diluted with water (100 mL) containing sodium sulfite. The mixture was extracted with $CH_2Cl_2$ and the extracts were dried ($MgSO_4$) and concentrated to give 2.70 g (58%) of **9** as a white solid, mp 144–145.5 °C (toluene): $^1H$ NMR ($CDCl_3$–$D_2O$) $\delta$ 7.49 (d, $J$ = 2.2 Hz, 1 H, C3-H), 4.28 (dd, $J_{4,5}$ = 4.8 Hz, $J_{4,3}$ = 2.2 Hz, 1 H, C4-H), 3.76 (s, 3 H, $CH_3$), 2.83–2.62 (m, 2 H, C7-$H_2$), 2.49 (ddd, $J_{5,4}$ = 4.8 Hz, $J_{5,6}$ = 7.5 Hz, $J_{5,6}$ = 2.8 Hz, 1 H, C5-H, 2.37–2.22 (m, 2 H, C6-$H_2$);[10] mass spectrum (70 eV, EI), $m/z$ 232 and 230 (molecular ions). Anal. Calcd for $C_8H_{11}BrN_2O$: C, 41.58; H, 4.80; N, 12.12. Found: C, 41.95; H, 4.83; N, 12.28.

**1-(Acetyloxy)-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-butanone (11).** To an ice-cold solution of 2.68 g (20.0 mmol) of **8** in THF (160 mL) and water (40 mL) was slowly added $HClO_4$ (40 mL of a 1.0 M solution; 40.0 mmol) followed by 5.52 g (40.0 mmol) of *N*-bromoacetamide, in portions. The reaction mixture was stirred at room temperature for 18 h and concentrated to half-volume. The concentrate was partitioned between $CH_2Cl_2$ and water (100 mL) containing sodium sulfite, and the organic phase was dried ($MgSO_4$) and concentrated to provide a yellow oil. This oil was diluted with acetone (250 mL) and 20 g of potassium acetate was added. The reaction mixture was heated at reflux for 18 h, cooled, and filtered. The precipitate was washed with acetone, and the combined filtrates were concentrated. The residue was reconstituted in $CH_2Cl_2$, and the solution was dried ($MgSO_4$) and concentrated to a viscous, amber oil, which was purified by flash chromatography on silica gel (9:1 acetone/$CH_2Cl_2$) to give 2.50 g (43%) of **13** as a yellow oil, bp 120–130 °C (2 mm): IR (neat) 1760 (ester C=O), 1740 (ketone C=O) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.30 (s, 1 H, C3-H), 4.55 (s, 2 H, $CH_2O$), 3.85 (s, 3 H, $NCH_3$), 3.00–2.70 (m, 4 H, $CH_2CH_2$), 2.15 (s, 3 H, $CH_3CO$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 203 (C2), 170 (ester C=O), 138 (pyrazole C3 and C5), 93.0 (pyrazole C4), 68.0 (C1), 38.0 ($NCH_3$), 37.0 (C3), 21.0 (C4), 18.0 (acetyl $CH_3$); mass spectrum (70 eV, EI), $m/z$ 288 and 290 (molecular ions). Anal. Calcd for $C_{10}H_{13}BrN_2O_3$: C, 41.54; H, 4.53; N, 9.69. Found: C, 41.52; H, 4.54; N, 9.31.

**$\alpha$,4-Dibromo-1-methyl-1*H*-pyrazole-5-butanal (12).** To an ice-cold solution of 2.68 g (20.0 mmol) of **8** in THF (160 mL) and water (40 mL) was slowly added $HClO_4$ (40 mL of a 1.0 M solution; 40.0 mmol) followed by 5.52 g (40.0 mmol) of *N*-bromoacetamide, in portions. The reaction mixture was stirred at room temperature for 18 h and concentrated. The residue was partitioned between $CH_2Cl_2$ and water (100 mL) containing sodium sulfite, and the organic phase was dried ($MgSO_4$) and concentrated. The resulting yellow oil was purified by flash chromatography on silica gel (9:1 $CH_2Cl_2$/acetone) to provide 4.80 g (78%) of **12** as a yellow oil: $^1H$ NMR ($CDCl_3$) $\delta$ 9.45 (d, $J$ = 2 Hz, 1 H, CHO), 7.40 (s, 1 H, C-3H), 4.45–4.15 (m, 1 H, CHBr), 3.85 (s, 3 H, $NCH_3$), 3.05–2.05 (m, 4 H, $CH_2CH_2$); mass spectrum (70 eV, EI), $m/z$ 308, 310, and 312 (molecular ions). Anal. Calcd for $C_8H_{10}Br_2N_2O$: C, 30.99; H, 3.25; N, 9.04. Found: C, 30.99; H, 3.32; N, 9.15.

