Guanidinium Ions. I. A Nuclear Magnetic Resonance Study of Proton Exchange in Methylguanidinium Salts[1,2]

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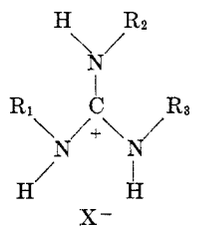
Received August 16, 1965

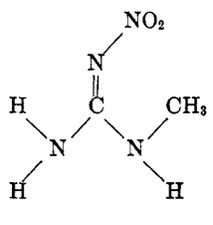
Activation energies were calculated for proton exchange of the amino proton in methylnitroguanidine and methyl derivatives of the guanidinium ion in solvents of different acid strengths by following the formation or collapse of the methyl doublet which is spin coupled to the exchanging nuclei. The activation energy decreases as the basicity of the methylguanidines and the acid strength of the solvent increases.

Nuclear magnetic resonance spectroscopy has been used by many workers to study exchange reactions in solutions.[3] In the present study of the methyl derivatives of nitroguanidine and guanidinium ions, the exchange reaction was followed by observing the formation or collapse (depending upon the temperature and solvent employed) of the resonance of the methyl doublet which is spin coupled to the exchanging nuclei (N–H proton).

The compounds studied are represented by the following formulas.



I, R_1 = CH_3; R_2,R_3 = H; X = Br^-
II, R_1,R_2 = CH_3; R_3 = H; X = Br^-
III, R_1,R_2,R_3 = CH_3; X = Br^-



IV

Hammond[4] made an nmr exchange rate study of methylamidinium salts which are similar to methylguanidinium salts and proposed a mechanism for proton exchange which involves backside attack of the methylamino group by protons from the solvent and exit of the exchanging amino proton from the front side of the methylamino group. The proton exchange processes of methylguanidinium salts can probably be explained by the same mechanism. There is, however, one important difference in the two series of compounds. The methyl groups in compounds II and III are equivalent as only one methyl signal was observed, whereas in the methylamidinium salts two methyl signals were observed which indicated nonequivalent methyl groups.

Discussion

The guanidinium ions (bromides) and the solvents employed are listed in Table I together with the activation energies obtained for amino proton exchange. Under the condition of slow passage and in the region of intermediate proton exchange an equation proposed by Gutowsky and Holm[5] may be used to calculate the lifetime of the exchanging amino proton (eq 1 below)

$$\frac{\text{separation of peaks}}{\text{separation of peaks at large } \tau} = \left[1 - \frac{1}{2\pi^2\tau^2(J_{\text{H-CH}_3})^2}\right]^{1/2} \quad (1)$$

where τ is the lifetime of exchanging amino proton in seconds, and $J_{\text{H-CH}_3}$ is the methyl doublet separation in cycles per second. The calculated values of τ at different temperatures may be used to obtain an activation energy for proton exchange using the equation[5]

$$\log \frac{1}{2\pi\tau J_{(\text{H-CH}_3)}} = \log \frac{k_0}{\pi J_{(\text{H-CH}_3)}} - \frac{E_a}{2.3RT} \quad (2)$$

where E_a is the activation energy and k_0 is the frequency factor. The activation energy may be obtained from the slope of the plot of log $1/2\pi\tau J$ *vs.* $1/T$. The condition of slow exchange was established by obtaining constant values for the methyl doublet separation (measurements were made below room temperature in some cases).

The data in Table I were interpreted on the basis of acid–base exchange where the guanidines act as strong bases.[6] For convenience, the results were divided into two categories: I, solvents systems A, B, and C; and II, guanidinium ions in different solvents (D and E).

System A. Water. Methylguanidinium (I), 1,3-Dimethylguanidinium (II), and 1,2,3-Trimethylguanidinium (III) Ions in Water.—It is well known that on the basis of inductive and resonance effects the base strength of the guanidines increase in the order I < II < III in water.[6] The activation energy for proton exchange was found to decrease as the base strength of the conjugate guanidine base increased. The activation energy decreased for each symmetrically placed methyl group. Although the E_a values only differ by ~1.5 kcal., which is within the experimental error, the relative values are believed to be significant because they were obtained under identical experimental conditions. In water I is a doublet below 17°. However, II and III coalesce into singlets above 50°.

