# Syntheses, Crystal Structures, and Metal Ion Complexation Studies of Novel Diaza-18-Crown-6 Ligands Containing Aromatic Thiol-Derived Side Arms

Ning Su,[†] Jerald S. Bradshaw,* Guoping Xue, N. Kent Dalley, Xian X. Zhang,
Paul B. Savage, Krzysztof E. Krakowiak,[#] and Reed M. Izatt

Department of Chemistry & Biochemistry, Brigham Young University, Provo, UT 84602
Received May 24, 1999

### Dedicated to the memory of Professor Raymond N. Castle

The Mannich aminomethylation reaction of aromatic thiols has been used to produce diaza-18-crown-6 ligands containing thiol-derived side arms. Thiophenols were attached to the azacrown through N-CH$_2$-S linkages even in the presence of hydroxy or acetamido groups. Heteroaromatic thiols containing N=C-SH (or NH-C=S) structural fragments were attached to diaza-18-crown-6 by N-CH$_2$-N linkages with the thiol becoming a thione function. X-ray crystal structural analyses show the N-CH$_2$-S and N-CH$_2$-N linkages for some of the new macrocyclic compounds. Interactions of four of the new diaza-18-crown-6 ligands with Na$^+$, K$^+$, Ba$^{2+}$, Ag$^+$, Zn$^{2+}$, Cd$^{2+}$, Ni$^{2+}$, and Cu$^{2+}$ were evaluated by calorimetric titration at 25° in methanol. The results show that these ligands form stable complexes with many of the metal ions studied.

Attachment of metal-ion chelating groups to macro-cyclic ligands has yielded compounds with marked improvements in ligating properties over the parent macro-cyclic ligands. In this context, we recently reported that 5-chloro-8-hydroxyquinoline-substituted diaza-18-crown-6 ligands (1 and 2, Figure 1) showed greatly improved ion-
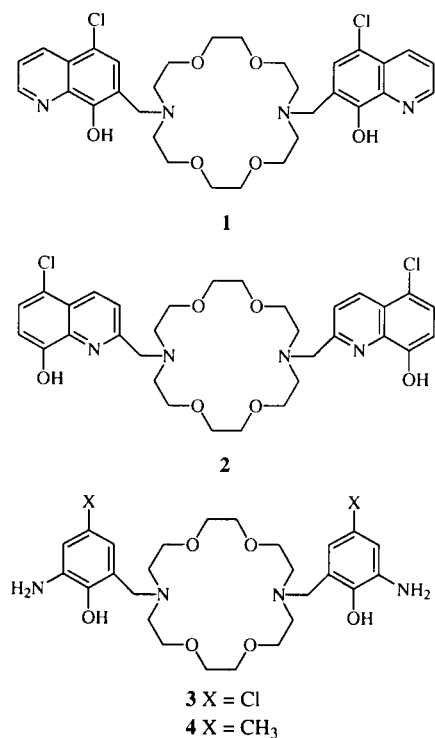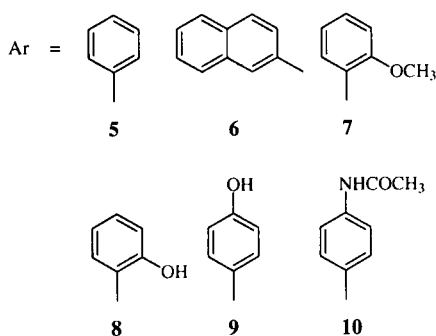


3 X = Cl
4 X = CH$_3$

Figure 1.

complexing ability and selectivity for certain metal ions compared to unsubstituted diaza-18-crown-6 [1,2]. For example, the log $K$ value for the 2-Ba$^{2+}$ complex (log $K$ =

12.2, in methanol) is of the same magnitude as that of the cryptand [2.2.2]-Ba$^{2+}$ complex. Indeed, 2 forms a pseudocryptand through π-π interaction between the 5-chloro-8-hydroxyquinoline rings when complexed with Ba$^{2+}$, and all ten donor atoms of 2 are involved in the coordination as shown by the $^1$H nmr spectrum and an X-ray crystal structure [1]. o-Aminophenol-substituted diaza-18-crown-6 ligands (3 and 4) have been shown to function as heterobinuclear receptors for Cu$^{2+}$ and Na$^+$ [3]. When solutions of 3-Cu$^{2+}$ and 4-Cu$^{2+}$ were titrated by a Na$^+$ solution, appreciable interactions of Na$^+$ with 3-Cu$^{2+}$ and 4-Cu$^{2+}$ were observed as shown by log $K$ values (1.41 and 1.86, respectively, valid in methanol at 25°).

We now report the syntheses of ten diaza-18-crown-6 ligands having two sulfur-containing aromatic side arms. Since sulfur interacts strongly with soft metal ions, we expect these ligands to selectively bind transition and post-transition metal ions. X-ray crystal structures of four of these ligands with aromatic substituents attached through an N-CH$_2$-S linkage and heteroaromatic substituents attached through N-CH$_2$-N linkages are described. Also, preliminary metal ion complexing properties of these ligands are reported.

Thiols have been used as reactants in the Mannich reaction [4]. In the presence of an aldehyde or a ketone, thiols condense with primary amines [5], secondary amines [6], hydroxylamine [7], primary and secondary amides [8], amino acids [9], or ammonia [10] leading to the formation of compounds containing N-CH$_2$-S linkages. Depending on the number of hydrogens on the nitrogen atom and the ratio of starting materials, one, two, or three thiol units can be attached to the same nitrogen atom. For example, secondary amines condense with one equivalent of thiol to give R-S-CH$_2$-NR'$_2$ groups.
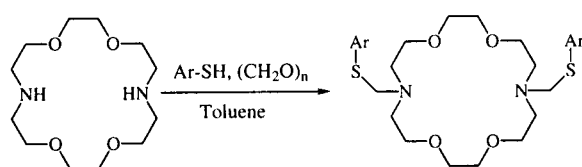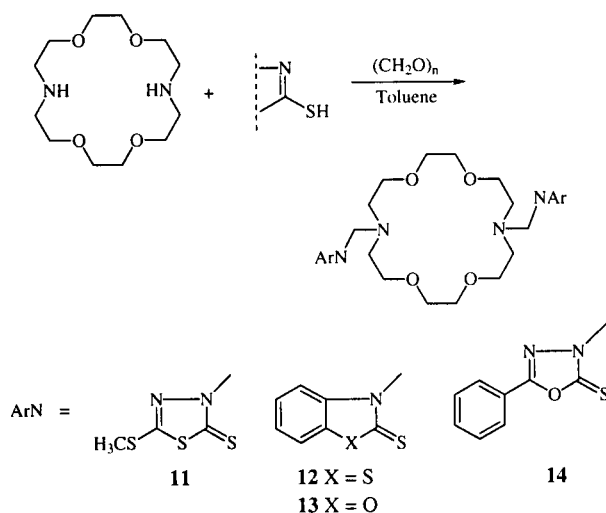
N. Su, J. S. Bradshaw, G. Xue, N. K. Dalley, X. X. Zhang, P. B. Savage,
K. E. Krakowiak, and R. M. Izatt

We have used the Mannich aminomethylation reaction with thiols and diazacrown ether to form azacrown ether ligands containing two thiol-derived side arms. The classical Mannich condensation reaction uses amines, formaldehyde and an appropriate receptor for aminomethylation and is usually conducted in polar solvents such as an alcohol, formic acid, or dimethylformamide [11]. In this study, we used solid paraformaldehyde instead of a formaldehye solution and performed the Mannich reaction with the thiols in toluene [12]. The one-pot Mannich reaction gave all aromatic thiol-derived diaza-18-crown-6 ligands (5-14, Schemes 1 and 2) in good yields [13]. All compounds were purified by sonication in a small amount of methanol followed by filtration and drying.

