REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	March 8, 1999	Technical Report

4. TITLE AND SUBTITLE
Synthesis of New Tetraazacrown Ethers Capable of Forming Metal Ion Ligating Agents Containing Two Fluoroionophores or Chromoionophores.

5. FUNDING NUMBERS
N00014-98-1-0485
98PR05020-00

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8. PERFORMING ORGANIZATION REPORT NUMBER
Technical Report No. 4

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
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Office of Naval Research
800 North Quincy Street
Arlington, VA 22217-5000

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES
Prepared for publication

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 words)

Four tetraazacrown ethers containing two unsubstituted ring nitrogen atoms were prepared *via* the crab-like cyclization reaction of two diamines with two bis-α-chloroamides followed by reduction of the resulting macrocyclic diamides. Thus, *N,N'*-dimethyltetraaza-15-crown-5 (**12**), *N,N'*-dimethyltetraaza-16-crown-5 (**13**), *N,N'*-dimethyltetraazathia-15-crown-5 (**14**), and *N,N'*-dimethyltetraazathia-16-crown-5 (**15**) macrocyclic ligands were prepared. X-ray crystal structures were determined for the macrocyclic diamide intermediates leading to **13** and **14**.

14. SUBJECT TERMS

15. NUMBER OF PAGES

16. PRICE CODE
NA

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

OFFICE OF NAVAL RESEARCH

Grant N00014-98-1-0485

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Results and Discussion

Synthesis of Tetraazacrown Ethers with Two Unsubstituted Macroring Nitrogen Atoms. A convenient way to functionalize the polyazacrown ethers with fluoroionophore (FIP) or chromoionophore (CIP) groups is *via* attachment to ring NH functions. To allow attachment of two FIP or CIP groups, it was necessary to prepare macrocycles containing two secondary amine groups. Application of crab-like bis(α-chloroacetamide)s for the synthesis of azacrown ethers with one or two secondary macroring nitrogen atoms has been reported.[1,2] In our syntheses, bis(α-chloroacetamide)s **6** and **7** were prepared by acylating the appropriate diamines with chloroacetyl chloride or chloroacetic anhydride. The bis(α-chloroamide)s were then treated with bis-secondary amines in MeCN using a carbonate base to form macrocyclic diamides **8-11** (Scheme1). These diamides were reduced to form the four tetraazacrown ethers containing two secondary ring nitrogen atoms (**12-15**) as shown in Scheme 1. The bis(α-chloroacetamide)s **6** and **7** were prepared in almost quantitative yields. The amide portions of the bis(α-chloroamide)s work as protecting groups for the nitrogen atoms and they increase the reactivity of the chloro-substituted carbon toward nucleophilic substitution.[2] Compounds **6** and **7** were reacted with two different bis-secondary amines by a cyclization reaction to form the four macrocyclic diamides **8-11** in 57-73% yields.

The crab-like cyclization reactions were carried out without using high dilution techniques and at room temperature. The relatively high yields may be attributable to hydrogen bonding between the amide oxygen atoms of the bis(α-chloroamide) and the amine hydrogen atoms of the bis-secondary amines which would keep the two chloride units in the positions needed for the cyclization reaction.[1] Satisfactory elemental analyses were obtained on the four

macrocyclic diamides (**8-11**).

Reduction of **8-11** with $LiAlH_4$ gave the four tetraazacrown ethers (**12-15**) in 71-83% yields. Reduction can also be achieved by using diborane in THF. Diborane reduction results in the formation of a borane complex which requires a complex work-up procedure.[2] To avoid the relatively more complicated work-up, reduction was done by $LiAlH_4$ and gave the products in good yields.

Experimental Section

The ^1H and ^{13}C NMR spectra were recorded at 200 or 300 MHz and 50 or 75 MHz in $CDCl_3$ unless otherwise noted. MS spectra were determined using chemical ionization (CI) and fast atom bombardment (FAB) methods. All starting materials were purchased from commercial sources.