System B. Trifluoroacetic Acid (TFA). Methyl-Nitroguanidine (IV) and Methylguanidinium Ion (I) in TFA.—It is known that methylguanidine is a stronger base than methylnitroguanidine.[6,7] In strong

(1) This work was supported by the Foundational Research Program of the Bureau of Naval Weapons.

(2) Presented in part at the 4th National Meeting of the Society for Applied Spectroscopy at Denver, Colo., Aug 1965.

(3) A. Lowenstein and T. M. Connor, *Ber. Bunsenges. Physik. Chem.*, **67**, 280 (1963).

(4) R. C. Neuman, Jr., and G. S. Hammond, *J. Phys. Chem.*, **67**, 1659 (1963).

(5) H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1956); W. F. Reynolds and T. Schaefer, *Can. J. Chem.*, **41**, 540 (1963).

(6) S. J. Angyal and W. K. Warburton, *J. Chem. Soc.*, 2492 (1951).

(7) T. G. Bonner and J. C. Lockhart, *ibid.*, 3852 (1958).

TABLE I

ACTIVATION ENERGY (KCAL) FOR AMINO PROTON EXCHANGE

	Methylnitroguanidine	Methylguanidine	1,3-Dimethylguanidine	1,2,3-Trimethylguanidine
Trifluoroacetic acid	8.8 ± 1.0	7.8 ± 1.0	*a*	*a*
Glacial acetic acid	12.9 ± 1.4	*d*	8.4 ± 1.0	*b*
Water	*b*	14.9 ± 1.0	13.6 ± 1.2	11.8 ± 1.5
Dimethyl sulfoxide-d_6	18.4 ± 1.0[c]	...	...	...
Dimethyl sulfoxide-d_6	*d*	*d*	*d*	*d*

[a] Exchange reaction is too fast at −40°. [b] Insoluble. [c] An equimolar amount of MNQ and TFA was used. [d] Exchange reaction is too slow at 110.

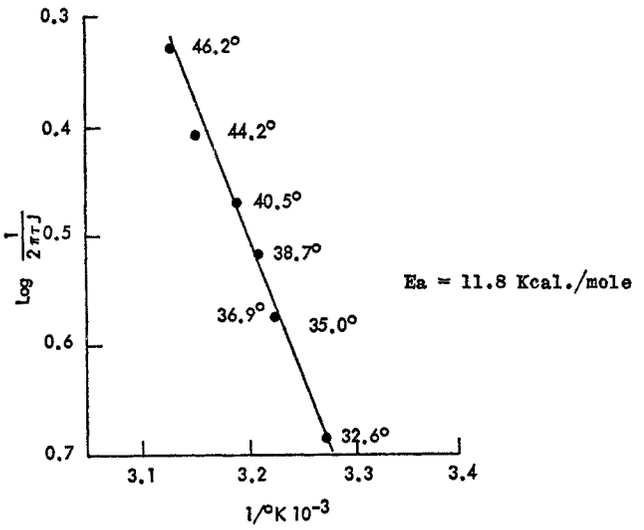


Figure 1.—Temperature dependence of amino proton of 1,2,3-TMB·Br in water.

acid solution (*i.e.*, 40% H_2SO_4), methylnitroguanidine exists mainly in the nitramino form ($NHNO_2$) rather than the nitrimino form (NNO_2).[7,8] Although the presence of the nitramino group increases the basicity of methylnitroguanidine, methylguanidine is still the stronger base and thus I has the lower activation energy.

System C. Glacial Acetic Acid (HAc). Methylnitroguanidine (IV) and 1,3-Dimethylguanidinium Ion (II) in Glacial Acetic Acid.—It was observed that II has an activation energy of 4.5 kcal/mole less than IV. This large difference in activation energy is due to the fact that in glacial acetic acid IV exists mainly in nitrimino form[8] which is a much weaker base than II.

