Calcd for $C_{37}H_{30}N_2P_2O$: C, 76.54; H, 5.20; N, 4.83; P, 10.67. Found: C, 76.40; H, 5.08; N, 4.80; P, 10.55.

***N*-[(*P*,*P*,*P*-Triphenylphospha-λ^5-azenyl)sulfonyl]-*P*,*P*,*P*-triphenylphospha-λ^5-azene (18c).** The same procedure described above was used with sulfamide (0.96 g, 10 mmol). The product was washed several times with THF and then recrystallized from ethanol: yield 5.2 g (84%), mp 243–244 °C (lit.[18] 245–246 °C and 242–244 °C); ^{1}H NMR δ 7.5–8.1 (m, Ar H); ^{31}P NMR (Me_2SO-d_6) δ 8.56.

Reaction of Bis(diphenylphosphino)methane (8) with Urea and DAD. To a mixture of bis(diphenylphosphino)methane (8; 1.02 g, 2.7 mmol) and urea (0.16 g, 2.7 mmol) in 10 mL of dry THF was added a solution of DAD (0.91 g, 5.2 mmol) in 5 mL of THF, under argon. The mixture was stirred at room temperature for 24 h and then refluxed for 0.5 h. The insoluble material (0.07 g) was filtered and identified as urea. Column chromatography of the residue after removal of the solvent [silica gel, ethyl acetate–methanol (0.5%)] gave several fractions as follows: DH_2D, 0.66 g, mp 131–132 °C, urea, 0.05 g, mp 115–130 °C, 0.53 g (40%) of [(*N*-cyano-*P*,*P*-diphenylphospha-λ^5-azenyl)methyl]diphenylphosphine oxide (11): mp 190–191 °C, ^{31}P NMR ($CDCl_3$) δ 23.96 (d, J = 12.1 Hz), 22.98 (d, J = 12.0 Hz); ^{1}H NMR and IR spectra as above. Anal. Calcd for $C_{26}H_{22}N_2OP_2$: C, 70.90; H, 5.04; N, 6.36. Found: C, 70.87; H, 5.36; N, 6.48. The final fraction, 0.46 g (38%), was identified as bis(diphenylphosphino)methane dioxide (12): mp 181–183 °C (lit.[20] mp 181–183 °C); ^{31}P NMR ($CDCl_3$) δ 25.20; ^{1}H NMR ($CDCl_3$) δ 3.53 (t, 2 H, CH_2, J = 14.6 Hz), 7.2–8.0 (m, 20 H, Ar H); IR (KBr) $\bar{\nu}$ 1435 (P—C), 1185 and 1197 (P=O), 1117.

Acknowledgment. We thank the Robert A. Welch Foundation of Houston, TX (Grant Y-684), The University of Texas at Arlington–Organized Research Fund, and The National Science Foundation for partial support of this work. We also thank Mr. Whe-Narn Chou and Mr. Mark Victor for some NMR spectra, Dr. Sanjay Basak for the FT-IR spectra, and Mr. Chou for the synthesis of 7.

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Synthesis and Complexing Properties of Diaza-Crown and Cryptand Ligands with Inward-Facing Phenolic Groups

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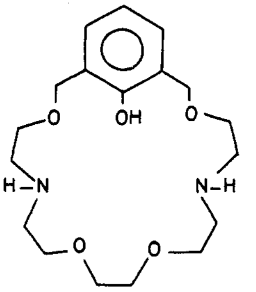
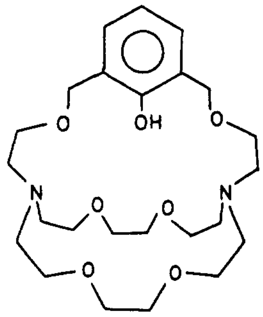
Novel diaza-crown and cryptand molecules with inward-facing phenolic group are synthesized and found to exhibit enhanced complexation of transition and heavy metal cations when compared with closely related cyclic and bicyclic ligands that do not possess this auxiliary binding site.

Crown ethers (macrocyclic polyethers) that contain a 1,3-xylyl unit and bear intraannular functionality at the 2-position have been prepared in several laboratories. The intraannular groups include hydroxyl,[1-5] hydroxymethyl,[6,7] methoxy,[1-5] methoxymethyl,[1,2] allyloxy,[5] carboxylic acid,[6,7] methoxycarbonyl,[6,7] amino,[8] nitro,[8] and sulfinic acid[9] substituents. Of particular interest has been the influence of such inward-facing groups upon metal ion complexation. Diaza-crown ethers and cryptands are efficient complexing agents for a variety of transition and heavy metal cations.[10] We now report syntheses of the first 1,3-xylyl unit based diaza-crown ether and cryptand ligands with inward-facing phenolic units, 1 and 2, respectively, and assessment of their complexation behaviors with Cd(II), Cu(II), Ni(II), Pb(II), and Zn(II) in water.



