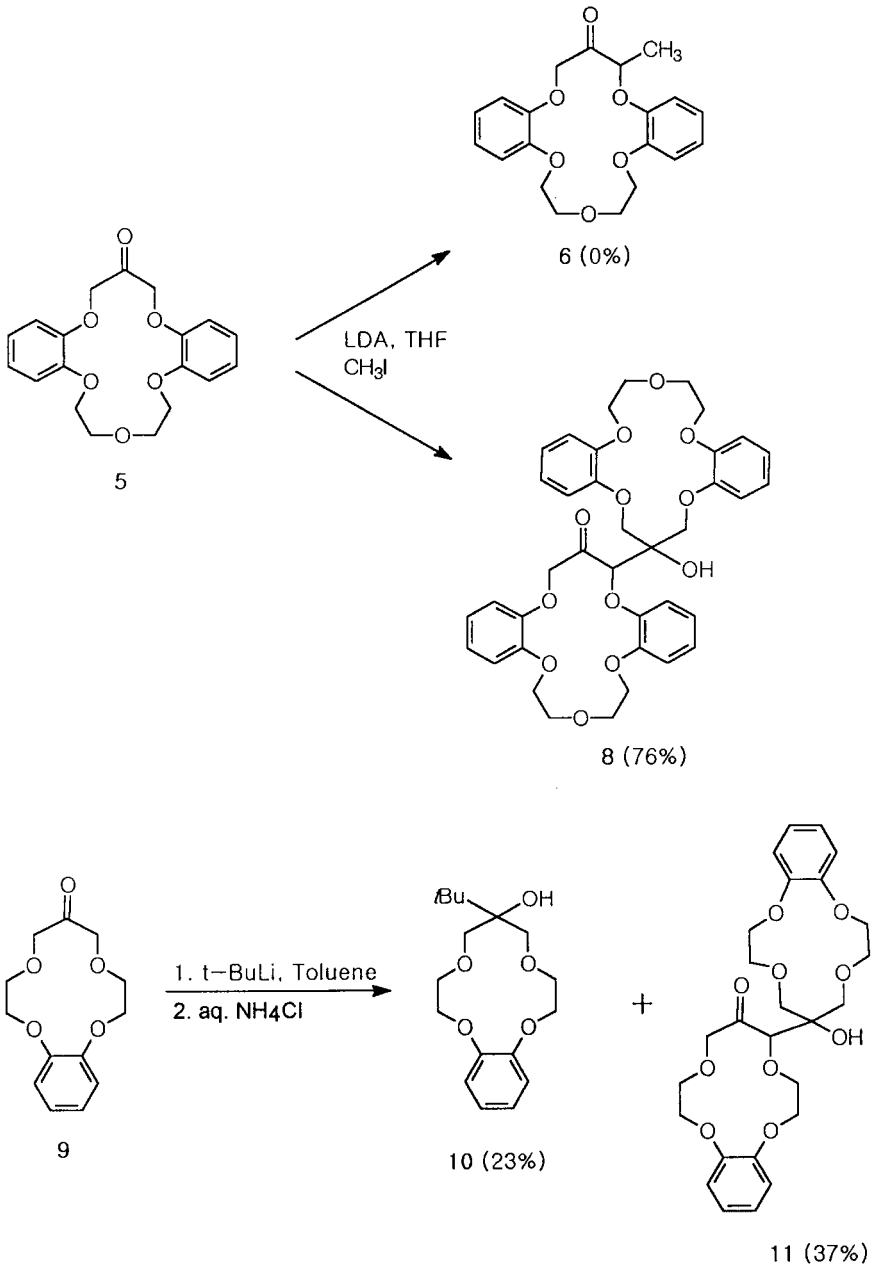
The alternative synthetic route is shown in Scheme 3. Epoxidation of commercially available 3-chloro-1-butene (**12**) with *m*-chloroperoxybenzoic acid (mCPBA) gave 3-chloro-1,2-epoxybutane (**13**) in 91% yield. According to the general liter-