## Scheme 1
### Syntheses of new thiophenol-derived diaza-18-crown-6 ligands with N-CH$_2$-S linkages



For the thiophenols, N-CH$_2$-S linkages were formed exclusively (5-10, Scheme 1). The exclusive formation of 8 and 9 from the corresponding hydroxythiophenols is somewhat surprising, since phenol is well known for its ability to direct aminomethylation to form a proton-ionizable *ortho* or *para* substituted phenol-containing azacrown ethers [13,14]. The exclusive formation of 10 is interesting because an amide nitrogen is also capable of undergoing the Mannich aminomethylation reaction to form an N-CH$_2$-N linkage [14].

For heteroaromatic thiols containing N=C-SH structural fragments, the Mannich reaction with diaza-18-crown-6 gave ligands 11-14 (Scheme 2) which contain the N-CH$_2$-N linkage and the thiol is converted to a thione function. In this case, no products with N-CH$_2$-S linkages were observed.

The formation of distinctive N-CH$_2$-S linkages from the thiophenols and N-CH$_2$-N linkages from the heteroaromatic thiols is further confirmed by the proton nmr spectra of the products. There are significant differences in the chemical shifts of the proton signals for -CH$_2$- groups among the various thiol-derived products (Table 1). The

## Table 1
Summary of $\delta_H$, $\delta_C$ (ppm, in dimethylsulfoxide-$d_6$) and Selected Bond Length (Å) Data of N-$CH_2$-S and N-$CH_2$-N Linkages

| Ligands | $\delta_H$ | $\delta_C$ | C6-S7 |
|---|---|---|---|
| 5 | 4.62 | 69.73 | N/A |
| 6 | 4.75 | 69.70 | N/A |
| 7 | 4.52 | 69.72 | N/A |
| 8 | 4.44 | 69.73 | 1.771(6) |
| 9 | 4.43 | 69.74 | N/A |
| 10 | 4.54 | 69.72 | N/A |
| Average | 4.55 | 69.72 | 1.770 |

| Ligands | $\delta_H$ | $\delta_C$ | C1-S1 |
|---|---|---|---|
| 11 | 5.22 | 69.92 | 1.666(3) |
| 12 | 5.32 | 70.03 | 1.656(3) |
| 13 | 5.17 | 69.99 | 1.644(2) |
| 14 | 5.14 | 69.91 | N/A |
| Average | 5.21 | 69.96 | 1.655 |

## Scheme 2
### Syntheses of new heteroaromatic thiol-derived azacrown ether ligands with N-CH$_2$-N linkages



average chemical shift of the signal for -CH$_2$- in N-CH$_2$-S linkages of 5-10 is 0.66 ppm upfield in the ^{1}H nmr spectra and 0.24 ppm upfield in the ^{13}C nmr spectra from that of the -CH$_2$- in N-CH$_2$-N linkages of 11-14. The presence of the two types of linkages was also observed in the solid state structures of 8, 11, 12, and 13 which were obtained by X-ray crystallographic studies. The crystal structures of 8, 11, 12, and 13 are shown in Figures 2-5, respectively. The C-S bond lengths of interest, C6-S7 in 8 and C1-S1 in 11, 12, and 13, are listed in Table 1. The average C1-S1 bond length [1.655(11) Å, where the number in parentheses is the standard deviation of the average of the three bond lengths] is significantly shorter (0.116 Å) than the C-S bond length [1.771(6)] in 8.
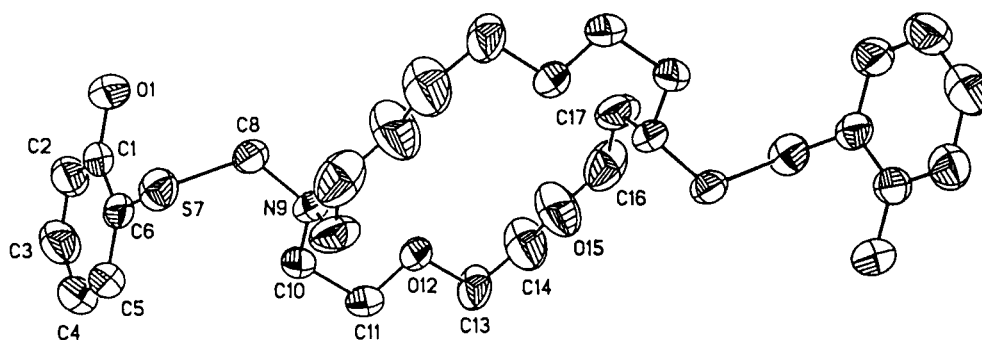
Figure 2. The solid state structure of **8**. The hydrogen atoms and C16' were omitted for clarity.
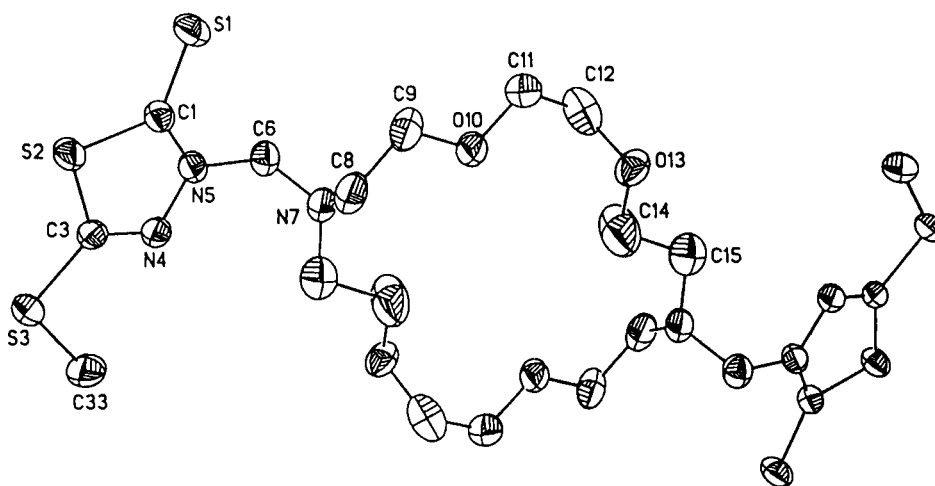


