**Registry No.**—**4**, 64201-22-5; **6**, 4521-28-2; **7**, 7021-11-6; **8**, 62889-58-1; **9**, 64201-23-6; **9** phenylurethane, 64201-24-7; **10**, 64201-25-8; **11**, 64201-26-9; **11** HCl, 64201-27-0; **12a**, 64201-28-1; **13b**, 64201-29-2; **17**, 64201-30-5; **18**, 64201-31-6; **19**, 64201-32-7; **21**, 64201-33-8; **22**, 64201-34-9; **23**, 64201-35-0; **24**, 64201-36-1; **25**, 64201-37-2; **25** phenylurethane, 64201-38-3; **26**, 64201-39-4; **27**, 64201-40-7; **28**, 64201-41-8; **29**, 64201-42-9; **29** phenylurethane, 64201-43-0; **30**, 64201-44-1; ethylene oxide, 75-21-8; *p*-toluenesulfonyl chloride, 98-59-9; ethyl bromoacetate, 105-36-2; ethyl bromopropionate, 539-74-2; acrylonitrile, 107-13-1; 3-amino-1-propanol, 156-87-6; isoamyl alcohol, 123-51-3; *N*-methyl-3-amino-1-propanol, 42055-15-2; xylene, 1330-20-7.

## References and Notes


(1) (a) Presented at the 173rd National Meeting of the American Chemical Society, New Orleans, La., March 1977, Abstract ORGN 14; (b) Taken in part from the thesis submitted by C. S. Yi to the Graduate School of the University of Georgia in partial fulfillment of the requirements for the Ph.D. degree, May, 1977; (c) Present address: School of Pharmacy, Creighton University, Omaha, Nebraska 68178.
(2) (a) E. E. Smissman and T. L. Pazdernik, *J. Med. Chem.*, **16**, 14 (1973); (b) E. E. Smissman and T. L. Pazdernik, *ibid.*, **16**, 18 (1973); (c) C. F. Barknecht, D. E. Nichols, D. B. Rusterholz, J. B. Long, J. A. Englebrecht, J. M. Beaton, R. J. Bradley, and D. C. Dyer, *ibid.*, **16**, 804 (1973); (d) E. Solomons and J. Sam, *ibid.*, **16**, 1330 (1973).
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(15) (a) Reference 4, pp 415–416; (b) N. L. Allinger, T. J. Walter, and M. C. Newton, *J. Am. Chem. Soc.*, **95**, 1680 (1973).
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(18) Reference 14, p 299.
(19) (a) Von Fritz Vogtle, *Chem.-Ztg.*, **96**, 396 (1972); (b) G. W. H. Potter, *Chem. Ind. (London)*, 1159 (1971).
(20) High-speed stirring was performed using a Labline Stir-O-Vac assembly (catalog No. 1280) coupled to a variable-speed motor (catalog No. 1285).
(21) Dry, oxygen-free nitrogen was obtained by passing through a column of drierite and then bubbling through a solution of benzophenone ketyl in xylene which was prepared from benzophenone and a sodium potassium alloy.[22]
(22) L. F. Fieser, "Experiments in Organic Chemistry", 3rd ed, Revised, D. C. Heath and Co., Boston, Mass., 1957, p 299.
(23) Isoamyl alcohol was distilled from anhydrous calcium chloride, bp 128–129 °C.
(24) Xylene was refluxed with sodium overnight and then distilled, bp 138–140 °C.
(25) Compound **30** taken directly from the column did not give acceptable elemental analysis: Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.00; H, 8.76; N, 5.03.
(26) Tetrahydrofuran was distilled from LAH, bp 68 °C.


# Chemistry of Heterocyclic Compounds. 26. Synthesis and Reactions of Multiheteromacrocycles Possessing 2,6-Pyrazino Subunits Connected by Carbon–Oxygen and/or –Sulfur Linkages[1]


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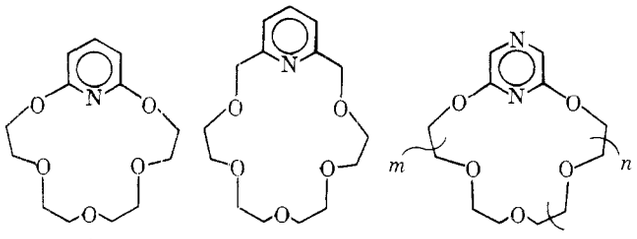
*Received June 24, 1977*


2,6-Dichloropyrazine (**4**) was treated with numerous glycol dianions, as well as the dianions of bis(2-mercaptoethyl) sulfide and bis(2-mercaptoethyl) ether, affording in most cases heteromacrocyclic ethers. Various expected uncyclized products were isolated and characterized. Quaternization of the N-4 position of the pyrazine ring was exclusively realized with these macrocycles. Diquaterization was accomplished with the 2:2-macrocycle **11**, and a new series of 1,3,5-cyclophanes (e.g., **40**) was generated from **5**.


Recently we described the preparation and characterization of carbon–oxygen bridged 2,6-pyridino macrocycles in which the bridging oxygens are directly attached to the pyridine nucleus (e.g., **1**).[2] This class of macrocycle[3] resulted from direct nucleophilic substitution of a ring halide by an alkoxide fragment and differs structurally and chemically from the macrocyclic class which possess a methylene group between the bridged heteroatoms and subring (e.g., **2**).[4] We herein describe the application of this procedure to the incorporation of the 2,6-pyrazino subunit into a "crown ether" (**3**) and the chemistry of these difunctional subheterocyclic rings.



1 2 3

In light of potential pharmaceutical and pesticidal interest in substituted pyrazines, numerous nonmacrocyclic 2,6-disubstituted pyrazines have been synthesized from the readily available 2,6-dihalopyrazine by nucleophilic substitution. Conditions for substitution of the 2- (or 6-) halides from 2,6-dihalopyrazines by alkoxide,[5] hydroxide,[5b–d] cyanide,[5b] amines,[5b,h,l,6] alkylsulfides,[5c,7] phenoxide,[8] sulfanilamide,[5g,9] alkyl,[10] and aryl[10] have been described. Based on the above chemical substitution studies and the $\pi$-electron density calculations in the pyrazine ring,[11] 2,6-dinucleophilic substitution on the pyrazine ring should be equally, or slightly more, facile to that of our previously studied pyridine cases.[2] Although the literature contains several examples of 1,2- and 1,3-diazine subunits incorporated into macrocyclic rings, prepared also by different procedures,[3] there are, to the best of our knowledge, no examples of the 2,6-pyrazino moiety incorporated in a "crown ether" ring.[12]

**A. Pyrazine Macrocycles with Carbon–Oxygen Bridges. 1. Diethylene Glycol.** Reaction of 2,6-dichloropyrazine (**4**) with diethylene glycol dianion, generated in situ from diethylene glycol and 2 equiv of oil-free sodium hydride,

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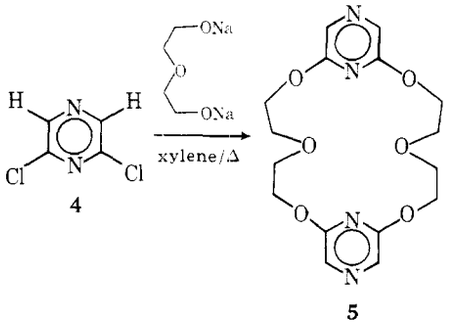
affords the 2:2- and 3:3-macrocycles (**5** and **6**, respectively) as well as the larger 40-membered 4:4-macrocycle **7**, which was isolated with difficulty. Although the smallest member (**8**) of this series was not isolated, it was not expected in view of the bridge size (ten-membered ring) and the general method of preparation. Only when the bridge possesses sulfur atoms which possess larger radii and diminished bond angle can such a ten-membered 1:1 macrocycle be generated, thus far, by this procedure; similar results have also been obtained in the related pyridine series.[2]

