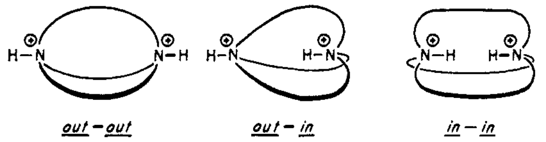
The shapes that the macrobicyclic amines assume is revealed by a remarkable isomerization of their ammonium salts. [8.8.8]-II gives a homogeneous, crystalline bishydrochloride from water whose 60-MHz spectrum in 50% aqueous trifluoroacetic acid (TFA) has broad absorptions at 8.9 (2 H), 3.1 (12 H), and 1.0–2.0 ppm (36 H). The N*H*$^+$ resonance at 8.9 ppm is similar to that of $(C_2H_5)_3N \cdot HCl$ (8.2 ppm). The bishydrochloride changed to an isomeric salt over 4 days in this solvent (Figure 1a,b), and addition of NaOH gave quantitative recovery of the amine. In the new ammonium ion, the N*H*$^+$ resonance is too broad to detect, and that of the α-CH_2 is a four-line multiplet centered at 3.2 ppm; the latter band is a sharp triplet (J = 5.5 Hz) in the corresponding bisdeuteriochloride, and the coupling is primarily to the β-CH_2. The lost N*H*$^+$ resonance, when irradiated at the ^{14}N decoupling frequency, appears far upfield at 4.6 ppm (2 H) (Figure 1c). The slow conversion of the initial ammonium ion to the isomer in 50% TFA is virtually complete (K_e > 100), but this equilibrium is established in ~30 min in water (K_e = 1.6). These and other data show that the initial ammonium ion is that isomer in which both NH^+ protons are *outside* the cavity, whereas both are *inside* in the new isomer. The 220-MHz spectra of the isomeric bisdeuteriochlorides clearly distinguish them (Figure 2).

We call the stereoisomerism of tetrahedral bridgehead atoms in three-stranded molecules "*out–in*."[3] Three stereoisomers of the bisammonium ions of II can exist when k, l, m > 6.



The $o^+o^+ \rightleftharpoons i^+i^+$ equilibrium has been detected in all amines in Table I, and in some cases crystalline isomers of both configurations have been isolated. For example, in the solid state the bishydrochloride of [8.8.8]-II exists as the o^+o^+ isomer, whereas the bisbifluoride is i^+i^+. Evidently the o^+i^+ isomers are of higher free energy than o^+o^+ or i^+i^+, probably because of torsional and nonbonded repulsion effects. The o^+i^+ ion is detected only when $k = l = m \geq 10$, and then as a fleeting intermediate during establishment of the equilibrium.

Equilibrium constants ($o^+o^+ \rightleftharpoons i^+i^+$) for the amines in 50% TFA are given in Table I, and hydrophobic bonding is thought to be important in determining the position of the equilibrium in aqueous media. An alternation effect is evident in the symmetrical ions; even chain lengths favor i^+i^+ isomers and odd, o^+o^+ isomers. The i^+i^+-[8.8.8] ion is particularly stable, and models suggest that it has a beautifully compact structure in which the chains contain a maximum of *trans* arrangements and are oriented for favorable nonbonded and dispersion interactions. It is thought that the o^+o^+ and i^+i^+ ions ($7 \leq k = l = m \leq 10$) have fewer preferred conformations than anticipated from their size and that the i^+i^+ ions exist with ellipsoidal shapes in which the hydrocarbon chains form a closed wall, giving them a sensible interior.

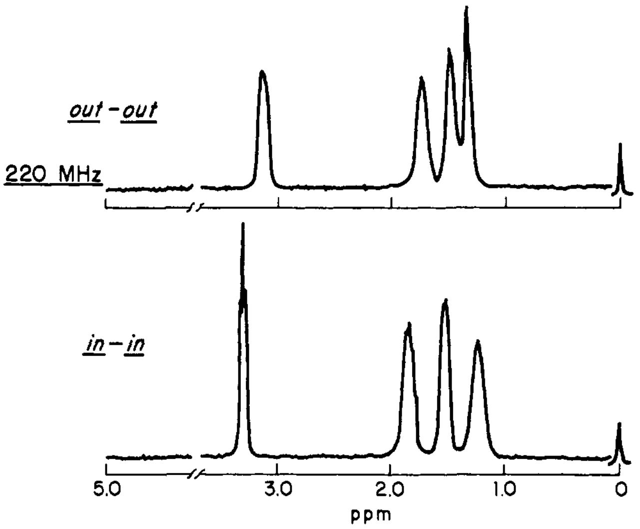


Figure 2. Pmr spectra (220-MHz) of *out,out*- and *in,in*-1,10-diazabicyclo[8.8.8]hexacosane bisdeuteriochloride in 50% CF_3CO_2D at 25°. The α-, β-, γ-, and δ-CH_2 absorptions occur at progressively higher fields.

