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1,4,7,10-TETRAAZATETRACYCLO[5.5.1.$0^{4,13}$.$0^{10,13}$]-TRIDECANE: DEGENERATE REARRANGEMENT OF ITS CONJUGATE ACID

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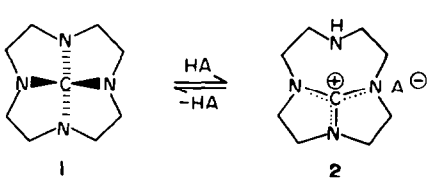
Abstract—The highly symmetrical 1,4,7,10-tetraazatetracyclo[5.5.1.$0^{4,13}$.$0^{10,13}$]tridecane (1) has been synthesized by two methods. The proton NMR spectrum of 1 is analyzed. The cyclic tetraaminomethane derivative undergoes a remarkable series of degenerate prototropic and conformational equilibria. The temperature dependence of the proton NMR spectra of 1 and its conjugate acid 3 are interpreted in terms of a large rate enhancement of intramolecular nucleophilic addition to guanidinium ion 3 (ring-chain tautomerism) compared to its acyclic counterpart.

Dialkylamide ions are normally poor leaving groups from tetrahedral carbon in ionization processes. In appropriately substituted molecules, however, protonated dialkylamino groups are well known to dissociate to carbonium ion intermediates and a secondary amine. The latter process is particularly facile in tetrakis(dimethylamino)methane,[1] a rare structural type which dissociates rapidly to hexamethylguanidinium ion and dimethylamine in water. Apparently, the reverse process has not been studied previously. Hydrolysis and other nucleophilic additions to guanidinium ions generally proceed very slowly.

In this paper we describe the synthesis of the highly symmetrical 1,4,7,10-tetraazatetracyclo-[5.5.1.$0^{4,13}$.$0^{10,13}$]tridecane (1), a molecule that dissociates readily and reversibly in water to an intramolecular guanidinium ion-amine pair (2). In aqueous solution, a remarkable sequence of degenerate prototropic and conformational equilibria accompanies dissociation and causes the magnetic equivalence of all protons.



1 2

†Salt 3 could not be isolated from the reaction of cyclen with phosgene, thiophosgene, phosgene imines, or trisalkoxycarbonium ion salts.

‡The reactants were refluxed in t-butanol with an equivalent of potassium t-butoxide. Intermediate 7 was isolated as the tetraphenylboron salt, m.p. 201–202°, from acetonitrile.

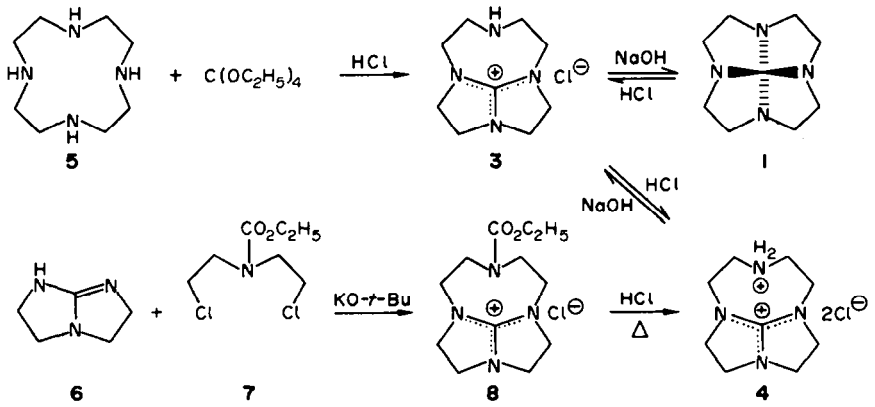
Synthesis

Two syntheses of the guanidinium salts 3 and 4 are illustrated in Scheme 1. The simpler route starts with 1,4,7,10-tetraazacyclododecane ("cyclen," 5),[2,3] one equivalent of hydrochloric acid, and ethyl orthocarbonate in ethanol giving 3, m.p. 133–136° (hydrate) in nearly quantitative yield.† Acidification of 3 with hydrochloric acid gives the guanidinium hydrochloride 4, m.p. 249–252°. Alternatively, the bicyclic guanidine 6[4] can be bridged‡ with the protected mustard 7[5] followed by hydrolysis to 4. The latter route suffers from low yield and difficult purification of intermediate 8 but confirms structure.

