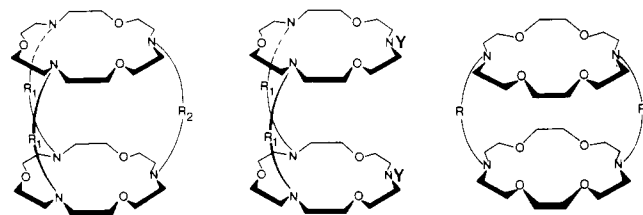
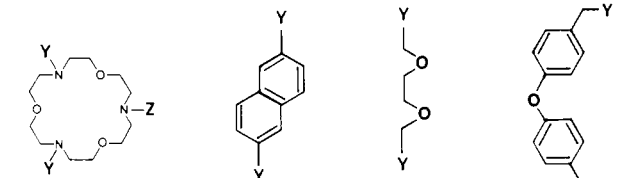


Chart I



- 1, $R_1 = R_2 = A$
 2, $R_1 = A$; $R_2 = B$
 11, $R_1 = A$; $R_2 = A^*$
 13, $R_1 = A$; $R_2 = B^*$
 14, $R_1 = R_2 = C$
 3, $R_1 = 1$; $Y = CH_3$
 8, $R_1 = A^*$; $Y = Tos$
 9, $R_1 = A$; $Y = Tos$
 10, $R_1 = A$; $Y = H$



- 5, $Y = Z = CH_3$
 6, $Y = H$; $Z = Tos$
 A, $Y = CH_2$
 A*, $Y = CO$
 7, $Y = COCl$
 B, $Y = CH_2$
 B*, $Y = CO$
 12, $Y = COCl$
 C, $Y = CH_2$
 15, $Y = COCl$

NMR spectroscopy have indicated that they are able to bind two primary ammonium cations $A-NH_3^+$ or a single diammonium substrate $^+H_3N-X-NH_3^+$, yielding, respectively, dinuclear monohapto or mononuclear dihapto complexes. Since cosystems might present a number of properties of general interest,¹ further exploration of these and other species is warranted.⁵

We now report the synthesis and some properties of another type of molecule belonging to this class, the macrotricycles **1** and **2**, and the macrotricycles **3** related to compound **4** described earlier (Chart I).¹ The macrocycle [18]- N_3O_3 **5**, which contains three symmetrically located nitrogen sites, is particularly well suited for binding primary ammonium groups, presumably by formation of three $^+N-H\cdots N$ hydrogen bonds.⁷ It was therefore of interest to incorporate two such rings into a polycyclic structure.

The monoprotected [18]- N_3O_3 macrocycle **6**, obtained earlier as an intermediate in the synthesis of a spherical cryptand,⁸ was condensed with the dichloride of naphthalene-2,6-dicarboxylic acid (**7**) in high dilution conditions,⁹ giving compound **8** (mp 152 °C; 80% yield). Compound **8** was converted into **10** (mp 138 °C) either in two steps via **9** (reduction with diborane; detosylation with HBr/AcOH/phenol; 55% yield) or directly by reduction with $LiAlH_4$ in tetrahydrofuran at reflux for 16 h (80% yield). A second high dilution condensation of **10** with **7** introduced the third bridge giving compound **11** (glass; 55% yield), which by reduction with diborane afforded the macrotricyclic hexamine **1** (mp >260 °C; 75% yield). The nonsymmetrically bridged macrotricyclic **2** (mp 140 °C) was obtained in 78% yield by diborane reduction of the diamide-tetramine **13** (glass), prepared in 46% yield by high dilution condensation of compound **10** with triglycolic acid dichloride **12**.⁹ Eschweiler-Clarke N-methylation of compound **10**