1



2

Results and Discussion

Synthesis. The preparation of diaza-crown ether 1 was accomplished by the method outlined in Scheme I.

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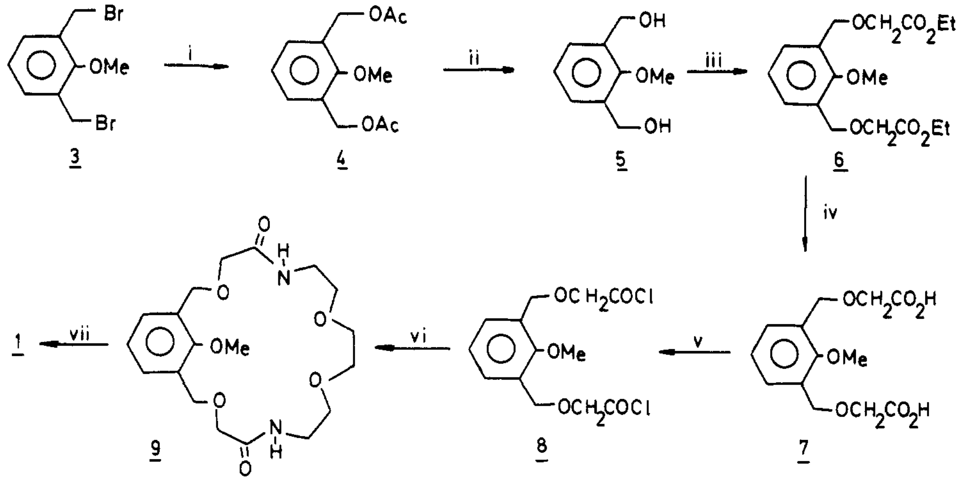
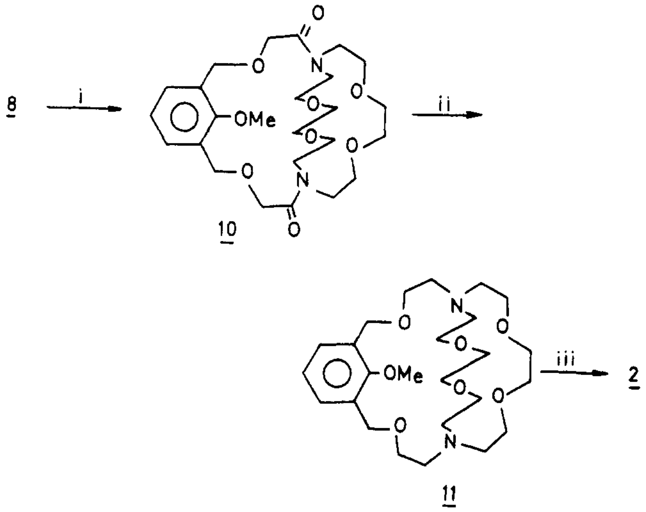
Scheme I[a]



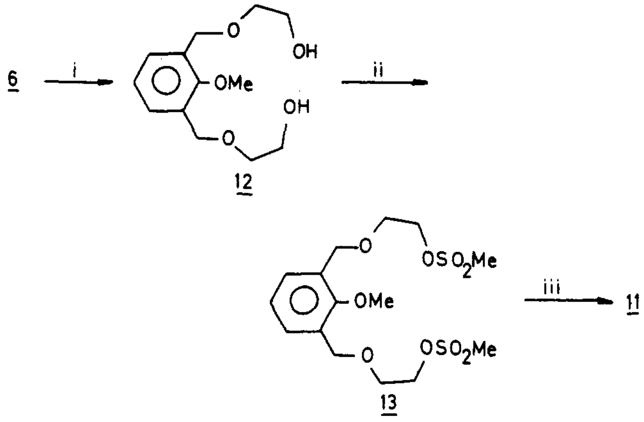
[a] (i) KOAc, AcOH; (ii) NaOH, aqueous EtOH; (iii) $ClCH_2CO_2H$, t-BuOK, t-BuOH, then PTSA, EtOH; (iv) NaOH, aqueous EtOH, then HCl; (v) $(COCl)_2$, C_6H_6; (vi) $NH_2CH_2CH_2OCH_2CH_2OCH_2CH_2NH_2$, Et_3N, toluene; (vii) $LiAlH_4$, THF.