The tetracyclic amine 1 was isolated by extraction into benzene from a basified aqueous solution of 3 or 4. After careful azeotropic drying, 1 was obtained as a hygroscopic, sublimable, colorless solid, m.p. 97–105°. This synthesis is remarkable considering the need for lithium dimethylamide to effect addition to hexamethylguanidinium ion.[1] Mass spectroscopy of 1 shows the parent ion at *m/e* 180. The IR spectrum is shown in Fig 1. Potentiometric titration of an aqueous solution of 1 shows end points at the addition of one and two equivalents of acid. These data are in accord with the interconversions of 1, 3, and 4 shown in Scheme 1. The quantitative reconversion of 1 to 8 on treatment with ethyl chloroformate provides additional structural evidence.

Structure

The proton NMR spectrum of 1 in benzene (Fig 2) or other aprotic solvents under anhydrous conditions is a symmetrical AA'BB' pattern. The parameters shown in Table 1 were calculated from the 100 MHz spectrum by standard methods.[6] In the iteration process the values of $J_{AA'}$ and $J_{BB'}$ were al-



SCHEME 1.

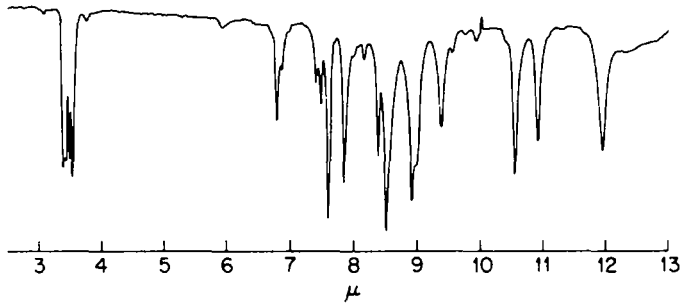
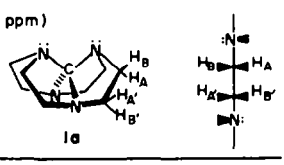


Fig 1. IR Spectrum of **1** in CCl_4.

Table 1. Calculated NMR parameters for **1** in benzene

	ΔA	156·0	(2·60 ppm)
	ΔB	180·7	(3·01 ppm)
J_{trans}	$J_{AA'}$	6·2±0·2	
J_{trans}	$J_{BB'}$	6·2±0·2	
J_{gem}	J_{AB}	−9·9	
J_{cis}	$J_{AB'}$	5·6	



lowed to vary independently but were calculated to be identical. This is an example of deceptive simplicity in the spectrum, only the sum of these coupling constants can be calculated accurately.

Consideration of the possible conformations for **1** suggests that the most stable form and the only form with equivalent methylene groups is **1a**. A molecular model of the conformer resulting from one nitrogen inversion in **1a** is considerably strained and those from successive inversions are prohibitively strained. The large negative value for J_{AB} identifies this as the coupling constant for geminal methylene protons.* The remaining values are consistent with the assignments in Table 1.

*P. J. Chivers and T. A. Crabb[7] report geminal coupling constants for methylene groups alpha to nitrogen in the range −8·6 to −13·6 Hz. Methylene groups with one CH bond eclipsing the nitrogen lone-pair orbital are presumed to have $J_{gem} \sim -8$ Hz.

