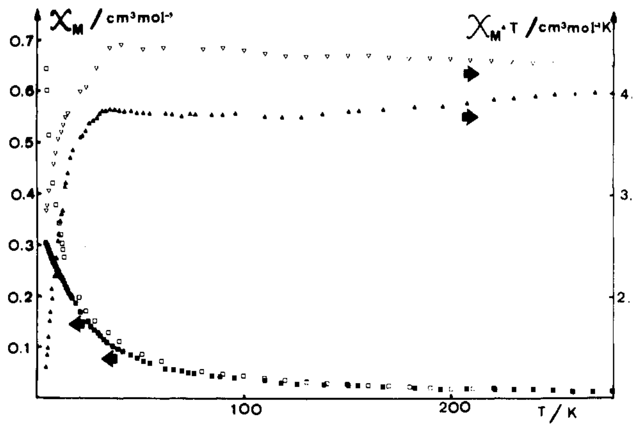

Figure 4. Temperature dependence of the magnetic susceptibility, χ_m, and of the product χ_mT for the compounds $\{NiMn(S_2C_2O_2)_2(H_2O)_{7.5}\}_\infty$, (Ni(II)-Mn(II)), and $\{CuMn(S_2C_2O_2)_2(H_2O)_{7.5}\}_\infty$, (Cu(II)-Mn(II)). The molar weight chosen is the weight of the above dimeric entities. Diamagnetic corrections were evaluated at 280 × 10^{-6} and 270 × 10^{-6} cm³ mol⁻¹, respectively. Ni(II)-Mn(II): χ_m (□), χ_mT (▽); Cu(II)-Mn(II): χ_m (■), χ_mT (▲).

S(2)-Ni-S(4) = 178.5 (3)°, and S(3)-Ni-S(4) = 92.5 (2)° and S(1)-Cu-S(2) = 91.9 (2)°, S(1)-Cu-S(3) = 178.0 (3)°, S(1)-Cu-S(4) = 89.1 (2)°, S(2)-Cu-S(3) = 87.7 (2)°, S(2)-Cu-S(4) = 177.5 (3)°, and S(3)-Cu-S(4) = 91.5 (2)°. The manganese atoms stand back from each side of the glide planes (y = 0.3512 (1) in both compounds) and are heptacoordinated to oxygen atoms located at the vertices of a nearly regular pentagonal bipyramid: four oxygen atoms from two dithiooxalate groups and one from water molecule w(3) are equatorial (69.0 (4)° ≤ O_{eq}-Mn-O_{eq} ≤ 75.9 (4)° in **1** and 69.0 (5)° ≤ O_{eq}-Mn-O_{eq} ≤ 75.7 (5)° in **2**; $\sum(O_{eq}\text{-Mn-}O_{eq})$ = 360.5 (20)° in both compounds); the axial positions are occupied by water molecules w(1) and w(2) (O_{ax}-Mn-O_{ax} = 178.0 (4)° in **1** and 178.4 (5)° in **2**; 86.1 (4)° ≤ O_{ax}-Mn-O_{eq} ≤ 94.2 (4)° in **1** and 86.1 (5)° ≤ O_{ax}-Mn-O_{eq} ≤ 95.0 (5)° in **2**. The Mn-O bond lengths and the interatomic distances in the dithiooxalate groups do not differ significantly in either compound (Figure 3). Within a chain, the atoms of the dithiooxalate groups, water molecules w(3), and nickel (copper) and manganese are almost coplanar with a mean plane approximately parallel to (10$\bar{2}$). Within a layer of chains, the planar groups NiS_4 or CuS_4 form stacks in which each of them is staggered with respect to the next one and is nearly perpendicular to the stacking direction [001]. The Ni-Ni and Cu-Cu separations are equal to 3.662 (1) and 3.681 (1) Å, respectively. The closest S-S separations between two successive chains range from 3.913 (7) to 3.981 (6) Å in **1** and from 3.917 (9) to 3.951 (9) Å in **2** and are therefore markedly larger than twice the sulfur van der Waals radius (1.85 Å). On the other hand, weak interchain hydrogen bonds involving water molecules w(1), w(2), and w(3) and oxygen atoms O(3), O(1), and O(2) are highly probable: O_w-O = 2.77 (2), 2.81 (2), and 2.78 Å in **1** and 2.77 (2), 2.87 (2), and 2.75 (2) Å in **2**; however, this point cannot be discussed further since the hydrogen atoms were not located. The shortest contacts between a layer of chains and a layer of water molecules involve only water molecules: 2.76 (2) Å ≤ O_w-O_w ≤ 2.81 (2) Å in **1** and 2.71 (2) Å ≤ O_w-O_w ≤ 2.86 (2) Å in **2**. Within a layer of water molecules the shortest O-O distances range from 2.65 (2) to 2.86 (2) Å in **1** and from 2.58 (2) to 2.84 (2) Å in **2**.