Scheme II[a]



[a] (i) 1,10-Diaza-18-crown-6, Et_3N, toluene; (ii) $Me_2S{\cdot}BH_3$, THF, then 9 N HCl, then LiOH; (iii) LiI, pyridine.

Scheme III[a]



[a] (i) $LiAlH_4$, THF; (ii) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (iii) BuLi, 1,10-diaza-18-crown-6, THF.

Treatment of 2,6-bis(bromomethyl)anisole[11] (**3**) with KOAc in AcOH produced a 96% yield of diacetate **4**, which upon basic hydrolysis gave diol **5**[12] in 68% yield. Reaction of **5** with t-BuOK and chloroacetic acid in t-BuOH followed by esterification of the crude product (for ease of purification) gave diester **6** in 62% yield. Basic hydrolysis of **6** followed by acidification produced 88% of diacid **7**, which was converted by reaction with oxalyl chloride into diacid chloride **8** in 96% yield. Cyclization of **8** with 1,8-diamino-3,6-dioxaoctane[13] under high dilution conditions provided 40% of cyclic diamide **9**. Treatment of **9** with lithium aluminum hydride in THF affected both reduction of the amide groups and demethylation[14] to afford a 79% yield of diazacrown ether **1**.

Two alternative synthetic routes to cryptand **2** are depicted in Schemes II and III. In the first method, diacid chloride **8** was condensed with 1,10-diaza-18-crown-6 under high dilution conditions to afford cryptand diamide **10** in 66% yield. Reduction of **10** with $Me_2S{\cdot}BH_3$ followed by treatment with 9 N HCl at room temperature and then with 5% aqueous LiOH afforded cryptand **11** in 67% yield. It was observed that hydrolysis of the adduct formed from **10** and $Me_2S{\cdot}BH_3$ under more forcing conditions (i.e., 6 N HCl at reflux) produced only a cleavage product, N,N'-bis(2-hydroxyethyl)-1,10-diaza-18-crown-6.[15,16] Demethylation of **11** with anhydrous LiI in pyridine[3,4] yielded 68% of **2**.

In the second route, diester **6** was reduced to diol **12** with lithium aluminum hydride in 23% yield. From **12**, dimesylate **13** was prepared in 94% yield and condensed with 1,10-diaza-18-crown-6 in the presence of n-BuLi in THF[17,18] to afford cryptand **11** in 7% yield. Due to the very low yield in this condensation step, the preparative route depicted in Scheme II is judged to be superior to that illustrated in Scheme III.

Metal Ion Complexation. Protonation constants of diaza-crown ether **1** and cryptand **2** and stability constants of their complexes with Cd(II), Cu(II), Ni(II), Pb(II), and

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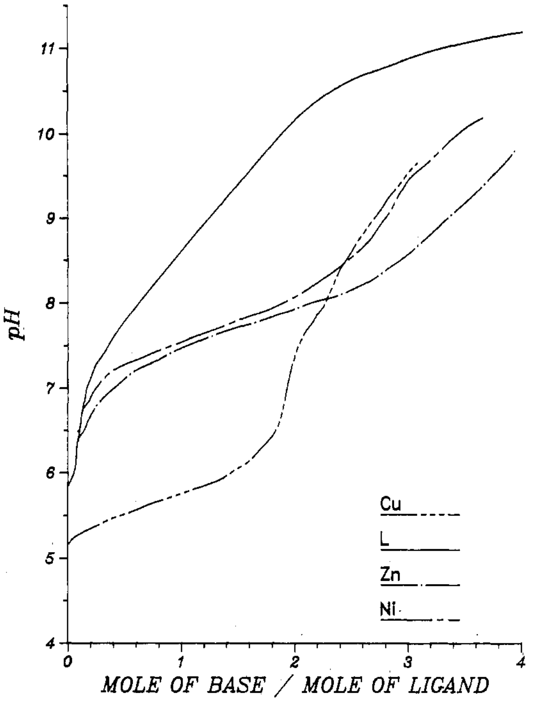

Figure 1. Potentiometric equilibrium curves for 1 and 1:1 ratios of 1 with selected metal ions ([1] = [M] = 1.0 × 10^{-3} M, 25 °C, μ = 0.10 (Me_4NCl)).