Bis[2-(α-chloroacetamido)ethyl] Ether (6) (Scheme 1). Chloroacetic anhydride (4.1 g, 24 mmol) in 10 mL of CH_2Cl_2 was added dropwise through a dropping funnel to a stirred solution of 2,2'-oxybis(ethylamine) (0.94 g, 10 mmol) at 0-5 °C over a 1-h period. The mixture was stirred for additional 1 h at rt. Saturated aqueous $NaHCO_3$ was added to neutralize the reaction mixture. The organic layer was separated and washed twice with 20 mL portions of saturated aqueous $NaHCO_3$, then twice with portions of water. The organic layer was dried (Na_2SO_4) and the solvent was evaporated under vacuum to give a crude product (2.52 g, 98%). The crude bis-α-chloroamide product was used to prepare the appropriate macrocycles without further purification; mp = 81-2 °C; ^1H NMR δ 6.94 (br s, 2H), 4.07 (s, 4H), 3.61-3.50 (m, 8H); ^{13}C NMR δ 166.3, 69.5, 42.9, 39.7; MS (CI) *m/z* 257 (M^+); HRMS (CI) Calcd for

$C_8H_{15}{}^{35}Cl_2N_2O_3$ (MH^+): 257.0460, found: 257.0472.

Bis[2-(α-chloroacetamido)ethyl] Sulfide (7) (Scheme 1). Compound 7 was synthesized from 2,2'-thiobis(ethylamine) (1.2 g, 10 mmol) and chloroacetic anhydride (4.1 g, 24 mmol) as above for **6**. A white precipitate formed gradually during the reaction. When the reaction was completed, the solution was cooled to 0 °C to complete the precipitation. The solid was filtered and washed with CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$ and water. The organic layer was dried (Na_2SO_4) and the solvent was evaporated to produce another portion of the product. Crude product **7** (2.71 g, 99%) was used without further purification; mp = 108-9 °C; ^{1}H NMR δ 6.99 (br s, 2H), 4.08 (s, 4H), 3.58-3.51 (m, 4H), 2.75 (t, J = 6.6 Hz, 4H); ^{13}C NMR δ 168.6, 42.9, 39.9, 31.4; MS (CI) *m/z* 273 (M^+); HRMS (CI) Calcd for $C_8H_{15}{}^{35}Cl_2N_2O_2S$ (MH^+): 273.0231, found: 273.0235.

General Procedure A: Cyclization of Bis(α-chloroamide)s 6 or 7 with Diamines (Scheme 1). A mixture of 3.89 mmol of **6** or **7**, 3.89 mmol of the appropriate diamine, and 1.5 g of Na_2CO_3 was stirred at reflux in 150 mL of MeCN for 24 h. The mixture was filtered, the solvent evaporated and 50 mL of $CHCl_3$ was added. The mixture was again filtered and evaporated. The crude cyclic diamide product was purified by flash chromatography on silica gel (40:5:1/CH_2Cl_2:MeOH:NH_4OH).

1,4-Dimethyl-1,4,7,13-tetraaza-10-oxacyclopentadecan-6,14-dione (8) (Scheme 1). Macrocyclic diamide **8** was obtained according to general procedure A from 1.00 g (3.9 mmol) of **6** and 0.34 g (3.8 mmol) of *N,N'*-dimethylethylenediamine. Compound **8** (0.86 g, 81%) was isolated after column chromatography and recrystallization in EtOAc as white crystals; mp = 151 °C; ^{1}H NMR δ 7.72 (br s, 2H), 3.58-3.47 (m, 8H), 3.03 (s, 4H), 2.57 (s, 4H), 2.27 (s, 6H); ^{13}C

NMR δ 170.8, 69.3, 61.9, 55.6, 42.8, 38.5; MS (FAB) *m/z* 295 (MNa^+); HRMS (FAB) Calcd for $C_{12}H_{25}N_4O_3$ (MH^+): 273.1926, found: 273.1927; Anal. Calcd for $C_{12}H_{24}N_4O_3$: C, 52.92; H, 8.88; Found: C, 52.70; H, 8.68.