Table I. Proton NMR Chemical Shifts of the CH_2 Signals of Diammonium Substrates Complexed by Receptor Molecules **1-5**^a

receptor	$^+H_3N-(CH_2)_5-NH_3^+$			$^+H_3N-(CH_2)_6-NH_3^+$		
	α	β	γ	α	β	γ
1	1.47	-1.35	-1.13	1.51	-0.76	-1.85
2	1.62	-0.23	-0.90			
3	2.06	0.67	-0.52			
4	1.95	-0.22	-1.10	2.5	0.31	-0.28
5	(~2.5) ^a	1.58	1.43	(~2.5) ^a	1.53	1.41

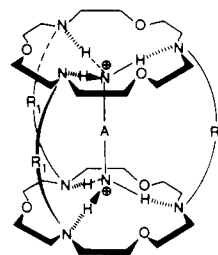
^a Approximate shifts. These signals are hidden under the NCH_2 signal of the macrocycles in the ligand.

afforded the macrotricyclic hexamine **3** (glass; 57% yield). The macrotricyclic **14**, which incorporates diphenyl ether bridges, has been synthesized via the same pathway as that described for **1**, using the diacid dichloride **15**. It will not be discussed further here. All compounds described gave analytical and spectral data in agreement with their structure. The three hexamines **1-3** should be stored in dry, inert atmosphere.

Compounds **1** and **2** represent a new type of macropolycyclic mesomolecules, *triply bridged, cylindrical macrotricycles*,⁶ built on two [18]- N_3O_3 macrocycles, which may serve as complexing sites for cationic species.⁷ The three bridges connected to the three nitrogens of the rings maintain the macrocycles at a fixed distance (about 7–8 Å for **1** and **2**) and delineate a central intramolecular cavity. Compared to the corresponding tricyclic system **4**,¹ the cavity of **1** (and, to a lesser extent, **2**) is rather tight and well insulated from the environment by the walls formed by the three surrounding naphthyl bridges.

The formation of complexes of compounds **1** and **2** with primary ammonium cations was studied by proton NMR spectroscopy.¹⁰ On addition of suitable ammonium picrates to a solution of the ligand, the resonances of both the receptor and the substrates were markedly shifted with respect to those of the free receptor and corresponding complexes of the macrocycle **5** taken as references.¹¹

When $^+H_3N-(CH_2)_5-NH_3^+$ dication was added to **1** or **2**, a complex of 1/1 stoichiometry was obtained which displayed remarkable high field shifts for the CH_2 NMR signals of the substrate.¹⁰ Even larger shifts were found for $[^+H_3N-(CH_2)_6-NH_3^+ + 1]$, reaching -1.85 ppm for the γ - CH_2 protons, i.e., an upfield shift of about 3.2 ppm from the reference complex formed with 2 equiv of **5**. The results obtained for compounds **1-3** are listed in Table I. As observed for the diammonium cryptates of macrotricycles,^{1,3,4} the protons of the substrate experience an intense shielding effect due to the aromatic groups in the bridges. The substrate must therefore be contained in the molecular cavity of the receptors **1-3**, forming a *mononuclear η^2 -cryptate* [$^+H_3N-(CH_2)_5-NH_3^+ \subset$ receptor] **16**, by simultaneous binding



(3) Johnson, M. R.; Sutherland, I. O.; Newton, R. F. *J. Chem. Soc., Chem. Commun.* **1979**, 309–311.

(4) Mageswaran, R.; Mageswaran, S.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1979**, 722–724.

(5) Dicrown ethers represent another type of ligands which have been shown to bind ammonium salts: Tarnowski, T. L.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1976**, 661–663. Goldberg, I. *Acta Crystallogr., Sect. B* **1977**, B33, 472–479. Johnson, M. R.; Sutherland, I. O.; Newton, R. F. *J. Chem. Soc., Perkin Trans. 1* **1980**, 586–600.

(6) A transversally bridged macrotricyclic has been described earlier: Lehn, J. M.; Simon, J.; Wagner, J. *Angew. Chem.* **1973**, 85, 621–622. *Angew. Chem. Int. Ed. Engl.* **1973**, 12, 578–579; *Nouv. J. Chim.* **1977**, 1, 77–84. For other types of macropolycyclics, see for instance: Wester, N.; Vögler, F. *Chem. Ber.* **1979**, 112, 3723–3727; **1980**, 113, 1487–1493.