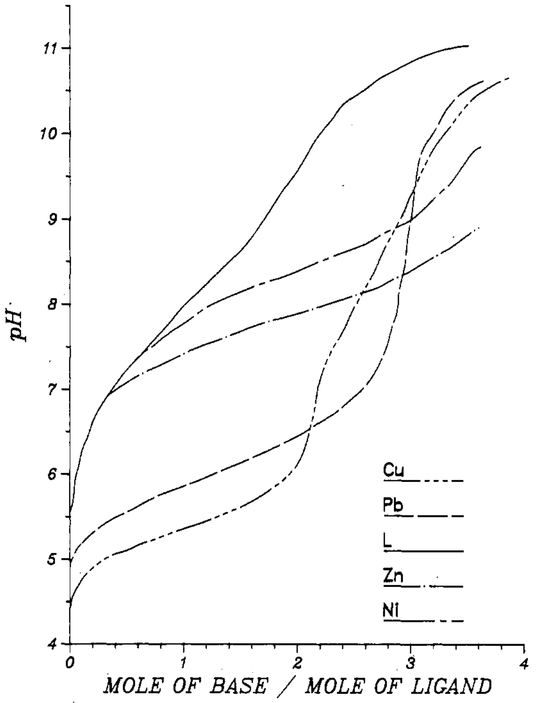

Figure 2. Potentiometric equilibrium curves for 2 and 1:1 ratios of 2 with selected metal ions ([2] = [M] = 1.0 × 10^{-3} M, 25 °C, μ = 0.10 (Me_4NCl)).

Zn(II) were determined by potentiometric titration.[19,20] For the protonation constant determinations, a standard HCl solution was added to protonate all basic sites on the ligands and the solutions were then titrated with standard Me_4NOH solution. For the stability constant determinations, 1 equiv of metal nitrate was added to the protonated ligand solutions ([ligand]:[metal ion] = 1.0), which were then titrated with standard Me_4NOH solution.

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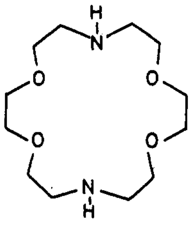
Table I. Protonation Constants for Compounds 1 and 2 and Stability Constants for Their Metal Ion Complexes in Water at 25.0 °C and μ = 0.1

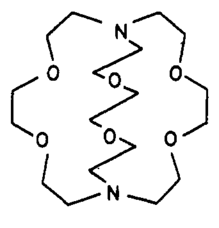
	1	14^{c}	2	15^{d}
	Protonation Constants^{a} (log K_{HL})			
	10.16 ± 0.04		10.96 ± 0.06	
	9.01 ± 0.04	9.20	9.49 ± 0.06	9.95
	7.49 ± 0.06	8.02	7.37 ± 0.08	7.59
	Stability Constants^{b} (log K_{ML})			
Cd(II)	5.70 ± 0.21	5.31	9.44 ± 0.05	7.10
Cu(II)	12.77 ± 0.17	6.18	14.80 ± 0.18	6.8
Ni(II)	6.75 ± 0.08	≤2.5	7.11 ± 0.02	≤3.5
Pb(II)	NM^{e}	6.90	13.33 ± 0.22	12.72
Zn(II)	7.21 ± 0.04	3.19	8.36 ± 0.07	≤2.5

$^{a}K_{HL}$ = [HL]/[H][L]. $^{b}K_{ML}$ = [ML]/[M][L]. ^{c}Data taken from ref 21. ^{d}Data taken from ref 22. ^{e}Not measurable.

Figures 1 and 2 show potentiometric equilibrium curves for diaza-crown ether 1 and cryptand 2, respectively. Calculated protonation constants for 1 and 2 and stability constants for their complexes with five divalent metal ions are given in Table I together with literature values[21,22] for the closely related ligands 1,10-diaza-18-crown-6 (14) and cryptand[2.2.2] (15), which do not possess inward-facing phenolic groups.



14



15

Both 1 and 2 exhibit three protonation constants. The largest one is attributed to protonation at the phenolate ion site. The lower protonation constants for the two amine groups are consistent with the values reported[21,22] for structural analogues 14 and 15, respectively.

Comparison of stability constants for complexation of Cd(II), Cu(II), Ni(II), Pb(II), and Zn(II) with diazacrown 1 and cryptand 2 reveals higher values for the latter ligand in each case. Differences in log K values range from 0.36 for Ni(II) to 3.74 for Cd(II). The difference is even larger in the case of Pb(II), which is strongly complexed by 2 but does not measurably associated with 1.