Figure 3. The solid state structure of **11**. The hydrogen atoms and C14' were omitted for clarity.
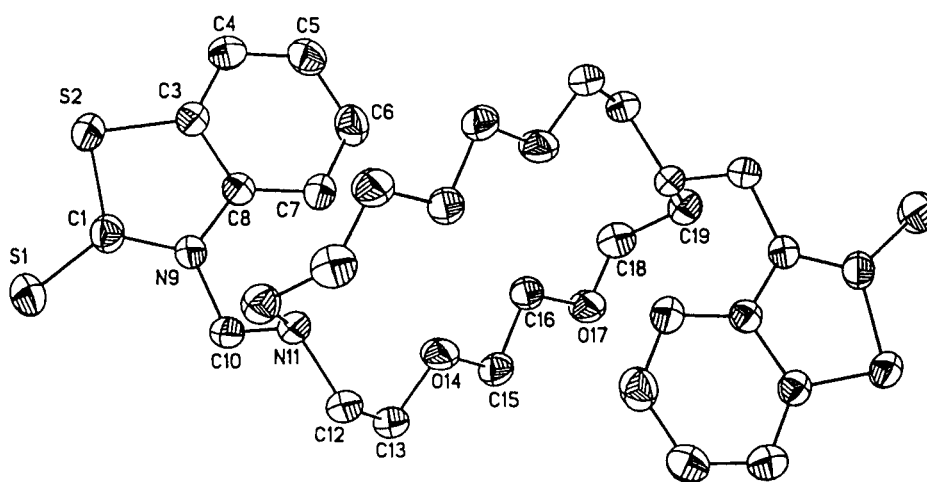


Figure 4. The solid state structure of **12**. The hydrogen atoms were omitted for clarity.

Interactions of ligands **5, 7, 8**, and **11** with Na+, K+, Ba$^{2+}$, Ag+, Zn$^{2+}$, Cd$^{2+}$, Ni$^{2+}$, and Cu$^{2+}$ were evaluated by a calorimetric titration technique [15] at 25° in an absolute methanol solution. The values of equilibrium constants (log $K$), enthalpy ($\Delta H$) and entropy changes (T$\Delta S$) for these interactions are listed in Table 2. In most cases, the ligands form stable complexes with the metal ions studied with log $K$ > 3. In methanol, ligands **5, 7, 8**, and **11** form precipitates with transition and post-transition metal ions in several cases (Table 2). The solubilities of compounds **6, 9, 10** and **12-14** in methanol are too low to perform a calorimetric titration.
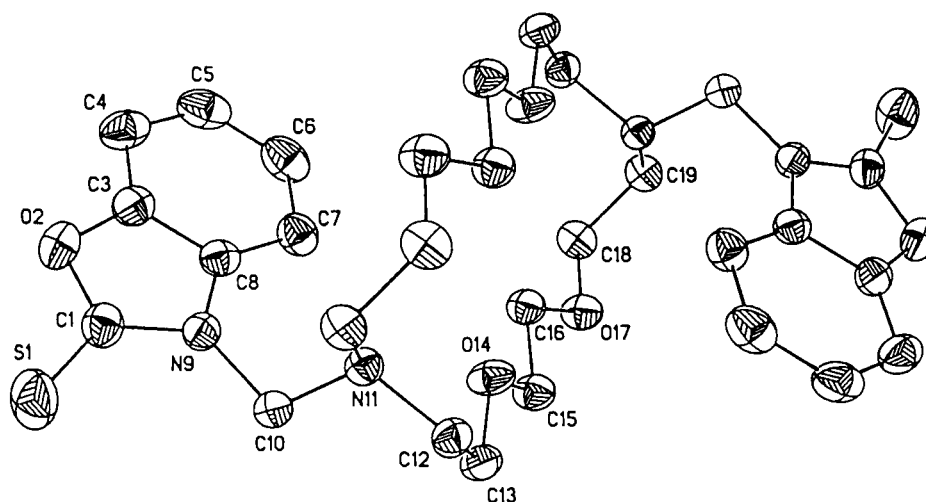
Figure 5. The solid state structure of **13**. The hydrogen atoms were omitted or clarity.

Phenylthio-substituted ligand **5** exhibits a high selectivity for Zn²⁺ (log $K$ = 5.19) over K⁺ and Ba²⁺, probably due to the four soft donor atoms (S and N). Ligand **11** selectively binds Ba²⁺ (log $K$ = 5.7) over Na⁺ and K⁺. The selectivities between K⁺ and Na⁺ demonstrated by ligands **8** and **11** are not high. Data in Table 2 show that complexation of the ligands with the metal ions studied is enthalpy driven in most cases. Except for the **8**-Ba²⁺, **11**-Na⁺, and **11**-Ba²⁺ interactions, all $\Delta H$ and $\Delta S$ values are negative. Large negative $\Delta H$ values were observed for complexation of K⁺ and Zn²⁺ with the ligands. Although

**7**-Zn²⁺, **8**-Cd²⁺, and **8**-Ni²⁺ interactions exhibit very large -$\Delta H$ values ($\geq$ 90 KJ/mol), the log $K$ values are not very large because of unfavorable entropy changes (large -T$\Delta S$ values), indicating that the ligands experience a large conformational change during complexation (a large loss of conformational entropy). Therefore, the sulfur and nitrogen atoms in these ligands may not be properly preorganized for coordination of transition and post-transition metal ions.

## EXPERIMENTAL

The ¹H nmr spectra (300 MHz) and ¹³C nmr spectra (75 MHz) were recorded in dimethylsulfoxide-$d_6$. Solvents and starting materials were purchased from commercial sources where available.

General Procedure for the Syntheses of Compounds **5-14** Using the One-Pot Mannich Reaction (Schemes 1 and 2).

An anhydrous toluene solution (180 ml) of 4,13-diaza-18-crown-6 (1.00 g, 3.82 mmoles), paraformaldehyde (280 mg, 9.30 mmoles), and the appropriate aromatic thiol (8.40 mmoles) was refluxed for 20 hours. The solvent was evaporated under reduced pressure, and a small amount of methanol was added. The mixture was sonicated for 20 to 30 minutes. The resulting solid was collected by filtration and dried.

7,16-Bis(phenylthiomethyl)-1,4,10,13-tetraoxa-7,16-diazacyclo-octadecane (**5**).

Ligand **5** (0.95 g, 49%) was prepared from thiophenol to give a white solid, mp 97-98°; ¹H nmr δ: 2.73 (t, $J$ = 5.4 Hz, 8H), 3.44 (m, 16H), 4.62 (s, 4H), 7.20 (m, 2H), 7.29 (m, 4H), 7.45 (m, 4H); ¹³C nmr δ: 52.2, 65.2, 68.8, 69.7, 126.7, 129.0, 131.2, 137.4.

*Anal.* Calcd. for C₂₆H₃₈N₂O₄S₂: C, 61.63; H, 7.56. Found: C, 61.59; H, 7.59.