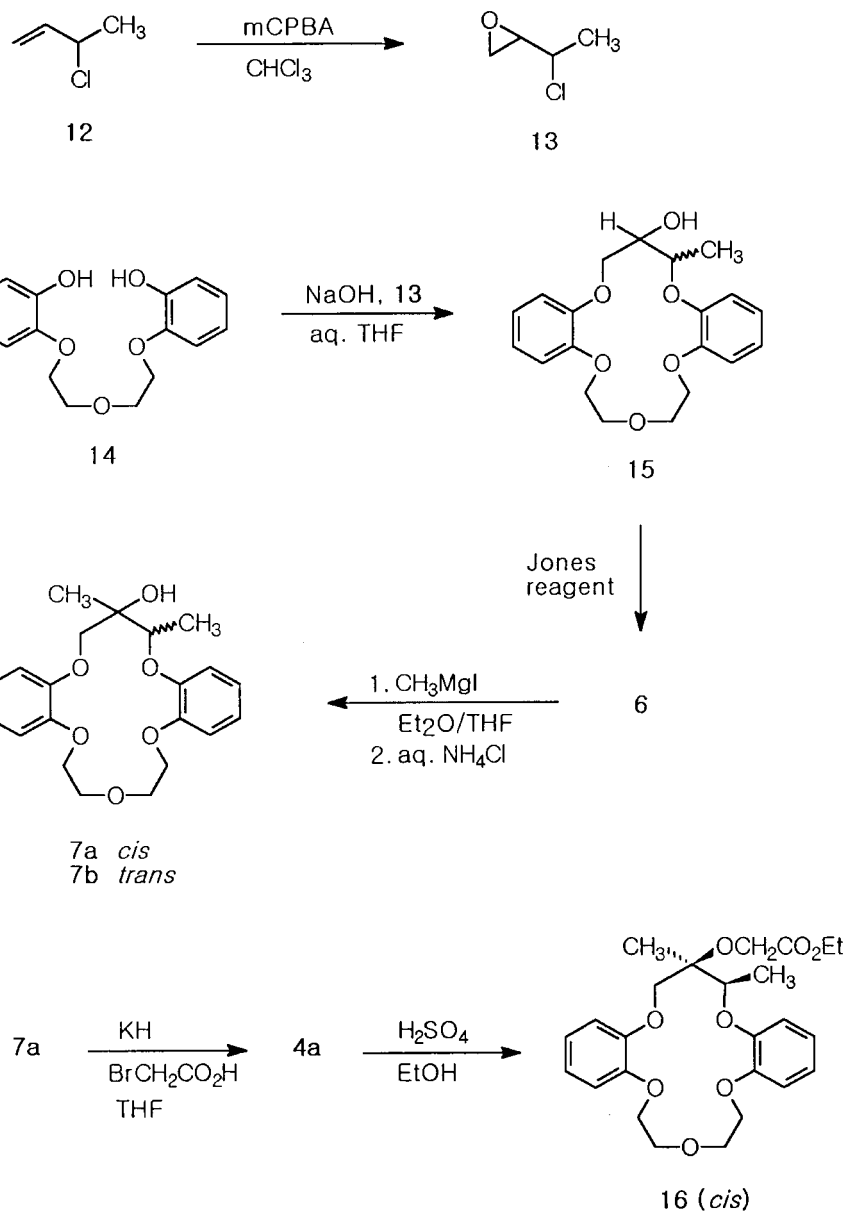
Scheme 1. Proposed synthetic route to asymmetric dibenzo-16-crown-5 (**4**).

ature for alkene epoxidation with mCPBA [10, 11], stirring for 20 min at 0 °C should be sufficient to insure complete reaction. However, in the present synthesis, stirring for at least 24 h at room temperature was required to complete the reaction. Cyclization of bisphenol **14** by reaction with NaOH and epoxide **13** in THF-water (1 : 1) provided the asymmetric crown ether alcohol **15** in 31% yield. TLC spots with R_f values of 0.4 and 0.5 on silica gel with EtOAc-hexane (1 : 1) as eluent were noted for the two stereoisomers of **15**, which has two chiral centers. NMR analysis indicated a 7 : 3 ratio of isomers.

Oxidation of crown ether alcohol **15** with Jones reagent provided crown ether ketone **6** in 74% yield. The Grignard reaction of **6** with methylmagnesium iodide gave lariat ether alcohol **7** in 87% yield. The ^{1}H NMR spectrum of crude **7** before chromatography indicated a mixture of two isomers in a 2 : 1 ratio. By TLC analysis on a silica gel with EtOAc as eluent, spots with R_f values of 0.40 and 0.43 were observed. Attempted separation of these two stereoisomers by column chromatography on silica gel and on alumina was unsuccessful. Only a small portion of the first fraction (R_f = 0.43) was separable. The use of radial thick-layer chromatography for this separation was more successful. One pure stereoisomer was obtained in 17% yield. Unfortunately, isolation of the pure second isomer could



Scheme 2. Preference of self-condensation over alkylation.



Scheme 3. Synthetic route for the preparation of **4a**.

not be achieved. To clarify the stereochemistry of the pure stereoisomer, a Nuclear Overhauser Effect (NOE) experiment was conducted, but the results were inconclusive. However, alkylation of the lariat ether alcohol isomer with bromoacetic acid gave lariat ether carboxylic acid **4a** which was shown to be the *cis*-isomer (the *vicinal* methyl and oxyacetic acid group are *cis*) by an NOE experiment. Therefore, the stereochemistry of the precursor lariat ether alcohol **7a** must also be *cis*.