The chemical shifts of the *out* protons decrease monotonically toward that of a simple tertiary aliphatic ammonium ion, such as $(C_2H_5)_3NH^+$, whereas those of the *in* protons similarly increase as the hydrocarbon chains lengthen (Table I). The unusually large upfield shifts (~4 ppm) of the *in* protons can be accounted for largely in terms of electrostatic effects, diamagnetic anisotropic shielding by the hydrocarbon chains, and less effective solvent hydrogen bonding.

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[3] We suggest names such as *out,out*-1,10-diazabicyclo[8.8.8]hexacosane bishydrochloride, conveniently abbreviated as *out,out*-$[8.8.8]^{2+}$, o^+o^+-[8.8.8], or simply o^+o^+ when the size is clear.

Macrobicyclic Amines. II.
out-out $\rightleftharpoons$ *in-in* Prototropy in 1,(k + 2)-Diazabicyclo[$k.l.m$] alkaneammonium Ions

Sir:

The interconversion of the o^+o^+ and i^+i^+ ammonium ions of 1,(k + 2)-diazabicyclo[$k.l.m$]alkanes[1] in aqueous solvents involves a sequence of prototropic reactions and nitrogen inversions, rather than a homeomorphic isomerization.[2] For example, when *out,out*-1,10-diazabicyclo[8.8.8]hexacosane bishydrochloride (o^+o^+) is dissolved in water at 25°, equilibrium with the *in,in* isomer (i^+i^+) is slowly established.

Our work has been guided strongly by studies of Grunwald[3] on the mechanism of NH^+ proton exchange

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[1] H. E. Simmons and C. H. Park, *J. Am. Chem. Soc.*, **90**, 2428 (1968).

[2] Homeomorphic isomerization is used here to mean a conformational change in which three-stranded molecules turn inside out by passage of one chain through the ring defined by the other two chains. Although this process can be demonstrated with Stuart–Briegleb models when $k = l = m \geq 8$, the free-energy barrier is so large that distinct atropisomers can be isolated.

[3] The observed exchange rate is independent of $[H^+]$ at pH 1–4 but inversely proportional at pH <1. See E. Grunwald, *J. Phys. Chem.*, **67**, 2208 (1963); **67**, 2211 (1963); E. K. Ralph, III, and E. Grunwald,

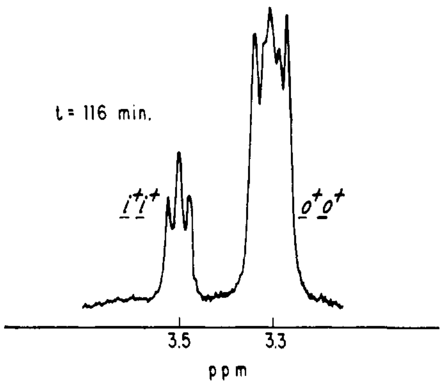

Figure 1. Pmr spectrum (220 MHz) of the α-CH_2 absorptions of 1,10-diazabicyclo[8.8.8]hexacosane bisdeuteriochloride in 0.1 *N* DCl at 23°.

in tertiary aliphatic ammonium ions in water. We have investigated six-, eight-, and ten-step mechanisms for the $o^+o^+ \rightleftharpoons i^+i^+$ isomerization and found that an eight-step mechanism best fits the experimental data.