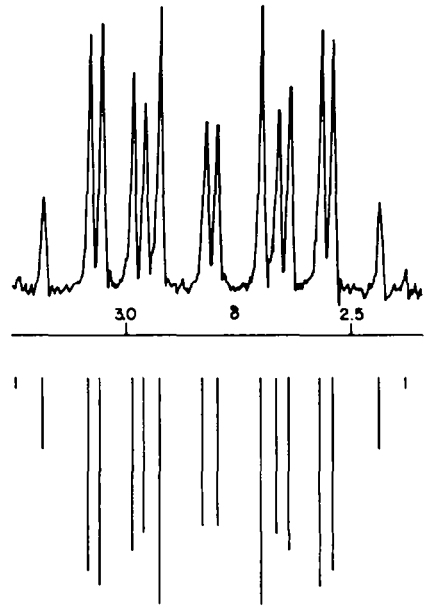


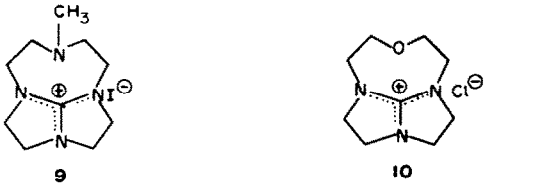
Fig. 2. 60 MHz proton NMR spectrum of **1** in benzene. The calculated spectrum is derived from the parameters in Table 1.

The coincidence of the values for the *trans* coupling constants $J_{AA'}$ and $J_{BB'}$ suggests that the ethylene units are eclipsed on the time average. Molecular models show that the conformation of **1a** with the lowest angle strain has eclipsed ethylene groups with one of the C–H bonds of each methylene eclipsing the nitrogen lone-pair orbital. The torsional strain introduced by four such ethano units should induce relaxation by rotation about these bonds. The eclipsed conformation probably represents a maximum on the energy profile separating conformations with slightly twisted ethylene groups. Tetramine **1** may therefore have the relatively rare D_2 symmetry, but D_{2d} on the time average.

The low-field protons were assigned as those protons (H_B) in **1a** which most nearly eclipse the nitrogen lone pair. There is evidence for staggered systems that an alpha methylene proton which is *gauche* to a nitrogen lone pair is deshielded relative to the *trans* proton.[8] Extrapolation of this behavior to systems which are nearly eclipsed seems questionable. Protons *syn* to the lone pair in aziridines are deshielded relative to the *anti* protons,[9] however aziridines are poor models for **1a** because of the ring strain. Data from model systems support our assignment and will be reported in a later publication.

The 60 and 220 MHz proton NMR spectra of the guanidinium chloride hydrochloride **4** are shown in Fig 3. The methylene proton region of these spectra is readily interpreted as two overlapping AA'BB' patterns. The multiplets centered at δ 4·24 and 3·60 closely resemble the symmetrical pattern of the hydrochloride salt of **6**. Since the spectra of **4** imply C_{2v} symmetry, apparently the most likely conformer, **4a**, undergoes rapid ring inversion (bridge flipping) at room temperature. At −48° the spectrum of **4** (Fig 3) shows dramatic broadening which implies that this bridge flipping is nearly frozen out.* Broadening is also observed in the low-temperature spectra of **9** and **10**, which should have similar barriers to bridge flipping.

4a



9 **10**

*Instrumental limitations precluded total resolution of the spectra at lower temperatures.