1,5-Dimethyl-1,5,8,14-tetraaza-11-oxacyclohexadecan-7,15-dione (9) (Scheme 1). Macrocyclic diamide **9** was obtained according to general procedure A from 2.57 g (0.01 mol) of **6** and 1.02 g (0.01 mol) of *N,N'*-dimethyl-1,3-propanediamine. Compound **9** (1.86 g, 65%) was isolated after column chromatography and recrystallization in EtOAc as white crystals; mp = 84-5 °C; ^{1}H NMR δ 7.46 (br s, 2H), 3.55-3.44 (m, 8H), 3.02 (s, 4H), 2.44 (t, J=7.1 Hz, 4H), 2.31 (s, 6H), 1.63 (p, J = 7.1 Hz, 2H); ^{13}C NMR δ 171.1, 69.9, 62.1, 55.1, 43.4, 39.1, 26.2; MS (FAB) *m/z* 287 (MH^+), 309 (MNa^+); HRMS (FAB) Calcd for $C_{13}H_{27}N_4O_3$ (MH^+): 287.2083, found: 287.2066; Anal. Calcd for $C_{13}H_{26}N_4O_3$: C, 54.52; H, 9.15; Found: C, 54.74; H, 8.93.

1,4-Dimethyl-1,4,7,13-tetraaza-10-thiacyclopentadecan-6,14-dione (10) (Scheme 1). Macrocyclic diamide **10** was obtained according to general procedure A from 2.72 g (0.01 mol) of **7** and 0.88 g (0.01 mol) of *N,N'*-dimethylethylenediamine. Compound **10** (1.64 g, 57%) was isolated after column chromatography and recrystallization in EtOAc as white crystals; mp = 151-152 °C; ^{1}H NMR δ 7.99 (br s, 2H), 3.49-3.44 (m, 4H), 3.05 (s, 4H), 2.75-2.71 (m, 4H), 2.56 (s, 4H), 2.34 (s, 6H); ^{13}C NMR δ 170.9, 61.9, 61.9, 55.9, 43.5, 36.5, 32.1; MS (FAB) *m/z* 289 (MH^+), 311 (MNa^+); HRMS (FAB) Calcd for $C_{12}H_{25}N_4O_2S$ (MH^+): 289.1698, found: 289.1693; Anal. Calcd for $C_{12}H_{24}N_4O_2S$: C, 49.97; H, 8.39; Found: C, 50.17; H, 8.16.

1,5-Dimethyl-1,5,8,14-tetraaza-11-thiacyclohexadecan-6,14-dione (11) (Scheme 1). Macrocyclic diamide **11** was obtained according to general procedure A from 2.72 g (0.01 mol) of **7** and 1.02 g (0.01 mol) of *N,N'*-dimethyl-1,3-propanediamine. Compound **11** (1.84 g, 61%)

was isolated after column chromatography and recrystallization in EtOAc as white crystals; mp = 128 °C; ^{1}H NMR δ 7.59 (br s, 2H), 3.52-3.46 (m, 4H), 3.00 (s, 4H), 2.79-2.75 (m, 4H), 2.45 (t, J = 7.1 Hz, , 4H), 2.31 (s, 6H), 1.70 (p, J = 7.1 Hz, 2H); ^{13}C NMR δ 171.0, 62.2, 55.7, 43.2, 37.2, 32.8, 26.2; MS (FAB) *m/z* 203 (MH^+), 325 (MNa^+); HRMS (FAB) Calcd for $C_{13}H_{27}N_4O_2S$ (MH+): 303.1855, found: 303.1872; Anal. Calcd for $C_{13}H_{26}N_4O_2S$: C, 51.63; H, 8.66; Found: C, 51.74; H, 8.44.

General Procedure B: Lithium Aluminum Hydride Reduction. The macrocyclic diamide was dissolved in dry THF and the solution was cooled in an ice bath. $LiAlH_4$ was carefully added to the solution. The mixture was refluxed in an oil bath. The reaction was monitored by TLC (40:4:1/CH_2Cl_2:MeOH:NH_4OH). When the reaction was completed, the mixture was cooled in an ice bath, then water, 15% NaOH solution, and more water were added. The white precipitate was filtered and the solid was washed with CH_2Cl_2. The combined organic solutions were evaporated to give the crude reduced product which was purified by flash chromatography on silica gel (50-100:5:1/CH_2Cl_2:MeOH:NH_4OH) to give the products as oils.

