Anion Receptor Molecules. Synthesis and Anion-Binding Properties of Polyammonium Macrocycles†

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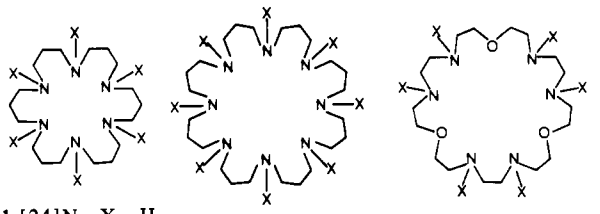
Anion-coordination chemistry, the binding of anions by organic ligands, has been much less investigated than cation complexation, although a multitude of new structures and properties may be expected in view of the role played by anionic species in chemical as well as in biological processes.[1] For instance, macropolycyclic ammonium salts yield katapinates[2] and anion cryptates;[3-5] polyguanidinium and polyammonium salts act as anion complexones;[6,7] quaternary ammonium salts allow selective extraction and transport of amino acids[8] and phosphates.[9]

We now report the synthesis of three new polyaza macrocycles **1** [24]N_6, **2** [32]N_8, and **3** [27]N_6O_3, and preliminary studies of the anion-binding properties of the corresponding polyammonium salts. The 1,3-propylenediamine unit incorporated in **1** and **2** was chosen for two reasons: (1) Polyammonium salts, based on the ethylenediamine pattern, require acidic pH for full protonation but bind anions more strongly than the pH-insensitive polyguanidinium salts.[7] The 1,3-propylenediammonium unit should represent a compromise between these two cases. Another possibility is to isolate ethylenediamine units by longer chains, as is the case in compound **3** where three such units are spread around the macrocycle. (2) Natural polyamines like putrescine, spermidine, and spermine contain amine functions separated by three or four methylene groups; they bind strongly to nucleotides,[10] and play an important role in many biological processes such as nucleic acid and protein synthesis and cell growth.[11]

The synthesis of **1-3** will be described very briefly. Tosylation of 1,7-diamino-4-azaheptane yields **4**, which is converted into the diol **5** ($ClCH_2CH_2CH_2OH$, K_2CO_3/DMF, 100 °C; 42% yield) and then into **6** (CH_3SO_2Cl, Et_3N, CH_2Cl_2; 97% yield); treatment of **4** with acrylonitrile in DMF gives the dinitrile **7** (80% yield) which is reduced to the diamine **8** (diborane/THF; 95% yield) and tosylated to **9** (TsCl/Et_3N; 80% yield). Reaction of $TsNHCH_2CH_2OH$ with $(ClCH_2CH_2)_2O$ yields **10** (K_2CO_3/DMF; 65% yield) which is converted successively into **11** (TsCl/pyridine; 95% yield), **12** (Gabriel reaction; 82% yield), and **13** (TsCl/H_2O, Et_2O; 57% yield). Reaction of ethylenediamine ditosylate with $ClCH_2CH_2OCH_2CH_2OH$ gives **14** (K_2CO_3/DMF; 80% yield) which yields **15** (TsCl/pyridine; 90% yield).

The disodium salt of **4** (NaH/DMF) is condensed with **6** in DMF at 110 °C,[12] affording the macrocyclic hexatosylate **16** (mp 197-198 °C; 50% yield). Similarly, reaction of the disodium salt of **9** with **6** gives **17**, after purification on a silica column (mp 185 °C, 35% yield). Finally, by use of **13** and **15**, the macrocycle **18** is obtained (mp 126-127 °C, 65% yield).

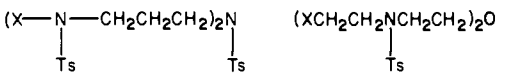
Removal of the tosyl groups of compounds **16**, **17**, and **18** by treatment with 30% HBr/AcOH/phenol at 80°C for 14 h gives



1 [24]N_6, X = H
16, X = Ts

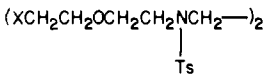
2 [32]N_8, X = H
17, X = Ts

3 [27]N_6O_3, X = H
18, X = Ts



4, X = H
5, X = $CH_2CH_2CH_2OH$
6, X = $CH_2CH_2CH_2OMs$
7, X = CH_2CH_2CN
8, X = $CH_2CH_2CH_2NH_2$
9, X = $CH_2CH_2CH_2NHTs$

10, X = OH
11, X = OTs
12, X = NH_2
13, X = NHTs



14, X = OH
15, X = OTs

the hydrobromides of the macrocyclic polyamines **1**, **2**, and **3** in 92%, 80%, and 90% yield, respectively. Anion exchange may be achieved by passing the hydrobromides over an anion exchange column, or by conversion into the parent polyamine and treatment with the desired acid. The fully protonated compounds (**1**-$6H^+$,$6Cl^-$), (**2**-$8H^+$,$6Cl^-$), (**3**-$6H^+$,$6Br^-$) have been isolated as crystalline solids (mp >230 °C). The unprotonated species are oily substances, unsuitable for storage. All new compounds were fully characterized by their physical and analytical properties.