Table 2

Log $K$, $\Delta H$ (kJ/mol), and T$\Delta S$ (kJ/mol) Values for the Interactions of Macrocyclic Ligands with Metal Ions in Methanol Solution at 25.0°

| Ligand | Cation | log $K$ | $\Delta H$ | T$\Delta S$ |
|---|---|---|---|---|
| 5 | K⁺ | 3.45 ± 0.02 | -61.6 ± 0.4 | -41.9 |
| | Ba²⁺ | 4.21 ± 0.08 | -26.5 ± 0.5 | -2.5 |
| | Zn²⁺ | 5.19 ± 0.07 | -61.5 ± 0.3 | -31.9 |
| | Cd²⁺ | (White precipitate) | | |
| | Ni²⁺ | (Brown precipitate) | | |
| 7 | K⁺ | 4.15 ± 0.02 | -57.2 ± 0.2 | -33.5 |
| | Ba²⁺ | 4.45 ± 0.04 | -28.8 ± 0.3 | -3.4 |
| | Zn²⁺ | 3.67 ± 0.05 | -99.6 ± 0.6 | -78.7 |
| | Cd²⁺ | (White precipitate) | | |
| | Ni²⁺ | (Brown precipitate) | | |
| 8 | Na⁺ | 3.48 ± 0.06 | -21.0 ± 0.5 | -1.2 |
| | K⁺ | 3.66 ± 0.02 | -53.2 ± 0.2 | -32.3 |
| | Ba²⁺ | 4.67 ± 0.07 | -26.0 ± 0.3 | 0.6 |
| | Ag⁺ | (White precipitate) | | |
| | Zn²⁺ | 4.21 ± 0.05 | -73.8 ± 0.2 | -49.8 |
| | Cd²⁺ | 2.79 ± 0.03 | -89.3 ± 0.4 | -73.4 |
| | Ni²⁺ | 3.43 ± 0.08 | -206.2 ± 3.2 | -186.6 |
| 11 | Na⁺ | 4.13 ± 0.07 | -9.7 ± 0.5 | 13.9 |
| | K⁺ | 3.81 ± 0.06 | -44.0 ± 0.8 | -22.3 |
| | Ba²⁺ | 5.7 ± 0.2 | -16.6 ± 0.5 | 15.9 |
| | Ag⁺ | (White precipitate) | | |
| | Zn²⁺ | (White precipitate) | | |
| | Cd²⁺ | (White precipitate) | | |
| | Cu²⁺ | (Blue precipitate) | | |

## Table 3

Crystal Data and Experimental Details for **8, 11, 12,** and **13.**

|  | **8** | **11** | **12** | **13** |
|---|---|---|---|---|
| Formula | $C_{26}H_{38}N_2O_6S_2$ | $C_{20}H_{34}N_6O_4S_6$ | $C_{28}H_{36}N_4O_4S_4$ | $C_{28}H_{36}N_4O_6S_2$ |
| Formula weight | 538.70 | 614.89 | 620.85 | 588.73 |
| F(000) | 576 | 1296 | 656 | 624 |
| Crystal size, mm | 0.55 x 0.4 x 0.07 | 0.45 x 0.3 x 0.2 | 0.45 x 0.35 x 0.3 | 0.5 x 0.4 x 0.35 |
| $\mu$, mm$^{-1}$ | 0.234 | 0.506 | 0.366 | 0.238 |
| Space group | $P2_1/c$ | C2/c | $P2_1/n$ | $P2_1/n$ |
| a, Å | 9.637(2) | 26.825(2) | 9.4652(12) | 9.3734(14) |
| b, Å | 17.867(4) | 9.7786(9) | 12.3873(14) | 12.461(3) |
| c, Å | 8.5848(12) | 11.876(2) | 12.6349(14) | 12.264(2) |
| $\beta$, deg. | 110.23(2) | 110.634(8) | 98.398(10) | 99.422(14) |
| Volume, Å$^3$ | 1386.9(4) | 2916.5(5) | 1465.5(3) | 1413.1(4) |
| Z | 2 | 4 | 2 | 2 |
| p calc., Mg/m$^3$ | 1.290 | 1.400 | 1.407 | 1.384 |
| $2\theta$ max. deg. | 52.00 | 55.00 | 50.00 | 55.0 |
| Independent data | 2714 | 3340 | 2571 | 3231 |
| Data/restraints/parameters | 2710/4/167 | 3339/0/165 | 2570/0/181 | 3231/0/183 |
| Goodness-of-fit on F$^2$ | 1.013 | 1.041 | 1.027 | 1.032 |
| Final R indices (I >2$\sigma$(I)) | $R_1 = 0.0767$ | $R_1 = 0.0546$ | $R_1 = 0.0407$ | $R_1 = 0.0473$ |
|  | $wR^2 = 0.1939$ | $wR^2 = 0.1304$ | $wR^2 = 0.0983$ | $wR^2 = 0.1170$ |
| Largest peak $\Delta$map, eÅ$^{-3}$ | 0.564 | 0.566 | 0.266 | 0.262 |
| Largest hole $\Delta$map, eÅ$^{-3}$ | -0.231 | -0.368 | -0.165 | -0.193 |

## Table 4

Atomic coordinates [ x 10$^4$] and equivalent isotropic displacement parameters [Å$^2$ x 10$^3$] for **8.** U(eq) is defined as one-third of the trace of the orthogonalized U$_{ij}$ tensor

|  | x | y | z | U(eq) |
|---|---|---|---|---|
| C1 | 11641(6) | 1178(3) | 1969(6) | 65(1) |
| O1 | 10967(4) | 702(2) | 2726(4) | 83(1) |
| C2 | 13134(7) | 1147(3) | 2258(7) | 83(2) |
| C3 | 13754(8) | 1647(4) | 1468(9) | 96(2) |
| C4 | 12910(9) | 2177(4) | 384(8) | 94(2) |
| C5 | 11428(8) | 2203(3) | 104(7) | 78(2) |
| C6 | 10762(6) | 1703(3) | 878(5) | 62(1) |
| S7 | 8839(2) | 1752(1) | 507(2) | 73(1) |
| C8 | 8178(6) | 879(3) | -719(5) | 62(1) |
| N9 | 7600(4) | 953(2) | -2497(4) | 59(1) |
| C10 | 8742(6) | 1171(3) | -3172(5) | 63(1) |
| C11 | 8314(7) | 1040(3) | -4993(6) | 74(2) |
| O12 | 7858(4) | 288(2) | -5363(4) | 71(1) |
| C13 | 7496(7) | 133(4) | -7067(6) | 94(2) |
| C14 | 6927(9) | -581(5) | -7489(9) | 124(3) |
| O15 | 5429(5) | -645(3) | -7322(7) | 131(2) |
| C16 | 4834(9) | -1325(6) | -7671(11) | 112(3) |
| C16' | 5140(26) | -1020(17) | -6149(28) | 98(9) |
| C17 | 3715(6) | -1417(4) | -6876(7) | 89(2) |
| H1 | 11589(4) | 375(2) | 3447(4) | 99 |
| H2 | 13720(7) | 792(3) | 2981(7) | 100 |
| H3 | 14766(8) | 1627(4) | 1670(9) | 115 |
| H4 | 13342(9) | 2510(4) | -146(8) | 112 |
| H5 | 10850(8) | 2562(3) | -617(7) | 93 |
| H8A | 8994(6) | 527(3) | -434(5) | 74 |
| H8B | 7413(6) | 660(3) | -368(5) | 74 |
| H10A | 9637(6) | 892(3) | -2602(5) | 75 |
| H10B | 8963(6) | 1698(3) | -2947(5) | 75 |
| H11A | 7514(7) | 1375(3) | -5590(6) | 89 |
| H11B | 9150(7) | 1143(3) | -5344(6) | 89 |
| H13A | 6775(7) | 496(4) | -7705(6) | 113 |
| H13B | 8376(7) | 188(4) | -7362(6) | 113 |
| H14A | 7593(9) | -945(5) | -6770(9) | 149 |