1,4-Dimethyl-1,4,7,13-tetraaza-10-oxacyclopentadecane (12) (Scheme 1). $LiAlH_4$ (170 mg, 4.4 mmol) was added slowly to a solution of **8** (300 mg, 1.1mmol) in 6 mL of dry THF at 0 °C. The resulting mixture was refluxing for 10 h and worked up as general procedure B. Macrocyclic diamine **12** (193 mg, 72%) was obtained as an oil; ^{1}H NMR δ 3.46 (dd, J = 4.8, 4.5 Hz, 4H), 2.83 (br s, 2H), 2.63 (dd, J = 4.8, 4.5 Hz, 4H), 2.52-2.49 (m, 4H), 2.39-2.35 (m, 4H), 2.27 (s, 4H), 2.05 (s, 6H); ^{13}C NMR δ 69.5, 57.4, 55.6, 49.4, 46.8, 41.9; MS (FAB) *m/z* 245 (MH^+), 267 (MNa^+); HRMS (FAB) Calcd for $C_{12}H_{29}N_4O$ (MH^+): 245.2341, found: 245.2328.

1,5-Dimethyl-1,5,8,14-tetraaza-11-oxacyclohexadecane (13) (Scheme 1). $LiAlH_4$ (260

mg, 6.8 mmol) was added slowly to a solution of **9** (500 mg, 1.7 mmol) in 6 mL of dry THF at 0 °C. The resulting mixture was refluxing for 48 h and worked up as general procedure B. Macrocyclic diamine **7** (333 mg, 76%) was obtained as an oil; ^{1}H NMR δ 3.48 (dd, J = 4.8, 4.5 Hz, 4H), 3.10 (br s, 2H), 2.68 (dd, J = 4.8, 4.5 Hz, 4H), 2.61-2.58 (m, 4H), 2.42-2.39 (m, 4H), 2.28 (t, J = 6.6 Hz, 4H), 2.08 (s, 6H), 1.48 (p, J = 6.6 Hz, 2H); ^{13}C NMR δ 70.0, 57.5, 54.5, 49.2, 46.6, 42.4, 25.8; MS (FAB) *m/z* 259 (MH^+); HRMS (FAB) Calcd for $C_{13}H_{31}N_4O$ (MH^+): 259.2498, found: 259.2489.

1,4-Dimethyl-1,4,7,13-tetraaza-10-thiocyclopentadecane (14) (Scheme 1). $LiAlH_4$ (1.6 g, 4 mol) was added slowly to a solution of **10** (3.0 g, 10 mol) in 90 mL of dry THF at 0 °C. The resulting mixture was refluxing for 24 h and worked up as general procedure B. Macrocyclic diamine **14** (2.24 g, 83%) was obtained as an oil; ^{1}H NMR δ 2.88 (br s, 2H), 2.68-2.67 (m, 8H), 2.64-2.56 (m, 4H), 2.45-2.42 (m, 4H), 2.35 (s, 4H), 2.14 (s, 6H); ^{13}C NMR δ 57.2, 55.7, 48.0, 46.7, 42.7, 33.3; MS (FAB) *m/z* 261 (MH^+), 283 (MNa^+); HRMS (FAB) Calcd for $C_{12}H_{29}N_4S$ (MH^+): 261.2113, found: 261.2100.

1,5-Dimethyl-1,5,8,14-tetraaza-10-thiocyclohexadecane (15) (Scheme 1). $LiAlH_4$ (1.31 g, 34 mmol) was added slowly to a solution of **11** (2.6 g, 8.6 mmol) in 100 mL of dry THF at 0 °C. The resulting mixture was refluxing for 18 h and worked up as general procedure B. Macrocyclic diamine **15** (1.67 g, 71%) was obtained as an oil; ^{1}H NMR δ 2.78-2.74 (m, 4H), 2.70-2.66 (m, 4H), 2.67 (br s, 2H), 2.62-2.59 (m, 4H), 2.42 (m, 4H), 2.34 (t, J = 12.6 Hz, 4H), 2.12 (s, 6H), 1.52 (p, J = 6.9 Hz, 2H); ^{13}C NMR δ 57.1, 54.3, 48.1, 46.3, 42.5, 32.6, 25.1; MS (FAB) *m/z* 275 (MH^+), 297 (MNa^+); HRMS (FAB) Calcd for $C_{13}H_{31}N_4S$ (MH^+): 275.2269, found: 275.2286.