The susceptibility vs. temperature curves of the Ni(II)-Mn(II) and Cu(II)-Mn(II) systems are shown in Figure 4. The magnetic behavior of Ni(II)-Mn(II) follows the Curie law expected for isolated Mn(II) ions down to 35 K (χ_mT = 4.3-4.5 cm³ mol⁻¹ K), in agreement with the planar surrounding of diamagnetic nickel(II) ions by sulfur. The decrease of χ_mT below 35 K could be due to the effects of a weak antiferromagnetic interaction or zero-field splitting of Mn(II) in heptacoordinated symmetry.

The magnetic behavior of Cu(II)-Mn(II) is more peculiar. The curves χ_m and χ_mT seem to look like those of Ni(II)-Mn(II) but the values are quite different: at 300 K, χ_mT is smaller (4.0 cm³ mol⁻¹ K) than expected for isolated Cu(II) and Mn(II) ions and even smaller than the value found for the Ni(II)-Mn(II) system. χ_mT very sharply decreases upon cooling from 300 to 30 K and then sharply decreases below 30 K to χ_mT = 1.3 cm³ mol⁻¹ K. These values and this behavior suggest that Cu(II) and Mn(II) are antiferromagnetically coupled. A complete interpretation of these magnetic data in terms of magnitude of interaction is not yet feasible. Indeed, the theoretical expression for the magnetic susceptibility of a chain of alternating $^1/_2$-$^5/_2$ spins has never been derived. Nevertheless, if the interaction between nearest neighbor Cu(II) and Mn(II) atoms is antiferromagnetic, the ground state of the chain is nonmagnetic and χ_mT should decrease continuously down to zero upon cooling to very low temperatures. This behavior contrasts with what is expected for an A-B heterobinuclear complex with $S_A = ^1/_2$ and $S_B = ^5/_2$. In this latter case, when the temperature is low enough for the $S = 3$ state to be totally depopulated, χ_mT is constant and equal to $2N\beta^2g^2/k$ (i.e., 3.0 cm³ mol⁻¹ K if $g = 2$).

This preliminary work demonstrates the feasibility of preparing structurally ordered magnetic bimetallic chains, in spite of the kinetic and entropic hindrances. Our groups are now engaged in further studies along similar lines.

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Supplementary Material Available: Listings of atomic positional and thermal parameters for $NiMn(S_2C_2O_2)_2(H_2O)_{7.5}$ and $CuMn(S_2C_2O_2)_2(H_2O)_{7.5}$ (2 pages). Ordering information is given on any current masthead page.

Synthesis of Macrocyclic Peptide Thiolactones as Models of the Metastable Binding Sites of α_2-Macroglobulin and Complement Protein C3b

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A macrocyclic thiolactone ring is common to the metastable binding sites of two serum proteins, the protease inhibitor α_2-macroglobulin[1,2] and the complement component C3b.[3] As shown in structure **1**, the macrocycle is believed to be a derivative of 1-thia-5,8,11-triazacyclopentadecane having a novel thiolester bond between the cysteine thiol group and the side-chain carboxyl group of the second glutamic acid residue of Cys-Gly-Glu-Glu. The 15-membered ring contains three amide bonds, one thioester bond, and three chiral centers (3*R*, 9*S*, 12*S*; Cys and both Glu residues in the L configuration). This paper describes the synthesis and characterization of three macrocyclic peptide thiolactones (**1b,d,f**) as initial models of these metastable binding sites.