## Table 4 (continued)

|  | x | y | z | U(eq) |
|---|---|---|---|---|
| H14B | 6846(9) | -691(5) | -8624(9) | 149 |
| H17A | 3189(6) | -1974(4) | -6951(7) | 107 |
| H17B | 3991(6) | -1637(4) | -5759(7) | 107 |

U values for C16' and the hydrogen atoms are isotropic displacement parameters.

## Table 5

Atomic coordinates [x 10$^4$] and equivalent isotropic displacement parameters [Å$^2$ x 10$^3$] for **11.** U(eq) is defined as one-third of the trace of the orthogonalized U$_{ij}$ tensor

|  | x | y | z | U(eq) |
|---|---|---|---|---|
| C1 | 2042(1) | 5680(3) | 578(3) | 42(1) |
| S1 | 2181(1) | 4017(1) | 758(1) | 57(1) |
| S2 | 2161(1) | 6850(1) | 1756(1) | 48(1) |
| C3 | 1902(1) | 8143(3) | 711(3) | 41(1) |
| S3 | 1858(1) | 9810(1) | 1172(1) | 56(1) |
| C33 | 1507(2) | 10600(4) | -257(4) | 70(1) |
| N4 | 1747(1) | 7763(3) | -396(2) | 45(1) |
| N5 | 1829(1) | 6372(3) | -456(2) | 41(1) |
| C6 | 1660(1) | 5760(4) | -1687(3) | 49(1) |
| N7 | 1111(1) | 5781(3) | -2328(3) | 56(1) |
| C8 | 801(1) | 4925(4) | -1825(3) | 63(1) |
| C9 | 798(2) | 3436(4) | -2125(3) | 64(1) |
| O10 | 512(1) | 3247(2) | -3374(2) | 60(1) |
| C11 | 515(2) | 1864(4) | -3725(4) | 69(1) |
| C12 | 258(2) | 1734(5) | -5035(4) | 86(1) |
| O13 | -302(2) | 1831(3) | -5402(3) | 108(1) |
| C14 | -404(4) | 3093(9) | -5937(8) | 72(2) |
| C14' | -613(5) | 3158(12) | -5762(10) | 76(3) |
| C15 | -889(2) | 2881(5) | -7133(4) | 78(1) |
| H33A | 1457(14) | 11542(12) | -94(36) | 105 |
| H33B | 1705(13) | 10548(37) | -791(28) | 105 |
| H33C | 1167(7) | 10171(34) | -626(31) | 105 |

N. Su, J. S. Bradshaw, G. Xue, N. K. Dalley, X. X. Zhang, P. B. Savage,
K. E. Krakowiak, and R. M. Izatt

Table 5 (continued)

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H6A | 1838(1) | 6248(4) | -2150(3) | 59 |
| H6B | 1781(1) | 4819(4) | -1615(3) | 59 |
| H8A | 437(1) | 5254(4) | -2110(3) | 76 |
| H8B | 941(1) | 5025(4) | -957(3) | 76 |
| H9A | 1160(2) | 3110(4) | -1924(3) | 77 |
| H9B | 630(2) | 2916(4) | -1660(3) | 77 |
| H11A | 326(2) | 1307(4) | -3328(4) | 83 |
| H11B | 878(2) | 1536(4) | -3481(4) | 83 |
| H12A | 389(2) | 2448(5) | -5425(4) | 103 |
| H12B | 352(2) | 859(5) | -5289(4) | 103 |
| H15A | -773(2) | 3801(5) | -6660(4) | 93 |
| H15B | -664(2) | 2199(5) | -6565(4) | 93 |

U values for C14, C14' and the hydrogen atoms are isotropic displacement parameters.

Table 6

Atomic coordinates [ x $10^4$ ] and equivalent isotropic displacement parameters [$Å^2$ x $10^3$] for 12. U(eq) is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor

| | x | y | z | U(eq) |
|---|---|---|---|---|
| C1 | 947(3) | 4671(2) | 2580(2) | 47(1) |
| S1 | 1780(1) | 5366(1) | 3605(1) | 75(1) |
| S2 | 1529(1) | 3392(1) | 2267(1) | 49(1) |
| C3 | 191(2) | 3272(2) | 1171(2) | 39(1) |
| C4 | -75(3) | 2420(2) | 468(2) | 48(1) |
| C5 | -1207(3) | 2502(2) | -347(2) | 56(1) |
| C6 | -2043(3) | 3433(2) | -459(2) | 55(1) |
| C7 | -1788(3) | 4289(2) | 248(2) | 45(1) |
| C8 | -659(2) | 4197(2) | 1076(2) | 37(1) |
| N9 | -219(2) | 4960(2) | 1878(2) | 40(1) |
| C10 | -963(3) | 5991(2) | 1941(2) | 44(1) |
| N11 | -2421(2) | 5811(2) | 2130(2) | 38(1) |
| C12 | -3268(3) | 6815(2) | 1986(2) | 47(1) |
| C13 | -3514(3) | 7245(2) | 861(2) | 50(1) |
| O14 | -4111(2) | 6417(1) | 158(1) | 53(1) |
| C15 | -4705(3) | 6786(2) | -871(2) | 47(1) |
| C16 | -5012(3) | 5797(2) | -1552(2) | 48(1) |
| O17 | -5791(2) | 6108(1) | -2556(1) | 53(1) |
| C18 | -6105(3) | 5227(2) | -3269(2) | 53(1) |
| C19 | -7513(3) | 4678(2) | -3185(2) | 48(1) |
| H4A | 496(3) | 1805(2) | 542(2) | 58 |
| H5A | -1415(3) | 1934(2) | -824(2) | 67 |
| H6A | -2790(3) | 3480(2) | -1023(2) | 66 |
| H7A | -2356(3) | 4905(2) | 170(2) | 54 |
| H10A | -461(3) | 6423(2) | 2518(2) | 52 |
| H10B | -968(3) | 6387(2) | 1278(2) | 52 |
| H12A | -2785(3) | 7365(2) | 2452(2) | 56 |
| H12B | -4188(3) | 6684(2) | 2214(2) | 56 |
| H13A | -4160(3) | 7857(2) | 818(2) | 60 |
| H13B | -2617(3) | 7486(2) | 657(2) | 60 |
| H15A | -4037(3) | 7253(2) | -1165(2) | 57 |
| H15B | -5577(3) | 7187(2) | -836(2) | 57 |
| H16A | -4125(3) | 5452(2) | -1660(2) | 57 |
| H16B | -5566(3) | 5287(2) | -1199(2) | 57 |
| H18A | -5344(3) | 4699(2) | -3129(2) | 64 |
| H18B | -6121(3) | 5484(2) | -3996(2) | 64 |
| H19A | -7683(3) | 4115(2) | -3780(2) | 57 |
| H19B | -8273(3) | 5226(2) | -3181(2) | 57 |

U values for the hydrogen atoms are isotropic displacement parameters.