The spectral data for **5–7** were virtually superimposable; however, the ring sizes were ascertained by both mass spectrometry and molecular weight determination, and the symmetrical macrocyclic structures were confirmed by their NMR patterns. In **5**, the 3,5-pyrazine hydrogens show up as a spike at $\delta$ 7.8, a downfield shift when compared with the 3,5-pyridine hydrogens, as in **1**, which appear as a doublet at $\delta$ 6.2–6.3. This comparative downfield shift of the pyrazine proton signal is caused by the second ring nitrogen at the 4 position. Since substituents on the pyrazine ring cause pronounced and in most cases predictable shifts in the chemical shifts, care must be taken in peak assignments. For example, in the uncyclized products, such as **9**, the 3- and 5-pyrazine hydrogens appear

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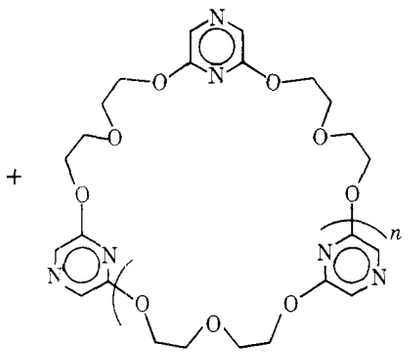
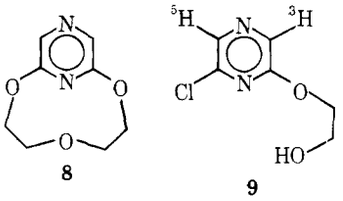


6, $n$ = 1
7, $n$ = 2



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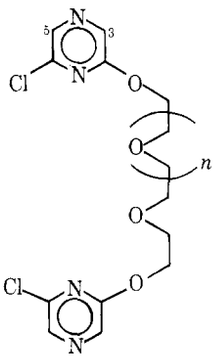
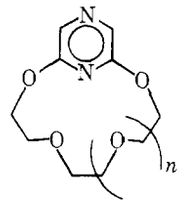
as a *singlet* at $\delta$ 8.15. This further downfield shift was always experienced in the uncyclized pyrazine products. The macrocyclic bridging methylene groups are readily characterized by NMR in that the $-OCH_2CH_2O-$ units appear as triplets [$\alpha$: $\delta$ 4.4–4.6; $\beta$: $\delta$ 3.8–3.9; $\gamma$: $\delta$ 3.5–3.7 (a singlet with an odd number of units); $\delta$-$\omega$: $\delta$ 3.4–3.6 (not defined)].

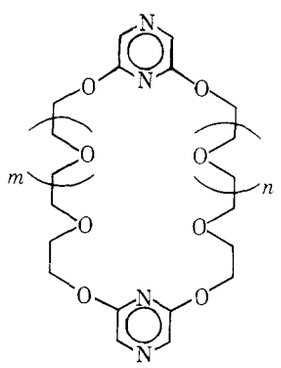
**2. Triethylene Glycol.** When 2,6-dichloropyrazine (**4**) was reacted with triethylene glycol dianion in refluxing xylene, besides the expected 1:1 and 2:2 macrocycles (**10** and **11**, respectively), a noncyclized product **12** was obtained in good yield. **12** could be converted into **11** upon treatment with additional dianion. The structures of these products were easily confirmed by $^1H$ NMR spectroscopy. In the macrocycles the 3,5-pyrazine hydrogens appeared as a singlet at $\delta$ 7.7–7.8; whereas, in **12** the pyrazine hydrogens appeared as two sepa-



12, $n$ = 1
15, $n$ = 2



10, $n$ = 1
13, $n$ = 2
17, $n$ = 3
19, $n$ = 4



11, $m = n$ = 1
14, $m = n$ = 2
16, $m$ = 1; $n$ = 2
18, $m = n$ = 3
20, $m = n$ = 4

rate singlets: $\delta$ 8.05 to H-3 and $\delta$ 8.10 to H-5 are the tentative assignments based on later examples. Numerous other products were obtained and upon cursory NMR analysis were shown to be minor noncyclized components; further characterizations of these compounds were not conducted.

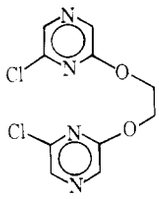
**3. Tetra-, Penta-, and Hexaethylene Glycols.** Reaction of the dianion of the commercially available tetraethylene glycol with **4** furnished the desired 1:1- and 2:2-macrocycles (**13** and **14**, respectively). The noncyclized products (e.g., **15**) were detected but not isolated; however, unlike our previous observation in the pyridine series,[2b] macrocycle **16** was not even detected in the reaction mixture. Prolonged reaction times caused a minor increase in the formation of the macrocyclic products.

Penta- and hexaethylene glycols were synthesized according to the procedure of Perry and Hibbert[13] by reacting ethylene glycol with 1,8-dichloro-3,6-dioxaoctane and 1,11-dichloro-3,6,9-trioxaundecane, respectively. The disodium salt of pentaethylene glycol was reacted with **4** to afford the expected 1:1 and 2:2 macrocycles as crystalline solids. Since polyglycols undergo both fragmentation as well as to a lesser extent oligomerization at reaction temperatures,[14] a 1% yield of the smaller 1:1 macrocycle **13** was realized. Similarly, hexaethylene glycolate fragmented under the reaction conditions to generate dianions which were the sources of both **10** and **13**. Macrocycles **19** and **20** were isolated from the later experiments in 15 and 2% isolated yields, respectively. In both the pyrazine as well as pyridine[2] studies, the 1:1 macrocycles derived from hexaethylene was obtained in unusually high yields

as compared with other reactions in these series, thus indicative of a possible template effect.[15]

**4. Ethylene Glycol.** Recently, Allison et al.[5j] treated the very reactive tetrafluoropyrazine with sodioglycolate at −15 °C for 30 min; only the 1:1 and 1:2 noncyclized products were obtained. Subsequent treatment of this 1:1 adduct, 1,3,5-trifluoro-6-(2′-hydroxyethoxy)pyrazine, with either potassium *tert*-butoxide at 20 °C or potassium carbonate in dimethylformamide at 120 °C afforded a polymeric material, which was assigned[5j] as poly[2,3-bis(ethylenedioxy)-5,6-difluoropyrazine].