The pK_a values and the anion-binding properties of the polyammonium salts of macrocycles **1-3** were determined by computer analysis of the pH metric titration curves measured in presence of the corresponding anion. The results are listed in Table I and illustrated in Figure 1.[14]

(1) All three fully protonated compounds **1**-$6H^+$, **2**-$8H^+$, and **3**-$6H^+$ form *strong complexes* with both inorganic and organic polyanions in aqueous solution. Since the pK_a's of **1-3** are close to or above 7, binding occurs in the neutral pH range. Complexation of monoanions has not been detected under the present conditions.[14]

(2) The nucleotide phosphate polyanions, AMP^{2-}, ADP^{3-}, ATP^{4-}, form complexes of much higher stability with the present macrocyclic polyammonium structures than with the acyclic tetraammonium ligand spermine.[10] Although the latter is not a direct reference compound, it is nevertheless probable that the enhanced stabilities of the complexes listed in Table I indicate a *macrocyclic effect on anion binding*, with respect to acylic ligands.

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(14) The pH metric titration and data analysis procedures were similar to those described earlier.[7] Ligands **1-3** were used as their fully protonated hydrochlorides. All measurements were performed on aqueous solutions containing 10^{-3} M ligand, a few 10^{-3} M anion (5.0×10^{-3} M, 2.5×10^{-3} M, or 1.5×10^{-3} M for anions of charge 2, 3, or 4, respectively) and 0.1 M supporting electrolyte Me_4NCl. Data analysis has been performed assuming 1/1 stoichiometry for the complexes, unless stated otherwise. Higher order complexes may, however, be present, especially for the larger macrocycle **2**-$8H^+$. For this reason the present discussion has been limited to general trends in anion-binding features. A more detailed analysis is in progress. The stability constants listed in Table I are apparent constants obtained in presence of a large excess of chloride ion. Although complexation of chloride appears to be weak, it competes with the other anion present; thus, the absolute K_s values are probably even higher than the relative values listed in Table I. In the case of singly charged anions like acetate, nitrate, and tetrafluoroborate no complex formation could be detected, presumably because of chloride competition. Stability constants with nonfully protonated ligands have also been obtained in the course of the data analysis; they will be reported in the final account of this work. In all cases, they decrease appreciably with the loss of a proton.

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Table I. Stability Constants, Log K_s (±0.2), for Anion Binding by the Polyammonium Macrocycles 1-6H$^+$, 2-8H$^+$, and 3-6H$^+$ in Aqueous Solution[14]

anion	macrocyclic ligand[a] 1-6H$^+$	2-8H$^+$	3-6H$^+$
sulfate^{2-}	4.0	4.0	4.5
oxalate^{2-}	3.8	3.7	4.7
malonate^{2-}	3.3	3.9	3.8
succinate^{2-}	2.4	3.6	2.8
tartrate^{2-}	2.5		2.9
maleate^{2-}	3.7	4.1	4.0
fumarate^{2-}	2.2	2.9	2.6
squarate^{2-}	3.2	3.6	3.4
citrate^{3-}	4.7	7.6	5.8
1,3,5-benzenetricarboxylate^{3-}	3.5	6.1	3.8
$Co(CN)_6^{3-}$	3.9	6.0	3.3
$Fe(CN)_6^{4-}$	6.9	8.9	6.3
AMP^{2-}	3.4	4.1 (7.2)[b]	4.7
ADP^{3-}	6.5	7.5 (10.2)[b]	7.7
ATP^{4-}	8.9	8.5 (12.8)[b]	9.1

[a] The following pK_a values (±0.1) were determined for the three ligands: 10.45, 10.35, 9.05, 7.90, 7.15, 6.60 for 1; 10.70, 10.45, 9.65, 9.00, 8.05, 7.50, 6.95, 6.45 for 2; 9.65, 9.15, 8.45, 6.80, 5.80, 5.70 for 3; aqueous solution, 0.1 M NMe_4Cl. [b] Log K_s values calculated for formation of 1/2 ligand/substrate complexes (see text).

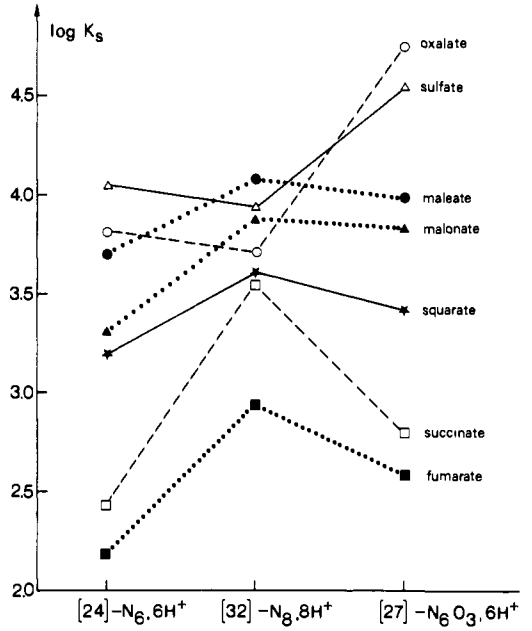

Figure 1. Graphical representation of the stability constants (log K_s) of the complexes formed by the polyammonium macrocycles 1-6H$^+$, 2-8H$^+$, and 3-6H$^+$ with various molecular anions (see also Table I).

