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THE [18]-N_3O_3 AZA-OXA MACROCYCLE: A SELECTIVE RECEPTOR UNIT FOR PRIMARY AMMONIUM CATIONS

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Abstract: A comparative study of the complexes formed by three [18]-macrocyclic ligands indicates that the triaza-trioxa macrocycle [18]-N_3O_3, **3**, displays by far the highest stability and selectivity for binding of primary ammonium cations.

Macrocyclic polyethers of the [18]-crown-6 type **1** are able to complex both metal cations and primary ammonium cations[1,2]. Extensive use has been made of the latter property for binding various organic ammonium substrates[2]. In general, however, these polyethers bind the alkali cations K^+ and Rb^+ appreciably stronger than $R\text{-}NH_3^+$ groups[3], whereas the opposite selectivity would be desirable for the design of receptor molecules aimed at the complexation of organic substrates .

Our work on aza-oxa-macropolycycles and on their cryptate inclusion complexes[4], lead us to consider such rings as potential binding sites for ammonium groups in synthetic molecular receptors[5]. They may serve as subunits for the edification of polycyclic molecular architectures capable of forming ammonium cryptates by binding one or more organic substrates. In particular, the cylindrical macrotricycles described earlier[4,5] yield dinuclear cryptates with metal ions and also bind ammonium salts[6,7].

It became desirable to design a macrocyclic subunit which would be a *receptor site for* $R\text{-}NH_3^+$ *cations*, displaying the following features:

1) a *suitable size* for fitting the $-NH_3^+$ group, i.e. an 18-membered ring[1,2];
2) a *ternary symmetry* complementary to that of the substrates;
3) *strong and selective binding of* $R\text{-}NH_3^+$ groups with respect to alkali cations;
4) three-coordinated *nitrogen sites for connection* of side-chains and building into large polycyclic structures.

Since $^+N\text{-}H\cdots N$ hydrogen bonding is stronger than $^+N\text{-}H\cdots O$[8] and since a very strong and selective NH_4^+ cryptate is formed by a tetraaza spherical receptor molecule[4,5], the triaza-trioxa-eighteen-membered ring, [18]-N_3O_3, **3**, appeared to be a suitable unit. We report here results on the binding of $R\text{-}NH_3^+$ substrates to macrocycles **2** and **3**. Extensive NMR studies led recently to the characterisation of ammonium complexes formed by other aza-oxa-macrocycles[9,10]. Compound **3** was obtained as a colourless liquid by Eschweiler-Clark N-methylation of the parent macrocycle **3'**, prepared earlier from an intermediate compound in the synthesis of a spherical cryptand[11].

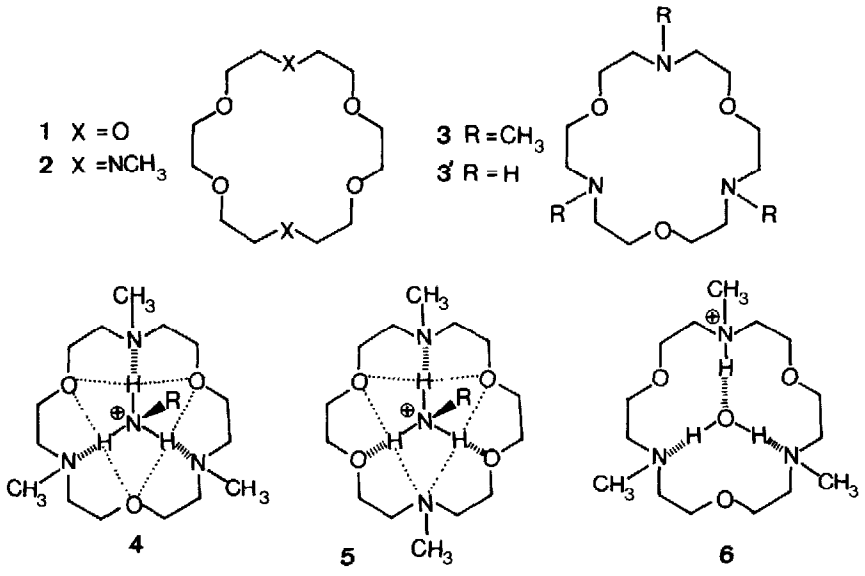

Table: *Stability Constants K_s for the Binding of Cationic Substrates by the Macrocycles* **1, 2, 3** [a].

Macrocycle	Na^+	K^+ [b]	$CH_3NH_3^+$	$CH_3CH_2NH_3^+$	$PhCH_2CH_2NH_3^+$
1 [18]-O_6	3200	1.7×10^5	2100	1600	1500
2 [18]-N_2O_4	1200	12500	2200	1500	2000
3 [18]-N_3O_3	1300	6000	65000[a,b]	31000[a,b]	50000[a,b]

[a] Solvent: methanol/water 9/1; 25°; supporting electrolyte: NMe_4Br 0.1M; *substrates added as* chlorides. All K_s values have been determined using a Na^+ cation specific glass electrode, either directly (Na^+) or by competition with Na^+ (other substrates) unless otherwise stated; accuracy ±10%.

[b] Values determined using a K^+ cation specific glass electrode, either directly (K^+) or by competition with K^+ (other substrates); accuracy ±10%.

The binding properties of **3** and of the related ligands **1**, [18]-O_6 and **2**, [18]-N_2O_4 (for other data on these ligands, see ref. 1, 3, 12) have been studied by determining the stability constants of the complexes formed with several cations (Table).

1) The *stability* of the *alkali cation complexes*, while retaining the expected $Na^+ < K^+$ selectivity, decreases markedly along the series **1** >> **2** ≥ **3** as O binding sites are replaced by N sites, in agreement with earlier result on macrocycles and cryptands[1,12,13].