Treatment of 2,6-dichloropyrazine with sodioglycolate in xylene at 140 °C gave six different noncyclized products (**9, 21–25**). Cyclic products were neither isolated nor detected from our procedures. Several attempts to prepare cyclic compounds from either **21, 22,** or **23** by reaction with sodium glycolate failed. When lithium hydride was used as the base, there were only minor changes in product distribution. If macrocyclic products were formed, they were generated in less than 1% of the product mixture. This lack of cyclic components, so evident in the ethylene glycol series, indicates that the heteroatoms must not be capable of attaining the proper disposition of metal ion coordination (template effect). Although the NMR spectra of **21** and **9** are quite simple, the spike at δ 8.15 for the 3,5-protons is indicative of a 2-oxy-6-chloropyrazine substitution pattern. Compounds **22–25,**



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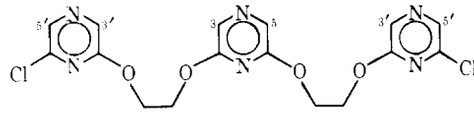

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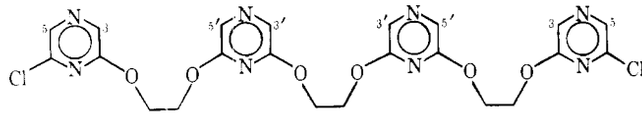

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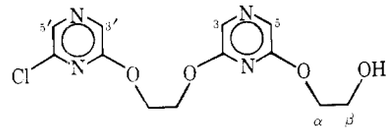

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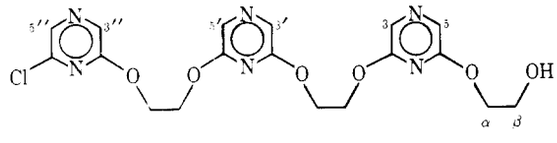
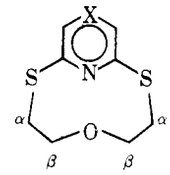


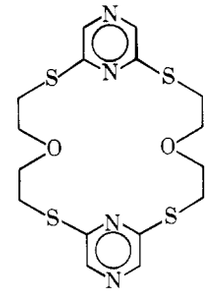
25

however, possess both a singlet at δ 8.15 for the terminal pyrazine hydrogens and a second singlet at ca. 7.8 for the internal pyrazine ring(s).

**B. Pyrazine Macrocycles with Carbon–Oxygen–Sulfur Bridges. Bis(2-mercaptoethyl) Ether.** Oxygen–sulfur mixed bridged macrocycles **26a** and **27** were isolated in good yield by reacting the disodium salt of bis(2-mercaptoethyl) ether with **4** in refluxing xylene. In both the pyrazine as well as pyridine series,[16] **26a** and **26b,** respectively, were the smallest isolable macrocycles possessing the corresponding subunit. The $^1$H NMR of **26a** showed a characteristic singlet at δ 8.2 for the pyrazine ring with 2,6-disulfur substitution and triplets at δ 3.25 and 3.91 corresponding to the β- and α-methylene groups, respectively. The sulfur functionality along with the "folded-under" conformation of the bridge in **26a** resulted in a slight upfield shift of the methylene absorptions. Macrocycle **27** showed the standard spike at δ 8.1 for the



**26a**, X = N
**b**, X = CH



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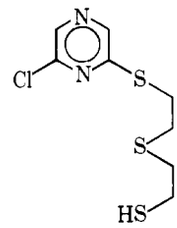
pyrazine hydrogens; however, the methylene groups appear as a complex multiplet centered at δ 3.5. This lack of differentiation of bridged methylenes was also experienced in the larger pyridine macrocycles which have sulfur atoms in the bridge(s).[16]

**C. Attempted Preparation of Pyrazine Macrocycles with Carbon–Sulfur Bridges. 1. Bis(2-mercaptoethyl) Sulfide.** When the disodium salt of bis(2-mercaptoethyl) sulfide was reacted with **4,** only three major components were isolated. The expected macrocycles in this carbon–sulfur series, such as **31,** were not detected; however, the noncyclic 1:1 product **28** was the key component and the remaining noncyclic products **29** and **30** were derived either from **28** or oligomers of the bis(2-mercaptoethyl) sulfide. The noncyclic nature of **28–30** was easily ascertained by NMR data, which showed two singlets at δ 8.2 and 8.3 for the H-3 and H-5 pyrazine hydrogens. The methylene region of these sulfur-containing side chains was too complex for interpretation.



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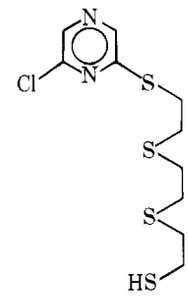

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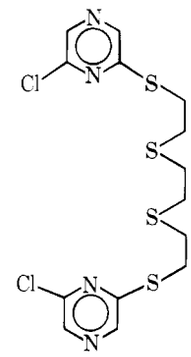

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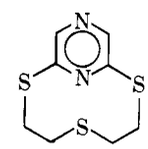

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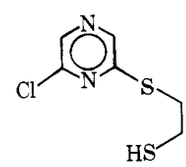
**2. Ethanedithiol.** Reaction of **4** with the disodio salt of ethanedithiol afforded only two major crystalline components which were shown to be 1:1 and 2:1 noncyclic compounds **32** and **33** via their NMR spectra. Attempted further cyclization of **32** was unsuccessful.



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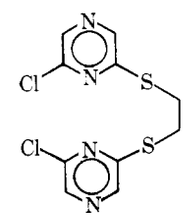
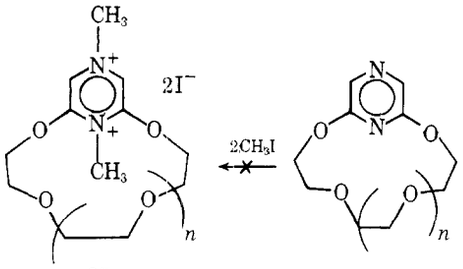


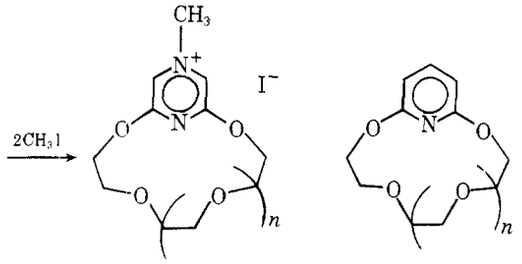
33

In general, the dithiols appear to undergo facile oligomerization prior to nucleophilic ring attack. Similar results were experienced in the preparation of pyridine–sulfur bridged macrocycles.[16] Further work in the carbon–sulfur bridged pyrazine-containing macrocycles was abandoned due to lack of isolable cyclic products and the general properties of the reactants.

**D. Quaternization of Selected Pyrazine Macrocycles. A Route to Cyclophanes.** From a limited number of literature examples of substituted pyrazine quaternization,[17] it appears that 2- (or 2,6-) substitution patterns give rise to N-4 alkylation as the major product. When the 1:1 carbon–oxygen bridged pyrazines were heated with excess methyl iodide, the N-4 methiodides (**34–36**) were obtained in near quantitative yields. Attempted further N-alkylation at the remaining N-1 position, to generate **37**, was unsuccessful. Similarly, the 1:1




**37**

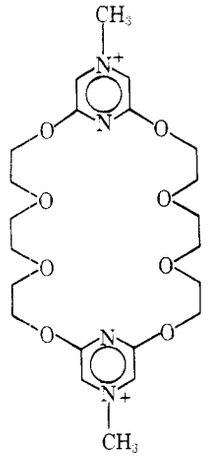



**34**, $n$ = 1
**35**, $n$ = 2
**36**, $n$ = 3

**38**

pyridine macrocycles **38** ($n$ = 1–4) also did not undergo quaternization under similar reaction conditions.[16]

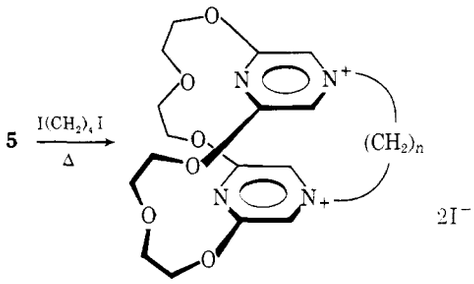
Similarly, when 2:2 macrocycle **11** was heated with excess methyl iodide, the dimethiodide **39** was isolated, in which only



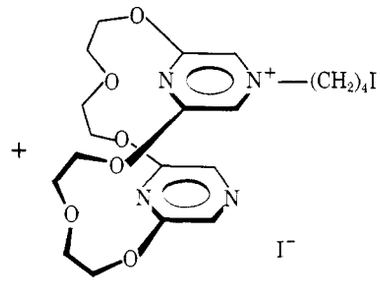

**39**

the two N-4 positions were alkylated. The NMR spectrum of **39** when compared to **11** indicated the expected downfield shift of the H-3,5 proton absorption ($\delta$ 8.37).