The ^{1}H NMR spectra of *sym*-(methyl)dibenzo-16-crown-5-oxyacetic acid (**2**) and of **4a** in deuterated benzene are presented in Figure 1. For **2**, absorptions for the methylene protons on the three-carbon bridge appear as a widely spaced AB pattern with a chemical shift difference ($\Delta\nu_{AB}$) of 259 Hz (300 MHz ^{1}H NMR) and a *geminal* coupling constant of 10 Hz. Such nonequivalence of the methylene protons demonstrates that their interconversion by inversion of the three-carbon bridge is slow on the NMR time scale due to strong intramolecular hydrogen bonding of the OH of oxyacetic acid side arm with one of polyether ring oxygens [8]. For compound **4a**, the AB splitting pattern for H_a and H_b is two doublets with a 10 Hz geminal coupling constant. The chemical shift difference ($\Delta\nu_{AB}$) of 260 Hz for the absorption at 4.77 and 3.87 ppm is similar to that for **2**. By this measure, the conformational flexibility of **4a** is similar to that of **2**. However, another set of AB splitting pattern signals is seen at 4.22 and 4.68 ppm from the diastereotopic hydrogens H_c and $H_{c'}$ with a 16 Hz geminal coupling constant. It should be noted that hydrogens H_c and $H_{c'}$ in **2** showed only a singlet because they are chemically equivalent. An examination of a CPK space-filling model for **4a** indicates that when the methyl group (H_e) has a pseudoequatorial orientation, this produces serious steric interactions with H_c (or $H_{c'}$). This leads to chemically different environments for H_c and $H_{c'}$, which suggests that **4a** may be conformationally more rigid than **2**.

Results of the NOE experiment for stereochemical identification of **4a** as the *cis* isomer are shown in Figure 2. The ^{1}H NMR spectrum (A) is consistent with that expected for lariat ether carboxylic acid **4a**. NOE spectra B-F were obtained for **4a**. Irradiation at 0.92 ppm (H_e) (spectrum B) enhances the peak for H_f which shows that hydrogens H_f and H_e are fairly close to each other. Similarly, irradiation at 1.52 ppm (H_f) (spectrum C) increases the absorption for H_e. From these results, it is clearly impossible for both methyl groups to be located in pseudoaxial positions. NOE spectra D and F provide convincing evidence for the *cis*-isomer. If the methyl group (H_e) were placed in a pseudoaxial position, the intensity of the H_e peak would not be affected by irradiation of the H_c or $H_{c'}$ protons due to the long distance involved and no NOE peak for H_e would be seen. However, the presence of an NOE peak for H_e in spectra D and F prove that the methyl group (H_e) is positioned in a pseudoequatorial orientation. Thus the stereochemistry of **4a** is ascertained.

Preorganization in a lariat ether carboxylic acid may be assisted by intramolecular hydrogen bonding between the carboxylic acid group and an oxygen of the crown ether ring. Such hydrogen bonding would contribute to the chemical nonequivalency of hydrogens H_c and $H_{c'}$ in **4a**. To probe this possible role of intramolecular hydrogen bonding for the lariat ether carboxylic acid, the correspond-