For titrations of both ligands in the presence of Cd(II), Ni(II), and Zn(II), metal hydroxides were observed to precipitate before sufficiently basic pH values for ionization of the phenolic functions could be reached. On the other hand, such precipitation did not occur for titrations of 2 in the presence of Cu(II) and Pb(II) and of 1 in the presence of Cu(II). For titrations of both ligands in the presence of Cu(II), phenol dissociation was noted to occur at considerably lower pH regions on the titration curves when compared to those for the other divalent metal ions. This indicates strong Cu(II)–phenolate interactions.

When stability constants for interactions of 1 and 2 with the divalent metal ions are compared with those reported[21,22] for diaza-crown 14 and cryptand 15, respectively, which do not contain inward-facing phenolic groups, it is found that the presence of the additional ligation site in 1 and 2 is beneficial in all cases except one (Table I).

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Hence, replacement of an ethylene bridge in **14** and **15** with a 1,3-xylyl unit that possess a hydroxyl group at the 2-position produces log *K* enhancements that vary from 0.45 to 8.0. The only exception is for ligand **1**, which does not measurably interact with Pb(II) even though this divalent metal ion is complexed by **14**.

The potential for lanthanide ion complexation by **1** and **2** was also briefly examined. Titrations in the presence of Eu(III), La(III), and Lu(III) gave only precipitation of the lanthanide hydroxides without complexation. This contrasts with reported lanthanide ion complexation by **15** although precipitates were noted at high pH values.[23]

In summary, it has been demonstrated that insertion of a structural unit that contains an inward-facing phenolic unit into diaza-crown and cryptand molecules generally enhances complexation of transition and heavy metal cations but not lanthanide cations. Of the divalent metal cations, ionization of the inward-facing phenolic units of **1** and **2** appears to be important only in the complexation of Cu(II).

Experimental Section

Melting points were taken with a Mel-Temp melting point apparatus and are uncorrected. IR spectra were obtained with a Nicolet MX-S infrared spectrophotometer and are given in reciprocal centimeters. ^{1}H NMR spectra were recorded with a Varian EM360 spectrometer and chemical shifts are reported in parts per million (δ) downfield from TMS. Mass spectra were obtained at 70 eV with a Hewlett Packard 5995B GC/MS instrument. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Unless specified otherwise reagent grade reactants and solvents were obtained from chemical suppliers and used directly. THF with purified by distillation from lithium aluminum hydride under nitrogen. Pyridine was dried over KOH pellets and *t*-BuOH was distilled from sodium metal.

Aqueous 0.010 M stock solutions of **1** and **2** were standardized by titration with standard HCl solution. The 0.10 M Me_4NOH solution was prepared by addition of 20 wt % Me_4NOH in MeOH to deionized water and standardized with potassium hydrogen phthalate.[19,20] Metal ion solutions were prepared from the chloride or nitrate salts and standardized by EDTA complexometric titrations.[19]

2,6-Bis(acetoxymethyl)anisole (4). In glacial HOAc (225 mL), 2,6-bis(bromomethyl)anisole (**3**)[11] (20.0 g, 68 mmol) and KOAc (27.8 g, 280 mmol) were refluxed for 1.5 h. Chloroform (400 mL) was added and the organic layer was neutralized with $NaHCO_3$. Filtration and evaporation of solvent in vacuo gave 16.3 g (96%) of **4** as a colorless liquid. An analytical sample was purified by chromatography on silica gel with $CHCl_3$ as eluent: IR (neat) 1740 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 6 H), 3.85 (s, 3 H), 5.18 (s, 4 H), 6.9–7.5 (m, 3 H).

Anal. Calcd for $C_{13}H_{16}O_7$: C, 61.90; H, 6.39. Found: C, 61.72; H, 6.42.

2,6-Bis(hydroxymethyl)anisole (5). Diacetate **4** (15.2 g, 60 mmol), NaOH (12.0 g, 300 mmol), EtOH (50 mL), and H_2O (100 mL) were refluxed for 4 h and the EtOH was evaporated in vacuo. The residue was neutralized with 6 N HCl, saturated with NaCl, and extracted with EtOAc (4 × 25 mL). The extracts were dried ($MgSO_4$) and evaporated in vacuo to give a crude product that was purified by chromatography on alumina with EtOAc as eluent to provide 6.80 g (68%) of **5** as white crystals: mp 93–95 °C (lit.[12] mp 93 °C).