Since both N-4 positions undergo facile quaternization, the 2:2 macrocycle **5** was treated with 1,4-iodobutane for 5 h at 100 °C, resulting in the formation of a novel new series of cyclophanes, e.g., **40**. The 1:1 cyclophane **40** was isolated from a complex mixture of predominately the 1:1 monoquaternized compound **41** along with numerous polyquaternary products. The structure of **40** is substantiated by its symmetrical NMR spectrum which shows a downfield singlet at $\delta$ 8.14 for the pyrazine ring protons, whereas **41** possesses two (1:1) singlets




**40**, $n = 4$




**41**

at $\delta$ 8.12 and 7.65 for the quaternized and free pyrazine ring protons, respectively. The chemistry of this class of 1,3,5-bridged cyclophanes will be the topic of a forthcoming publication.

## Experimental Section

**General Comments.** All melting points were taken in capillary tubes with a Thomas-Hoover Uni-Melt and are uncorrected. Infrared (IR) and ultraviolet (UV) spectra were recorded on Beckman IR-7 and Cary 14 spectrophotometers, respectively. Unless otherwise noted, $^1$H NMR spectra were in deuteriochloroform solutions with $Me_4Si$ as internal standard ($\delta$ = 0 ppm) whereas quaternary salts were in $D_2O$ with an external standard and recorded on either Varian A-60A or HA-100 spectrometers. Molecular weights were determined with a Hewlett-Packard 302 vapor pressure osmometer and/or a Hitachi-Perkin-Elmer RMS-4 mass spectrometer. The recorded $R_f$ values were determined by a standardized thin-layer chromatograph (TLC) procedure: 0.25-mm Brinkman silica gel HF eluting with cyclohexane–ethyl acetate (1:1). For preparative TLC, 2-mm Brinkman silica gel PF-254-366 plates were used, eluting with the stipulated solvent system. Elemental analyses were performed by Mr. R. Seab in these laboratories.

All reaction solvents were distilled from lithium aluminum hydride or sodium under nitrogen. Sodium hydride (57% oil dispersion) was initially washed with petroleum ether (bp 30–60 °C) and then dried in vacuo prior to the reaction.

Ethylene glycol and di-, tri-, and tetraethylene glycols were purchased from Aldrich Chemical and were distilled in vacuo prior to use. 3,6,9,12-Tetraoxa-1,14-tetradecanediol [pentaethylene glycol, bp 185–190 °C (0.15 mm) (lit.[13] bp 174–176 °C (0.14 mm)] and 3,6,9,12,15-pentaoxa-1,17-octadecanediol [hexaethylene glycol, bp 201–205 °C (0.7 mm) (lit.[13] bp 203.0–205.0 °C (0.3 mm)] were prepared according to the procedure of Perry and Hibbert.[13a]

Ethanedithiol, bis(2-mercaptoethyl) ether, and bis(2-mercaptoethyl) sulfide were purchased from Fairfield Chemical Co. and were used directly without further purification.

Although the noncyclized products could in most cases be isolated, in general complete characterization was undertaken only when they were a major product of the reaction. The cited yield data are based on analytically pure components and are not maximized.

**Reaction of 2,6-Dichloropyrazine with Diethylene Glycol. General Procedure.** To a suspension of oil-free sodium hydride (480 mg, 20 mmol) in anhydrous xylene (200 mL), diethylene glycol (1.10 g, 10 mmol) was added slowly with stirring under nitrogen. After 15

min, a solution of 2,6-dichloropyrazine (1.5 g, 10 mmol) in xylene (50 mL) was added, then the mixture was refluxed for 24 h. The reaction was cooled and the unreacted sodium hydride, if any, was carefully decomposed with water. The organic layer was separated, washed with water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford a viscous residue which was chromatographed (TLC), eluting two times with cyclohexane–ethyl acetate (1:1), to give the following components.

**Fraction A** gave unreacted 2,6-dichloropyrazine, mp 51–52 °C.

**Fraction B** afforded 2:2 macrocycle **5**, which was recrystallized from 95% ethanol as colorless plates: mp 137–138 °C; 75 mg (4%); $R_f$ 0.2; NMR ($CDCl_3$) δ 3.85 (t, β-$CH_2O$, $J$ = 5 Hz, 8 H), 4.5 (t, α-$CH_2O$, $J$ = 5 Hz, 8 H), 7.75 (s, 3,5-pyrazine-H, 4 H); IR ($CHCl_3$) 2950, 1560, 1440, 1350, 1300, 1220, 1060, 850 $cm^{-1}$.

Anal. Calcd for $C_{16}H_{20}N_4O_6$: C, 52.74; H, 5.49; N, 15.38; mol wt 364. Found: C, 52.47; H, 5.56; N, 15.26; mol wt (MS) $m/e$ 364 ($M^+$).

**Fraction C** yielded 3:3 macrocycle **6**, which was recrystallized from 95% ethanol as colorless needles: mp 111–112 °C; 90 mg (5%); $R_f$ 0.07; NMR ($CDCl_3$) δ 3.80 (t, β-$CH_2O$, $J$ = 5 Hz, 12 H), 4.42 (t, α-$CH_2O$, $J$ = 5 Hz, 12 H), 7.8 (s, 3,5-pyrazine-H, 6 H); IR ($CHCl_3$) 2900, 1590, 1540, 1300, 1280, 1180, 1050, 850 $cm^{-1}$.

Anal. Calcd for $C_{24}H_{30}N_6O_9$: C, 52.74; H, 5.49; N, 15.38; mol wt 546. Found: C, 52.42; H, 5.49; N, 15.42; mol wt (MS) $m/e$ 546 ($M^+$).

The combined baselines from the preparative plates were extracted with ethanol–chloroform (1:1). The residue was rechromatographed (TLC), eluting three times with cyclohexane–ethyl acetate (1:2) to afford the 4:4 macrocycle **7**, as a beige solid, which was recrystallized from 95% ethanol to give colorless needles: mp 115–116 °C; 55 mg (3%); $R_f$ 0.03; NMR ($CDCl_3$) δ 3.87 (t, β-$CH_2O$, $J$ = 5 Hz, 16 H), 4.4 (t, α-$CH_2O$, $J$ = 5 Hz, 16 H), 7.75 (s, 3,5-pyrazine-H); IR ($CHCl_3$) 2910, 1520, 1410, 1340, 1250, 1180, 1050, 850 $cm^{-1}$.

Anal. Calcd for $C_{32}H_{40}N_8O_{12}$: C, 52.74; H, 5.49; N, 15.38; mol wt 728. Found: C, 52.70; H, 5.59; N, 15.07; mol. wt. (MS) $m/e$ 728 ($M^+$).

**Diquaternization of 5 with 1,4-Diiodobutane.** A mixture of macrocycle **5** (370 mg, 1 mmol) and 1,4-diiodobutane (310 mg, 1 mmol) in ethanol (25 mL) was refluxed for 24 h. After cooling, a yellow solid, which separated, was filtered and washed several times with anhydrous ether and finally recrystallized from ethanol to afford cyclophane **40**, as yellow needles: mp 214 °C (dec), 500 mg (80%); NMR ($D_2O$) δ 3.95 (m, β-$CH_2O$; β-$CH_2$, 12 H), 4.60 (m, α-$CH_2O$, 8 H), 5.25 (m, α-$CH_2$, 4 H), 8.14 (s, 3,5-pyrazine-H, 4 H).