Proteolytic cleavage of complement protein C3 into C3a anaphylatoxin and the activated protein C3b exposes both the COOH-terminal inflammatory site[4] of C3a and the internal

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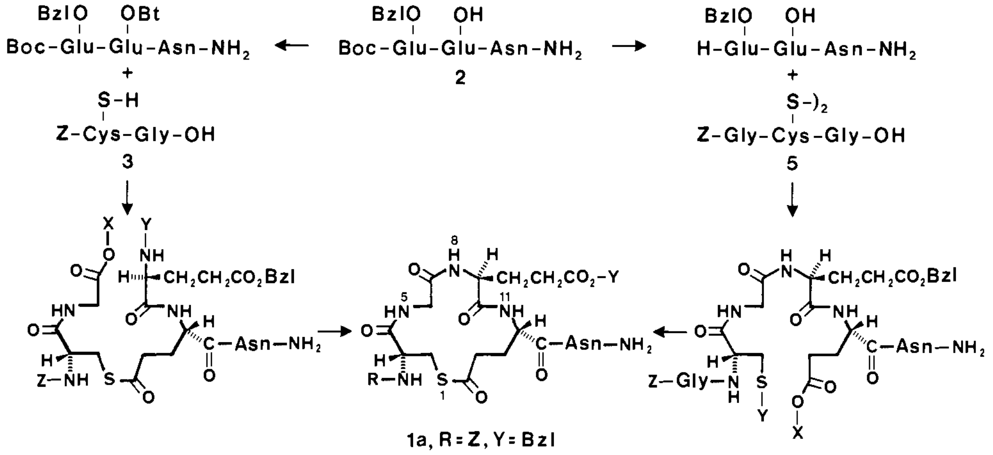
Scheme I



4a, X = H, Y = Boc
4b, X = Tcp, Y = Boc
4c, X = Tcp, Y = H

1a, R = Z, Y = Bzl
1b, R = Y = H
1c, R = Z-Gly, Y = Bzl
1d, R = H-Gly, Y = H
1e, R = Ac-Gly, Y = Bzl
1f, R = Ac-Gly, Y = H

6a, X = H, Y =)$_2$
6b, X = Y = H
6c, X = Bt, Y = H

metastable binding site[3,5] of C3b. Nascent C3b can react with a hydroxyl group on the surface of a receptive cell or other biological particle to form a covalent ester bond.[6] Similarly, proteolytic cleavage of α_2-macroglobulin exposes a metastable binding site, which can covalently react with the protease.[1] The metastable binding sites of both serum proteins contain a common 7-residue segment,[2,3]-Gly-Cys-Gly-Glu-Glu-Asn-Met-.

Six macrocyclic thiolactones (**1a–f**) containing five or six of these residues were assembled from glycine and L-amino acids by two synthetic strategies, which differed by the type of bond (amide, thiolester) formed on ring closure. Common intermediate **2** was prepared by mixed anhydride coupling[7] of Boc-Glu(OBzl) and Asn-NH$_2$ (86% yield), removal of the benzyl group from Boc-Glu(OBzl)-Asn-NH$_2$ by catalytic transfer hydrogenolysis[8] (Pd black, formic acid, CH$_3$OH, 15 min, 96% yield) removal of the Boc group by acidolysis,[9] and mixed anhydride coupling[7] of Boc-Glu(OBzl)-OH and H-Glu-Asn-NH$_2$ (85% yield).

The first synthetic strategy involved formation of the thiolester bond followed by ring closure through formation of the Gly–Glu amide bond. Dipeptide thiol **3** was obtained by mixed anhydride coupling[7] of bis-Z-cystine and Gly-OCH$_3$ (82% yield), saponification[10] of the methyl ester (81% yield), and reduction of the disulfide bond with tri-1-butylphosphine.[11,12] The thiolester linkage was established by coupling[15,16] of the 1-benzotriazolo ester of tripeptide **2** with dipeptide thiol **3** (77% yield), and the resulting thiolester **4a** was converted[17] into the 2,4,5-trichlorophenyl ester **4b**. After acidolysis[9] of the Boc group, crude amino ester **4c** was cyclized under dilute conditions (0.3 mM in 5:1 (v/v) THF/pyridine, 25 °C, 24 h) to furnish the protected thiolactone **1a** (45% yield from thiolester **4a**) (Scheme I).