Table 7

Atomic coordinates [x $10^4$] and equivalent isotropic displacement parameters [$Å^2$ x $10^3$] for 13. U(eq) is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| C1 | 872(2) | 4612(2) | 2513(2) | 43(1) |
| S1 | 1832(1) | 5152(1) | 3619(1) | 66(1) |
| O2 | 1224(2) | 3634(1) | 2116(1) | 49(1) |
| C3 | 206(2) | 3406(2) | 1191(2) | 42(1) |
| C4 | 118(3) | 2504(2) | 532(2) | 54(1) |
| C5 | -1023(3) | 2474(2) | -332(2) | 60(1) |
| C6 | -2014(3) | 3310(2) | -519(2) | 58(1) |
| C7 | -1923(2) | 4218(2) | 155(2) | 46(1) |
| C8 | -778(2) | 4237(2) | 1015(2) | 38(1) |
| N9 | -331(2) | 4977(1) | 1858(1) | 36(1) |
| C10 | -1030(2) | 6006(2) | 1991(2) | 39(1) |
| N11 | -2494(2) | 5832(1) | 2201(1) | 33(1) |
| C12 | -3361(2) | 6822(2) | 2046(2) | 39(1) |
| C13 | -3592(3) | 7266(2) | 886(2) | 43(1) |
| O14 | -4093(2) | 6429(1) | 137(1) | 47(1) |
| C15 | -4643(3) | 6796(2) | -945(2) | 45(1) |
| C16 | -4922(2) | 5814(2) | -1654(2) | 42(1) |
| O17 | -5787(2) | 6104(1) | -2673(1) | 46(1) |
| C18 | -6095(3) | 5215(2) | -3402(2) | 45(1) |
| C19 | -7495(2) | 4647(2) | -3294(2) | 40(1) |
| H4A | 788(3) | 1950(2) | 663(2) | 65 |
| H5A | -1133(3) | 1881(2) | -799(2) | 72 |
| H6A | -2764(3) | 3263(2) | -1115(2) | 70 |
| H7A | -2592(2) | 4774(2) | 31(2) | 55 |
| H10A | -479(2) | 6398(2) | 2604(2) | 46 |
| H10B | -1054(2) | 6433(2) | 1327(2) | 46 |
| H12A | -2888(2) | 7366(2) | 2545(2) | 47 |
| H12B | -4298(2) | 6681(2) | 2254(2) | 47 |
| H13A | -4297(3) | 7842(2) | 820(2) | 51 |
| H13B | -2691(3) | 7553(2) | 718(2) | 51 |
| H15A | -3946(3) | 7259(2) | -1216(2) | 54 |
| H15B | -5531(3) | 7196(2) | -947(2) | 54 |
| H16A | -4012(2) | 5511(2) | -1787(2) | 50 |
| H16B | -5418(2) | 5278(2) | -1282(2) | 50 |
| H18A | -5305(3) | 4705(2) | -3256(2) | 54 |
| H18B | -6147(3) | 5465(2) | -4157(2) | 54 |
| H19A | -7678(2) | 4121(2) | -3773(2) | 48 |
| H19B | -8318(2) | 5162(2) | -3377(2) | 48 |

U values for the hydrogen atoms are isotropic displacement parameters.

U values for the hydrogen atoms are isotropic displacement parameters.

7,16-Bis(2-naphthylthiomethyl)-1,4,10,13-tetraoxa-7,16-diaza-cyclooctadecane (6).

Ligand 6 (1.25 g, 54%) was prepared from 2-thionaphthol to give a white solid, mp 112-113°; $^1H$ nmr δ: 2.76 (t, $J$ = 5.5 Hz, 8H), 3.42 (s, 16H), 4.75 (s, 4H), 7.50 (m, 6H), 7.83 (m, 6H), 8.00 (s, 2H); $^{13}C$ nmr δ: 52.3, 65.0, 68.9, 69.7, 125.7, 126.5, 127.0, 127.6, 128.2, 128.8, 129.1, 131.3, 133.4, 135.1.

Anal. Calcd. for $C_{34}H_{42}N_2O_4S_2$: C, 67.29; H, 6.98. Found: C, 67.05; H, 6.82.

7,16-Bis(2-methoxyphenylthiomethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (7).

Ligand 7 (0.95 g, 44%) was prepared from 2-methoxythiophenol to give a white solid, mp 84-86°; $^1H$ nmr δ: 2.73 (t, $J$ = 5.5 Hz, 8H), 3.44 (s, 16H), 3.82 (s, 6H), 4.52 (s, 4H), 6.88 (t, $J$ = 7.6 Hz, 2H), 6.98 (d, $J$ = 8.3 Hz, 2H), 7.22 (t, $J$ = 7.6 Hz, 2H), 7.42 (d, $J$ = 7.6 Hz, 2H); $^{13}C$ nmr δ: 52.1, 55.6, 63.1, 68.8, 69.7, 111.2, 120.8, 124.5, 127.9, 132.6, 158.1.

*Anal.* Calcd. for $C_{28}H_{42}N_2O_6S_2$: C, 59.34; H, 7.47. Found: C, 59.06; H, 7.43.

7,16-Bis(2-hydroxyphenylthiomethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (**8**).

Ligand **8** (1.21 g, 59%) was prepared from 2-hydroxythiophenol to give a light yellow solid, mp 87-88°; $^1$H nmr δ: 2.76 (t, $J$ = 5.4 Hz, 8H), 3.43 (s, 16H), 4.44 (s, 4H), 6.72 (td, $J$ = 1.2, 7.6 Hz, 2H), 6.82 (dd, $J$ = 1.0, 8.1 Hz, 2H), 7.07 (td, $J$ = 1.5, 8.1 Hz, 2H), 7.34 (dd, $J$ = 1.5, 7.6 Hz, 2H), 9.87 (br s, 2H); $^{13}$C nmr δ: 52.0, 63.4, 68.7, 69.7, 115.5, 119.5, 121.9, 128.3, 133.8, 157.2.