Anal. Calcd for $C_{20}H_{28}N_4O_6I_2$: C, 35.60; H, 4.15; N, 8.30. Found: C, 35.50; H, 4.20; N, 8.25.

The mother liquor after concentration gave a pale yellow crystalline mass corresponding to **41**: mp 198 °C (dec); 60 mg (5%); NMR ($D_2O$) δ 2.4 (m, β,γ-$CH_2$, 4 H), 3.9 (br t, β-$CH_2O$, δ-$CH_2$, 10 H), 4.62 (br t, α-$CH_2O$, 8 H), 5.2 (br t, α-$CH_2N^+$, 2 H), 7.65 (s, free pyrazine-ring H, 2 H), 8.12 (s, charged pyrazine-ring H, 2 H). Attempted recrystallization failed to afford an analytical sample.

**Reaction of 2,6-Dichloropyrazine with Triethylene Glycol.** The above general procedure was followed except for the substitution of triethylene glycol (10 mmol). The crude reaction mixture was chromatographed (TLC) eluting three times with cyclohexane–ethyl acetate (1:1) to afford the following fractions.

**Fraction A** afforded a small quantity (10 mg) of unreacted dichloropyrazine, mp 51–52 °C.

**Fraction B** afforded 6,6′-dichloro-2,2′-[oxytris(ethylenoxy)]dipyrazine (**12**) as colorless flakes (recrystallized from absolute ethanol): mp 58–60 °C; 100 mg (2%); $R_f$ 0.4; NMR δ 3.7 (s, γ-$CH_2O$, 4 H), 3.85 (t, β-$CH_2O$, $J$ = 5 Hz, 4 H), 4.55 (t, α-$CH_2O$, $J$ = 5 Hz, 4 H), 8.05 (s, 3-pyrazine-H, 2 H), 8.10 (s, 5-pyrazine-H, 2 H); IR ($CHCl_3$) 2900, 1570, 1540, 1430, 1410, 1360, 1300, 1175, 1125, 1100, 1050, 1000, 990, 880, 750 $cm^{-1}$.

Anal. Calcd for $C_{14}H_{16}N_4O_4Cl_2$: C, 44.80; H, 4.26; N, 14.93; mol wt 375. Found: C, 44.71; H, 4.26; N, 14.74; mol wt (MS) $m/e$ 375 ($M^+$).

**Fraction C** gave 1:1 macrocycle **10** as a white solid, which was recrystallized from 95% ethanol as colorless needles: mp 128–130 °C; 80 mg (2.5%); $R_f$ 0.18; NMR ($CDCl_3$) δ 3.65 (s, γ-$CH_2O$, 4 H), 3.8 (t, β-$CH_2O$, $J$ = 5 Hz, 4 H), 4.6 (t, α-$CH_2O$, $J$ = 5 Hz, 4 H), 7.7 (s, 3,5-pyrazine-H, 2 H); IR ($CHCl_3$) 2930, 1580, 1540, 1480, 1340, 1210, 1180, 1050, 920, 830 $cm^{-1}$.

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.19; N, 12.38; mol wt 226. Found: C, 53.01; H, 6.23; N, 12.24; mol wt (osmometry) 229.5 (average).

The methiodide of **10** was prepared: a mixture of **10** (113 mg) was heated with methyl iodide (0.5 mL) in a sealed tube for 8 h at 90 °C. Excess of methyl iodide was evaported and the residue was crystallized from ethanol as pale yellow needles: mp 203 °C (dec); 150 mg (90%); NMR ($D_2O$) δ 3.85 (s, γ-$CH_2O$, 4 H), 3.95 (m, β-$CH_2O$–, 4 H), 4.3 (s, N-Me, 3 H), 4.95 (t, α-$CH_2O$, $J$ = 5 Hz, 4 H), 8.15 (s, 3,5-pyrazine-H, 2 H).

Anal. Calcd for $C_{11}H_{17}N_2O_4I$: C, 35.86; H, 4.61; N, 7.60. Found: C, 35.70; H, 4.72; N, 7.47.

**Fraction D** yielded 2:2 macrocycle **11**, which was recrystallized from 95% ethanol as colorless needles: mp 138–140 °C; 200 mg (8%); $R_f$ 0.12; NMR ($CDCl_3$) δ 3.70 (s, γ-$CH_2O$, 8 H), 3.85 (t, β-$CH_2O$, $J$ = 5 Hz, 8 H), 4.5 (t, α-$CH_2O$, $J$ = 5 Hz, 8 H), 7.8 (s, 3,5-pyrazine-H, 4 H); IR ($CHCl_3$) 2900, 1580, 1500, 1450, 1400, 1300, 1280, 1160, 1110, 950, 850 $cm^{-1}$.

Anal. Calcd for $C_{20}H_{28}N_4O_8$: C, 53.09; H, 6.19; N, 12.38; mol wt 452. Found: C, 53.02; H, 6.53; N, 12.20; mol wt (osmometry) 436 (av).

The dimethiodide **39** was prepared: a mixture of **11** (113 mg) and methyl iodide (0.5 mL) was heated in a sealed tube for 8 h. The crystalline residue was recrystallized from ethanol as yellow needles: mp 211 °C (dec); 132 mg (75%); NMR ($D_2O$) δ 3.75 (s, γ-$CH_2O$, 8 H), 3.9 (m, β-$CH_2O$, 8 H), 4.45 (s, N-$CH_3$, 6 H), 4.75 (t, α-$CH_2O$, $J$ = 5 Hz, 8 H), 8.37 (s, 3,5-pyrazine-H, 4H); IR ($CHCl_3$) 2950, 1540, 1490, 1450, 1370, 1320, 1240, 1210, 1150, 1050, 940, 830 $cm^{-1}$.

Anal. Calcd for $C_{22}H_{34}N_4O_8I_2$: C, 35.86; H, 4.61; N, 7.60. Found: C, 35.72; H, 4.48; N, 7.52.

**Reaction of 2,6-Dichloropyrazine with Tetraethylene Glycol.** The general procedure was followed except for the substitution of tetraethylene glycol (1.94 g, 10 mmol). The crude reaction mixture was chromatographed (TLC), eluting four times with cyclohexane–ethyl acetate (1:1), to give the following fractions.

**Fraction A** afforded unreacted 2,6-dichloropyrazine, mp 51–52 °C.

**Fraction B** gave 1:1 macrocycle **13**, which was recrystallized from ethanol as colorless plates: mp 86–87 °C; 100 mg (3%); $R_f$ 0.12; NMR ($CDCl_3$) δ 3.54 (m, γ-$CH_2O$, 8 H), 3.85 (t, β-$CH_2O$, $J$ = 5 Hz, 4 H), 4.61 (t, α-$CH_2O$, $J$ = 5 Hz, 4 H), 7.75 (so 3,5-pyrazine-H, 2 H); IR ($CHCl_3$) 2910, 1545, 1350, 1280, 1145, 1050, 940, 850 $cm^{-1}$.

Anal. Calcd for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.66; N, 10.37; mol wt 270. Found: C, 53.30; H, 6.81; N, 10.10; mol wt (osmometry) 272.8 (av).

