Anion Receptor Molecules. Synthesis and Some Anion Binding Properties of Macrocyclic Guanidinium Salts

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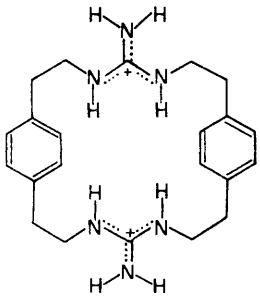
Summary A method for the introduction of guanidinium groups into macrocyclic molecules has been developed and applied to the synthesis of three such macrocycles (**1**), (**3**), and (**5**) which display enhanced binding of phosphate anion.

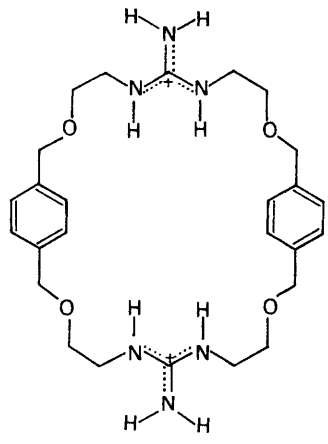
ANION co-ordination chemistry has received little attention compared to the numerous studies devoted to the co-ordination of cations, although anion complexation by organic ligands should offer exciting developments in organic, inorganic, and biological chemistry. The main task lies in the design of organic receptors for efficient and selective binding of inorganic anions and of negatively charged functional groups (carboxylate, phosphate, *etc.*) on organic and biological substrates. Anion inclusion complexes[1-4] have recently been described where the anion is bound inside a molecular cavity by ionic hydrogen bonds with ammonium sites yielding highly stable and selective anion cryptates of spherical[2,3] and triatomic anions.[4]

Macropolycyclic structures possess the architectural flexibility which should allow the designed arrangement in space of suitable anion binding sites, *i.e.* cationic sites like ammonium[1,2,4] and guanidinium groups. The guanidinium group presents several interesting features: it may form several zwitterionic hydrogen bonds $N\text{–}H^{+}\cdots X^{-}$ which provide binding strength by their charge and structural specificity by their arrangement as seen in the crystal structures of many guanidinium salts;[5] it has a very high pK_a (13·5)[6] and is therefore little affected by pH changes; in the arginyl residues of proteins it has an important function in the maintenance of protein conformations and in the binding and recognition of anionic substrates by enzymes, receptor sites, and antibodies (see for example ref. 7).

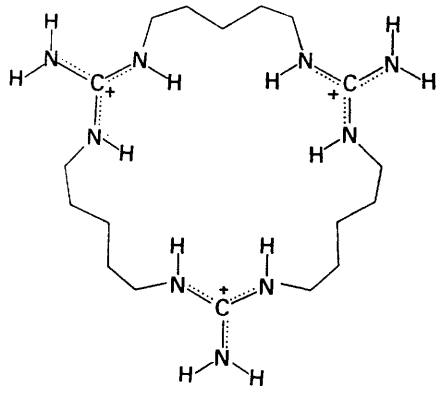
We report a scheme for the introduction of guanidinium sites into macrocyclic molecules, the synthesis of the three cationic guanidinium macrocycles (**1**), (**3**), and (**5**), and some preliminary anion complexation properties of these substances.



(1), $2Br^-$ or $2Cl^-$
(2), S instead of NH_2^+



(3), $2Br^-$ or $2Cl^-$
(4), S instead of NH_2^+

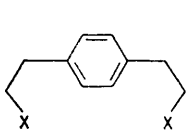


(5), $3Br^-$ or $3Cl^-$
(6), S instead of NH_2^+

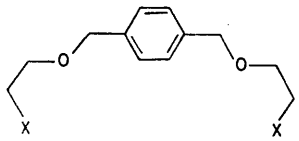
Reduction of αα′-dicyano-*p*-xylene with diborane gives the diamine (**7**) (m.p. 36 °C; lit.,[8] 36 °C; 65% yield). Reaction of αα′-dibromo-*p*-xylene with the monosodium salt of ethylene glycol in ethylene glycol affords the diol (**11**) (b.p. 195—200 °C at 0·6 mmHg; 65% yield), which, *via* its ditosylate (m.p. 70—71 °C) and the phthalimide method of Gabriel (see ref. 9), gives the diamine (**12**) [b.p. 154—158 °C at 0·2 mmHg; 55% yield from (**11**)].

The diamines (**7**), (**12**), and diaminopentane are converted respectively into the bis-isothiocyanates (**9**) [m.p. 97 °C, lit.[10] 99 °C; 65% yield from (**7**)], (**14**) [m.p. 35 °C; 65% yield from (**12**)], and (**17**) (b.p. 110—115 °C at 0·5 mmHg; 57% yield) *via* the intermediate dithiocarbamate derivatives (**8**), (**13**), and (**16**).[11] Controlled hydrogenolysis of the bis-carbamate (**18**) (m.p. 102—103 °C) affords the monocarbamate (**19**) (oil; 36% yield) which by reaction with thiophosgene gives (**20**) (m.p. 110 °C; 48% yield); deprotection with HBr–AcOH affords the diamine (**21**) (oil; 95% yield).