$$o^+o^+ + 2H_2O \rightleftharpoons o^+o\cdots HOH + H_3O^+ \tag{1}$$

$$o^+o\cdots HOH \rightleftharpoons o^+i + H_2O \tag{2}$$

$$o^+i + H_2O \rightleftharpoons o^+i\cdots HOH \tag{3}$$

$$o^+i\cdots HOH + H_3O^+ \rightleftharpoons o^+i^+ + 2H_2O \tag{4}$$

$$2H_2O + o^+i^+ \rightleftharpoons H_3O^+ + HOH\cdots oi^+ \tag{5}$$

$$HOH\cdots oi^+ \rightleftharpoons ii^+ + H_2O \tag{6}$$

$$H_2O + ii^+ \rightleftharpoons HOH\cdots ii^+ \tag{7}$$

$$H_3O^+ + HOH\cdots ii^+ \rightleftharpoons 2H_2O + i^+i^+ \tag{8}$$

In the scheme, *o* and *i* indicate the stereochemistry of free amine lone pairs in the monocations. Solvent hydrogen bonding to NH^+ protons is omitted for clarity, and only that to nitrogen lone pairs is shown. Steps 1, −4, 5, and −8 are simply ionizations of ammonium ions. Steps 2 and 6 involve inversion of free amine nitrogens during which a hydrogen bond is lost; it is reasonable that kinetically significant *o* species are solvated, *e.g.*, $o^+o\cdots HOH$. Reestablishment of the hydrogen bond in steps 3 and 7, preparatory to proton transfer from hydronium ion in the solvent shell, requires the water molecule to diffuse into the hydrocarbon cavity.

The kinetic expression for the eight-step scheme, treated as coupled, pseudo-first-order reactions, is

$$\ln\left\{\frac{C_0 - C_\infty}{C_t - C_\infty}\right\} = \frac{\alpha + \beta}{\gamma[H^+] + \delta}t$$

where α, β, γ, and δ are complicated expressions of $k_1\cdots k_{-8}$, and *C* is the concentration of o^+o^+ or i^+i^+. All uncharged species are considered unstable intermediates, as is o^+i^+, whose concentration is too small to detect experimentally.[1] Evidently the rate can be a function of the acidity, depending on the relative magnitudes of γ and δ.

The isomerization of o^+o^+ in aqueous HCl was followed at 23° by monitoring the α-CH_2 resonances (o^+o^+, 3.3 ppm; i^+i^+, 3.5 ppm) in the 220-MHz pmr spectrum[1] (Figure 1). The isomerization exhibited clean, first-order kinetics when $[H^+] = 0.05$–1.00 *M*, and an acid dependence was found. At pH >0.65 the observed rate constant for isomerization is 1.9×10^{-4} sec^{-1} and independent of $[H^+]$, whereas at pH <0.65 it is inversely proportional to $[H^+]$, requiring $\gamma = 5.2\delta$ (Figure 2).

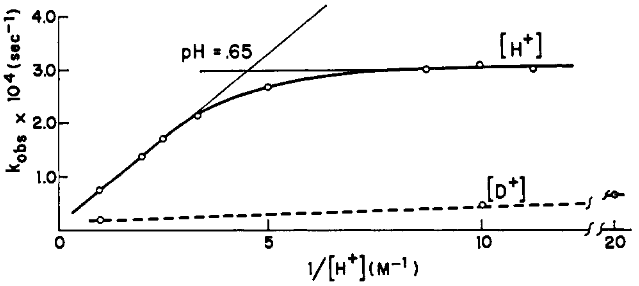

Figure 2. Dependence of observed isomerization rate constants on $[H^+]^{-1}$ (full line) and $[D^+]^{-1}$ (dotted line) for o^+o^+-[8.8.8] $\rightleftharpoons$ i^+i^+-[8.8.8] in aqueous HCl at 23°; $[o^+o^+]_0 = 0.18$ *M*.

Steps 1 and 8 were studied independently by measuring NH^+ proton-exchange rates of o^+o^+-[8.8.8] $2Cl^-$ and i^+i^+-[8.8.8] $2HF_2^-$ in deuterium oxide. It was found that $k_1 > 0.1$ sec^{-1} (the fast exchange of *out* protons could not be measured accurately by line-broadening methods[3]), but that $k_{-8} = 6.4 \times 10^{-5}$ sec^{-1}. Unlike simple tertiary aliphatic ammonium ions, the exchange rate of *in* protons was independent of $[H^+]$ over the range studied; this suggests that rotation of the *in* hydrogen-bonded water molecule may be the mechanism for exchange rather than diffusion[3] into the bulk solvent.