X-ray Structural Analysis of 9 and 10. X-ray structures of **9** and **10** with atom labels are shown in Figures 1 and 2, respectively. The compounds have some structural similarities. Both compounds contain two rigid amide groups which play an important role in determining the conformations of the molecules. It is apparent from the figures that the conformations of the upper halves of the two molecules are similar with the exception of the replacement of O1 in **9** by S1 in **10**. The three carbon bridge which joins the two nitrogen atoms (N7 and N11) in **9** allows the ring of that molecule to have more flexibility than the ring of **10** where only two carbons link N7 and N10. Because of this, the conformations of the lower portion of the molecules differ considerably. This is illustrated by the differences in that dihedral angles between the least-square planes of the amide groups in the two molecules. The value of that dihedral angle in **9** is 44.21° while it is 5.2° in **10**. The four nitrogen atoms of **10** are nearly planar with the average deviation of a nitrogen atom from their least square plane is 0.033Å. By contrast, the average deviation of a nitrogen from their least square plane in **9** is 0.117Å.

X-ray Structure Determinations. Tables of crystal data and structure determination information, experimental details, atomic coordinates and thermal parameters for all atoms, anisotropic thermal parameters for non-hydrogen atoms, and bond lengths and angles for **9** and **10** are contained in the Supporting Information.

References

(1) Bradshaw, J. S.; Krakowiak, K. E.; Izatt, R. M. *J. Heterocyclic Chem.* **1989**, *26*, 1431.

(2) Krakowiak, K. E.; Bradshaw, J. S.; Izatt, R. M. *J. Org. Chem.* **1990**, *55*, 3364.