The second strategy involved formation of all of the amide bonds followed by ring closure through formation of the thiolester bond. Tripeptide dimer **5** was prepared by mixed anhydride coupling[7] of bis-Boc-cystine and Gly-OCH$_3$ (87% yield), acidolysis[9] of the Boc group, mixed anhydride coupling[7] of Z-Gly (2 equiv) and the disulfide dimer of Cys-Gly-OCH$_3$ (82% yield), and saponification[10] of the methyl ester (85% yield). After acidolysis[9] of peptide **2**, the Gly–Glu peptide bond was formed by mixed anhydride coupling[7] of dimeric tripeptide acid **5** and the free amine derivative of tripeptide **2** (1:2 molar ratio, DMF, 84% yield). Dimeric hexapeptide acid **6a** was reduced with tri-1-butylphosphine,[11] mercapto acid **6b** was esterified[18] with 1-hydroxybenzotriazole, and crude mercapto ester **6c** was cyclized[18] under dilute conditions (0.4 mM) to provide crude thiolactone **1c** (55–60% yield from **6a**).

The second synthetic strategy was also used for preparation of the acetylated thiolactone **1e**. Since dimeric tripeptide acid **5**, Ac replacing Z, and its methyl ester precursor were difficult to isolate because of their high solubility in water, the linear hexapeptide was assembled from three segments. Mixed anhydride coupling[7] of the disulfide dimer of Boc-Cys-Gly and the free amine derivative of tripeptide **2** (1:2 molar ratio, THF/DMF) afforded the dimer of Boc-Cys-Gly-Glu(OBzl)-Glu-Asn-NH$_2$ in 81% yield.

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(7) Except as noted, the mixed anhydride was formed by reaction of the peptide acid with *N*-methylmorpholine and isobutyl chloroformate in THF for 5 min at −15 °C. The amine was added and the solution was stirred for 0.5 h at −15 °C and 2–20 h at 25 °C.

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(9) Reaction with 1:1 (v/v) CF$_3$CO$_2$H/CH$_2$Cl$_2$ for 0.5 h at 25 °C gave quantitative removal of the Boc group.

(10) Treatment with 0.1 M NaOH (2.2 equiv) in 9:1 (v/v) CH$_3$OH/water for 2–3 h at 25 °C.

(11) Reduction was essentially complete after reaction with 0.2 M Bu$_3$P (2 equiv) in 9:1 (v/v) CH$_3$OH/water for 2 h at 25 °C. The dried peptide was triturated with ether to remove most Bu$_3$PO and residual Bu$_3$P. Although alkyl and aryl disulfides[12] and cystine disulfide[13] and S-SO$_3$ bonds[14] in proteins have been reduced with Bu$_3$P, to our knowledge a trialkylphosphine has not been used previously for reduction of cystine during peptide synthesis.

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(15) Amine-free DMF was flushed with N$_2$ to remove dissolved O$_2$. Tripeptide acid **2** (0.1 mmol) was treated with 1-hydroxybenzotriazole (HOBt; 0.12 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (DCC; 0.1 mmol) in DMF (5 mL) for 1 h at 0 °C and 18 h at 25 °C. A solution of dipeptide thiol **3** (0.105 mmol) in DMF (2 mL) was added, the temperature was raised to 40 °C, triethylamine[16] (0.4 mmol) was added, and the solution was stirred for 4 h at 40 °C. After precipitation with ether, crude thioester **4a** was twice dissolved in DMF and precipitated with THF to remove unreacted **2** and **3**.

(16) Thiophenol and benzyl mercaptan react with 1-benzotriazolo esters of *Z*-amino acids using triethylamine as the base at room temperature, but the alkanethiol (CH$_3$)$_3$CSH is reported to require prior conversion into its thallous salt (Horiki, K. *Synth. Commun.* **1977**, *7*, 251–259). In our experience, near 40 °C triethylamine promotes reaction of cysteinethiols with 1-benzotriazolo esters.

(17) Reaction of thiolester **4a** (0.1 mmol) in N$_2$-flushed DMF (5 mL) with 2,4,5-trichlorophenol (0.11 mmol) and DCC (0.11 mmol) for 1 h at 0 °C and for 18 h at 25 °C.