(7) Lehn, J. M.; Vierling, P. *Tetrahedron Lett.* **1980**, 1323–1326.

(8) Graf, E.; Lehn, J. M. *J. Am. Chem. Soc.* **1975**, 97, 5022–5024; *Helv. Chim. Acta* **1981**, 64, 1040–1057.

(9) Dietrich, B.; Lehn, J. M.; Sauvage, J. P.; Blanzat, J. *Tetrahedron* **1973**, 29, 1629–1645.

(10) All proton NMR spectra have been measured at 250 MHz on $CDCl_3/CD_3OD$ 9/1 solutions at 18 °C, unless otherwise stated.

(11) Since the macrocyclic subunit [15]- N_3O_3 is quite basic,⁷ protonation of the amino groups of the receptor by proton transfer from the ammonium substrates may be a complicating factor. The distinction between complexation and transprotonation is usually quite straightforward, since they induce characteristic and markedly different chemical shift changes for the NMR signals of both receptor and substrate. Protonation of compound **1** leads to marked downfield shifts of its proton NMR signals. Conversely, deprotonation of the ammonium substrate causes upfield shifts of its resonances. Protonation of **1-3** might also result from traces of acid present in the solvent and/or proton abstraction from the solvent. In general, compounds **1-3** appear to undergo protonation rather readily, so that sample preparation requires special care.

of the two $-\text{NH}_3^+$ groups to the $[\text{18}]\text{-N}_3\text{O}_3$ macrocyclic subunits. The shifts observed provide information about the location of the included substrate with respect to the aromatic residues.

As for macrotricycles,^{4,12} complexation with chain length discrimination among $^+\text{H}_3\text{N}-(\text{CH}_2)_n-\text{NH}_3^+$ substrates was observed. Whereas **1** binds the $n = 5$ and $n = 6$ species, no complexes were formed with the $n = 4$ and $n = 8$ dications in the same conditions.

Binding of two A-NH_3^+ substrates by receptors **1-4** may in principle yield three types of *dinuclear monohapto*¹ species, depending on whether the two substrates are both inside the central molecular cavity, one in and one out, or both outside. Which form predominates depends on toposelective factors which direct substrate binding either into or out of the central cavity. Steric repulsions between the A group of A-NH_3^+ and the bridges in **1-4** hinder inside binding, whereas inside orientation of the nitrogen sites (which are the strongest binding sites)¹³ and eventual attractive interactions between A and the bridges favor inside binding. The balance between these effects rests on the nature of the macrocycles, the bridges, and group A. For compound **4**¹ and other macrotricycles,^{3,4} NMR data indicated that internal complexation occurs but external binding could not be excluded.^{1,14} The tighter internal cavity of **1** and **2** should hinder inside binding more than with **4**. When CH_3NH_3^+ picrate was added to **1** or **2**, complexation occurred and peaks appeared at high field in the 0.7-1.7-ppm region in the ^1H NMR spectrum at -55°C .¹⁰ It is not possible at present to decide which species were formed, but the marked high field shifts indicate that internal binding presumably occurs to some extent. A-NH_3^+ substrates where A is larger than CH_3 , gave transprotonation under the same conditions.

The complexation data described above indicate that substrate binding is more restricted for **1** and **2** than for **4**, implying that these macrotricycles display *very high selectivity* of complexation at the expense, of course, of the ability to bind a broader range of substrates. There is probably a close to total discrimination against internal binding of a more bulky derivative of $^+\text{H}_3\text{N}-(\text{CH}_2)_5-\text{NH}_3^+$ or CH_3NH_3^+ by receptor **1**.