**4,5,6,7-Tetrahydro-1,4-dimethyl-1*H*-indazol-4-ol (13).** A solution of 15.0 g (0.100 mol) of ketone **6** in THF (100 mL) was added, dropwise, to a solution of methylmagnesium bromide (40.0 mL of a 2.80 M solution in ethyl ether; 0.112 mol) in THF (100 mL) at such a rate that the reaction temperature remained at 20–30 °C. The mixture was stirred at room temperature for 90 min and slowly poured onto ice containing $NH_4Cl$ and NaCl. The resulting slurry was extracted with $CH_2Cl_2$, and the combined extracts were dried ($MgSO_4$) and concentrated. The residue was dissolved in warm toluene and the crystalline solid which formed on cooling was collected to give 11.2 g (67%) of **13**, mp 108–110 °C: $^1H$ NMR ($CDCl_3$) $\delta$ 7.40 (s, 1 H, C3-H), 3.65 (s, 3 H, $NCH_3$), 2.70–2.30 (m, 2 H, $CH_2$), 2.40 (s, 1 H, OH), 2.20–1.65 (m, 4 H, $CH_2CH_2$), 1.55 (s, 3 H, $CCH_3$); mass spectrum (70 eV, EI), $m/z$ 166 (molecular ion). Anal. Calcd for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.86. Found: C, 65.00; H, 8.38; N, 16.67.

**4-Bromo-1-methyl-1*H*-pyrazole-5-butanal (14).** Preparation of **14** was analogous to that of **12**. Thus, 1.00 g (6.57 mmol) of carbinol **7**, $HClO_4$ (7.00 mL of a 1.0 M solution; 7.00 mmol), and 1.00 g (7.25 mmol) of *N*-bromoacetamide provided 1.40 g (92%) of **14** as a yellow oil, which was purified by flash chromatography on silica gel (9:1 $CH_2Cl_2$/acetone): IR (neat) 1720 (C=O) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 9.70 (t, $J$ = 1 Hz, 1 H, CHO), 7.35 (s, 1 H, C3-H), 3.80 (s, 3 H, $NCH_3$), 2.90–2.20 (m, 4 H, $CH_2CH_2CH_2$), 2.15–1.70 (m, 2 H, $CH_2$); mass spectrum (70 eV, EI), $m/z$ 230 and 232 (molecular ions). Anal. Calcd for $C_8H_{11}BrN_2O$: C, 41.58; H, 4.80; N, 12.12. Found: C, 41.66; H, 4.81; N, 12.03.

**5-(4-Bromo-1-methyl-1*H*-pyrazol-5-yl)-2-pentanone (15).** Preparation of **15** was analogous to that of **12**. Thus, 3.32 g (20.0 mmol) of carbinol **13**, $HClO_4$ (20.0 mL of a 1.0 M solution; 20.0 mmol), and 2.76 g (20.0 mmol) of *N*-bromoacetamide provided crude **15** as a yellow oil. Purification by flash chromatography on silica gel (9:1 $CH_2Cl_2$/acetone) gave 3.70 g (76%) of **15** as a colorless oil: IR (neat) 1715 (C=O) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.40 (s, 1 H, C3-H), 3.85 (s, 3 H, $NCH_3$), 2.85–2.40 (m, 4 H, $CH_2CH_2CH_2$), 2.20 (s, 3 H, $CH_3CO$), 2.10–1.70 (m, 2 H, $CH_2$); mass spectrum (100 eV, CI), 245 and 247 ($M^+$ + 1), 273 and 275 ($M^+$ + 29), 285 and 287 ($M^+$ + 41). Anal. Calcd for $C_9H_{13}BrN_2O$: C, 44.10; H, 5.34 N, 11.43. Found: C, 44.46; H, 5.54; N, 11.20.

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**Registry No.** **4**, 30581-70-5; **5**, 85302-07-4; **6**, 85302-16-5; **7**, 109801-13-0; **8**, 109801-14-1; **9**, 109801-15-2; **11**, 109801-16-3; **12**, 109801-17-4; **13**, 109801-18-5; **14**, 109801-19-6; **15**, 109838-57-5; DMFDMA, 4637-24-5; MeMgBr, 75-16-1; $MeNHNH_2$, 60-34-4.