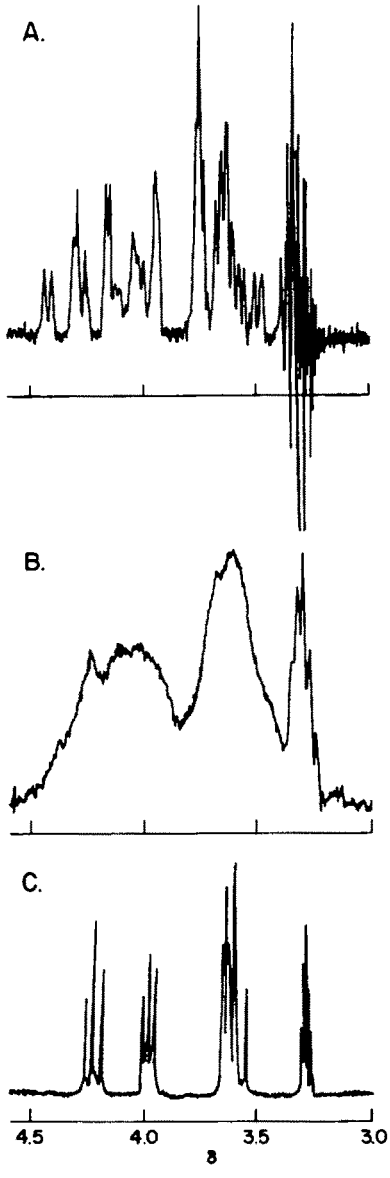


Fig. 3. Proton NMR spectra of **4** in CD_3OD. (A) 60 MHz at 68°C. (B) 60 MHz at −48°C. (C) 220 MHz at 20°C. Solvent multiplet appears at δ3·31.

A tertiary amine, one of whose alpha-carbons is bound to three electronegative N atoms as in **1**, would be expected to show reduced basicity. Hexamethylenetetramine and 1,4-diazabicyclo[2.2.2]-octane have acidity constants $5{\cdot}0 \times 10^{-7}$ and $2{\cdot}5 \times 10^{-9}$ (mol/l), respectively.[10] Yet tetramine **1** shows an apparent acidity constant $5{\cdot}0 \times 10^{-11}$ (mol/l) by potentiometric titration, indicating that **1** is an unexpectedly strong base. It will be shown in the following section that this small equilibrium constant is due to a subsequent transformation of the conju-

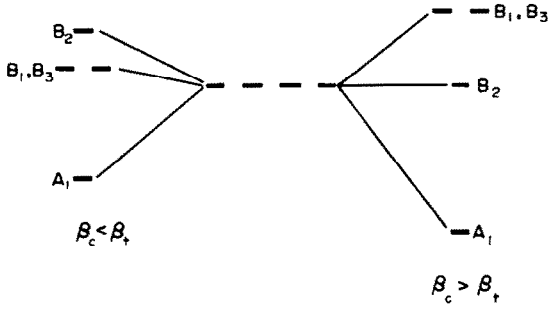
gate acid of 1 in water. The basicity of 1 can be estimated from the infrared stretching frequencies of $CDCl_3$ containing the amine.[11] Values of $\Delta\nu = \nu_{C\text{-}D} - \nu_{CD\cdot N}$ are 84 cm^{-1} for both triethylamine and quinuclidine.* 1,4-Diazabicyclo[2.2.2]octane, whose tertiary amine sites are influenced by a beta nitrogen substituent on each alkyl chain, shows $\Delta\nu = 69\ cm^{-1}$, whereas the still less basic hexamethylenetetramine has $\Delta\nu = 34\ cm^{-1}$. Tetramine 1 shows $\Delta\nu = 48\ cm^{-1}$. If the acidity constants for this series of similar amines are proportional to the frequency shifts, then K_{A_1} for 1 can be estimated as 6×10^{-8} (mol/l).

Since nitrogen inversion is unimportant in 1, the four lone-pair orbitals maintain D_2 symmetry. Such an array of four hybrid orbitals can be considered a distorted spiroconjugated[12] arrangement. The molecular orbitals resulting from such interaction are $\psi(A_1) = 1/2(h_1 + h_2 + h_3 + h_4)$, $\psi(B_1) = 1/2(h_1 + h_2 - h_3 - h_4)$, $\psi(B_2) = 1/2(h_1 - h_2 + h_3 - h_4)$, and $\psi(B_3) = 1/2(h_1 - h_2 - h_3 + h_4)$, where h_i is a hybrid orbital on nitrogen *i*. The corresponding energies are $\epsilon(A_1) = \alpha + \beta_c + 2\beta_t$, $\epsilon(B_1) = \epsilon(B_3) = \alpha - \beta_c$, and $\epsilon(B_2) = \alpha + \beta_c - 2\beta_t$, where β_c is the exchange integral for the *cisoid* 1,3 lone-pair interaction and β_t that of the *transoid* interaction. It is immediately apparent from these expressions and from the energy level diagram that the highest occupied molecular orbital depends critically on the relative magnitudes of β_c and β_t. (The diagrams refer arbitrarily to $\beta_c = 1/2\beta_t$ and $\beta_c = 2\beta_t$. Photoelectron spectroscopy measurements in progress may distinguish between the two possible cases. Interestingly, a peak in the mass spectrum of 1 appears at *m/e* 90 (P^{++}), indicating that the amine readily loses two electrons. Ionization may occur from the relatively high energy B_2 orbital resulting in a closed-shell stable dication.

