Stable Ammonium Cryptates of Chiral Macrocyclic Receptor Molecules Bearing Amino-acid Side-chains

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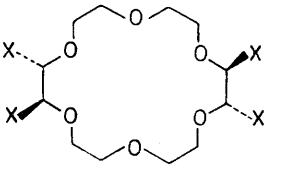
Summary The chiral 18-crown-6-tetracarbonyl-[1]-cryptands (**3**), (**5**), and (**6**) are molecular receptors for primary ammonium salts, forming stable complexes whose stability and selectivity depends on interactions with the side chains of the ligands.

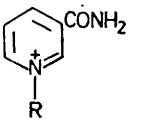
AMONG the most interesting features of macrocyclic polyethers is the ability of 18-crown-6 to form complexes with primary ammonium salts.[1] This property has been used to effect resolution of racemic ammonium salts,[2,3] especially by means of chiral crown ethers containing the binaphthyl group;[2] however, this group causes a large decrease in association constant.[4]

Our own efforts in the field of ammonium complexation were directed towards the synthesis of a chiral, polyfunctional, macrocyclic polyether unit where the functionalities are attached to the aliphatic carbons of 18-crown-6. This has been realized[5] by the one-step synthesis from *NNN'N'*-tetramethyltartramide of the tetra-functional chiral macrocyclic polyether[1]-cryptand (**1**).[6] The derivative (**2**) has been prepared from (**1**)[5] as well as by another route.[7]

The cryptand (**1**) complexes ammonium salts.[5] Its carboxylic groups may be used for the attachment of various structural units X which will line the periphery of the central cavity. One may thus hope to be able: (i) to influence complexation selectivity by choosing the 'recognizing' residues X and the type of interactions (electrostatic, hydrophobic, hydrogen bonding, *etc.*), *i.e.* study the *receptor* properties, and (ii) to perform molecular polyfunctional *catalysis* if the X units incorporate catalytic groups; it is important that the complexes be stable enough for performing tasks (i) and (ii) in water.

(1) X = $CONMe_2$
(2) X = CH_2OH
(3) X = CO_2H or CO_2^-
(4) X = COCl
(5a) X = L-CONH-CH(CO_2Me)-CH_2-(3-indole)
(5b) X = L-CONH-CH($CO_2^-NMe_4^+$)-CH_2-(3-indole)
(6a) X = -CONH-CH_2-CO_2Me
(6b) X = -CONH-CH_2-$CO_2^-NMe_4^+$
(7) X = -CO-NH-CH_2-CH_2-(4-imidazole)
(8) X = L-CO-NH-CH(CO_2Me)-CH_2-SH

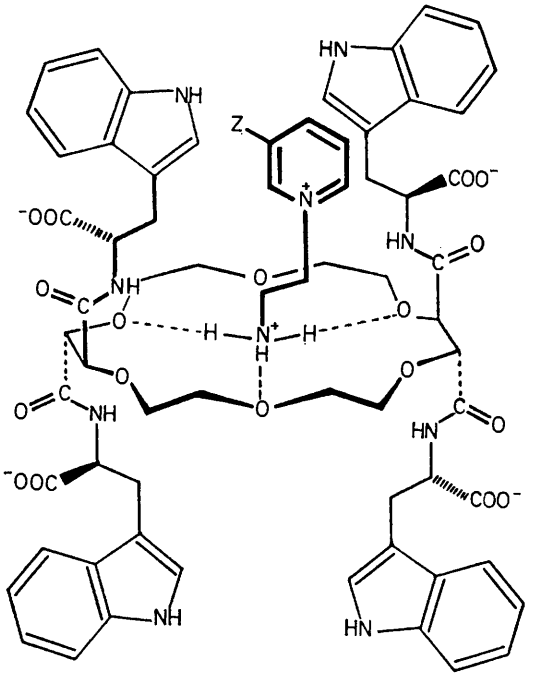




(10a) R = $-CH_2CH_2NH_3^+$
(10b) R = $-[CH_2]_4-NH_3^+$

We report here some of our results on stable R–NH_3^+ complexes obtained with compounds (**5**) and (**6**) containing respectively tryptophan and glycine residues. The corresponding tetrahistamido (**7**) and tetracysteinyl (**8**) compounds have also been prepared.[8]

Hydrolysis of (**1**) (2·5N-HCl, 12 h; 80 °C) yields the tetra-acid (**3**) (m.p. 211 °C) which forms a crystalline $H_3O^+Cl^-$ complex. (**3**) is converted into (**4**) with PCl_5 [crystalline, m.p. 180 °C (decomp.)]. Condensation of (**4**) with the amino-acid methyl esters gives (**5a**) (m.p. 135—138 °C) and (**6a**) (m.p. 188 °C) which may be hydrolysed to (**5b**) and (**6b**) using Me_4NOH.



Z = $CONH_2$

(**9**)

The stability constants of the complexes formed by ligands (**3**), (**5**), and (**6**) with a series of primary ammonium salts in aqueous solution are listed in the Table.