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## Enhancement of Alkali Metal Cation Binding in Water by Ring Sulfonation of Dibenzo-16-crown-5 Carboxylic Acids

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The presence of aromatic ring substituents on benzo- and dibenzocrown ethers may substantially influence the selectivity and binding strength for alkali metal cations.[1-3] In general, it has been observed that electron-donating substituents enhance cation binding as a result of increased basicity of oxygen atoms bonded to the aromatic ring. We now report the ring sulfonation of dibenzo-16-crown-5 carboxylic acids **1–3** to form crown carboxylic disulfonic acids **4–6** and an assessment of interactions of these novel proton-ionizable crown ethers with $Na^+$ and $K^+$ in water.

The first recorded crown ether sulfonation was by Pederson[4] who prepared dibenzo-18-crown-6 disulfonic acid as a dihydrate. Later, Cram and co-workers[5] reported tetrasulfonation of optically active bisnaphtho-22-crown-6. In neither instance were the alkali metal cation binding properties of the sulfonated crown ether examined.

Syntheses of crown carboxylic disulfonic acids **4–6** were accomplished in high yields (82–93%) by treatment of crown carboxylic acids **1–3** with a solution of $H_2SO_4$, $Ac_2O$, AcOH, and $CHCl_3$ (Scheme I). The presence of AcOH prevented sulfone formation.[6] The crown carboxylic disulfonic acids were isolated as solids that contained waters of hydration in the case of **4** and **5**. Increased lipophilicity within the crown carboxylic disulfonic acid reduced the number of water molecules present in the solid.

Sulfonated crown compounds **4–6** possess high water solubility and the *n*-butyl compound **6** was found to be soluble in acetone as well. These crown carboxylic disulfonic acids decomposed when stored for periods longer than a few weeks but could be converted into stable disulfonate salts when neutralized with calcium, sodium, or potassium carbonates. Stoichiometries of the disulfonate salts, as determined by atomic absorption, were two metal cations to one crown species for $K^+$ and $Na^+$ and one metal

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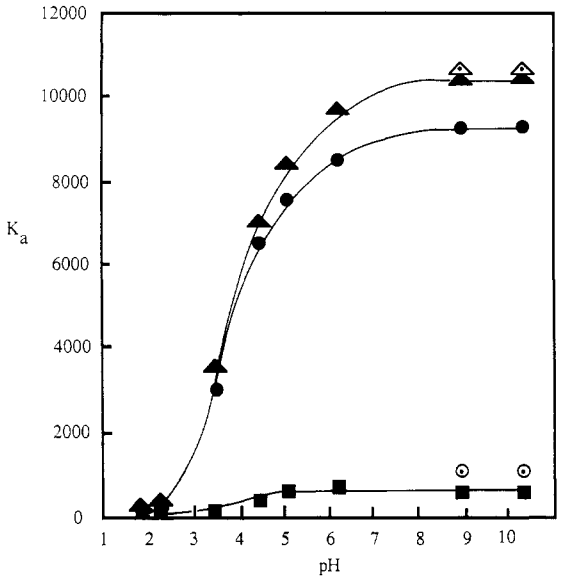



**Figure 1.** Plot of association constants vs. pH for complexation of $Na^+$ in buffered water by **1**, ■; **2**, ○; **4**, ●; **5**, ▲; **6**, △.

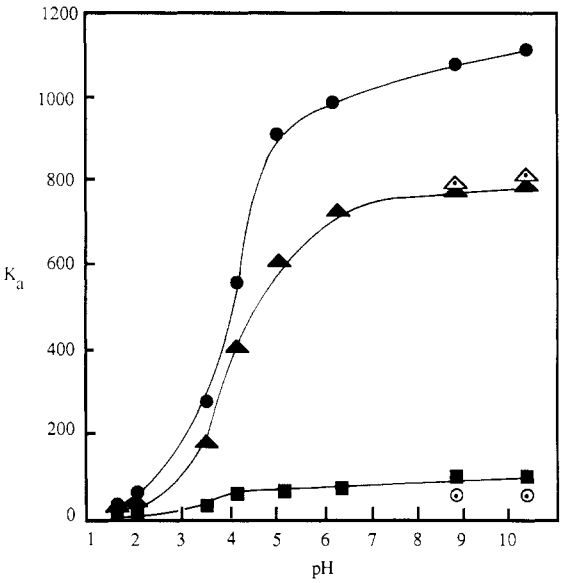
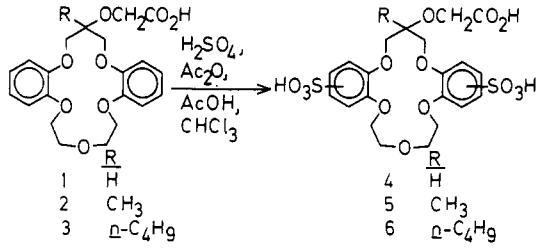