Degenerate rearrangements. The most interesting feature of tetramine 1 is the isomerization and resulting degenerate rearrangement of its conjugate acid in water. The proton NMR spectra of guanidinium chloride 3 and its N-Me analogue 9 are similar at −31° in methanol-d_4 (Fig 4). At room temperature the spectrum of 3 collapses to a broad signal at about δ 3·6. Similar behavior is observed in D_2O. In acetonitrile-d_3 at −50° the 60 MHz spectrum is a pair of broad lines which coalesce and sharpen to a singlet on warming. The coalescence temperature (T_c) is higher for more dilute samples.

These data indicate that 3 undergoes a rapid dynamic process which equilibrates the four types of methylene groups. Scheme 2 provides a mechanism consistent with these observations. Accordingly, 3 isomerizes rapidly and reversibly to 11, the conjugate acid of 1. In a subsequent bimolecular process, 3 abstracts a proton from 11 to give 1 and 4. The net reaction is the reversible disproportionation of 3 to 1 and 4. The methylenes of 1 are equivalent, and therefore these processes interchange the four unique methylenes in 3.

The equilibrium for the net reaction in Scheme 2 lies far to the left in neutral media. We conclude this from the low-temperature NMR spectrum of 3 in methanol-d_4, from the IR spectra, and from experimental estimation of the equilibrium constant. Tetramine 1 shows two breaks in its titration curve



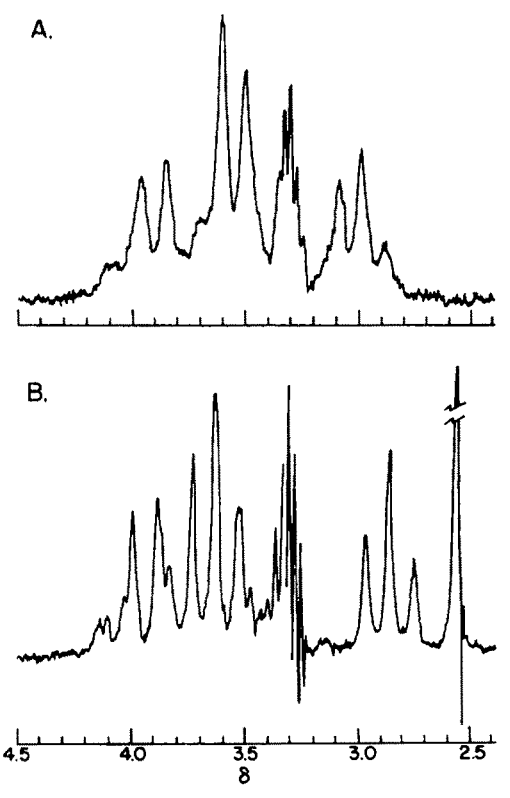
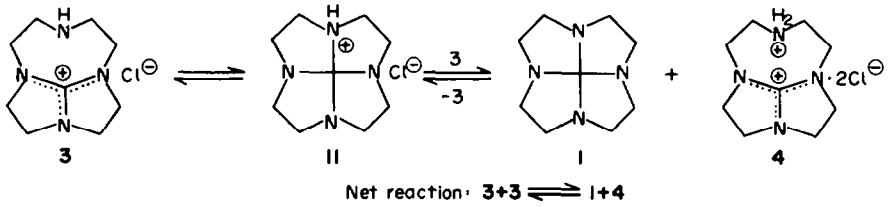


Fig. 4. Proton NMR spectra at 60 MHz in CD_3OD at −31°C. (A) Spectrum of 3. (B) Spectrum of 9. Solvent multiplet appears at δ3·31.