Diester 6. Under nitrogen, a solution of chloroacetic acid (7.55 g, 80 mmol) in 32 mL of freshly distilled *t*-BuOH was added slowly to a stirred and refluxing solution of **5** (5.2 g, 31 mmol) and *t*-BuOK (17.3 g, 154 mmol) in *t*-BuOH (190 mL). After overnight reflux, the solvent was removed in vacuo and the residue was neutralized with 6 N HCl and evaporated in vacuo. The crude diacid was dissolved in C_6H_6 (100 mL) and EtOH (60 mL) and 1.0 g of *p*-toluenesulfonic acid was added. The mixture was refluxed for 15 h with circulation of the condensate through anhydrous Na_2SO_4 in a Soxhlet thimble. The solvent was evaporated in vacuo and the residue was dissolved in Et_2O (100 mL), neutralized by washing with 5% aqueous $NaHCO_3$, washed with H_2O, and dried ($MgSO_4$). After evaporation of the solvent in vacuo, the residue was chromatographed on alumina with petroleum ether–EtOAc (2:1) as eluent to afford 6.54 g (62%) of **6** as a colorless oil: IR (neat) 1753 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 6 H), 3.80 (s, 3 H), 4.0–4.5 (s + q, 8 H), 4.65 (s, 4 H), 6.9–7.55 (m, 3 H).

Anal. Calcd for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11. Found: C, 59.88; H, 7.12.

Diacid 7. Diester **6** (2.72 g, 8.0 mmol) was dissolved in EtOH (20 mL), 20 mL of 20% aqueous NaOH was added, the mixture was refluxed overnight, and the EtOH was evaporated in vacuo. The residue was acidified with 6 N HCl and extracted with $CHCl_3$ (2 × 20 mL). Evaporation of the $CHCl_3$ in vacuo gave 2.0 g (88%) of **7** as a white solid: mp 101–103 °C: IR (neat) 3300–2400 (OH), 1736, 1701 (C=O), 1124 (CO) cm^{-1}; ^{1}H NMR (CD_3SOCD_3) δ 3.80 (s, 3 H), 4.10 (s, 4 H), 4.67 (s, 4 H), 6.95–7.55 (m, 3 H), 10.93 (s, 2 H).

Anal. Calcd for $C_{13}H_{16}O_7$: C, 54.93; H, 5.67. Found: C, 55.05; H, 5.83.

Diacid Chloride 8. Diacid **7** (2.25 g, 7.9 mmol) was suspended in dry C_6H_6 (17 mL) and oxalyl chloride (6.6 mL) and 2 drops of pyridine were added. The mixture was stirred at room temperature for 48 h and filtered. The filtrate was evaporated in vacuo and dry C_6H_6 (10 mL) was added and evaporated in vacuo. After a second addition and evaporation of dry C_6H_6, 2.44 g (96%) of **8** was obtained as a white solid: mp 55–57 °C; IR (neat) 1813 (C=O), 1122 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3 H), 4.45 (s, 4 H), 4.68 (s, 4 H), 6.95–7.50 (m, 3 H).

Cyclic Diamide 9. To 250 mL of rapidly stirred toluene at 0 °C under nitrogen were simultaneously added solutions of **8** (1.88 g, 5.9 mmol) in 30 mL of toluene (solution A) and 1,8-diamino-3,6-dioxaoctane[13] (0.87 g, 5.9 mmol) and Et_3N (1.61 g, 16 mmol) in 30 mL of toluene (solution B) during 5 h. The reaction mixture was stirred at room temperature overnight and filtered. The filtrate was evaporated in vacuo to give a residue that was chromatographed on alumina with $CHCl_3$ as eluent to yield 0.93 g (40%) of **9** as a white solid: mp 145–146 °C; IR (neat) 3433, 3288 (NH), 1672 (C=O), 1105 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.2–3.75 (m, 14 H), 3.95 (s, 3 H), 4.15 (s, 4 H), 4.60 (s, 4 H), 6.95–7.65 (m, 5 H); mass spectrum, *m/e* 396.3 (M$^+$).

Anal. Calcd for $C_{19}H_{28}N_2O_7$: C, 57.56; H, 7.12. Found: C, 57.97; H, 7.01.

