Proton Cryptates

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Summary Structures of the 1,6-diazabicyclo-[5,5,5] type have been synthesized and tertiary mono- and diammonium salts have been obtained in which the protons are "cryptated", *i.e.* located inside the molecular cavity and therefore efficiently shielded from the environment, so that deprotonation is extremely slow even in strong base.

BICYCLIC molecules of the [*k,l,m*] type (*k,l,m* $\neq$ 0) have been the subject of much interesting chemistry. Bicyclo-[*k,l,m*] structures, having *k,l,m* = 1—3, have been important substrates for mechanistic and conformational studies. Macrobicyclic molecules (*k,l,m* $\geqslant$ 6) have recently revealed new facets of organic chemistry.[1—5] Medium size bicyclic systems with *k,l,m* = 4,5 would be expected to have strong interactions between the bridges; no such molecule has yet been reported, the two bicyclic structures at the limit of the gap being of the [4,4,2][6] and [5,5,8][7] type. In addition, if the bridgeheads are nitrogen atoms these structures may present two other interesting properties:

(i) they lie at the borderline where *in–in* (*ii*), *out–in*(*oi*), *out–out*(*oo*) isomerism[1] becomes possible (all smaller systems are *oo*);

(ii) since the central molecular cavity is small and highly shielded, inside protonation would lead to ammonium salts which could be considered as "proton cryptates" in which, by analogy with the metal cation cryptates described earlier,[5,7] the protons are hidden inside the molecular cavity.

Inside protonation of macrobicyclic diamines has already been described;[1,2] the rates of deprotonation reported, although slower than for acylic amines, are still much faster than in the systems discussed below.

We describe here the synthesis and some unusual properties of molecules of the 1,6-diazabicyclo-[5,5,5] type.

Condensation of the cyclic diamine (I) with diglycolic acid dichloride under high dilution conditions gives the bicyclic diamide (II) (10%; m.p. 178—180°) and a tricyclic dimer (30%).† Treatment of (II) with diborane affords a mono-borane amine (III) (95%; m.p. 151°).

Using a large excess of diborane, (III) could not be converted into a bis-borane amine, which is the type of product usually obtained with larger bicyclic systems.[4]

(III) affords the bicyclic diamine (IV) on treatment with a solution of KOH in methanol (33%; m.p. 81—83°). Spectral and analytical data of (III) and (IV) agree with the assigned structures. The n.m.r. spectrum of (IV) (in $CDCl_3$) displays two triplets (*J* 4·7 Hz) at 2·63 and 3·60 p.p.m. for the CH_2–N and CH_2–O protons, respectively.

When (III) is hydrolysed by boiling 6N-HCl for 2 h, a dihydrochloride (V) is obtained. The n.m.r. spectrum of (V) contains a "quartet" and a "triplet" at 3·70 and 3·95 p.p.m. for the CH_2–N^+ and CH_2–O groups, respectively, and a very broad signal, integrating for 2 H–N^+ protons at 7·5 p.p.m. (linewidth *ca.* 80—100 Hz). Strong irradiation of this signal leads to a CH_2–N^+ "triplet" similar to the CH_2–O signal, indicating that the additional splitting

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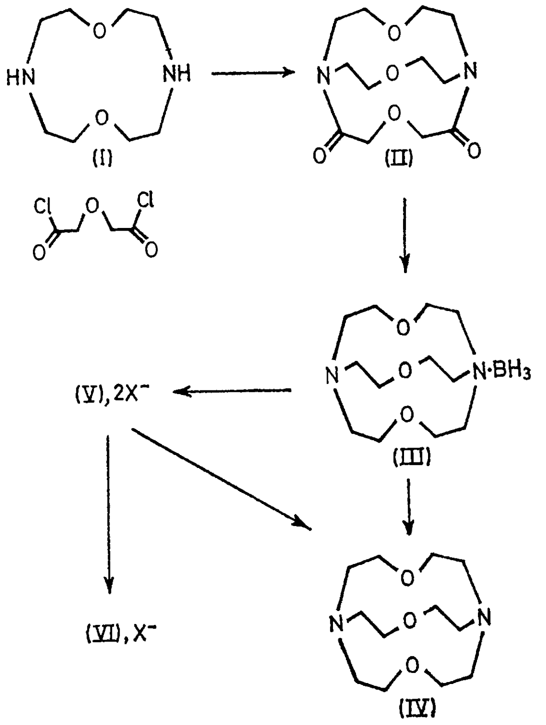
† The chemistry of this compound will be described later.[8]

(*ca.* 5 Hz) is due to coupling to the slowly exchanging ammonium proton.