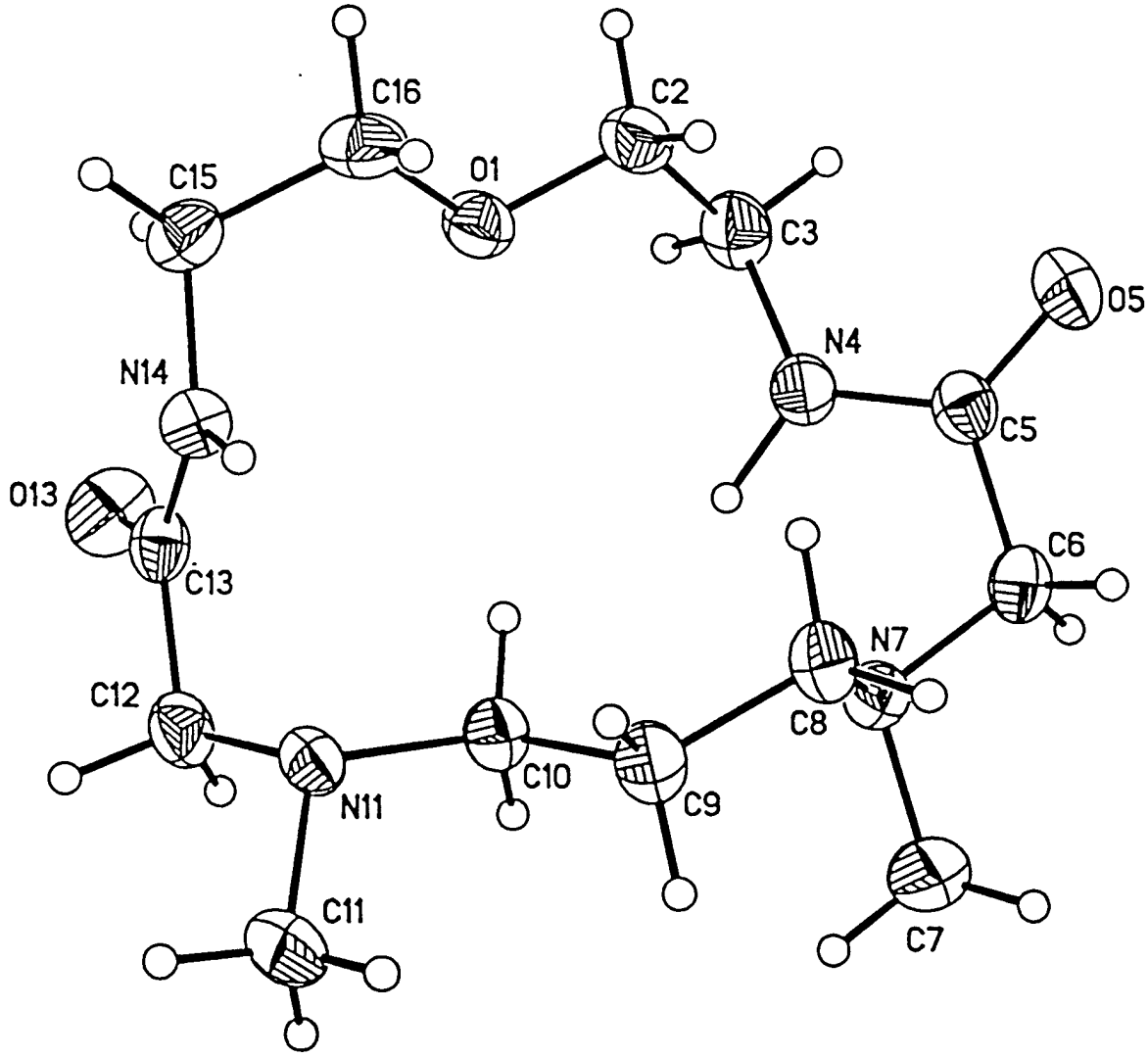


Figure 1 The solid state structure of 9 with the thermal ellipsoids drawn at the 30 percent probability level.