**Figure 2.** Plot of association constants vs. pH for complexation of $K^+$ in buffered water by **1**, ■; **2**, ○; **4**, ●; **5**, ▲; **6**, △.

**Scheme I**




cation to one crown moiety for $Ca^{2+}$. Water solubility of the calcium salts was noted to be higher than that of the potassium and sodium salts.

Heating **4** in 25% aqueous HCl produced proto-desulfonation, whereas halo-desulfonation with bromine resulted in a tetrabrominated derivative of **1**.

Association constants ($K_a$) for complexation of $Na^+$ and $K^+$ by compounds **1**, **2**, **4**, **5**, and **6** in buffered aqueous solutions at 25 °C were determined by potentiometric titration.[7] Compound **3** had insufficient water solubility to be studied. In Figures 1 and 2, association constants for complexation of $Na^+$ and $K^+$, respectively, are plotted vs. the pH of the buffered aqueous solutions. For crown carboxylic acid **2** and crown carboxylic disulfonic acid **6**, association constants were determined only at alkaline pH values.

A p$K_a$ of 3.69 has been determined[8] for crown carboxylic acid **1** in water at 25 °C, while p$K_a$ values for aromatic sulfonic acids are typically 1.0–1.5.[9] The uniformly low binding of $Na^+$ and $K^+$ by crown carboxylic acids **1** and **2** and crown carboxylic disulfonic acids **4** and **5** at pH 2 and below reveals that the presence of two ring sulfonate groups in the latter has only a minor influence upon metal ion binding when the pendant carboxylic acid group is in its un-ionized form. However as the pH is increased, marked enhancements in $K_a$ values for complexation of $Na^+$ and $K^+$ with crown carboxylic disulfonic acids **4**–**6** compared with crown carboxylic acids **1** and **2** are readily apparent.

At pH 9, the stability constant for association of $Na^+$ with crown carboxylic disulfonic acid **4** is enhanced by a factor of 12 over its nonsulfonated analogue **1**. Similarly binding of $Na^+$ by **2** increases by a factor of 14 in its disulfonated derivative **5**. Such elevation of $Na^+$ binding when sulfonate groups are attached to the aromatic rings of crown carboxylic acids **1** and **2** cannot be attributed to a simple electronic effect since a Hammett $\sigma_p$ value of 0.09 for the $SO_3^-$ substituent[10] shows it to be weakly electron withdrawing. Instead, a simple electrostatic rationalization is advanced in which the controlling factor is the stronger association of a trivalent anion with a monovalent cation compared with a monovalent anion–monovalent cation interaction.

In all cases, association constants for complexation of $Na^+$ are higher than those for $K^+$ as would be predicted for the 16-crown-5 ring size.[11] For **1** and **4**, the maximum association constant ratio $K_a^{Na^+}/K_a^{K^+}$ is 8; whereas for **2** and **5**, it is 14. The ratio for **6** is 17. Examination of CPK space-filling models suggests that in **2**, **5**, and **6** the alkyl group on the three-carbon bridge prefers to point away from the more polar polyether ring. This would orient the carboxylate group over the crown ether cavity and produce greater cation selectivity by preorganization of the binding site.[12]

In summary, the new crown carboxylic disulfonic acids **4**–**6** are effective complexing agents for $Na^+$ in water at all except highly acidic pH values and exhibit good $Na^+/K^+$ selectivity.

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## Experimental Section

For the potentiometric measurements, a Fisher Accumet Model 825 MP pH/mV meter was utilized together with a Corning sodium ion electrode (Cat. No. 476210) and a Corning monovalent ion electrode (Cat. No. 476220) for $Na^+$ and $K^+$ binding determinations, respectively. A Brinkman 50-mL titration vessel (Model No. EA 876-50) was utilized for all determinations. Demineralized water was prepared by passing distilled water through three Barnstead D8992 combination cartridges in series.