2) The *stability* of the *ammonium cation complexes* increases markedly for macrocycle **3**, which complexes CH_3-NH_3^+ about 30 times more strongly than either **1** or **2**. The gain in stability is about 2 kcal/mole and is expected to be even larger in less polar solvents.

3) The *ammonium/potassium selectivity* is greatly in favour of K^+ for **1** and **2** while compound **3** complexes the primary ammonium salts more strongly (by a factor of 5-10). The stability ratio RNH_3^+/K^+ increases by a factor of about 1000 from **1** (∿ 0.01) to **3** (∿ 10).

It is much higher for **3** than the NH_4^+/K^+ selectivity exhibited by natural macrocyclic ligands[14], but is nevertheless lower than the NH_4^+/K^+ ratio displayed by a spherical macrotricyclic NH_4^+ receptor molecule[4,5].

4) The 1/1 *stoichiometry* of the complexes has been determined both from the potentiometric measurements and from shifts of the proton NMR signals of the ligands on complexation. Thus addition of $PhCH_2CH_2NH_3^+ Cl^-$ to a solution of macrocycles **2** or **3** in $CDCl_3$ (or addition of $CH_3NH_3^+Cl^-$ to MeOH/H_2O 9/1 solutions) causes an *upfield* shift ($\sim$0.1 ppm) of the CH-N proton signals of the ligand up to 1/1 ratio. The shifts of the N-CH_3 and N-CH_2 signals amount respectively to 5Hz and 8.5Hz for **2** and to 6Hz and 5Hz for **3** (at 60 MHz in $CDCl_3$).

5) A potentially complicating factor is proton transfer from the ammonium substrate to a nitrogen site in the macrocycle. If it occurs, the NMR signals of the CH protons next to the nitrogen sites should shift upfield and downfield respectively for the substrate and for the macrocycle. In fact, as mentioned in 4), shifts in the opposite direction (upfield) are observed for the ligand signals and the substrate resonances remain almost unaffected. Thus, *no transprotonation* occurs and the complexed species is indeed an ammonium salt. Furthermore, *ab initio* computations (with optimization of the $^+$N,N distances) have shown that when a NH_4^+ cation is bound to three surrounding NH_3 molecules by three linear $^+$N-H$\cdots$$NH_3$ hydrogen bonds (along the symmetry axis of NH_3), the system is appreciably more stable (by about 15 kcal/mole) than the corresponding species which results from proton transfer from the central NH_4^+ to one of the three NH_3^+ units and contains one N$\cdots$H-N^+ and two N$\cdots$H-N hydrogen bonds[15].

6) The *high affinity* and *considerable selectivity* displayed by macrocycle **3**, [18]-N_3O_3 for the complexation of primary ammonium salts may be ascribed to the presence of three symmetrically located tertiary N sites. The R-NH_3^+ group binds into the circular cavity of the macrocycle via three $^+$N-H$\cdots$N hydrogen bonds completed by six electrostatic interactions between the oxygen sites and the hydrogens of the -NH_3^+ group as schematically represented in structure **4***. The macrocycle **3** is thus a selective *receptor site* for anchoring *primary ammonium substrates* via the -NH_3^+ group. The binding to macrocycle **2** may involve one $^+$N-H$\cdots$N and two $^+$N-H$\cdots$O hydrogen bonds as pictured in structure **5** (or perhaps two $^+$N-H$\cdots$N bonds)**. The bonding schemes **4** and **5** are supported by the crystal structure of the *ter*Bu-NH_3^+ complex of the monopyridine macrocycle [18]-O_5Py (derived from **1** by replacing one oxygen site by the nitrogen site of a pyridine ring) which indicates that the -NH_3^+ group binds to the pyridine N site and to two oxygens[19]. Hydrogen bonding to a tertiary amine site is appreciably stronger than to an ether oxygen or to a pyridine nitrogen[8] ‡.

7) The pK_a values of the triamine **3** are 10.23, 7.53 and 5.42 in aqueous solution at 25°. The high basicity of the first value and the large ΔpK_a between the first two figures may

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* The positive charge of an -NH_3^+ group has been shown to be located on the hydrogens by both theoretical[15,16] and experimental[17] studies.

** Low temperature NMR studies of the primary ammonium complexes of **2**[9] and **3**[18] indicate the presence of species differing by the orientations of the N-CH_3 groups.

‡ The tris-pyridyl macrocycle corresponding to compound **3** complexes ammonium salts less well than **1**[20].

indicate the cooperation of a complexed water molecule for the first protonation. A large cooperativity effect of this type has been found for a spherical macrotricyclic molecule[4,5]. Monoprotonation of **3** with one equivalent picric acid in $CDCl_3$ solution causes a marked downfield shift of the N-CH proton signals as expected. On addition of about one equivalent of water these signals shift slightly upfield; there is no further shift when more water is added. These observations agree with the formation of an inclusion complex **6** between the monoprotonated macrocycle **3**-H^+ and a water molecule, bound by accepting one $^+$N-H···O hydrogen bond and donating two O-H···N bonds to two unprotonated nitrogen sites. The crystal structure of a closely related species, the water complex of monoaza-18-crown-6 hydrochloride, has been reported[21].

The unique properties of the macrocycle [18]-N_3O_3, **3**, as a strong and selective binding site for ammonium cations, together with the presence of ternary nitrogen sites for connection of bridges, make this system of particular interest for *incorporation as a subunit into large macropolycyclic structures*. The synthesis and properties of such receptor molecules will be described in another report.

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