*Comparison with known tetrakis(dimethylamine)-methane is not possible because of its rapid reaction with $CDCl_3$.



SCHEME 2.

in water at 25° corresponding to equilibrium constants $K_1 = 5{\cdot}0 \times 10^{-11}$ and $K_2 = 3{\cdot}2 \times 10^{-6}$ (mol/l).

$$3 \overset{K_1}{\rightleftharpoons} 1 + H^+$$

$$4 \overset{K_2}{\rightleftharpoons} 3 + H^+$$

The equilibrium constant for the net reaction in Scheme 2 is

$$K = \frac{[1][4]}{[3]^2} = \frac{K_1}{K_2} = 1{\cdot}6 \times 10^{-5}$$

Hence, about 0·4% of **1** is present when **3** is dissolved in water. The equilibrium constant K_{iso} for the isomerization **3** ⇌ **11** can be calculated from K_1 and an estimate of K_{A_1}. From the frequency shift

$$K_{A_1} = \frac{[1][H^+]}{[11]} = K_1 \cdot \frac{[3]}{[11]} = \frac{K_1}{K_{iso}}$$

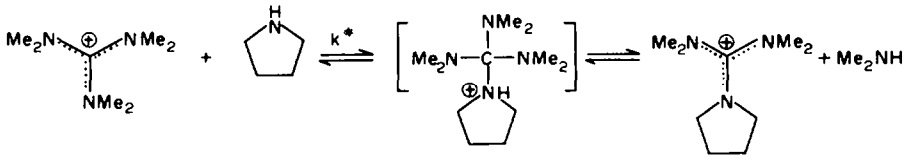
of **1** in $CDCl_3$ as discussed above, the value of K_{A_1} was estimated to be 6×10^{-8} (mol/l). K_{iso} is then 8×10^{-4}. The dissociation of **11** to the guanidinium ion-amine pair **3** is favored by 4 kcal/mol, apparently much less favorable than in acyclic tetraaminomethanes.

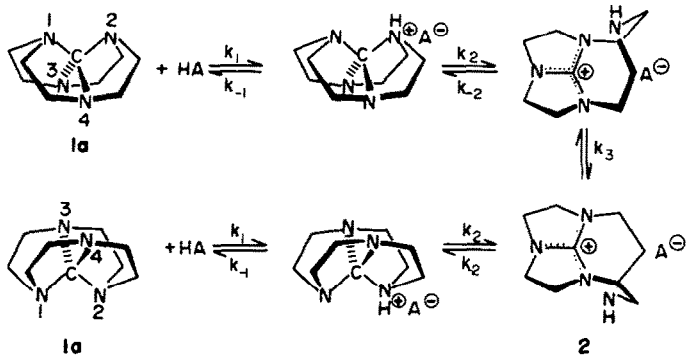
The surprising rapidity of the processes in Scheme 2 led us to examine the acyclic model reaction of pyrrolidine with hexamethylguanidinium chloride in methanol-d_4. The exchange was slow at 100°, requiring several minutes before dimethylamine was detected by NMR and several hours before equilibrium was reached. From the approximate half-life of this reaction, k* was estimated at 10^{-4} l/mol-sec. An estimate of $k_{-2} \sim 200\ sec^{-1}$ (Scheme 3) was made from coalescence temperature measurements on **3**. If all analogous proton transfer steps occur rapidly and at comparable rates, then we can estimate the effect of intramolecularity by the "effective concentration" $\simeq 200/10^{-4} = 2 \times 10^6$ mol/l, a value consistent with the entropic advantage observed in other intramolecular reactions.[13] Furthermore, the equilibrium constant for the addition of amines to acyclic guanidinium ions must be much smaller than 10^{-5} (l/mol) since the dissociation of protonated acyclic tetraaminomethanes should be at least as rapid as the dissociation of **11** (k_2).