Melting points were taken with a Fisher Johns melting point apparatus and are uncorrected. IR spectra were obtained on neat samples (unless specified otherwise) with a Nicolet MW-S infrared spectrophotometer and are recorded in reciprocal centimeters. $^1H$ NMR spectra were recorded with a Varian EM 360A or EM 360 spectrometer in deuteriochloroform and chemical shifts are reported in parts per million ($\delta$) downfield from TMS. Elemental analysis was performed by Galbraith Laboratories of Knoxville, TN.

Unless specified otherwise, reagent grade reactants and solvents were obtained from chemical suppliers and used as received. (Dibenzo-16-crown-5-oxy)acetic acid (**1**),[8] *sym*-*n*-butyl(dibenzo-16-crown-5-oxy)acetic acid (**3**),[13] and *sym*-hydroxymethyldibenzo-16-crown-5[14] were prepared by reported methods.

**Preparation of *sym*-Methyl(dibenzo-16-crown-5-oxy)acetic Acid (2).** Under nitrogen, 1.0 g (21.3 mmol) of NaH (60% dispersion in mineral oil) was washed with dry pentane to remove the mineral oil and was suspended in 200 mL of THF. *sym*-Hydroxymethyldibenzo-16-crown-5 (5.3 mmol) in 50 mL of THF was added and the mixture was stirred for 1 h. A solution of 1.64 g (11.8 mmol) of bromoacetic acid in 25 mL of THF was added dropwise and the mixture was stirred at room temperature for 48 h and then at reflux for 1 h. To the cooled reaction mixture was added $H_2O$ (50 mL), and the pH was adjusted to 1 with 6 N HCl. The THF was evaporated in vacuo and the residual aqueous mixture was extracted with $CH_2Cl_2$ (3 × 100 mL). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo to give a crude product which chromatographed twice on silica gel with $CH_2Cl_2$–MeOH (10:1) as eluent. Recrystallization from 30–60 °C petroleum ether–EtOAc (10:1) gave an 84% yield of **2** as a white crystalline solid: mp 102–103 °C; IR (deposited from $CDCl_3$) 3620–3200 (OH), 1730 (C=O), 1250, 1121 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.30 (s, 3 H), 3.4–4.55 (m, 12 H), 4.75 (s, 2 H), 6.9–7.1 (m, 8 H). Anal. Calcd for $C_{22}H_{26}O_8$: C, 63.15; H, 6.26. Found: C, 62.81; H, 6.34.

**Preparation of Crown Carboxylic Disulfonic Acids 4–6.** A solution of $Ac_2O$ (36 mL), AcOH (5 mL), $CH_2Cl_2$ (24 mL), and 2.0 g of concentrated $H_2SO_4$ was added to 5.0 g of crown carboxylic acid **1–3** under nitrogen. The white mixture was heated to 50 °C to produce a reddish solution which was cooled and stirred overnight at room temperature. Volatile components were removed with a rotary evaporator (heating to 45 °C). The resultant dark oil was held under vacuum (0.05 Torr) for 6 h at room temperature and then heated to 40 °C to produce off-white crystals which were dissolved in MeOH (10 mL). The MeOH solution was added to $Et_2O$ (100 mL) and placed in a refrigerator overnight. The mother liquor was decanted and the residue was evaporated in vacuo (0.05 Torr, heating to 40 °C) to produce white crystals which were further purified by twice repeating the dissolution in MeOH, precipitation with $Et_2O$, and drying procedure. The final products were extremely hygroscopic white solids. Due to decomposition of **4–6** after several weeks at room temperature, they were converted into their calcium salts for storage by neutralizing an aqueous solution of the crown carboxylic disulfonic acid with 1 equiv of $CaCO_3$ and evaporation of the $H_2O$ in vacuo to yield a white powder.

**(Bis[4(5)-sulfobenzo]-16-crown-5-oxy)acetic acid (4):** mp 127–128 °C; 93%; IR (deposited film from $CDCl_3$) 3408 (OH), 1734 (C=O), 1124 (CO), 1033 (S=O) $cm^{-1}$; $^1H$ NMR ($CD_3SOCD_3$) $\delta$ 3.5–4.5 (m, 15 H), 5.60 (s, 13 H), 6.75–6.85 (m, 6 H). Anal. Calcd for $C_{21}H_{24}O_{14}S_2 \cdot 5.0H_2O$: C, 39.51; H, 5.42. Found: C, 39.16; H, 5.33. Calcium salt: mp >300 °C dec; IR (KBr) 3400 (OH), 1603 (C=O), 1107 (CO), 1039 (SO) $cm^{-1}$; $^1H$ NMR ($D_2O$) $\delta$ 3.5–4.3 (m, 15 H), 6.7–7.4 (m, 6 H).