(18) Mercapto acid **6b** (0.1 mmol) in N$_2$-flushed DMF (10 mL) was treated with HOBt (0.3 mmol) and DCC (0.1 mmol) at 0 °C for 1 h and at 25 °C for 18 h. The mixture was added to N$_2$-flushed THF (250 mL) stirring at 40 °C. Triethylamine[16] (2 mmol) was added and stirring was continued for 20 h.

After acidolysis[9] of the Boc group, mixed anhydride coupling[7] of Ac-Gly and the resulting pentapeptide dimer (2:1 molar ratio, THF/DMF) gave the acetylated hexapeptide **6a**, Ac replacing Z, in 76% yield. The latter was reduced, activated, and cyclized to thiolactone **1e** in 55–60% yield as described[11,18] for the conversion of **6a** into **1c**.

The protected thiolactones **1a**, **1c**, and **1e** were deprotected (9:1 (v/v) HF/anisole, 0 °C, 15 min) and purified by reverse-phase liquid chromatography to furnish 10-mg quantities of the desired[19] macrocyclic thiolactones **1b**, **1d**, and **1f**. The yields over four steps were 16% from thiolester **4a** to **1b** by the first strategy and both 24% from dimeric hexapeptide **6a** to **1d** and 22% from **6a**, Ac replacing Z, to **1f** by the second strategy. In order to study the binding of thiolactone **1f** to biological particles,[21] tritiated **1f**, R = [^{3}H]Ac-Gly (2960 cpm/nmol), was prepared from [^{3}H]Ac-Gly and the pentapeptide dimer as described above.

These results (1) constitute the first chemical synthesis of the 1-thia-5,8,11-triazacyclopentadecane ring system, (2) present the first examples of reduction of a peptide disulfide with a trialkylphosphine,[11] and (3) introduce the formation of peptide thiolesters[15] and thiolactones[18] by coupling of cysteine thiol groups with 1-benzotriazolo esters.

The 300-MHz NMR spectrum[22,23] of macrocyclic thiolactone **1f** revealed that the chemical shifts of the β-methylene protons of Cys differ by 0.58 ppm and those of the γ-methylene protons of the second Glu differ by 0.20 ppm. In addition, the coupling constant between one of the Cys β-methylene protons and the α proton is only 2 Hz. A plausible explanation for these large chemical shift differences and the small coupling constant is that the 15-membered thiolactone ring exists in a single, relatively rigid conformation.

Thiolactones **1d** and **1f** undergo hydrolytic ring opening about 2000 times faster than the acyclic model thiolester *N*,*S*-diacetylcysteine methylamide.[24] Macrocyclic thiolactone **1f** (half-life[24] 0.20 h) hydrolyzes about 10^3 times faster than the latent binding site of C3 (half-life[24] 186 h) but about 10^7 times slower than the metastable binding site of nascent C3b (estimated half-life[5] 30 μs). The 15-membered thiolactone ring **1** is evidently necessary but not sufficient to explain the pronounced biological reactivity of the metastable binding site of human C3b.