The rapidly established equilibrium **3** ⇌ **11** proposed in Scheme 2 is crucial to understanding the dynamic behavior exhibited by **1** in protic solvents. The NMR spectrum of **1** in D_2O, in methanol-d_4, or in moist acetonitrile-d_3 at 38° is a singlet (δ 2·97, width at half height 1·5 Hz in CD_3OD). A solution of **1** in methanol-d_4 made 1N in sodium methoxide was examined for temperature dependence of the 60 MHz NMR spectrum. At − 41° the spectrum is a symmetrical broad multiplet which coalesces at − 10° and sharpens to a singlet on further warming (width at half height 0·9 Hz at 70°).

In protic solvents the two proton sites in **1a** must be rapidly exchanging. The equilibration mechanism outlined in Scheme 3 is consistent with the above results. These five steps lead to a net inversion of the central carbon atom in **1a** and interconvert the two proton types. The bridge-flipping motion k_3 is essential to this mechanism. The model compounds **9** and **10** apparently undergo the bridge-flipping process rapidly (*vide supra*). The other steps in Scheme 3 are similar to steps in Scheme 2 except that the acid HA is the protic solvent. Rapid exchange in strongly basic methanol-d_4 implies that methanol itself acts as the acid HA.

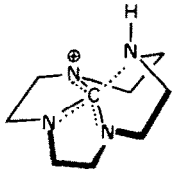
We do not have direct evidence for the intermediate tetracyclic ammonium ion **11** in Scheme 2 or its counterpart in Scheme 3. Although it is likely that **11** is a discrete intermediate, it is possible that protonation of **1** is accompanied by C–N bond cleavage or conversely that **3** deprotonates with concomitant C–N bond formation. Protic acids in highly polar media are not required for the facile C–N bond cleavage in **1** since methylation with methyl iodide in anhydrous benzene gives **9** di-





SCHEME 3.

rectly. It is also possible that the guanidinium-amine pair **3** is better described as a hybrid **12**. We are presently examining the X-ray crystal structure of this unusual compound to see if the guanidinium group is distorted from planarity by interaction with the secondary nitrogen.



12

REFERENCES

[1]H. Weingarten and W. A. White, *J. Am. Chem. Soc.* **88**, 2885 (1966)

[2]H. Stetter and K.-H. Mayer, *Chem. Ber.* **94**, 1410 (1961); J. P. Collman and P. W. Schneider, *Inorg. Chem.* **5**, 1380 (1966)

[3]J. E. Richman and T. J. Atkins, submitted for publication

[4]A. F. McKay, W. G. Hatton and R. O. Braun, *J. Am. Chem. Soc.* **78**, 6144 (1956)

[5]H. E. Skipper, C. E. Bryan, W. H. Riser, Jr., M. Welty and A. Stelzenmuller, *J. Nat. Cancer Inst.* **9**, 77 (1948)

[6]S. Castellano and A. A. Bothner-By, *J. Chem. Phys.* **41**, 3863 (1964)

[7]P. J. Chivers and T. A. Crabb, *Tetrahedron* **26**, 3389 (1970)

[8]C. C. Price, *Tetrahedron Letters* 4527 (1971)

[9]T. Yonezawa and I. Morishima, *J. Mol. Spectrosc.* **27** 210 (1968)

[10a]A. Farkas and K. G. Flynn, *J. Am. Chem. Soc.* **82**, 642 (1960); [b]D. D. Perrin, *Dissociation Constants of Organic Bases in Aqueous Solutions.* Butterworth, London (1965)

[11]R. C. Lord, B. Nolin and H. D. Stidham, *J. Am. Chem. Soc.* **77**, 1365 (1955) and personal communication

[12]H. E. Simmons and T. Fukunaga, *Ibid.* **89**, 5208 (1967)

[13]M. I. Page, *Chem. Soc. Rev.* **2**, 295 (1973)