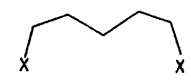
Reaction of an amine with an isothiocyanate is a very fast reaction which should be well suited for the formation of macrocycles by cyclization under high dilution conditions. Indeed, condensation of the diamine (**7**) with the bis-isothiocyanate (**9**) in toluene, using the high dilution procedure previously described for amine–acid chloride reactions,[9] affords the macrocyclic bis-thiourea (**2**) (m.p. 252 °C, decomp.) in 75% yield. Reaction of (**12**) with (**14**) gives (**4**) (m.p. 216—217 °C; 80% yield). Finally, condensation of (**17**) with (**21**) leads to the tris-thiourea macrocycle (**6**) (m.p. 192 °C) in 40% yield.



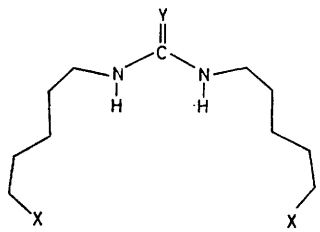
(7), $X = NH_2$
(8), $X = NHCS_2CO_2Et$
(9), X = NCS
(10), $X = [NHC(NH_2)NHEt]^+, 2\ Cl^-$



(11), X = OH
(12), $X = NH_2$
(13), $X = NHCS_2CO_2Et$
(14), X = NCS
(15), $X = [NHC(NH_2)NHEt]^+, 2\ Cl^-$



(16), $X = NHCS_2CO_2Et$
(17), X = NCS
(18), $X = NHCO_2CH_2Ph$
(19), $X = NH_2$ and $NHCO_2CH_2Ph$



(20), $X = NHCO_2CH_2Ph$, Y = S
(21), $X = NH_2$, Y = S
(22), $X = [NHC(NH_2)NHEt]^+$, $Y = NH_2$, $3\ Cl^-$

Conversion of a thiourea into a guanidinium salt may be achieved by various procedures.[12] In the present case where several thiourea groups are present in the same molecule the following conditions were found satisfactory: conversion of the thioureas (**2**), (**4**), and (**6**) into their *S*-ethyl-thiouronium derivatives by treatment with ethyl bromide in ethanol at reflux for 4—6 h followed by evaporation to dryness and reaction of the residue with ammonia in ethanol at 70 °C in a sealed tube for 6—8 h affords the macrocyclic guanidinium bromides (**1**), (**3**), and (**5**) respectively. Recrystallization from ethanol gives pure (**1**) (m.p. > 300 °C; 75% yield) and (**3**) (m.p. 209—210 °C; 80% yield). Purification of the tris-guanidinium salt (**5**) is achieved through conversion into its tris-picrate, recrystallization from MeOH–H_2O (tris-picrate: m.p. 170 °C, decomp.; 90% yield) and back-conversion into the tris-chloride salt. Whereas the thioureas (**2**), (**4**), and (**6**) are sparingly soluble or insoluble in common solvents the guanidinium chlorides are soluble in water and in methanol or ethanol.†

† All new compounds described have spectral (^1H and ^{13}C n.m.r.; mass spectra) and microanalytical properties in agreement with the assigned structures.

In order to be able to ascertain the effect of cyclization on complexation properties we also prepared the non-cyclic analogues (**10**), (**15**), and (**22**) of (**1**), (**3**), and (**5**) respectively, *via* the corresponding thiourea derivatives.†

Some preliminary measurements on the anion complexation properties of ligands (**1**), (**3**) and (**5**)‡ and of the reference compounds (**10**), (**15**), and (**22**)‡ have been performed for the phosphate anion. The stability constants K_S have been determined by computer analysis[13] of the pH titration curves[14] of the anion obtained in the absence and in the presence of the ligand. The results for the PO_4^{3-} species agree with the formation of 1:1 complexes having log K_S ($\pm$0·2): 1·7 (**1**), 2·2 (**3**), 2·4 (**5**), 1·05 (**10**), 1·7 (**15**), 2·1 (**22**), 0·95 (*NN'*-diethylguanidinium), and 0·7 (guanidinium)[15] in aqueous solution; 3·1 (**1**), 3·4 (**3**), 4·3 (**5**), 2·8 (**10**), 2·9 (**15**), 4·1 (**22**), and 2·1 (*NN'*-diethylguanidinium) in methanol–water (9:1) solution (at 20 °C). Both a chelate and a macrocyclic effect are found when comparing diethylguanidinium with the polyguanidinium species (**15**) and (**22**), and the acyclic species (**10**), (**15**), and (**22**) with the corresponding macrocycles (**1**), (**3**), and (**5**).

Although these effects are still quite weak compared to those observed for alkali cation complexation,[16] compounds (**1**), (**3**), and (**5**) represent a step in the design of anion receptor molecules based on the guanidinium binding site, which would display high stabilities and selectivities of complexation, for instance, towards phosphate, diphosphate and, triphosphate anions and their biologically most important derivatives AMP, ADP, and ATP.

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‡ The relative orientations of the substituents at the guanidinium centres are not known at present. The *trans*, *trans* forms indicated would probably be best suited for anion complexation.

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