Rate constants were computed which met the following criteria: (1) $\gamma = 5.2\delta$, (2) k_f^{obsd} and k_r^{obsd} were a function of $[H^+]$, (3) K_e, (4) $[o^+i^+] < 0.05[o^+o^+]_0$, (5) NH^+ exchange rates, (6) nitrogen inversion frequency in [8.8.8] amine, and (7) steady-state assumptions.[1] In this way, it has been determined that $k_1 \sim k_5 \sim 1$, $k_{-1} \sim k_{-5} \sim 10^{10}$, $k_2 \sim k_{-2} \sim k_6 \sim k_{-6} \sim 10^6$, $k_3 \sim k_{-3} \sim k_7 \sim k_{-7} \sim 10^5$, $k_4 \sim k_8 \sim 10^6$, $k_{-4} \sim 10^{-3}$, $k_{-8} \sim 10^{-5}$. The refinement of these values, which suggest that $\Delta pK = -[\log (k_1/k_{-1}) - \log (k_{-8}/k_8)]$ is small (≤ 1), is in progress, but the orders of magnitude are believed correct.

Significantly, $k_{\pm 3}$ and $k_{\pm 7}$ are *ca.* 100,000 times smaller, and k_4 and k_8 are at least 10,000 times smaller than in simple tertiary aliphatic amines.[3] This is understandable on steric grounds since steps 3 and 7 involve diffusion of a water molecule into the hydrocarbon cavity and steps 4 and 8 involve a proton transfer from hydronium ion to this hindered water molecule. Perhaps as important, a water molecule must leave its stable environment in the bulk solvent and diffuse into a lipophilic region. The half-life for establishment of the $o^+o^+ \rightleftharpoons i^+i^+$ equilibrium is 40 min in D_2O, 15 min in 25% CD_3OD, and <1 min in CD_3OD. Acceleration of isomerization in methanol relative to water may reflect hydrophobic interactions in water which tend to compress the hydrocarbon chains and slow diffusion processes into the cavity. Preliminary measurements show that the temperature dependence of K_e in aqueous media is small, suggesting that the equilibria are largely entropy controlled.

The deuterium isotope effect on the isomerization rate (Figure 2) is in accord with the eight-step mechanism and will be discussed in a later publication. The isotope effect on the equilibrium is inverse, K_D/K_H =

J. Am. Chem. Soc., **89**, 2963 (1967); E. Grunwald and E. K. Ralph, III, *ibid.*, **89**, 4405 (1967).

1.19 ± 0.10, and not sensibly a function of acidity (0.05–1.00 *N*), showing that deuterons are favored over protons by 20% inside the molecular cavity.

The equilibrium and rate constants of the isomerization of the [7.7.7] and [8.8.8] ammonium ions are not influenced by the nature of the counterion; however, this is no longer so when the hydrocarbon chains contain nine or more methylenes due to a remarkable kind of ion pairing in the larger ammonium ions.[4]

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(4) C. H. Park and H. E. Simmons, *J. Am. Chem. Soc.*, **90**, 2431 (1968).

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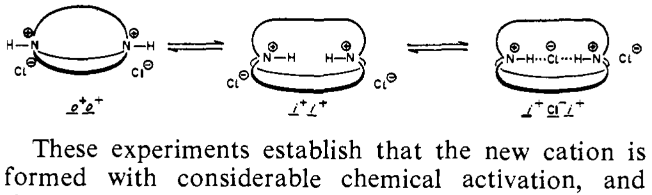
Macrobicyclic Amines. III. Encapsulation of Halide Ions by *in,in*-1,($k + 2$)-Diazabicyclo[*k.l.m*]alkane-ammonium Ions

Sir:

Certain *in,in*-1,($k + 2$)-diazabicyclo[*k.l.m*]alkane-ammonium ions[1,2] ($k = l = m \geq 9$) exhibit an unprecedented kind of ion pairing in aqueous media which involves diffusion of halide ions into the hydrocarbon cavity. This encapsulation does not occur in the smaller ammonium ions; furthermore, the o^+o^+ and i^+i^+ ions generally show no appreciable ion pairing in the usual sense, as judged from pmr concentration studies with a variety of anions.

out,out-1,11-Diazabicyclo[9.9.9]nonacosane bis(deuteriochloride), dissolved in 50% deuteriotrifluoroacetic acid (DTFA), is slowly converted to the *in,in* isomer ($K_e = 0.41$),[1] and subsequently a second equilibrium is established more slowly to produce a new monocation. The three ions are readily distinguished by their 220-MHz pmr spectra: the α-CH_2 absorptions occur at 2.90 (multiplet) in o^+o^+, 3.07 (triplet) in i^+i^+, and 2.80 ppm (triplet) in the monocation. In another experiment, 1.0 equiv (2 moles) of chloride ion (DCl, NaCl, or LiCl) was added to an equilibrium mixture of the o^+o^+ and i^+i^+ bis(trifluoroacetates) in 50% DTFA at 23°. The spectrum was unchanged shortly after mixing, but during several days the absorption at 2.80 ppm emerged (Figure 1a,b). The spectrum sharpened on heating at 65°, and all three absorptions were well differentiated (Figure 1c). This shows that the equilibrium constant of $o^+o^+ \rightleftharpoons i^+i^+$ is not disturbed and that interconversion of the monocation with either isomer is slow on the nmr time scale, even at elevated temperatures. Furthermore, basification gives quantitative recovery of the amine.