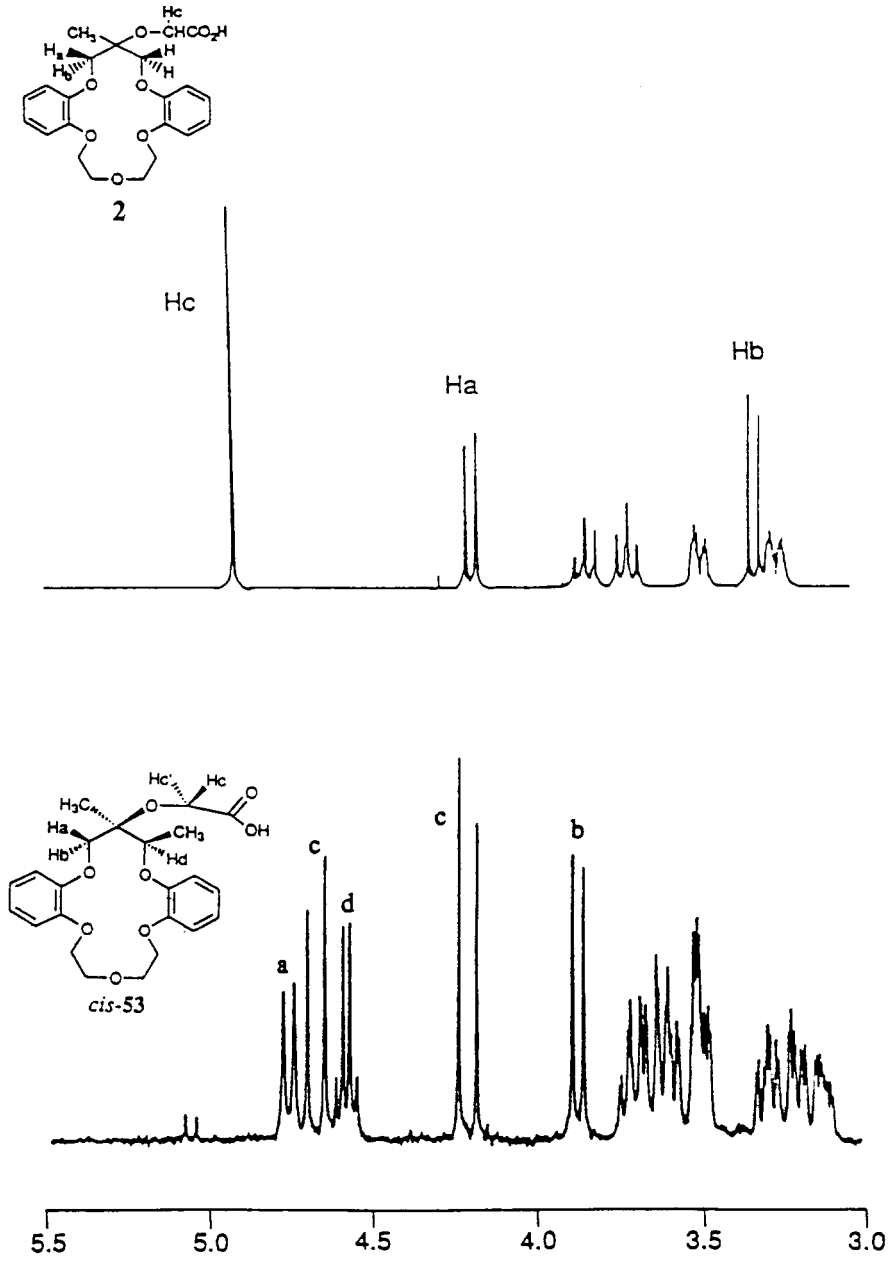


Figure 1. ^{1}H NMR spectra of compounds **2** and **4a** in deuterated benzene (300 MHz).

