One-step synthesis of a quaternary tetrapyridinium macrocycle as a new specific receptor of tricarboxylate anions

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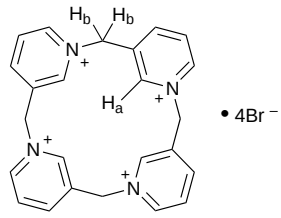
A new type of quaternary tetrapyridinium macrocycle has been readily prepared *via* a one-step reaction, which showed characteristic selectivity for certain tricarboxylate anions upon 1 : 1 complexation.

Because anion recognition plays an important role in many biological processes, much effort has been devoted to designing specific anion receptors in molecular recognition chemistry.[1,2] In most of the reported receptors, positively charged groups such as ammonium and guanidinium units have been commonly introduced as binding sites, with electrostatic attraction between ion pairs predominantly contributing to the stability of the complexes.[3] Structural complementarity also affects both the selectivity and stability of the anion complexation. Kimura and Hosseini and Lehn demonstrated[4] that some protonated polyazamacrocycles bound carboxylates and phosphates, and exhibited interesting anion selectivity. Since the number of synthetic receptors specific for anions is still limited, a new class of macrocycles having well-defined geometrical and binding features should be developed, especially for specific recognition of biologically important organic polyanions.

Here, we present the one-step synthesis, crystal structure and anion binding property of a new macrocyclic receptor **1**.† Although polyammonium macrocycles have been presented as effective anion receptors, macrocycle **1** is remarkable for the following reasons. (1) Macrocycle **1** was directly derived from 3-bromomethylpyridine and its synthetic procedure was extremely simple. (2) The macro-ring is composed of four pyridinium rings having structurally and electrostatically well-defined features. (3) The positive charge of **1** is permanent and active even under neutral or weakly alkali conditions, while corresponding aliphatic polyammoniums are not fully protonated under such conditions.



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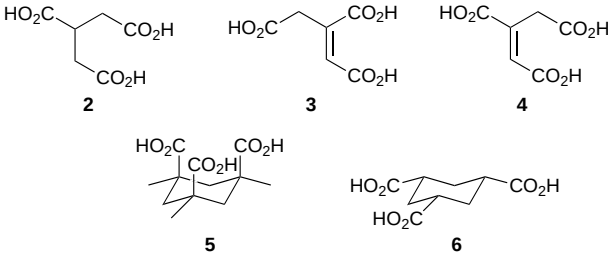
An aqueous solution of 3-bromomethylpyridinium bromide (4.5 g, 18 mmol) was neutralized with $NaHCO_3$ and the resulting 3-bromomethylpyridine was immediately extracted in CH_2Cl_2 (40 ml). When the solvent was evaporated at room temperature, *N*-alkylation vigorously occurred to yield a mixture of quaternary pyridinium salts. Hydrated single crystals of the tetrapyridinium bromide **1**, $C_{24}H_{24}N_4Br_4{\cdot}2H_2O$,‡ were isolated by recrystallization from water (230 mg, 0.32 mmol). A mixture of linear oligomeric pyridinium salts was obtained as major products, but product analysis by capillary electrophoresis revealed that cyclic compounds having different ring sizes were not formed under the employed conditions. *N*-Alkylation also occurred in refluxing CH_2Cl_2, which gradually yielded cyclic tetramer and linear polymer.

The crystal structure§ of **1**·$2H_2O$, determined by an X-ray diffraction study, indicates that the 16-membered ring containing four pyridine nitrogen atoms with positive charges is almost in one plane (Fig. 1). Of the four counter bromide anions, two are located inside the macrocycle, while the others are located outside the macrocycle. The distances between these bromide anions and the H_a protons of the pyridine rings are in the range 2.65–2.79 Å, which are shorter than the sum of the van der Waals radius of a hydrogen atom and the ionic radius of a bromide anion (3.17 Å).[5]

The binding property¶ of **1** for tricarboxylate anions was investigated by ^1H NMR titration experiments in D_2O in which the pH value was initially adjusted to be 7–8 with $NaHCO_3$ to make guest anions in the trivalent forms. Five tricarboxylic acids were employed: acyclic tricarboxylic acids **2**–**4** and cyclohexane tricarboxylic acids **5** and **6**. When **3** was employed as a guest, large downfield shifts ($\Delta\delta$ = 0.83 ppm, 1 equiv.) were observed for the H_a proton signal†† while the signals for other aryl protons shifted slightly upfield ($\Delta\delta$ = 0.13 ppm, 1 equiv.). Other tricarboxylates **2**, **4** and **5** gave similar ^1H NMR spectral changes and the observed titration curves showed saturation and were well fitted by the 1 : 1 complexation, although **6** provided too small changes in the ^1H NMR spectra to precisely analyze. The binding constants *K* were calculated