These experiments establish that the new cation is formed with considerable chemical activation, and they are consistent with encapsulation of chloride ion in the molecular cavity of an *in,in* isomer. The N*H*$^+$ absorption (2 H) of this bishydrochloride occurs at 8.0 ppm in 50% TFA, and the large downfield shift from the i^+i^+ ion (4.8 ppm)[1] can be accounted for by hydrogen bonding with the chloride ion. The upfield shift of the α-CH_2 resonance in the monocation can be explained in terms of anisotropic shielding effects of the ellipsoidally polarized chloride ion within the cavity.

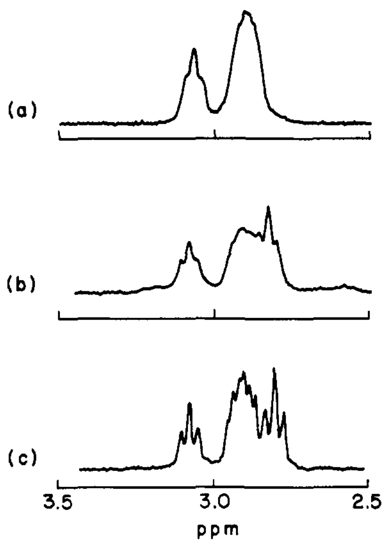


Figure 1. Pmr spectra (220 MHz) of α-CH_2 absorptions of 1,11-diazabicyclo[9.9.9]nonacosane in 50% DTFA; equilibrium mixture of o^+o^+ and i^+i^+ isomers to which 1.0 equiv of NaCl has been added; (a) t = 1 min, 23°; (b) t = 21 days, 23°; (c) t = 21 days, 65°.

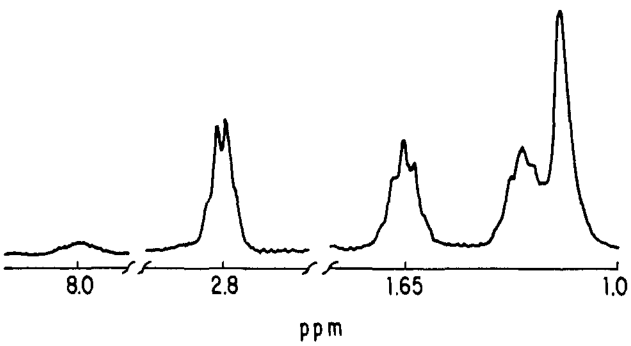


Figure 2. Pmr spectrum (220 MHz) of chloridekatapinate-*in,in*-1,11-diazabicyclo[9.9.9]nonacosanebis(ammonium) chloride in 50% DTFA at t = 12 min, 23°.

A new, crystalline bishydrochloride deposited when a solution of the [9.9.9] amine in 10% HCl was allowed to stand 5 days at 25°. The 220-MHz spectrum of this bishydrochloride in 50% TFA immediately after solution showed the presence of only the katapinate[3] $i^+Cl^-i^+$-[9.9.9] Cl^- (Figure 2). When this solution was allowed to stand, the equilibria among o^+o^+, i^+i^+, and $i^+Cl^-i^+$ are slowly reestablished. Bromide ion is encapsulated by i^+i^+-[9.9.9] less favorably than chloride, and no encapsulation of iodide can be detected (Table I).

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(1) H. E. Simmons and C. H. Park, *J. Am. Chem. Soc.*, **90**, 2428 (1968).

(2) C. H. Park and H. E. Simmons, *ibid.*, **90**, 2429 (1968).

(3) We define katapinosis (Greek, καταπινω = swallow up, engulf) as diffusion of molecules into a larger molecule with a sensible cavity to give a discrete molecular species. An appropriate name for the complex ammonium ion is chloridekatapinato-*in,in*-1,11-diazabicyclo[9.9.9]nonacosanebis(ammonium) chloride (a chloridekatapinate chloride) or simply $i^+Cl^-i^+$-[9.9.9] Cl^-.