Diaza-Crown Phenol 1. Diamide **9** (0.70 g, 1.8 mmol) in 20 mL of THF was added to a suspension of $LiAlH_4$ (0.50 g, 13.6 mmol) in THF (20 mL) and the mixture was refluxed for 18 h. To the cooled mixture was added 2.5 mL of 5% aqueous NaOH and the solid material was filtered and washed with hot THF. Evaporation of the filtrate and washings in vacuo gave the crude product, which was chromatographed on alumina with $CHCl_3$ as eluent to give 0.46 g (79%) of **1** as a pale yellow oil: IR (neat) 3300 (NH, OH), 1101 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.6–3.0 (m, 8 H), 3.35–3.85 (m, 12 H) 4.55 (br s, 7 H), 6.6–7.25 (m, 3 H); mass spectrum, *m/e* 354.4 (M$^+$).

Anal. Calcd for $C_{18}H_{30}N_2O_5$: C, 61.00; H, 8.53. Found: C, 60.74; H, 8.49.

Cryptand Diamide 10. Using the procedure given for **9**, solutions of 2.45 g (7.6 mmol) of **8** in 100 mL of toluene and of 2.00 g (7.6 mmol) of 1,10-diaza-18-crown-6 and 1.98 g (19.6 mmol) of Et_3N in a mixture of toluene (70 mL) and THF (30 mL) were simultaneously added to 250 mL of rapidly stirred toluene during 4 h. After workup, the residue was chromatographed on alumina with $CHCl_3$–EtOH (100:1) as eluent to give 2.55 g (66%) of **10** as a very hygroscopic, white solid: mp 115–117 °C; IR (neat) 1645 (C=O), 1103 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.6–3.9 (m, 27 H), 4.12 (br s, 4 H), 4.62 (br s, 4 H), 6.95–7.5 (m, 3 H); mass spectrum, *m/e* 510.4 (M$^+$).

Anal. Calcd for $C_{25}H_{38}N_2O_9 \cdot 0.25H_2O$: C, 58.30; H, 7.53. Found: C, 58.38; H, 7.34.

Cryptand 11. Diamide **10** (2.45 g, 4.8 mmol) was dissolved in THF (25 mL) and 2.4 mL (12 mmol) of $Me_2S \cdot BH_3$ was added. The mixture was stirred at room temperature for 6 h and then

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[23] Burns, J. H.; Baes, C. F., Jr. *Inorg. Chem.* **1981**, *20*, 616–619.

refluxed for 15 h. After addition of H_2O (2 mL), the solvent was removed in vacuo and the residue was extracted with $CHCl_3$ (2 × 15 mL). Evaporation of the $CHCl_3$ in vacuo gave a white solid, which was dissolved in THF (40 mL), and 80 mL of 9 N HCl was added. The mixture was stirred at room temperature for 5 h and evaporated in vacuo. The residue was treated with 50 mL of 5% aqueous LiOH and extracted with Et_2O (5 × 100 mL). The combined extracts were dried over $MgSO_4$ and evaporated in vacuo to give a crude product, which was chromatographed on alumina with $CHCl_3$ as eluent to afford 1.55 g (67%) of **11** as a colorless oil: IR (neat) 1113 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35–2.9 (m, 12 H), 3.15–3.4 (m, 23 H), 4.55 (s, 4 H), 6.85–7.5 (m, 3 H); mass spectrum, *m/e* 482.6 (M^+).

Anal. Calcd for $C_{25}H_{42}N_2O_7$: C, 62.22; H, 8.77. Found: C, 62.19; H, 8.59.

Cryptand Phenol 2. Cryptand **11** (1.38 g, 2.9 mmol) was dissolved in 6 mL of anhydrous pyridine and 1.5 g of anhydrous LiI was added. The mixture was heated at 100 °C for 15 h and the pyridine was evaporated in vacuo. Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The CH_2Cl_2 extracts were dried over $MgSO_4$ and evaporated in vacuo. Chromatography of the residue on alumina with $CHCl_3$ as eluent gave a semisolid product that was dissolved in $CHCl_3$ and washed with deionized H_2O (3 × 10 mL). Evaporation of the $CHCl_3$ and removal of H_2O by coevaporation with C_6H_6 in vacuo gave 0.91 g (67%) of **2** as a pale yellow viscous oil: IR (neat) 3304 (OH), 1132–1109 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.5–3.0 (m, 12 H), 3.3–3.9 (m, 20 H), 4.63 (s, 4 H), 6.6–7.4 (m, 3 H), 7.33 (s, 1 H); mass spectrum, *m/e* 468.6 (M^+).

Anal. Calcd for $C_{24}H_{40}N_2O_7$: C, 61.52; H, 8.60. Found: C, 61.47; H, 8.56.