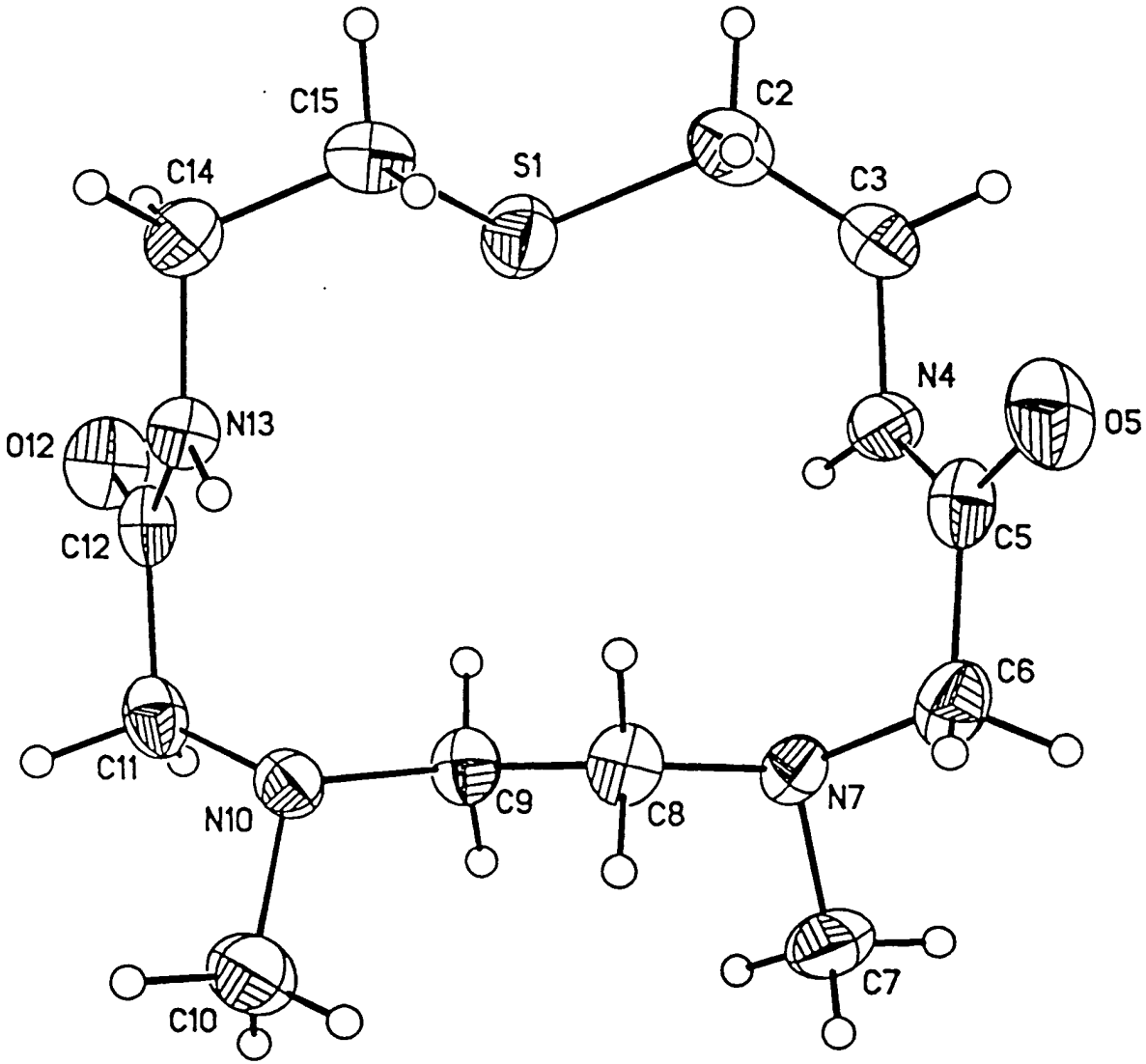
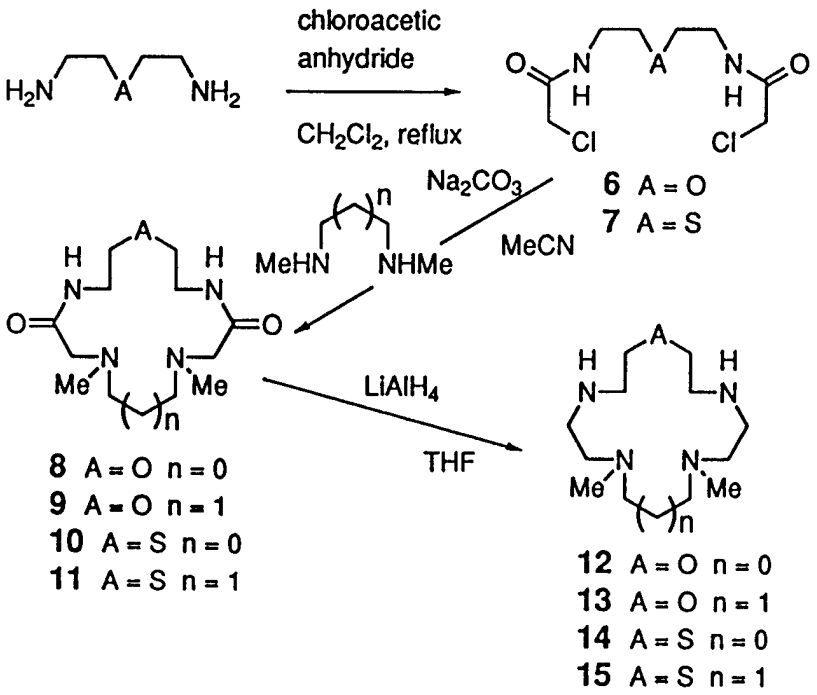


Figure 2 The solid state structure of 10 with the thermal ellipsoids drawn at the 30 percent probability level.



Scheme 1. Syntheses of tetraazacrown ethers with two unsubstituted nitrogens