These results indicate the following. (i) As portrayed in formula (**9**),† anchoring of the NH_3^+ group of R–NH_3^+ salts into the ring allows the operation of secondary interactions with the residues X, which may influence both the stability and the selectivity of the complexes. The periphery is hydrophobic in the case of (**5**) and may be uncharged (**5a**, **6a**) or negatively charged (**5b**, **6b**). Compounds (**5**), (**6**), and (**8**) represent the first combination of the 'crown' unit with amino-acids *via* a peptide bond, forming a 'parallel' tetrapeptide (as compared to linear oligopeptides).

(ii) Whereas (**1**) has complexation properties close to those of the parent compound (**1**) (with X=H) for K^+ and NH_4^+,[5] compound (**3**) as the tetracarboxylate forms by far the most stable K^+ and NH_4^+ complexes reported to date for a macrocyclic polyether.

(iii) The stabilities‡ of the R–NH_3^+ complexes reported here are much higher than those of the parent 18-crown-6 (K_s *ca.* 5 for $MeNH_3^+$[9]). These complexes are consequently also much more stable than those formed by a large number of modified 18-crown-6 type macrocycles, the stabilities of which at most equal that of complexes of the parent system.[4]

TABLE. Stability constants, K_s, of macrocyclic ammonium cryptates.[a]

Cryptand	Substrate	K_s[a]
(**1**)	K^+	70
	NH_4^+	<5
(**3**)	K^+	$3\pm1\times10^5$
	NH_4^+	3200 ± 200
	$MeNH_3^+$	750 ± 60
	$PhCH_2CH_2NH_3^+$	260 ± 40
(**5b**)	K^+	$5{\cdot}5\pm1\times10^4$
	NH_4^+	340 ± 20
	$CH_3NH_3^+$	95 ± 20
	$PhCH_2NH_3^+$	145 ± 15
	$PhCH_2CH_2NH_3^+$	100 ± 20
	$^+H_3NCH_2CH_2NH_3^+$	3000 ± 900[b]
	$^+H_3N(CH_2)_3NH_3^+$	800 ± 100
	$^+H_3N(CH_2)_4NH_3^+$	570 ± 90
	(**10a**)	2300 ± 700[b]
	(**10b**)	400 ± 50
(**6b**)	K^+	180 ± 20
	NH_4^+	10 ± 5
	$MeNH_3^+$	<10

[a] Determined with K^+ or NH_4^+ ion-selective electrodes, by competition with NH_4^+ for the substituted salts R–NH_3^+; in water at 25 °C; 0·1 M; tetramethylammonium phosphate buffer at pH 7·0. The error limits indicated are valid for comparing stabilities within a series of substrates; the absolute error on K_s is estimated to be *ca.* ± 20%. [b] Less accurate values because of correction for incomplete protonation of the substrate at pH 7·0.

From the stability sequence of the K^+, NH_4^+ complexes, (**3**) > (**5b**) >> (**6b**) > (**1**), two main points emerge: (a) carboxylate groups increase complex stability, and especially strongly when they are close to the ring [compare (**6b**) and (**3**) with (**1**)], (b) most striking is the very large increase in stability from (**6b**) to (**5b**); it may be due at least in part to two effects: a better arrangement of the carboxylate groups for interaction with the cation and/or the increase in ion-pair interaction over solvation owing to shielding by the bulky, hydrophobic indole groups. The latter effect appears to dominate since the stability of the NH_4^+ complex increases more from (**6b**) to (**5b**) than from (**1**) to (**6b**); it may also be of importance in increasing enzyme substrate interactions in active sites containing hydrophobic residues.

(iv) The selectivities of complexation display electrostatic and hydrophobic effects. Whereas (**3**) complexes $MeNH_3^+$ more strongly than $PhCH_2CH_2NH_3^+$, the latter is bound as strongly as the former by the more hydrophobic receptor (**5b**). Electrostatic interactions between the carboxylate groups and the free NH_3^+ end group in the complexes of (**5b**) with the diammonium salts lead to a marked increase in stability (Table). Finally, the remark-

† The small (*ca.* 2 Hz) coupling found between the vicinal C–H protons of the tartaric-type residues in derivatives of (**1**) bearing different X groups at each residue agrees with an arrangement of the X groups close to the diaxial type represented in (**9**).

‡ Solvent effects on stabilities are very important. The K_s values listed in the Table are for aqueous solutions. They are expected to be much higher in methanol (factor $>10^3$) and in chloroform (factor $>10^5$—10^6).[1,2,5,6]

able stability of the nicotinamide complex (**9**) may also incorporate a contribution from a donor–acceptor interaction (see also below).

(v) Confirmation that interactions between side chains and complexed substrate (as pictured in **9**) do indeed occur is provided by the presence of a charge transfer (C.T.) band in the u.v. spectrum of complex (**9**) (shoulder at 305 nm; ϵ *ca.* 500; aqueous solution). This band may be ascribed to pyridinium-indole interaction and resembles the intramolecular C.T. band (diffuse band, 300—400 nm; ϵ *ca.* 1000 at *ca.* 320 nm, MeOH) found in model systems where both groups are linked in the same molecule.[10] When excess of K^+ is added to (**9**) the C.T. band disappears owing to displacement of the pyridinium salt.

Further variations in receptor structure and substrate nature will help to define the elementary structural units required for controlling complex stability and receptor selectivity. Such model studies also provide quantitative data on elementary interactions occurring in biological receptor sites.

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