*Anal.* Calcd. for $C_{26}H_{38}N_2O_6S_2$: C, 57.97; H, 7.11. Found: C, 58.06; H, 7.27.

7,16-Bis(4-hydroxyphenylthiomethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (**9**).

Ligand **9** (1.38 g, 67%) was prepared from 4-hydroxythiophenol to give a light yellow solid, mp 160-161°; $^1$H nmr δ: 2.72 (t, $J$ = 5.6 Hz, 8H), 3.43 (m, 16H), 4.43 (s, 4H), 6.70 (dt, $J$ = 2.9, 8.5 Hz, 4H), 7.28 (dt, $J$ = 2.9, 8.5 Hz, 4H), 9.55 (br s, 2H); $^{13}$C nmr δ: 52.2, 66.6, 68.8, 69.7, 116.1, 125.1, 134.6, 156.7.

*Anal.* Calcd. for $C_{26}H_{38}N_2O_6S_2$: C, 57.97; H, 7.11. Found: C, 58.01; H, 6.96.

7,16-Bis(4-acetamidophenylthiomethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (**10**).

Ligand **10** (1.37 g, 58%) was prepared from 4-acetamidothiophenol to give a white solid, mp 175-176°; $^1$H nmr δ: 2.03 (s, 6H), 2.71 (t, $J$ = 5.4 Hz, 8H), 3.59 (t, $J$ = 5.4 Hz, 8H), 3.43 (s, 8H), 4.54 (s, 4H), 7.38 (d, $J$ = 8.5 Hz, 4H), 7.51 (d, $J$ = 8.5 Hz, 4H), 9.96 (s, 2H); $^{13}$C nmr δ: 24.0, 52.2, 66.0, 68.8, 69.7, 119.4, 130.4, 132.6, 138.0, 168.3.

*Anal.* Calcd. for $C_{30}H_{44}N_4O_6S_2$: C, 58.04; H, 7.14. Found: C, 58.07; H, 6.94.

7,16-Bis(5-methylthio-1,3,4-thiadiazole-2-thione-3-ylmethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (**11**).

Ligand **11** (1.23 g, 52%) was prepared from 5-methylthio-1,3,4-thiadiazole-2-thiol to give a white solid, mp 110-112°; $^1$H nmr δ: 2.64 (s, 6H), 2.98 (br s, 8H), 3.52 (m, 8H), 5.22 (s, 4H); $^{13}$C nmr δ: 15.5, 51.9, 69.3, 69.6, 69.9, 156.9, 185.9.

*Anal.* Calcd. for $C_{20}H_{34}N_6O_4S_6$: C, 39.07; H, 5.57. Found: C, 39.10; H, 5.48.

7,16-Bis(benzothiazole-2-thione-3-ylmethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (**12**).

Ligand **12** (0.85 g, 36%) was prepared from 2-mercaptobenzothiazole to give a light yellow solid, mp 152-154°; $^1$H nmr δ: 2.94 (br s, 8H), 3.47 (m, 16H), 5.32 (s, 4H), 7.30 (t, $J$ = 7.6 Hz, 2H), 7.42 (t, $J$ = 7.6 Hz, 2H), 7.54 (d, $J$ = 8.3 Hz, 2H), 7.71 (d, $J$ = 7.8 Hz, 2H); $^{13}$C nmr δ: 51.6, 65.7, 69.1, 70.0, 114.4, 121.3, 125.0, 126.7, 127.2, 142.7, 163.2.

*Anal.* Calcd. for $C_{28}H_{36}N_4O_4S_4$: C, 54.17; H, 5.84. Found: C, 54.19; H, 5.77.

7,16-Bis(benzoxazole-2-thione-3-ylmethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (**13**).

Ligand **13** (1.18 g, 53%) was prepared from 2-mercaptobenzoxazole to give a white solid, mp 153-155°; $^1$H nmr δ: 2.95 (t, $J$ = 5.4 Hz, 8H), 3.43 (s, 8H), 3.51 (t, $J$ = 5.4 Hz, 8H), 5.17 (s, 4H), 7.30 (m, 4H), 7.52 (m, 4H); $^{13}$C nmr δ: 51.9, 66.9, 69.2, 70.0, 109.8, 112.1, 124.1, 124.8, 132.2, 146.7, 180.1.

*Anal.* Calcd. for $C_{28}H_{36}N_4O_6S_2$: C, 57.12; H, 6.16. Found: C, 57.34; H, 6.31.

7,16-Bis(5-phenyl-1,3,4-oxadiazole-2-thione-3-ylmethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (**14**).

Ligand **14** (1.13 g, 46%) was prepared from 5-phenyl-1,3,4-oxadiazole-2-thiol to give a white solid, mp 156-157°; $^1$H nmr δ: 3.02 (t, $J$ = 5.4 Hz, 8H), 3.54 (s, 8H), 3.58 (t, $J$ = 5.4 Hz, 8H), 5.14 (s, 4H), 7.60 (m, 6H), 7.89 (m, 4H); $^{13}$C nmr δ: 51.8, 69.2, 69.3, 69.9, 122.4, 126.1, 132.3, 158.8, 177.1.

*Anal.* Calcd. for $C_{30}H_{38}N_6O_6S_2$: C, 56.06; H, 5.96. Found: C, 55.96; H, 5.96.

### X-Ray Crystal Structure Analyses.

Crystals of **8**, **11**, **12**, and **13** suitable for single crystal X-ray studies were prepared. Crystal and intensity data were obtained for the four compounds using a Bruker P4 automated diffractometer using MoKα (λ = 0.70173 Å) radiation. The lattice parameters and orientation matrix for each crystal were obtained using a least-squares procedure involving a suitable number of carefully centered reflections. The intensity data for each crystal were collected using a variable speed θ-2θ scanning procedure. The crystal and experimental data are listed in Table 3.

The four structures were solved using direct methods. Positional and thermal parameters for the atoms of **8**, **11**, **12**, and **13** are listed in Tables 4-7, respectively. Compounds **12** and **13** are isomorphous with only slight differences in the lattice parameters and the positional parameters of the respective atoms (see Tables 3, 6, and 7). The only difference in the compounds is that the ring sulfur atom in **12** is replaced by an oxygen atom in **13**. The disorder of C16 in **8** (occupancy of C16 is 0.80, of C16' is 0.80) and of C14 in **11** (occupancy of C14 is 0.55, of C14' is 0.45) was resolved. All nonhydrogen atoms except C16' in **8** and C14 and C14' in **11** were refined anisotropically. Positions for all hydrogen atoms bonded to nondisordered atoms with the exceptions of C17 in **8**, C15 in **11**, and C19 in **12** and **13** were calculated. The hydrogen atoms attached to these carbon atoms were located in the respective difference maps. In the refinement process, all of the hydrogen atoms were allowed to ride on their neighboring atoms and the magnitudes of their isotropic thermal parameters were a function of the equivalent isotropic thermal parameter of the carbon atom to which they were bonded. The methyl group of C33 in **11** was refined as a rigid group. Hydrogen atoms bonded to the disordered carbon atoms were not included in the refinement of the structures of **8** and **11**. The four structures were solved, refined and displayed using the program package SHELXTL PC version 5.03 [17] supplied by Bruker Analytical X-ray Systems.