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[19] The following thiolactones were homogeneous by thin-layer chromatography and reverse-phase liquid chromatography and gave acceptable mass spectral molecular weights, amino acid molar ratios, and elemental analyses. Thin-layer systems: A, 4:1:1 (v/v/v) 1-butanol/acetic acid/water; B, 23:10:3 (v/v/v) ethanol/acetic acid/water; C, 3:1:1:1 (v/v/v/v) 1-butanol/ethyl acetate/acetic acid/water. Reverse-phase conditions: 30-cm μBondapak C_{18} column was eluted isocratically with 2% CH_3CN in water; $k' = (t_{\mathrm{compd}}/t_{\mathrm{solvent}}) - 1$, where t = retention time. Molecular ions were observed as $(M + \mathrm{Na})^+$ in the positive-ion portion of the ^{252}Cf fission fragment-induced mass spectrum.[20] Molar ratios for Cys are uncorrected for losses due to oxidation during acid hydrolysis (6 N HCl, 110 °C, 24 h). The counterion for the protonated amines **1b** and **1d** is assumed to be fluoride because the only acid present during purification was HF. (a) Pentapeptide **1b**: R_f (A) 0.73, (B) 0.17, (C) 0.21; $k' = 2.27$; *m/e* ($C_{19}H_{29}N_7O_9SNa$) calcd 554.16, found 554.22; $\mathrm{Asp}_{1.07}\mathrm{Glu}_{1.97}\mathrm{Gly}_{1.00}\mathrm{Cys}_{0.27}$; Anal. ($C_{19}H_{29}N_7O_9S{\cdot}HF{\cdot}0.5\ H_2O$) C, H, N. (b) Hexapeptide **1d**: R_f (A) 0.69, (B) 0.13, (C) 0.14; $k' = 2.10$; *m/e* ($C_{21}H_{32}N_8O_{10}SNa$) calcd 611.19, found 611.23; $\mathrm{Asp}_{1.05}\mathrm{Glu}_{2.10}\mathrm{Gly}_{2.00}\mathrm{Cys}_{0.74}$; Anal. ($C_{21}H_{32}N_8O_{10}S{\cdot}HF$) C, H, N. (c) Acetylated hexapeptide **1f**: R_f (A) 0.85, (B) 0.42, (C) 0.24; k' 3.64; *m/e* ($C_{23}H_{34}H_8O_{11}SNa$) calcd 653.20, found 653.27; $\mathrm{Asp}_{1.07}\mathrm{Glu}_{2.05}\mathrm{Gly}_{2.00}\mathrm{Cys}_{0.47}$; Anal. ($C_{23}H_{34}N_8O_{11}S{\cdot}1.5H_2O$) C, H; N, calcd 17.04, found 16.58. Thiolactones **1d** and **1f** contained <2% free thiol as measured with 5,5′-dithiobis(2-nitrobenzoic acid) (Ellman's reagent).

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[22] ^{1}H NMR (CF_3CO_2D) 2.2–2.6 (4 H, m, Glu β), 2.40 (3 H, s, Ac), 2.78 (2 H, t7, Glu γ), 2.93 (1 H, m, Glu γ1), 3.13 (1 H, m, Glu γ2), 3.23 (2 H, d5, Asn β), 3.38 (1 H, d15 d6, Cys β1), 3.96 (1 H, d15 d2, Cys β2), 4.24 and 4.31 (2 H, ABq17.5, Gly α), 4.38 and 4.42 (2 H, ABq17.5, Gly α), 4.98 (1 H, d9 d5, Glu α), 5.03 (1 H, d9 d3, Glu α), and 5.17–5.28 ppm (2 H, m, Cys α and Asn α).

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Encircling of Water by Crown Compounds

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Despite the fact that various authors have stressed the importance of water complexation by crown ethers[1] and although several stoichiometric water complexes of crown-type ligands have been reported,[2] in no previous case has water been found to be encircled by an uncharged[3] host molecule. We report here on the first proven "neutral-component complexes" of crown hosts[4] (**1** and **2**) which contain water bound exclusively in the center of the cavity by hydrogen bonding with several crown ether oxygen atoms.

Polar guest compounds have recently been found to be bound by crowns.[11,12] Water has been proven to interact strongly with

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[3] The definitions for complex, adduct, addition compound, molecular compound, molecular complex associates, inclusion compound, clathrate, host–guest complex, key–lock complex, etc. seem not to be used consistently in the literature.[2] We propose that the above overall "neutral complexes" can be further subdivided into two classes: (a) those which are composed of two or more neutral (or uncharged) components, to be considered "neutral-component complexes"; and (b) those which are formed from one or more charged components, resulting in the formation of "charged-component complexes".

[4] Previously described water complexes of uncharged crown ethers possess either phenolic (acidic) OH[5] or pyridine *N*-oxide[6] groups to which the hydrogen bond(s) form; the remainder of the reports are actually of aza crown cations as hosts[7] or hydronium ion complexes. Older claims of water-containing macrocyclic polyamines[8] or diketones,[9] based mainly on IR data, have never been proven by X-ray analysis to bind the water molecules *inside* the cavity. A triple crown ether has been analyzed as a dihydrate, but X-ray analysis has not been conducted.[10]

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