The monomethiodide of **13** was prepared: macrocycle **13** (270 mg, 10 mmol) was heated with excess methyl iodide in a sealed tube at 80 °C for 8 h. Excess methyl iodide was evaporated, and the yellow residue was washed several times with anhydrous ether to remove unreacted starting materials and then recrystallized from ethanol to afford **35** as yellow needles: mp 186–189 °C (dec); 400 mg (95%); NMR ($CDCl_3$) δ 3.58 (s, γ-$CH_2O$, 8 H), 3.85 (m, β-$CH_2O$, 4 H), 4.6 (s, N-Me, 3 H), 4.75 (m, α-$CH_2O$, 4 H), 8.35 (s, 3,5-pyrazine-H, 2 H); IR ($CHCl_3$) 2950, 1525, 1500, 1450, 1325, 1230, 1110, 1052, 950, 850 $cm^{-1}$.

Anal. Calcd for $C_{13}H_{21}N_2O_5I$: C, 37.86; H, 5.09; N, 6.79. Found: C, 37.70; H, 5.13; N, 6.69.

**Fraction C** was initially isolated as an oil; however, upon dissolution in alcohol and prolonged standing (ca. 1 week) 2:2 macrocycle **14** crystallized: mp 75–76 °C; 75 mg (3%); $R_f$ 0.05; NMR ($CDCl_3$) δ 3.62 (m, γ-$CH_2O$, 16 H), 3.8 (t, β-$CH_2O$, $J$ = 5 Hz, 8 H), 4.4 (t, α-$CH_2O$, $J$ = 5 Hz, 8 H), 7.75 (s, 3,5-pyrazine-H, 4 H).

Anal. Calcd for $C_{24}H_{36}N_4O_{10}$: C, 53.33; H, 6.66; N, 10.37; mol wt 540. Found: C, 53.23; H, 6.63; N, 10.16; mol wt (osmometry) 540 (av).

**Reaction of 2,6-Dichloropyrazine with Pentaethylene Glycol.** The general procedure was followed except for the substitution of pentaethylene glycol (2.38 g, 10 mmol). After standard workup procedures, the reaction residue was chromatographed (TLC), eluting four times with cyclohexane–ethyl acetate (1:1), to afford the following fractions.

**Fraction A** gave unreacted 2,6-dichloropyrazine, mp 51–52 °C.

**Fraction B** was recrystallized from ethanol to afford 1:1 macrocycle **13** as colorless plates: mp 86–87 °C; 50 mg (1%).

**Fraction C** afforded after recrystallization from 95% ethanol the desired 1:1 macrocycle **17**: mp 72–74 °C; 100 mg (4%); $R_f$ 0.11; NMR ($CDCl_3$) δ 3.55 (br d, γ,ε-$CH_2O$, 12 H), 3.85 (t, β-$CH_2O$, $J$ = 5 Hz, 4 H), 4.5 (t, α-$CH_2O$–, $J$ = 5 Hz, 4 H), 7.72 (s, 3,5-pyrazine-H, 2 H); IR ($CHCl_3$) 2950, 1600, 1540, 1450, 1430, 1300, 1250, 1175, 1050, 940, 840 $cm^{-1}$.

Anal. Calcd for $C_{14}H_{22}N_2O_6$: C, 53.50; H, 7.00; N, 8.91; mol wt 314. Found: C, 53.21; H, 6.98; N, 8.63; mol wt (MS) $m/e$ 314 ($M^+$).

The monomethiodide **36** was prepared from the macrocycle **17** (160 mg) with methyl iodide (0.5 mL) by heating in a sealed tube on a water bath for 5 h. After removing unquaternized macrocycle by repeated washing with anhydrous ether, a residue was recrystallized from ethanol, affording **36** as yellow needles: mp 204 °C (dec); 180 mg (70%); NMR ($D_2O$) 3.6 (br d, γ,ε-$CH_2O$, 12 H), 3.95 (t, β-$CH_2O$, $J$ = 5 Hz, 4 H), 4.65 (t, α-$CH_2O$–, $J$ = 5 Hz, 4 H), 8.35 (s, 3,5-Pyr-H, 2 H).

Anal. Calcd for $C_{15}H_{25}N_2O_6I$: C, 39.47; H, 5.48; N, 6.14. Found: C, 39.21; H, 5.56; N, 6.10.

The baseline was extracted with a solvent mixture of chloroform

and ethanol (1:1) and the residue rechromatographed (TLC), eluting four times with cyclohexane–ethyl acetate (1:2), to afford 2:2 macrocycle **18** as colorless crystalline plates: mp 80–81 °C; 60 mg (2%); $R_f$ 0.04; NMR ($CDCl_3$) $\delta$ 3.60 (br d, $\gamma,\epsilon$-$CH_2O$, 24 H), 3.85 (t, $\beta$-$CH_2O$, $J$ = 5 Hz, 8 H), 4.5 (t, $\alpha$-$CH_2O$–, $J$ = 5 Hz, 8 H), 7.80 (s, 3,5-pyrazine-H, 4 H); IR ($CHCl_3$) 2900, 1600, 1570, 1440, 1300, 1230, 1100, 1070, 1050, 950, 840 $cm^{-1}$.

Anal. Calcd for $C_{28}H_{44}N_4O_6$: C, 53.50; H, 7.00; N, 8.91; mol wt 628. Found: C, 53.36; H, 8.72; mol wt (osmometry) 600 (av).

**Reaction of 2,6-Dichloropyrazine with Hexaethylene Glycol.** The general procedure was followed except for the substitution of hexaethylene glycol (2.82 g, 10 mmol). The reaction residue, after standard workup, was chromatographed (TLC), eluting two times with cyclohexane–ethyl acetate (1:1). The following fractions were isolated and characterized.

**Fraction A** gave unreacted 2,6-dichloropyrazine, mp 52 °C.

**Fraction B** afforded 30 mg of a crystalline compound, which corresponded physically and spectrally to 1:1 macrocycle **10**, mp 130–131 °C.

**Fraction C** afforded 1:1 macrocycle **13**, which was recrystallized from 95% ethanol as colorless plates: mp 86–87 °C; 30 mg (<1%).

The residual baseline was extracted with chloroform–ethanol (1:1), and then after concentration the residue was rechromatographed (TLC), eluting three times with cyclohexane–ethyl acetate (1:3) to give the following fractions.

**Fraction D** was recrystallized from petroleum ether (bp 60–90 °C), affording colorless needles of 1:1 macrocycle **19:** mp 59–60 °C; 500 mg (15%); $R_f$ 0.08; NMR ($CDCl_3$) $\delta$ 3.65 (m, $\gamma,\omega$-$CH_2O$, 16 H), 3.82 (t, $\beta$-$CH_2O$, $J$ = 5 Hz, 4 H), 4.52 (t, $\alpha$-$CH_2O$, $J$ = 5 Hz, 4 H), 8.71 (s, 3,5-pyrazine-H, 2 H); IR ($CHCl_3$) 2900, 1590, 1530, 1440, 1380, 1270, 1180, 1025, 950, 850 $cm^{-1}$.

Anal. Calcd for $C_{16}H_{26}N_2O_7$: C, 53.63; H, 7.26; mol wt 358. Found: C, 53.45; H, 7.42; mol wt (MS) $m/e$ 358 ($M^+$).

**Fraction E** was obtained as colorless plates (recrystallized from ethanol) corresponding to 2:2 macrocycle **20:** mp 68–69 °C; 80 mg (2%); $R_f$ 0.03; NMR ($CDCl_3$) $\delta$ 3.6 (m,$\gamma,\omega$-$CH_2O$, 32 H), 3.8 (t, $\beta$-$CH_2O$–, $J$ = 5 Hz, 8 H), 4.5 (t, $\alpha$-$CH_2O$–, $J$ = 5 Hz, 8 H), 8.75 (s, 3,5-pyrazine-H, 4 H); IR ($CHCl_3$) 2900, 1590, 1540, 1425, 1320, 1250, 1200, 1145, 1100, 1050, 1000, 930, 850, 750 $cm^{-1}$.