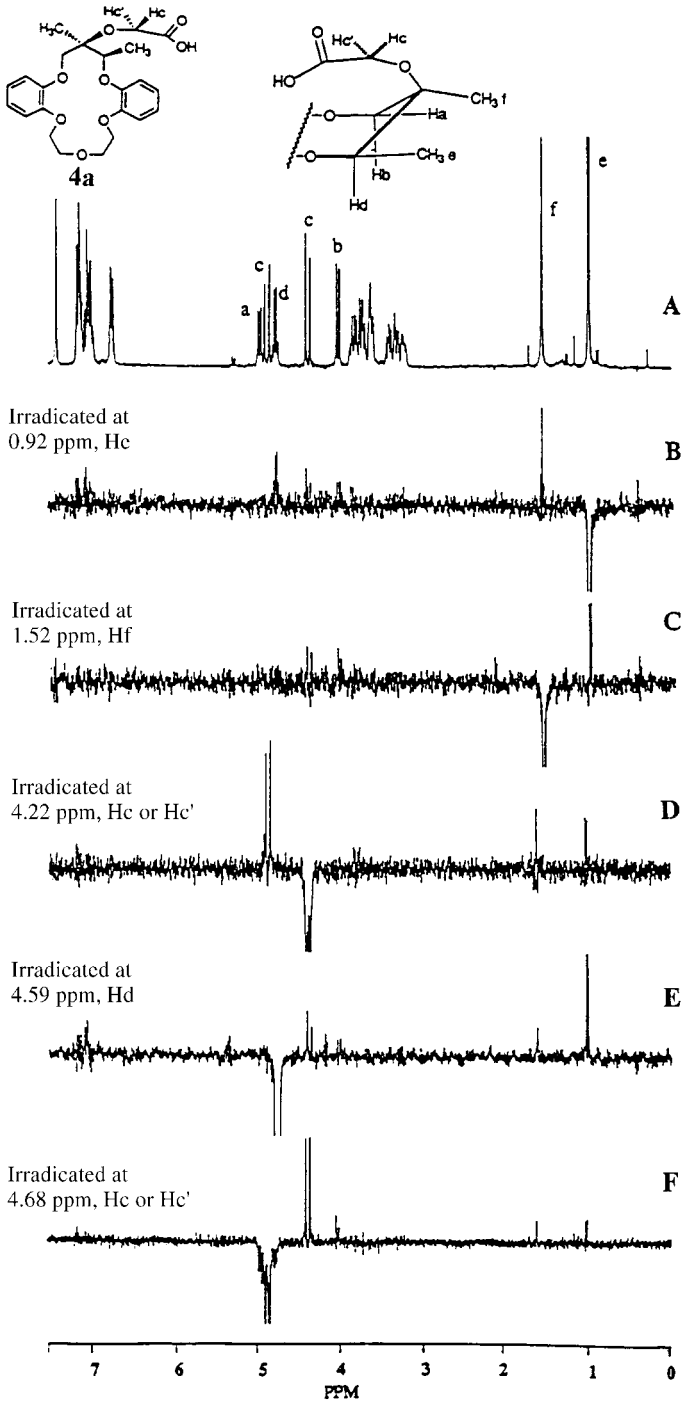


Figure 2. NOE spectra of **4a**.

ing ethyl ester **16** was prepared and its ^{1}H NMR spectrum was taken. For ethyl ester **16,** there is no possibility for intramolecular hydrogen bonding. In agreement, the chemical shift difference value ($\Delta\nu_{AB}$) for H_a and H_b decreases markedly from 260 Hz for compound **4a** to 119 Hz for **16** in deuterated benzene. In addition, the chemical shift difference for H_c and $H_{c'}$ of **16** decreases remarkably to 14 Hz compared to a value of 148 Hz for **4a** in deuterated benzene. These remarkable changes of the chemical shift difference values ($\Delta\nu_{AB}$) for H_a, H_b, H_c, and $H_{c'}$ strongly suggests that the conformational rigidity in this dibenzo-16-crown-5 carboxylic acid system results appreciably from an intramolecular hydrogen bonding.

Stability constants for complexation of alkali metal cations by the ionized forms of crown ether carboxylic acids **2** and **4a** in 90% aqueous methanol were determined by titration calorimetry. The stability values (log K) of Na^+ and K^+ for **4a** are 2.40 and 2.19, respectively, while those for **2** are 4.69 and 3.56, respectively. These data demonstrate that the introduction of a second methyl group into compound **2** to give **4a** seriously inhibits complexation of the alkali metal cations probably due to steric congestion in **4a**.

3. Experimental

3.1. CHEMICALS AND INSTRUMENTS FOR ANALYSIS

Melting points were obtained on either a Fisher-Johns (glass plate) or Mel-Temp (capillary tube) melting point apparatus. Infrared (IR) spectra were recorded with either a Nicolet MX-S FT-IR or a Perkin-Elmer 1600 Series FT-IR on NaCl plates (neat or film deposited from solution) or as KBr pellets and are reported in wavenumbers (cm^{-1}). ^{1}H NMR spectra were recorded with an IBM AF-200 or AF-300 spectrometer with the chemical shifts (δ) reported downfield from TMS. Commercial benzene-d_6 was used as received. Splitting patterns in the ^{1}H NMR spectra are identified as: s, singlet; d, doublet; t, triplet; q, quartet; br s, broad singlet; m, multiplet; J_{gem} (AB), geminal coupling constant in an AB splitting pattern. Thin layer chromatography (TLC) was performed using either Alumina GF or Silica Gel GF Uniplat
es from Analtech. Column chromatography was performed with 80–200 mesh alumina or 60–200 mesh silica gel from Fisher Scientific and Mallinckrodt, respectively. Flash chromatography was performed using silica gel for flash chromatography from Baker. Radial thick-layer chromatography was performed on a Harrison Research Chromatotron Model 7924T using Silica Gel 60 PF-254 with gypsum or Alumina Oxide 60 PF-254 from EM Science as absorbants. THF was freshly distilled from sodium ribbon or chunks. Pentane was stored over sodium ribbon. CH_2Cl_2 was freshly distilled from $LiAlH_4$. Elemental analyses were performed by either Galbraith Laboratories of Knoxville, Tennessee, or Desert Analytics of Tucson, Arizona. Compounds **5** [12] and **14** [13] were synthesized by reported procedures.