Information about substrate exchange rates and relative stabilities of the complexes was obtained from competition experiments. Addition of 1 equiv of **1** to the $[\text{H}_3\text{N}-(\text{CH}_2)_5-\text{NH}_3^+ \text{C } \mathbf{4}]$ cryptate or addition of 1 equiv of **4** to the $[\text{H}_3\text{N}-(\text{CH}_2)_5-\text{NH}_3^+ \text{C } \mathbf{1}]$ cryptate gave the same ^1H NMR spectrum, displaying the high field signals of the substrates in *both* complexes.¹⁰ The equilibrium mixture $[\text{C } \mathbf{1}] + \mathbf{4} \rightleftharpoons \mathbf{1} + [\text{C } \mathbf{4}]$ contained about 40% and 60% of the cryptates of **1** and **4**, respectively.

Thus, substrate exchange was slow on the NMR time scale, and the two complexes have about the same stability. The tighter cavity of **1** probably causes larger steric interactions between the substrate and the bridges as compared to **4**, thus compensating the expected stronger binding of $-\text{NH}_3^+$ groups by the $[\text{18}]\text{-N}_3\text{O}_3$ subunit **5** of **1** as compared to the $[\text{18}]\text{-N}_3\text{O}_4$ ring of **4**.⁷

Further studies are required to ascertain the precise structure of the complexes formed by the macrotricyclic receptors **1** and **2**, as well as the nature of the binding scheme (tentatively represented by **16**). The triply bridged nature of these systems provides a closer control of cavity properties; bent bridges (as in **14**) open up the cavity, presumably expanding the range of complexable substrates. Comparison of systems like **1**, **4**, and **14** should allow delineating the respective properties of "closed" and "open" macropolycycles (complexation stability, selectivity, exchange rates, etc.).

Acknowledgment. We thank Pierre Plumeré for the preparation of macrocycle **6**⁸ used in the present work.

(12) Kintzinger, J. P.; Kotzyba-Hibert, F.; Lehn, J. M.; Pagelot, A.; Saigo, K., *J. Chem. Soc., Chem. Commun.*, in press.

(13) In the crystal structure of the tricycle **4**, all four nitrogen sites are found to be oriented toward the interior of the molecule: Arnoux, B.; Pascard-Billy, C., unpublished results.

(14) Low-temperature NMR measurements on the complexes of **4** with CH_3NH_3^+ or $\text{CH}_3\text{CH}_2\text{NH}_3^+$ point to the presence of more than one species, indicating that both internal and external binding occurs; work in progress.

Oxygen Activation by Radical Coupling between Superoxide Ion and Reduced Methyl Viologen

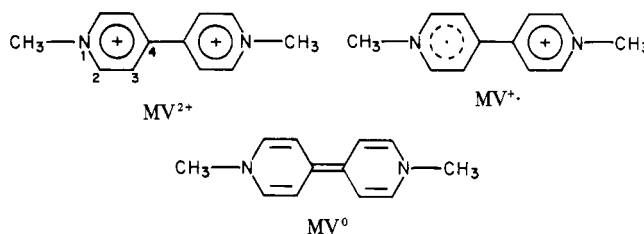
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Superoxide ion, O_2^- , has been cited as a major factor in the toxicity of methyl viologen (1,1'-dimethyl-4,4'-bipyridinium ion (MV^{2+}) or paraquat).^{1,2} The methyl viologen radical cation



($\text{MV}^{\bullet+}$) reacts with O_2 rapidly ($k_2 = 7.7 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$) to generate O_2^- .³ MV^{2+} augments the production of O_2^- by chloroplasts,^{4,5} lung microsomes,⁶ and homogenates of lung, liver, and kidney;⁷ and O_2 augments the toxicity of MV^{2+} in plants,⁸⁻¹⁰ rats,¹¹ and *E. coli*.¹² However, the role of O_2^- , if any, in paraquat toxicity remains unclear.¹² To propose that O_2^- is the penultimate toxin in paraquat toxicity is unverified and may be fallacious; the studies to date indicate that O_2^- is fairly innocuous to aerobic organisms.¹³⁻¹⁵