***sym*-Methyl(bis[4(5)-sulfobenzo]-16-crown-5-oxy)acetic acid (5):** mp 110–111 °C; 86%; IR (deposited film from $CDCl_3$) 3421 (OH), 1730 (C=O), 1107 (CO), 1033 (SO) $cm^{-1}$; $^1H$ NMR ($CD_3SOCD_3$) $\delta$ 1.40 (s, 3 H), 3.2–4.4 (m, 14 H), 6.4–7.2 (m, 6 H), 8.40 (s, 7 H). Anal. Calcd for $C_{22}H_{26}O_{14}S_2 \cdot 2H_2O$: C, 42.99; H, 4.92. Found: C, 43.07; H, 4.98. Calcium salt: mp >270 °C dec; IR (KBr) 3400 (OH), 1587 (C=O), 1100 (CO), 1039 (SO) $cm^{-1}$.

***sym*-*n*-Butyl(bis[4(5)-sulfobenzo]-16-crown-5-oxy)acetic acid (6):** mp 173–175 °C; 82%; IR (deposited film from $CDCl_3$) 3418 (OH), 1745 (C=O), 1113 (CO), 1035 (SO) $cm^{-1}$; $^1H$ NMR ($CD_3SOCD_3$) $\delta$ 0.8–1.9 (m, 9 H), 3.4–4.7 (m, 14 H), 6.7–7.3 (m, 6 H). Anal. Calcd for $C_{25}H_{32}O_{14}S_2$: C, 46.72; H, 5.04. Found: C, 46.47; H, 5.02. Calcium salt: mp >330 °C dec; IR (KBr) 3400 (OH), 1595 (C=O), 1110 (CO), 1035 (SO) $cm^{-1}$.

**Potentiometric Determination of Stability Constants.** The ion-selective electrode was preconditioned by soaking overnight in a 0.1 M solution of the alkali metal chloride in buffered solution at the pH of interest. For pH 1–6, a phosphoric acid–trimethylammonium hydroxide buffer was used, while a phosphoric acid–tris(2-hydroxyethyl)ammonium buffer was utilized for pH >6.[15] The buffer concentrations were 0.001 M in both cases and the buffer pH was measured to 0.001 pH unit. At pH 5.2 and 9.0, calibration plots of mV vs. log a were linear from 0.01 to 0.0001 M alkali metal chloride. In a typical run, the titration cell was filled with 25 mL of 0.01–0.001 M alkali metal chloride in the appropriate buffer while flushing with nitrogen. The ion-selective electrode and silver/silver chloride reference electrode were inserted into the cell and the solution was stirred magnetically for 15 min. The stirring was interrupted and mV readings were taken until a change no greater than 0.2 mV was observed during 5 min. This solution was titrated by adding weighed amounts of **1–6** (0.025–0.0025 M), stirring until all the crown compound had dissolved, and taking mV readings on the unstirred solution until a change no greater than 0.2 mV was observed during 5 min. The cell was emptied and refilled with a fresh solution of the alkali metal chloride in buffer and the mV reading was taken and averaged with that for the original solution. The difference in mV readings in the presence and absence of crown was used with Frensdorf's equations[7] to calculate $K_1$. The possible participation of $K_2$ was evaluated[7] and found to be negligible in all cases. All calculations were carried out with a program written in Microsoft Basic (v 2.0) on a Macintosh 512 K microcomputer.

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**Registry No.** **1**, 78708-41-5; **2**, 109686-79-5; **3**, 87598-63-8; **4**, 109719-22-4; **5**, 109719-23-5; **6**, 100107-44-6; *sym*-hydroxymethyldibenzo-16-crown-5, 69496-29-3; bromoacetic acid, 79-08-3.

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## Ruthenium-Catalyzed Reaction of Carbon Dioxide, Amine, and Acetylenic Alcohol

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Esters of carbamic acid have directly been prepared by the reactions of carbon dioxide and amines with 2-bromoalkanophenone,[1] epoxide,[2] alkyl halide,[3] and alk-

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