(3) The complexation of AMP, ADP, and ATP has also been studied by following the changes in ^{31}P NMR chemical shifts on addition of ligand to a solution of substrate anion at pH 6.5. The smaller macrocycle ([24]N_6, 6H$^+$) forms a 1/1 complex with ATP, whereas for ADP both 1/1 and 1/2 species are detected. The larger ring system ([32]N_8, 8H$^+$) binds two substrate molecules in all three cases.

(4) *Electrostatic interactions* play a major role in both strength and selectivity of anion binding. Thus, for a given receptor molecule, the anions most strongly complexed are usually the smallest and most highly charged ones, i.e., those of highest charge density (see for instance the sequence oxalate > malonate > succinate and maleate > fumarate).

(5) *Structural effects* are observed in the trends represented in Figure 1. The larger dianions, like squarate, fumarate, and especially succinate, form more stable complexes with the larger [32] macrocycle, 2-8H$^+$, than with the [24] macrocycle, 1-6H$^+$; this is not the case for the smaller sulfate and oxalate anions. Ligand 3-6H$^+$ binds sulfate and oxalate more strongly than the smaller cycle 1-6H$^+$ of same charge; this may be due to a higher local charge density in an ethylenediammonium group than in a propylenediammonium group. Large polyanions like citrate, 1,3,5-benzenetricarboxylate, $Co(CN)_6^{3-}$, and $Fe(CN)_6^{4-}$, form very strong complexes with the large and highly charged 2-8H$^+$ receptor.

(6) In terms of *structural complementarity* between the anionic substrate and the macrocyclic receptor, 1-6H$^+$ and 3-6H$^+$ correspond to substrates of threefold symmetry and 2-8H$^+$ to substrates of fourfold symmetry. Molecular models show that indeed planar XO_3^{n-} or tetrahedral XO_4^{n-} anions fit well into the cavity of 1-6H$^+$, forming hydrogen bonds with all six ammonium sites. On the other hand, squarate dianion and the square-planar structural fragment in the equatorial plane of the octahedral $M(CN)_6^{n-}$ complex anions fit into the 2-8H$^+$ macrocycle in an eightfold hydrogen-bonding pattern.[15] This apparently agrees with the particularly high stabilities displayed by $Co(CN)_6^{3-}$ and $Fe(CN)_6^{4-}$ with 2-8H$^+$.

(7) The binding of anions like $Fe(CN)_6^{4-}$, $Co(CN)_6^{3-}$, or other complex anions of transition metals yield species which may be considered as *complexes of complexes*: the central cation is complexed by cyanide anions and the resulting species is in turn bound by the polyammonium macrocycle.[16] Such complexation may permit regulation of the physical properties of the substrate. Indeed, electrochemical measurements show that $Fe(CN)_6^{4-}$ forms 1/1 complexes with 1-6H$^+$ and 2-8H$^+$, resulting in a strong shift of its redox potential toward more positive values.[18]

In conclusion, the macrocyclic polyammonium cations 1-6H$^+$, 2-8H$^+$, and 3-6H$^+$ are *anion receptor molecules* forming strong and selective complexes with a variety of molecular anions. Since the selectivity of complexation depends both on electrostatic and structural effects, modification of size and shape of the macrocyclic system should allow controlling the selectivity sequence. More accurate structural control should be achievable in macropolycyclic systems which may be expected to yield even stronger and more selective complexes (see for instance ref 4). The selective complexation of biologically important anions (like AMP, ADP, ATP, citrate, and other carboxylates) is of particular interest, especially if, by attachment of hydrocarbon chains, the ligands are converted into selective *anion carriers*. Binding of anionic functional groups may result in *catalysis*. Finally, applications in the areas of analytical chemistry (for instance anion selective electrodes) and separation science may be envisaged. Various extensions of the present work along these lines are being studied.[19]

(15) It has not yet been possible to produce crystals suitable for X-ray structure determination. A crystalline complex of 2-8H$^+$ with $Pt(CN)_4^{2-}$ having the composition 2-8H$^+$/4 $Pt(CN)_4^{2-}$ has been isolated.

(16) Complexation of anionic clusters may also be envisaged. Conversely, the binding of cationic transition-metal complexes to a hexacarboxylate macrocyclic polyether[17] has been detected: Vierling, P., unpublished observations.

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(19) The macrocyclic polyamines 1, 2, and 3 also form complexes with transition-metal cations (work in progress).

A Highly Stereoselective Synthesis of Trans Epoxides via Arsonium Ylides[1]

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We wish to report a useful new method for the direct epoxidation of carbonyl compounds. The procedure involves the

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