Anal. Calcd for $C_{32}H_{52}N_4O_{14}$: C, 53.63; H, 7.26; N, 7.92; mol wt 716. Found: C, 53.39; H, 7.35; N, 7.63; mol wt (osmometry) 678 (av).

**Reaction of 2,6-Dichloropyrazine with Ethylene Glycol. Method A. With Sodium Hydride.** To a stirred suspension of oil-free sodium hydride (2 g, 80 mmol) in anhydrous xylene (300 mL), ethylene glycol (2.5 g, 40 mmol) was added dropwise under argon. The mixture was stirred for 30 min, and then a xylene solution of 2,6-dichloropyrazine (6 g, 40 mmol) was added over 10 min. The mixture was refluxed for 24 h and worked up as previously described. The gummy residue was chromatographed (TLC), eluting two times with cyclohexane–ethyl acetate (1:1), affording the following fractions.

**Fraction A** gave unreacted 2,6-dichloropyrazine, mp 52 °C.

**Fraction B** was recrystallized from 95% ethanol as colorless needles of 6,6′-dichloro-2,2′-(ethylenedioxy)dipyrazine (**21**): mp 125–126 °C; 150 mg (3%); $R_f$ 0.5; NMR ($CDCl_3$) $\delta$ 4.75 (s, –$OCH_2CH_2O$–, 4 H), 8.15 (s, 3,5-pyrazine-H, 4 H); IR ($CHCl_3$) 2900, 1550, 1425, 1400, 1300, 1175, 1075, 925 $cm^{-1}$.

Anal. Calcd for $C_{10}H_8N_4O_2Cl_2$: C, 41.11; H, 2.78; N, 19.51; mol wt 287. Found: C, 41.15; H, 2.72; N, 19.49; mol wt (MS) 287 ($M^+$).

**Fraction C** afforded 2,6-bis(6′-chloro-2′-pyrazyloxyethylenoxy)-pyrazine (**22**) as colorless needles (95% ethanol): mp 115–116 °C; 100 mg (2%); $R_f$ 0.35; NMR ($CDCl_3$) $\delta$ 4.7 (s, –$OCH_2CH_2O$–, 8 H), 7.82 (s, 3,5-pyrazine-H, 2 H), 8.2 (s, 3′,5′-pyrazine-H, 4 H); IR ($CHCl_3$) 2900, 1550, 1500, 1400, 1300, 1250, 1175, 1000, 950, 850 $cm^{-1}$.

Anal. Calcd for $C_{16}H_{14}N_6O_4Cl_2$: C, 45.17; H, 3.29; N, 19.76; mol wt 425. Found: C, 45.39; H, 3.18; N, 19.72; mol wt (MS) $m/e$ 425 ($M^+$).

**Fraction D** was shown to be 2-(6′-chloro-2′-pyrazyloxy)ethanol (**9**), as a brown viscous oil: bp 103–104 °C (0.1 mm, short path); 250 mg (4%); $R_f$ 0.2; NMR ($CDCl_3$) $\delta$ 3.5 [s, –OH (exchanged with $D_2O$), 1 H], 3.95 (m, $\beta$-$CH_2O$, 2 H), 4.45 (m, $\alpha$-$CH_2O$, 2 H), 8.15 (s, 3′,5′-pyrazine-H, 2 H); IR (neat) 3150, 2975, 1525, 1475, 1300, 1275, 1145, 1050, 945, 840 $cm^{-1}$.

Anal. Calcd for $C_6H_7N_2O_2Cl$: C, 41.26; H, 4.01; N, 16.04; mol wt 174.5. Found: C, 41.03; H, 4.16; N, 15.87; mol wt (osmometry) 172 (av).

**Fraction E** afforded the tetrapyrazyl dichloride **23** as lemon-yellow plates, which were recrystallized from 95% ethanol: mp 143–145 °C; 60 mg (1%); $R_f$ 0.17; NMR ($CDCl_3$) $\delta$ 4.6 (s, –$OCH_2CH_2O$–, 12 H), 7.85 (s, 3′,5′-pyrazine-H, 4 H), 8.2 (s, 3,5-pyrazine-H, 4 H); IR ($CHCl_3$) 2900, 1550, 1500, 1450, 1300, 1250, 1155, 1045, 1000, 850 $cm^{-1}$.

Anal. Calcd for $C_{22}H_{20}N_8O_6Cl_2$: C, 46.89; H, 3.55; N, 19.89; mol wt 563. Found: C, 46.75; H, 3.58; N, 19.61; mol wt (MS) $m/e$ 563 ($M^+$).

**Fraction F** was isolated as a viscous oil shown to be **24:** bp 125–126 °C (0.8 mm, short path); 125 mg (2%); $R_f$ 0.10; NMR ($CDCl_3$) $\delta$ 3.7 [s, –OH (exchanged with $D_2O$), 1 H], 3.90 (t, $\beta$-$CH_2O$, $J$ = 4 Hz, 2 H), 4.45 (t, $\alpha$-$CH_2O$, $J$ = 4 Hz, 2 H), 4.75 (s, –$OCH_2CH_2O$–, 4 H), 7.85 (s, 3,5-pyrazine-H, 2 H), 8.2 (s, 3′,5′-pyrazine, 2 H); IR (neat) 3400, 2900, 1575, 1525, 1400, 1300, 1000, 850 $cm^{-1}$.

Anal. Calcd for $C_{12}H_{13}N_4O_4Cl$: C, 46.09; H, 4.19; mol wt 312.5. Found: C, 45.96; H, 4.17; mol wt (osmometry) 320 (av).

**Fraction G** was recrystallized from 95% ethanol as a microcrystalline solid and shown to be **25:** mp 125–127 °C; 200 mg (3%); $R_f$ 0.07; NMR ($CDCl_3$) $\delta$ 3.75 [s, –OH (exchanged with $D_2O$), 1 H], 3.95 (m, $\beta$-$CH_2O$, 2 H), 4.4 (m, $\alpha$-$CH_2O$, 2 H), 4.55 (s, –$OCH_2CH_2O$–, 8 H), 7.8 (s, 3,3′,5,5′-pyrazine-H, 4 H), 8.15 (s, 3″,5″-pyrazine-H, 2 H); IR ($CHCl_3$) 3300, 2900, 1525, 1475, 1375, 1250, 1150, 1000, 740 $cm^{-1}$.

Anal. Calcd for $C_{18}H_{19}N_6O_6Cl$: C, 47.90; H, 4.25; N, 18.64; mol wt 450.5. Found: C, 47.84; H, 4.17; N, 18.49; mol wt (osmometry) 444 (av).

**Method B. With Lithium Hydride.** To a suspension of lithium hydride (0.64 g, 80 mmol) in anhydrous xylene (400 mL), ethylene glycol (2.5 g, 40 mmol) was added dropwise. To this warm suspension, 2,6-dichloropyrazine (6 g, 40 mmol) was added and the mixture was refluxed for 24 h. The workup procedure mimicked the general procedure, and the crude reaction products were chromatographed (TLC) affording the same noncyclic products, except product distribution: **21** (mp 125–126 °C; 5%), **22** (mp 115–116 °C; 1%), **23** (mp 143–145 °C; 2%), **9** [bp 103–104 °C (0.1 mm, short path); 5%], and **25** (mp 125–127 °C; 1%). Compound **24** was not isolated in this reaction.

**Reaction of 2,6-Dichloropyrazine with Bis(2-mercaptoethyl) Ether.** The above general procedure was followed except for the substitution of bis(2-mercaptoethyl) ether (10 mmol) with 2,6-dichloropyrazine (10 mmol). After the workup, the residue was chromatographed (TLC), eluting two times with cyclohexane–ethyl acetate (4:1), to afford two macrocycles along with starting material.