The ability to form electrochemically stable solutions of O_2^- ¹⁶ and $\text{MV}^{\bullet+}$,^{17,18} in aprotic media prompted us to investigate the reactivity of O_2^- with $\text{MV}^{\bullet+}$. On the basis of electrochemical, spectroscopic (UV-vis, ESR, NMR, MS), and chromatographic measurements, we now report that when 1 equiv of O_2^- is combined with 1 equiv of $\text{MV}^{\bullet+}$, a diamagnetic adduct is the initial product, which is consistent with a primary radical-radical coupling mechanism.

- (1) Hassan, H. M.; Fridovich, I. *J. Biol. Chem.* **1979**, *254*, 10846.
- (2) Hassan, H. M.; Fridovich, I. *J. Biol. Chem.* **1978**, *253*, 8143.
- (3) Farrington, J. A.; Ebert, M.; Land, E. J.; Fletcher, K. *Biochim. Biophys. Acta* **1973**, *314*, 372.
- (4) Miller, R. W.; MacDowell, F. D. H. *Biochim. Biophys. Acta* **1975**, *387*, 176.
- (5) Harbour, J. J.; Bolton, J. R. *Biochem. Biophys. Res. Commun.* **1975**, *64*, 803.
- (6) Montgomery, M. R. *Res. Commun. Chem. Pathol. Pharmacol.* **1977**, *16*, 155.
- (7) Baldwin, R. C.; Pasi, A.; MacGregor, J. T.; Hine, C. H. *Toxicol. Appl. Pharmacol.* **1975**, *32*, 298.
- (8) Mees, G. C. *Ann. Appl. Biol.* **1960**, *48*, 601.
- (9) Calderbrook, A. *Adv. Pest Control Res.* **1968**, *8*, 127.
- (10) Conning, D. M.; Fletcher, K.; Swan, A. A. B. *Br. Med. Bull.* **1969**, *25*, 245.
- (11) Fisher, H. K. "Biochemical Mechanisms of Paraquat Toxicity"; Auro, A. P., Ed.; Academic Press: New York, 1977; pp 57-65.
- (12) Ross, W. E.; Block, E. R.; Chang, R.-W. *Biochem. Biophys. Res. Commun.* **1979**, *91*, 1302.
- (13) Nilsson, R.; Pick, F. M. Bray, R. C. *Biochim. Biophys. Acta* **1969**, *192*, 145.
- (14) Schmidt, M.; Bipp, H. Z. *Anorg. Allg. Chem.* **1960**, *303*, 190, 201.
- (15) LeBeine, A.; Berguer, Y. *Bull. Soc. Chim. Fr.* **1966**, 2363.
- (16) Sawyer, D. T.; Roberts, J. L., Jr. *J. Electroanal. Chem.* **1966**, *12*, 90.
- (17) Bard, A. J.; Ledwith, A.; Shine, H. J. *Adv. Phys. Org. Chem.* **1976**, *13*, 155.
- (18) Electrolysis of MV^{2+} in DMF at -0.55 V vs. SCE requires 1.05 e^- and yields a deep blue solution that is attributable to the methyl viologen radical cation, $\text{MV}^{\bullet+}$, with absorption bands at 311 nm (ϵ 4560 $\text{M}^{-1} \text{ cm}^{-1}$) 370 (13 100), 387 (22 000), 398 (40 200), 580 (8440), 608 (10 760), 665 (4980), and 740 (1940). The ESR spectrum for this solution is similar to published spectra for $\text{MV}^{\bullet+}$.^{19,20}
- (19) Johnson, C. S., Jr.; Gutowsky, H. S. *J. Chem. Phys.* **1963**, *39*, 58.
- (20) Kosower, E. M.; Cotter, J. L. *J. Am. Chem. Soc.* **1964**, *86*, 5524.