3.2. 1,2-EPOXY-3-CHLOROBUTANE (**13**) [10]

To a slurry solution of *m*-chloroperoxybenzoic acid (49.5 g, 0.14 mol) in 350 mL of $CHCl_3$ at 0 °C was added dropwise 10.0 g (0.11 mol) of 3-chloro-1-butene (**12**) during a period of 20 min under nitrogen. The mixture was stirred for 24 h at room temperature and then treated with 5% aqueous $NaHCO_3$ until the reaction mixture no longer gave a positive test with starch iodide paper. The starch iodide paper (KI) turned purple (positive) if unreacted *m*-CPBA remains in the reaction mixture. The mixture was filtered. The organic layer was separated, washed with brine (2 × 100 mL), dried over $MgSO_4$, and *in vacuo* at room temperature to provide 11.0 g (94%) of **13** as a colorless oil. IR (neat): 1123 (C–O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.56 (q, 3H); 2.67–2.74 (m, 1H); 2.85–2.90 (m, 1H); 3.00–3.15 (m, 1H); 3.60–3.67 (m, 0.5H); 3.76–3.85 (m, 0.5H).

3.3. 6-HYDROXY-5-METHYL-(2,3)(9,10)-DIBENZO-16-CROWN-5 (**15**)

A solution of 3.70 g (0.012 mol) of bis[2-(*o*-hydroxyphenoxy)ethyl]ether (**14**), 0.96 g (0.024 mol) of NaOH, 150 mL of dry THF, and 300 mL of water was stirred for 2 h at 90 °C under nitrogen. After cooling to 50 °C, 1.70 g (0.015 mol) of **10** in 10 mL of dry THF was added dropwise during a period of 3 h followed by refluxing for 10 h. After cooling to 50 °C, 0.96 g (0.024 mol) of NaOH was added and 1.27 g (0.012 mol) of **14** was added dropwise during a 3 h-period followed by refluxing for 10 h. After the THF was removed *in vacuo*, EtOAc and 20% NaOH solution (100 mL of each) were added to the crude product. The organic layer was separated and washed with 20% aqueous NaOH solution (4 × 100 mL) to remove the unreacted **14**. The EtOAc layer was dried over $MgSO_4$ and evaporated *in vacuo* to provide a yellowish solid. Chromatography of the crude product on silica gel with EtOAc-hexanes (1 : 6) as eluent gave 1.34 g (31%) of **15** as a white solid (mixture of *cis* and *trans* isomers) with mp 82–83 °C. By TLC [silica gel with EtOAc-hexanes (1 : 1) as eluent], spots with R_f values of 0.4 and 0.5 (7 : 3 ratio by ^1H NMR integration) were noted for the two stereoisomers. IR (deposit from CH_2Cl_2 solution): 3444 (O–H); 1123 (C–O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.21–1.38 (two d, 3H); 3.08, 3.52 (br s, 1H); 3.85–4.29 (m, 12H); 4.41–4.70 (m, 1H); 6.84–7.03 (m, 8H). Anal. Calcd. for $C_{20}H_{24}O_6 \cdot 0.05CH_2Cl_2$: C, 66.04; H, 6.60. Found: C, 65.91; H, 6.26.

3.4. 5-METHYL-6-OXO-(2,3)(9,10)-DIBENZO-16-CROWN-5 (**6**)

To 2.40 g (6.6 mmol) of **15** in 100 mL of acetone was added dropwise 10 mL of Jones reagent [14] during a period of 2 h at −10 °C and then the reaction mixture was stirred for 4 h at room temperature. The yellowish tan solution was decanted from the green residue and the residue was washed with acetone (3 × 100 mL). After the combined acetone solution and washings were evaporated *in vacuo*, 100 mL of CH_2Cl_2 and 100 mL of water were added to the dark yellowish solid. The organic layer was separated, washed with 5% aqueous $NaHCO_3$ (2 × 100 mL),

dried over $MgSO_4$, and evaporated *in vacuo* to afford a yellowish solid. Chromatography of the crude product on silica gel with EtOAc-hexanes (1 : 2) as eluent gave 1.75 g (74%) of **6** as a white solid [15] with mp 124–125 °C. IR (deposit from CH_2Cl_2 solution): 1736 (C=O); 1123 (C–O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.52 (d, 3H); 3.88–3.94 (m, 4H); 4.10–4.19 (m, 4H); 4.94 (q, 1H); 5.15 (d, J_{gem} = 18.6 Hz, 1H); 5.37 (d, J_{gem} = 18.6 Hz, 1H); 6.82–7.15 (m, 8H). Anal. Calcd. for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19. Found: C, 66.82; H, 5.97.