Diol 12. Diester **6** (4.10 g, 12 mmol) was refluxed with $LiAlH_4$ (1.18 g, 31 mmol) in 30 mL of THF for 3 h. The reaction mixture was treated consecutively with a solution of H_2O (1.2 mL) and THF (6 mL), 15% aqueous NaOH (1.2 mL), and a mixture of H_2O (6 mL) and THF (6 mL). Solid material was filtered and washed with THF. The filtrate and washings were combined and evaporated in vacuo and the residue was chromatographed on alumina with EtOAc–MeOH (10:1) as eluent to afford 0.80 g (27%) of **12** as a colorless, viscous liquid: IR (neat) 3416 (OH), 1109, 1070 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.87 (br s, 2 H), 3.35–3.9 (s + m, 11 H), 4.58 (s, 4 H), 6.9–7.5 (m, 3 H).

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.75; H, 7.81.

Dimesylate 13. A solution of diol **12** (2.34 g, 9.1 mmol) and Et_3N (2.95 g, 29 mmol) in CH_2Cl_2 (40 mL) was cooled to −10 °C and a solution of methanesulfonyl chloride (2.60 g, 22 mmol) in CH_2Cl_2 (40 mL) was added dropwise. The mixture was stirred at 0 °C for 1 h, diluted with cold CH_2Cl_2 (50 mL), washed consecutively with 5% HCl, H_2O, 5% aqueous $NaHCO_3$, and H_2O, dried ($MgSO_4$), and evaporated in vacuo to give 3.52 g (94%) of **13** as a colorless oil: IR (neat) 1354, 1172 (S=O), 1107 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.03 (s, 6 H), 3.80 (m, 7 H), 4.1–4.5 (m, 4 H), 4.60 (s, 4 H), 6.9–7.6 (m, 3 H).

Anal. Calcd for $C_{15}H_{24}O_9S_2$: C, 43.68; H, 5.87. C, 43.43; H, 5.93.

Cryptand 11 from Dimesylate 13. Under nitrogen, BuLi (0.49 g, 7.6 mmol) was added slowly to a stirred solution of 1,10-diaza-18-crown-6 (2.00 g, 7.6 mmol) in THF (40 mL) at room temperature. After 1 h, a solution of **13** (3.14 g, 7.6 mmol) in THF (25 mL) was added and the mixture was stirred at room temperature for 12 h and then refluxed for 4 days. The solvent was evaporated in vacuo and the residue was chromatographed on alumina with EtOAc as eluent to give 0.25 g (7%) of **11**.

Potentiometric Titrations. Determination of protonation constants for **1** and **2** and stability constants for their complexes were performed by potentiometric titrations at 25.0 ± 0.1 °C in a manner similar to that described earlier.[19,20] For determination of a protonation constant, 25.0 mL of a 1.0×10^{-3} M ligand solution was prepared and the ionic strength was adjusted to 0.10 with Me_4NCl. An excess of standard HCl solution was added to protonate all basic sites and then the solution was titrated with 0.10 M Me_4NOH solution. An equivalent amount of metal salt solution was added to the protonated ligand solution ([ligand]:[metal ion] = 1.0) while the total titrate volume was kept constant to determine a stability constant. The resulting solution was then titrated with the 0.10 M Me_4NOH solution. All calculations were performed with a Hewlett-Packard HP87 personal computer using the methods and programs described earlier.[24]

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(24) Chang, C. A.; Douglas, B. E. *J. Coord. Chem.* **1981**, *11*, 91–97.

Utilization of α,β-Unsaturated Acids as Michael Acceptors for the Synthesis of Thieno[2,3-*b*]thiopyrans

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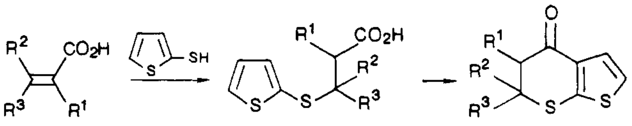
A general and versatile method that extends the synthetic utility of the Michael reaction is described for the preparation of substituted propionic acids of the type II. The addition of 2-mercaptothiophene to commercially available acrylic acids I, instead of the commonly employed esters, provides a facile and high-yielding synthesis of II. In turn, these compounds are useful intermediates for the construction of the heteroaryl thieno[2,3-*b*]thiopyrans III. An example of an anti-Michael addition, involving the use of 3-(4-pyridyl)propionic acid, is also presented.



I II III

The pharmacological properties of 1[1] have stimulated interest in developing a general and versatile method for the construction of the thieno[2,3-*b*]thiopyran nucleus. The preparation of the parent heterocycle has been de-

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