**Fraction A** gave a small amount (<20 mg) of unreacted 2,6-dichloropyrazine: mp 52 °C.

**Fraction B** afforded 1:1 macrocycle **26a** as colorless plates (recrystallized from ethanol): mp 118–119 °C; 100 mg (4%); $R_f$ 0.6; NMR ($CHCl_3$) $\delta$ 3.25 (t, $\beta$-$CH_2O$, $J$ = 4 Hz, 4 H), 3.91 (t, $\alpha$-$CH_2O$, $J$ = 4 Hz, 4 H), 8.17 (s, 3,5-pyrazine-H, 2 H); IR ($CHCl_3$) 2850, 1480, 1390, 1180, 1140, 1100, 990, 840 $cm^{-1}$.

Anal. Calcd for $C_8H_{10}N_2S_2O$: C, 44.85; H, 4.67; N, 13.08; mol wt 214. Found: C, 44.56; H, 4.72; N, 12.86; mol wt (MS) $m/e$ 214 ($M^+$).

**Fraction C** was recrystallized from 95% ethanol to afford 2:2 macrocycle **27** as colorless needles: mp 155–156 °C; 140 mg (6%); $R_f$ 0.5; NMR ($CDCl_3$) $\delta \sim$ 3.5 (m, $\alpha$- and $\beta$-$CH_2O$, 16 H); 8.1 (s, 3,5-pyrazine-H, 4 H); IR ($CHCl_3$) 2900, 1500, 1450, 1250, 1140, 1080, 990, 830 $cm^{-1}$.

Anal. Calcd for $C_{16}H_{20}N_4S_4O_2$: C, 44.85; H, 4.67; N, 13.08; mol wt 428. Found: C, 44.80; H, 4.92; N, 12.83; mol wt (osmometry) 430 (av).

**Reaction of 2,6-Dichloropyrazine with Bis(2-mercaptoethyl) Sulfide.** The general procedure was followed except for the substitution of bis(2-mercaptoethyl)sulfide (1.54 g, 10 mmol). The crude reaction mixture was chromatographed (TLC), eluting two times with cyclohexane–ethyl acetate (20:1) to afford the major fast-moving 2[2-[2-(6-chloropyrazylthio)]thioethoxy]ethanethiol (**28**) as a colorless viscous oil: bp 145 °C (0.5 mm; short path); 210 mg (8%); $R_f$ 0.85; NMR ($CDCl_3$) $\delta$ 1.77 [m, –SH (exchanged slowly with $D_2O$), 1 H], 2.8 (m, $SCH_2CH_2SCH_2$, 6 H), 3.35 (m, S-$\alpha$-$CH_2$, 2 H), 8.18 (s, 3-pyrazine-H, 1 H), 8.30 (s, 5-pyrazine-H, 1 H), IR (neat) 2900, 2550, 1540, 1490, 1400, 1350, 1260, 1190, 1150, 1100, 990, 860, 830, 740 $cm^{-1}$.

Anal. Calcd for $C_8H_{11}N_2S_3Cl$: C, 36.02; H, 4.12; N, 10.60; mol wt 266.5. Found: C, 35.93; H, 4.06; N, 10.38; mol wt (osmometry) 272 (av).

The baseline was extracted with a mixture of chloroform–ethanol (1:1) and after concentration the residue was rechromatographed (TLC), eluting three times with cyclohexane–ethyl acetate (10:1) to afford the following fractions.

**Fraction B** afforded **29** as a viscous oil: bp 162 °C (0.5-mm short path); 80 mg (2%); $R_f$ 0.70; NMR ($CDCl_3$) $\delta$ 1.71 [m, –SH (exchanged slowly with $D_2O$), 1 H], 2.9 [m, $-CH_2S(CH_2)_2S(CH_2)_2-$, 10 H], 3.35 (m, $\alpha$-$SCH_2$, 2 H), 8.25 (s, 3-pyrazine-H, 1 H), 8.35 (s, 5-pyrazine-H, 1 H), IR (neat) 2900, 2550, 1490, 140, 1400, 1375, 1350, 1260, 1190, 1120, 1040, 990, 850, 830, 750 $cm^{-1}$.

Anal. Calcd for $C_{10}H_{15}N_2S_4Cl$: C, 36.75; H, 4.58; N, 8.57; mol wt 326.5. Found: C, 37.00; H, 4.49; N, 8.68; mol wt (osmometry) 338 (av).

**Fraction C** afforded **30** as a viscous oil: bp 187 °C (1-mm short path); 55 mg (2%); $R_f$ 0.65; NMR ($CDCl_3$) 2.9 (m, $CH_2SCH_2$, 8 H), 3.4

(m, α-$SCH_2$, 4 H), 8.19 (s, 3-pyrazine-H, 2 H), 8.36 (s, 5-pyrazine-H, 2 H); IR (neat) 2910, 1700, 1500, 1475, 1390, 1350, 1250, 1175, 1125, 990, 860, 830, 750 $cm^{-1}$.

Anal. Calcd for $C_{14}H_{16}N_4S_4Cl_2$: C, 38.10; H, 3.64; N, 12.75; mol wt 439. Found: C, 38.35; H, 3.71; N, 12.45; mol wt (osmometry) 446 (av).

**Reaction of 2,6-Dichloropyrazine with Ethanedithiol.** The general procedure was followed except for the substitution of ethanedithiol (940 mg, 10 mmol). The gummy residue, after usual workup, was chromatographed (TLC), eluting with cyclohexane–ethyl acetate (4:1) to afford the following fractions.

**Fraction A** gave 2-(6′-chloro-2′-pyrazylthio)ethanethiol (**32**) as pale yellow microcrystals (recrystallized from 95% ethanol): mp 91 °C; 70 mg (4%); $R_f$ 0.52; NMR ($CDCl_3$) δ 1.7 [t, –SH (exchanged slowly with $D_2O$), 1 H], 2.9 (t, β-$CH_2O$–, $J$ = 5 Hz, 2 H), 3.4 (t, α-$CH_2O$–, $J$ = 5 Hz, 2 H), 8.15 (s, 3-pyrazine-H, 1 H), 8.35 (s, 5-pyrazine-H, 1 H); IR ($CHCl_3$) 2900, 1480, 1390, 1350, 1340, 1250, 1175, 1150, 1125, 1080, 990, 860, 830, 720 $cm^{-1}$.

Anal. Calcd for $C_6H_7N_2S_2Cl$: C, 34.86; H, 3.38; N, 14.04; mol wt 206.5. Found: C, 34.75; H, 3.21; N, 13.80; mol wt (osmometry) 208 (av).

**Fraction B** was recrystallized from ethanol as pale yellow needles of 6,6′-dichloro-2,2′-(ethylenedithio)dipyrazine (**33**): mp 106 °C; 100 mg (6%); $R_f$ 0.43; NMR ($CDCl_3$) δ 4.55 (s, $SCH_2CH_2S$, 4 H), 8.4 (s, 3,3′-pyrazine-H, 2 H), 8.5 (s, 5,5′-pyrazine-H, 2 H); IR ($CHCl_3$) 2980, 1540, 1500, 1375, 1175, 1150, 1125, 990, 960, 830, 740 $cm^{-1}$.

Anal. Calcd for $C_{10}H_8H_{N4}S_2Cl_2$: C, 37.61; H, 2.50; N, 17.55; mol wt 319. Found: C, 37.42; H, 2.46; N, 17.46; mol wt (osmometry) 322 (av).

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