### Determination of Thermodynamic Quantities.

Values of log $K$ and Δ$H$ were determined as described earlier [15] in absolute methanol solutions at 25.0 ± 0.1° by titration calorimetry using a Tronac Model 450 calorimeter equipped with a 20-ml reaction vessel. Values of TΔ$S$ were calculated from $K$ and Δ$H$ values. The metal ion solutions were titrated into the macrocyclic ligand solutions and the titrations were carried out to a twofold excess of the metal ions. The method used to process the calorimetric data and to calculate the log $K$ and Δ$H$ values has been described [16].

## REFERENCES AND NOTES

* To whom correspondence should be addressed: Telephone: (801) 378-2415; Fax: (801) 378-5474; E-mail: jerald_bradshaw@byu.edu

† Current address for N. S., Bayer Corp., Pharmaceutical Division, West Haven, CT 06516

# Current address for K. E. K., IBC Advanced Technologies, Inc., P. O. Box 98, American Fork, UT 84003.

[1] A. V. Bordunov, J. S. Bradshaw, X. X. Zhang, N. K. Dalley, X.-L. Kou, and R. M. Izatt, *Inorg. Chem.*, **35**, 7229 (1996).

[2] X. X. Zhang, A. V. Bordunov, J. S. Bradshaw, N. K. Dalley, X.-L. Kou, and R. M. Izatt, *J. Am. Chem. Soc.*, **117**, 11507 (1995).

[3] N. Su, J. S. Bradshaw, X. X. Zhang, P. B. Savage, K. E. Krakowiak, and R. M. Izatt, *J. Org. Chem.*, **64**, 3825 (1999).

[4] S. Pawlenko and S. Lang-Fugmann, S/N-Acetale in Methoden Der Organischen Chemie; H. Hagemann and D. Klamann, Eds.; Houben-Weyl: New York; 1992; Band E14a/3; p.483.

[5a] Y. Terao, K. Matsunaga, and M. Sekiya, *Chem. Pharm. Bull.*, **25**, 2964 (1977); [b] J. Szabó, G. Bernáth, and P. Sohár, *Heterocycles*, **26**, 2381 (1987); [c] G. F. Grillot and R. E. Schaffrath, *J. Org. Chem.*, **24**, 1035, (1959); [d] K. Kellner, W. Hanke, and A. Tzschach, *Z. Chem.*, **21**, 403 (1981); [e] W. Ando, T. Takata, L. Huang, and Y. Tamura, *Synthesis*, 139 (1986); [f] T. Takata, M. Kuo, Y. Tamura, Y. Kabe, and W. Ando, *Chem. Lett.*, 939 (1985); [g] A. B. Kuliev, M. I. Abdullaeva, N. O. Akhadov, M. A. Abdulvagabova, and B. R. Gasanov, *Neftekhimiya*, **33**, 62 (1993); *Chem. Abstr.*, **119**, 99414y (1993).

[6a] G. F. Grillot, H. R. Felton, B. R. Garrett, H. Greenberg, R. Green, R. Clementi, and M. Moskowitz, *J. Am. Chem. Soc.*, **76**, 3969 (1954); [b] I. E. Pollak, A. D. Trifunac, and G. F. Grillot, *J. Org. Chem.*, **32**, 272 (1967); [c] P. Wipf, R. Prewo, J. H. Bieri, and H. Heimgartner, *Helv. Chim. Acta*, **70**, 1380 (1987); [d] H. Chikashita, S. Komazawa, N. Ishimoto, K. Inoue, and K. Itoh, *Bull. Chem. Soc. Jpn.*, **62**, 1215 (1989); [e] A. B. Kuliev, A. G. Mamedov, M. M. Dzhavadov, N. O. Akhadov,

M. A. Abdulvagabova, F. V. Ibragimova, and M. I. Abdullaeva, *Neftehimiya*, **30**, 841 (1990); *Chem. Abstr.* **115**, 139296n (1991); [f] I. E. Pollak and G. F. Grillot, *J. Org. Chem.*, **32**, 2891 (1967).

[7] K. Ito and M. Sekiya, *Chem. Pharm. Bull.*, **27**, 1691 (1979).

[8a] A. D. Dunn and R. Norrie, *Z. Chem.*, **28**, 212 (1988); [b] M. Yokoyama, *Bull. Chem. Soc. Jpn.*, **44**, 1610 (1971); [c] M. Yokoyama, *J. Org. Chem.*, **36**, 2009 (1971); [d] Z. Z. Sapozhnikova, A. F. Prokofeva, V. N. Volkova, and N. N. Mel'nikov, *Zh. Obshch. Khim.*, **61**, 2451 (1991); *Chem. Abstr.* **116**, 194269b (1992); [e] D. F. Veber, J. D. Milkowski, S. L. Varga, R. G. Denkewalter, and R. Hirschmann, *J. Am. Chem. Soc.*, **94**, 5456 (1972).

[9] K. Ito, R. Komaki, and M. Sekiya, *Chem. Pharm. Bull.*, **25**, 3385 (1977).

[10a] I. E. Pollak and G. F. Grillot, *J. Org. Chem.*, **32**, 2891 (1967); [b] F. Asinger and H. Offermanns, *Angew. Chem. Int. Ed. Engl.*, **6**, 907 (1967).

[11a] M. Tramontini, *Synthesis*, 703 (1973); [b] M. Tramontini and L. Angliolini, *Tetrahedron*, **46**, 1791 (1990).

[12] A. Chimirri, S. Grasso, P. Monforte, G. Romeo, and M. Zappalà, *Synthesis*, 244 (1988).

[13a] K. W. Chi, H. C. Wei, T. Kottke, and R. J. Lagow, *J. Org. Chem.*, **61**, 5684 (1996); [b] N. Su, J. S. Bradshaw, P. B. Savage, K. E. Krakowiak, R. M. Izatt, S. L. De Wall, and G. W. Gokel, *Tetrahedron*, **55**, 9737 (1999).

[14] A. V. Bordunov, J. S. Bradshaw, V. N. Pastushok, and R. M. Izatt, *SynLett.*, 933 (1996).

[15a] J. L. Oscarson and R. M. Izatt, in Physical Methods of Chemistry; B. W. Rossiter and R. C. Baetzold, Eds.; Wiley: New York, 1992; Vol. 6, Chapter 7; [b] R. M. Izatt, X. X. Zhang, H. Y. An, C. Y. Zhu, and J. S. Bradshaw, *Inorg. Chem.*, **33**, 1007 (1994).

[16] D. J. Eatough, J. J. Christensen, and R. M. Izatt, *Thermochim. Acta*, **3**, 219 and 233 (1972).

[17] G. M. Sheldrick, SHELXTL PC Version 5.03, Bruker Analytical X-ray Systems, Madison Wisconsin (1994).