3.5. CIS-5,6-DIMETHYL-6-HYDROXY-(2,3)(9,10)-DIBENZO-16-CROWN-5 (**7a**)

To 6.80 mg (2.77 mmol) of magnesium turnings in 15 mL of Et_2O was added 0.39 g (2.77 mmol) of iodomethane under nitrogen and the mixture was stirred for 3 h at room temperature. To the gray suspension was added 500 mg (1.38 mmol) of **6** in 15 mL of dry THF during a period of 1 h followed by stirring for 5 h at room temperature. After cooling to 0 °C, 10 mL of saturated NH_4Cl solution was added dropwise and the mixture was stirred for 30 min at room temperature. After the Et_2O and THF were evaporated *in vacuo*, 20 mL of CH_2Cl_2 and 30 mL of water were added to the yellowish oil. The organic layer was separated, washed with brine (2 × 30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to provide a white solid. Radial thick-layer chromatography of the white solid on silica gel with EtOAc-hexanes (1 : 4) gave 90 mg (17%) of **7a** as a colorless oil. IR (neat): 3310 (O–H); 1123 (C–O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.23 (d, 3H); 1.54 (s, 3H); 3.03 (br s, 1H); 3.87–4.23 (m, 10H); 4.64 (q, 1H); 6.83–7.00 (m, 8H); Anal. Calcd. for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00. Found: C, 67.15; H, 6.95.

3.6. CIS-5,6-DIMETHYL-6-OXYACETOXY-(2,3)(9,10)-DIBENZO-16-CROWN-5 (**4a**)

After removal of the protecting mineral oil from KH (0.86 g, 65% dispersion in mineral oil, 7.5 mmol) by washing with pentane under nitrogen, dry THF (100 mL) then **7a** (0.57 g, 1.51 mmol) were added with stirring at room temperature. After the mixture had been stirred for 30 min, bromoacetic acid (0.42 g, 3.03 mmol) in 10 mL of dry THF was added dropwise during a period of 30 min. The reaction mixture was stirred for an additional 3 h at room temperature. After careful addition of water to destroy the excess KH, the THF was evaporated *in vacuo*. The resulting alkaline solution was extracted with EtOAc (2 × 50 mL) to remove unreacted **7a** and organic impurities. The aqueous layer was acidified to pH 1 with 6 N HCl and extracted with CH_2Cl_2 (3 × 30 mL). The CH_2Cl_2 layer was dried over $MgSO_4$ and concentrated *in vacuo* to give a pale yellowish oil. Crystallization from 50 mL of Et_2O provided 0.56 g (87%) of **4a** as a white solid with mp 127–128 °C. IR (deposit from CH_2Cl_2 solution): 3420–2800 (O-H); 1710 (C=O); 1123 (C–O) cm^{-1}. ^1H NMR (C_6D_6): δ 0.94 (d, 3H); 1.50 (s, 3H); 3.06–3.72 (m, 8H); 3.97 (d,

J_{gem} = 10 Hz, 1H); 4.22 (d, J_{gem} = 16.2 Hz, 1H); 4.57 (q, 1H); 4.68 (d, J_{gem} = 16.2 Hz, 1H); 4.77 (d, J_{gem} = 10 Hz, 1H); 6.48–6.91 (m, 8H). Anal. Calcd. for $C_{23}H_{28}O_8$: C, 63.87; H, 6.52. Found: C, 64.04; H, 6.72.

3.7. ETHYL CIS-5,6-DIMETHYL-6-OXYACETOXY-(2,3)(9,10)-DIBENZO-16-CROWN-5 (**16**)

A solution of **4a** (30.0 mg, 0.093 mmol), 20 mL of 100% EtOH, and a catalytic amount of sulfuric acid was refluxed for 10 h with the condensate passing through a Soxhlet thimble containing anhydrous Na_2SO_4. After 10 mL of water was added, the EtOH was removed *in vacuo* and 10 mL of CH_2Cl_2 was added. The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo* to provide 39.5 mg (93%) of **16** as a colorless oil. IR (neat): 1732.5 (C=O); 1122 (C–O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.24 (d, 3H); 1.68 (s, 3H); 3.85–4.33 (m, 12H); 4.69 (s, 2H); 4.75 (q, 1H); 6.79-7.00 (m, 8H). Anal. Calcd. for $C_{25}H_{32}O_8$: C, 65.19; H, 7.01. Found: C, 65.09; H, 6.81.