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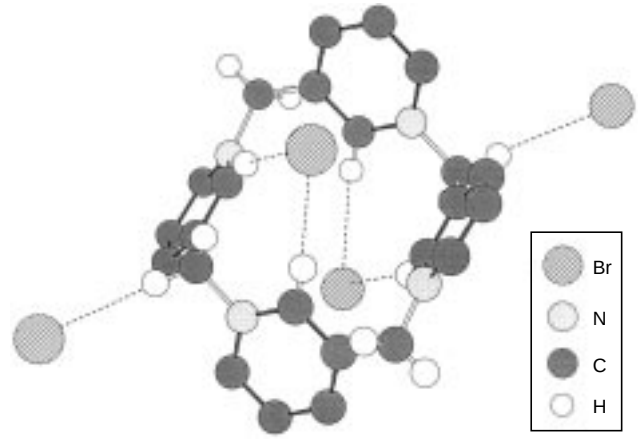

Fig. 1 Crystal structure of **1**·$2H_2O$. Hydrogen atoms other than H_a and H_b are omitted for clarification.

from the computer analysis,[6] indicating that **1** offered interesting anion selectivity for the four tricarboxylates; **3** (log K = 5.1) > **4** (4.5) ≈ **2** (4.4) > **5** (4.1). Among the acyclic tricarboxylates **2**–**4**, **3**, having two carboxylates fixed at the *cis*-1,2 positions, offered the largest K value. Because the employed tricarboxylates have the same net charges, the geometry of the three carboxyl groups should be an important factor for determining the stability and selectivity.[7] The order of the log K values parallels that of the chemical shift changes ($\Delta\delta$) of the H_a protons.‖

We have successfully prepared a new type of macrocyclic receptor *via* a one-step synthesis. Because of the pre-organized macrocyclic structure and highly positive charge, it specifically binds tricarboxylate anions at pH 7. Since its anion recognition behavior varied considerably from those observed with common protonated macrocyclic polyamines,[4,7] this study presents a new aspect of anion recognition chemistry with wide applications in related fields.

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Footnotes and References

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† R. E. Cramer and co-workers (ref. 8) prepared cyclic tetramers containing positive charge from vitamin B_1. Although they formed crystalline complexes with inorganic anions such as chloride, nitrate and $[Hg_2I_7]^{3-}$, their receptor functions have not been characterized in aqueous solutions.

‡ *Selected data* for **1**: mp 290 °C (decomp.) (Calc. for $C_{24}H_{24}N_4Br_4{\cdot}2H_2O$: C, 39.81; H, 3.90; N, 7.74. Found: C, 39.88; H, 3.81; N, 7.73%.) $\delta_H(D_2O)$ 9.43 (s, 4 H), 9.27 (d, 4 H), 8.91 (d, 4 H), 8.30 (t, 4 H) and 6.21 (s, 8 H); $\delta_C(D_2O)$ 151.02, 149.20, 147.21, 137.05, 132.98 and 63.25; λ_{max} (H_2O)/nm 263. With 3-chloromethylpyridine as a starting material, cyclic products were also found to be formed from the ^{1}H NMR spectrum of the reaction mixture. Unlike the bromide salt, they did not crystallize from the reaction mixture.

§ *Crystallographic data* for **1**·$2H_2O$: $C_{24}H_{28}O_2N_4Br_4$, triclinic, space group $P\bar{1}$ (#2), a = 9.664(6), b = 10.955(5), c = 7.115(2) Å, α = 108.11(3), β = 104.60(3), γ = 67.17(3)°, V = 652.3(5) Å^3, Z = 1; 3004 independent reflections measured at 296 K using a Rigaku AFC7S diffractometer; Mo-Kα; 2185 reflections with $I > 3\sigma(I)$ and 155 variables yields R = 0.045, R_w = 0.066. CCDC 182/692.

¶ The complexation between **1** and **5** was confirmed by ESI-MS spectroscopy in H_2O–MeOH (pH 7); $[(\mathbf{1}–4Br^-)^{4+} + (\mathbf{5}–3\ H^+)^{3-}]^+$ was found at 623, $[(\mathbf{1}–3\ Br^-)^{3+} + (\mathbf{5}–2\ H^+)^{2-}]^+$ at 703 and $[(\mathbf{1}–4\ Br^-)^{4+} + (\mathbf{5}–2\ H^+)^{2-}]^{2+}$ at 312.

‖ Similar NMR spectral changes were reported in non-cyclic pyridinium molecule systems and some contributions from the hydrogen bonding between anion guests and protons of the pyridinium ring were suggested. See K.-S. Jeong and Y. L. Cho, *Tetrahedron Lett.*, 1997, **38**, 3279.

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