This diammonium salt (V) has unusual properties. It is unchanged (<5% deprotonation) after 18 days in 5N-KOH at room temperature. When heated to 60° in 5N-KOH for *ca.* 80 h, (V) is 50% converted into a new compound (VI) (k *ca.* $5 \times 10^{-7}\,\mathrm{l\,M^{-1}\,s^{-1}}$). (VI) may also be obtained by passing an aqueous solution of (V) over a quaternary ammonium hydroxide anion exchange column, in a yield depending on the length of contact between the solution of (V) and the strongly basic column.

When (V) is passed quickly through the column, no (VI) is obtained and the eluate is shown by n.m.r. and titration to be still a diammonium salt in the form of its dihydroxide. Thus, one obtains a ditertiary ammonium dihydroxide behaving like a diquaternary ammonium dihydroxide. The nature of (VI) is no less surprising: analytical and n.m.r. data show that it is still an ammonium salt: a monoprotonated derivative of diamine (IV). The n.m.r. spectrum of (VI) contains a "sextet" at 3·30 p.p.m. and a "triplet" at 3·70 p.p.m. for the CH_2–O and CH_2–N protons, respectively, and a broad singlet (linewidth *ca.* 10–15 Hz) at 8·65 p.p.m., integrating for 1 N–H proton.

Strong irradiation of this last signal leads to a "triplet" for the CH_2–N protons similar to the CH_2–O "triplet", indicating that the additional splitting (*ca.* 2·5 Hz) is due to the coupling to a single proton, jumping rapidly back and forth between the two nitrogens but not exchanging with other protons of D_2O deuterons. Treatment of (VI) with a boiling conc. DCl–D_2O solution (90 min) leads to the mono-H^+–mono-D^+ diammonium species (V) (with H^+, D^+ inside).

The interconversions (1), (2), and (3) have also been effected.

(V) → (IV) (excess of Na–liq. NH_3) (15%) (1)
(III) or (IV) → (VI) (acid at room temperature) (2)
(VI) → (V) (6N-HCl, 2 h reflux)‡ (3)

Reactions (2) and (3) are almost quantitative. Conversion of (VI) directly into (IV) has not yet been achieved.

In addition, an aqueous solution of (IV) is basic and becomes slightly more basic with time while the n.m.r. spectrum shows the progressive formation of a small amount of (VI). In a typical experiment *ca.* 15% [IV, H]$^+$ OH$^-$ is obtained after 24 h.

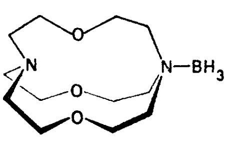
The structures of the various compounds described are confirmed by analytical and spectral data and their chemical properties.

The results described can be rationalized in terms of the possible topologies of the bicyclic system:

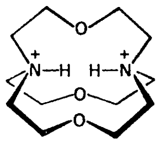
—the mono-borane amine (III) must have the (*io*) form since only one nitrogen is available for complexation with BH_3;

—because of their great resistance to deprotonation, the disalt (V) and the monosalt (VI) must be ammonium salts having the proton(s) located inside the molecular cavity of the *ii* form: i^+i^+ and i^+i, respectively (see diagrams). Molecular models show that such "cryptated" protons are well shielded from attack by an OH^- ion. (VI) could also be formed of two rapidly equilibrating inside protonated *io* forms: $i^+o \rightleftharpoons oi^+$. Some data indicate that a very small amount of this form may be present but the i^+i form is expected to be much more stable. The two nitrogens being far apart (*ca.* 3·5 Å) the proton is probably not located symmetrically between them but jumps rapidly from one to the other: $i^+i \rightleftharpoons ii^+$.

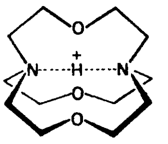
—since (a) an aqueous solution of (IV) is basic, (b) inside protonation is irreversible, and (c) the n.m.r. spectrum of (IV) shows only one type of CH_2N proton, (IV) must be either an *oo* form, or a rapid (on the n.m.r. time scale) $oi \rightleftharpoons io$ equilibrium or a rapidly equilibrating mixture of all forms.



(III)



(V),2X⁻



(VI),X⁻

It has also been found that the diamine (IV) leads to a lithium cryptate[5] when a $CDCl_3$ solution is treated with solid LiSCN. In water the complex is also formed but only

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‡ The protonation of (IV) to (VI) and of (VI) to (V) are complex processes, as seen in the n.m.r. spectra, and will be discussed in detail in the full paper.

with a large excess of LiSCN present, indicating that it is unstable, as expected from the small size of the molecular cavity. No complex has been observed with the other alkali or the alkaline-earth cations.§

(*Received, 17th January* 1972; *Com.* 074.)

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§ Be^{2+} has not yet been tried.

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