3.8. SELF-CONDENSATION (ALDOL) PRODUCT **8**

To 2.00 g (5.8 mmol) of *sym*-(keto)dibenzo-16-crown-5 (**5**) in 60 mL of dry THF at −45 °C under nitrogen was added dropwise 5.80 mL (8.71 mmol) of LDA with a syringe. After stirring for 1 h at −45 °C, 0.98 g (8.71 mmol) of iodomethane in 5 mL of dry THF was added during a period of 30 min at −45 °C. The reaction mixture was stirred for 2 h at room temperature and then 20 mL of 5% aqueous NH_4Cl was added slowly. The THF was evaporated *in vacuo* and 30 mL of EtOAc and 30 mL of water were added. The organic layer was separated, washed with 20 mL of 5% HCl and then with 30 mL of brine. The EtOAc layer was dried over $MgSO_4$ and concentrated *in vacuo* to give a yellowish oil. Chromatography of the crude product on silica gel with EtOAc-hexanes (1 : 4) as eluent afforded a white solid which was recrystallized from 50 mL of Et_2O to give 1.50 g (76%) of **8** with mp 89 °C (shrinking), 102 °C (melting). IR (deposit from CH_2Cl_2 solution): 3507 (O–H); 1734 (C=O); 1125 (C–O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.89–3.93 (m, 9H); 4.05–4.29 (m, 16H); 4.26 (d, 1H); 4.50 (q, 1H); 4.58 [d, J_{gem}(AB) = 9.7 Hz, 1H]; 5.1 [d, J_{gem}(AB) = 18.1 Hz, 1H]; 5.32 (d, J_{gem}(AB) = 18.1 Hz, 1H]; 5.34 (s, 1H); 6.68–7.20 (m, 16H). MS: m/z (M+) Calc: 688.72, Found: 670.72 [17]. Anal. Calcd for $C_{38}H_{40}O_{12}$: C, 66.27; H, 5.85. Found: C, 66.54; H, 5.69.

3.9. TITRATION CALORIMETRY

The calorimetric determination was carried out using a TRONAC model 1250 isoperibol titration calorimeter equipped with a 25 mL-glass Dewar flask as the reaction vessel and a 10 mL-precision constant-rate burette for titrant delivery. The thermostat was maintained at 25 ± 0.02 °C with a TRONAC model 40 precision

temperature controller. The ligand solution (4 mM of the ligand, 20 mL) was titrated with 40 mM MNO_3 in 90% methanol-water solution. The heat of dilution for the metal nitrate was measured in separate experiments by titrating the metal nitrate into 90% methanol-water solution. Stability constant, enthalpy changes, and entropy changes were simultaneously obtained by the use of the least square program.

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References

1. C. J. Pedersen: *J. Am. Chem. Soc.* **89**, 2495 (1967).
2. D. J. Cram and N. K. Trueblood: in F. Vögtle and E. Weber (eds), *Host Guest Complex Chemistry. Macrocycles. Synthesis, Structures, and Applications*, Springer-Verlag, New York, U.S.A. (1985).
3. B. Dietrich, P. Viout, and J.-M. Lehn: in *Macrocyclic Chemistry*, VCH, New York, U.S.A. (1993).
4. G. W. Gokel, D. M. Dishong, and C. J. Diamone: *J. Chem. Soc., Chem. Commun.*, 1053 (1980).
5. R. A. Bartsch: *Solvent Extn. Ion Exch.* **7**, 829 (1989).
6. W. Walkowiak, W. A. Charewicz, S. I. Kang, I. W. Yang, M. Pugia, and R. A. Bartsch: *Anal. Chem.* **62**, 2018 (1990).
7. R. A. Bartsch, J. S. Kim, U. Olser, D. M. Purkiss, V. Ramesh, N. K. Dalley, and T. Hayashita: *Pure Appl. Chem.* **65**, 399 (1993).
8. R. A. Bartsch, J. S. Kim, U. Olser, and D. M. Purkiss: *Supramol. Chem.* **6**, 327 (1996).
9. H. Jatzke and R. R. Schmidt: *Liebigs Ann. Chem.*, 753 (1991).
10. H. C. Brown, D. Van der Jagt, L. I. Rothberg, W. J. Hammer, and J. H. Kawakami: *J. Org. Chem*. **50**, 2179 (1985).
11. H. C. Brown, J. H. Kawakami, and S. Ikegami: *J. Am. Chem. Soc*. **92**, 6914 (1970).
12. R. A. Bartsch, Y. Liu, S. I. Kang, B. K. Son, G. S. Heo, P. G. Hipes, and L. J. Bills: *J. Org. Chem.* **48**, 4864 (1983).
13. G. S. Heo, R. A. Bartsch, L. L. Schlobohm, and J. G. Lee: *J. Org. Chem.* **46**, 3574 (1981).
14. Chromium trioxide anhydride (16.2 g) and concentrated sulfuric acid (3.8 mL) were added to 20 mL of water and then diluted to 60 mL with water.
15. Sometimes, the product was a pale yellowish solid which could be decolorized by washing with cold Et_2O.
16. NOE experiments performed to indicate which isomer was present (*cis* or *trans*) were unsuccessful. However, the product (*cis*-**7**) of the next step (coupling with bromoacetic acid) shows that the *cis* isomer was present.
17. A dehydration reaction ($-H_2O$) might take place during mass spectrometry to give the α,β-unsaturated ketone.