System D. Methylguanidinium Ion (I) in TFA and Water.—The activation energy for proton exchange was found to decrease as the acid strength of the solvent increased.

System E. Methylnitroguanidine (IV) in TFA, HAc, and DMS-d_6.[9]—The acid strength of the solvent in this series decreases in the order TFA > HAc > DMS-d_6. The observed activation energy increases in the order TFA < HAc < DMS-d_6. In this series it was found that the methyl doublet coalesces at 68° in TFA and at approximately 46° for the other two solvents.

It is interesting to note that the activation energies for the methylnitroguanidine and methylguanidinium ions practically double as one goes from a strong acid to a neutral solvent. Typical data obtained in this study are shown in Table II in which calculated exchange rates are obtained from doublet separation and are plotted in Figure 1 to give an activation energy for amino proton exchange.

TABLE II

EXCHANGE RATE OF 1,2,3-TRIMETHYLGUANIDINIUM BROMIDE IN WATER AS CALCULATED FROM MEASURED DOUBLET SEPARATION

Temp, °C	Doublet separation	τ, sec	Exchange rate, sec^{-1}
11.0	4.85 ± 0.02		
32.6	4.64 ± 0.04	0.160 ± 0.008	6.25 ± 0.31
35.0	4.51 ± 0.03	0.126 ± 0.002	7.94 ± 0.12
36.9	4.49 ± 0.03	0.123 ± 0.002	8.13 ± 0.10
38.7	4.38 ± 0.02	0.108 ± 0.002	9.26 ± 0.10
40.5	4.26 ± 0.01	0.097 ± 0.0009	10.3 ± 0.1
44.2	4.03 ± 0.02	0.084 ± 0.0002	11.9 ± 0.1
46.2	3.42 ± 0.03	0.066 ± 0.0003	15.2 ± 0.2
50.5	Singlet		

As the acid strength of the solvent is decreased there is a shift to higher field of the methyl resonance relative to tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate as internal standard. As an example, in going from trifluoroacetic acid to dimethyl sulfoxide-d_6, methyl nitroguanidine resonance shifts 28 cps (196 to 168 cps) and 1,2,3-trimethylguanidinium ion 12 cps (180 to 168). In trifluoroacetic acid the methyl resonance of methyl nitroguanidine comes at 16 cps lower field than the methyl analogs of guanidinium ions while in the other solvents the methyl resonances are nearly equal.

Frequency factors were calculated and their order of magnitude paralleled the order of activation energies obtained. The values found for methyl nitroguanidine were (in sec^{-1}) 4.2×10^6 (TFA), 7.5×10^9 (HAc), and 4.2×10^{13} (DMS-d_6); for methylguanidine 1.2×10^7 (TFA) and 1.7×10^{12} (H_2O); for 1,3-dimethylguanidine 6.4×10^5 (HAc) and 3.2×10^7 (H_2O); for 1,2,3-trimethylguanidine 7.8×10^8 (H_2O).

A relationship has been found between the trend in activation energies and the basicity of methyl analogs of guanidine and the acid strength of the solvent. As the basicity of the guanidines and acid strength of the solvent increase, the activation energy decreases.

Experimental Section

Materials.—Dimethyl sulfoxide (DMS-d_6, Volk Radiochemical Co., 98% purity) and trifluoroacetic acid (TFA, Eastman White Label) were used without further purification. Glacial acetic acid was fractionally recrystallized, mp 16.8°. Water was doubly distilled from alkaline permanganate solution. The solutions (0.8 to 1.4 *M*) were degassed and vacuum sealed in 5-mm glass tubes.

Methylnitroguanidine.—Methylnitroguanidine was conveniently prepared by the reaction of methylamine with 2-

(8) J. U. Lowe, Jr., R. D. Barefoot, R. Evans, and A. S. Tompa, Pittsburgh Conference on Applied Spectroscopy and Analytical Chemistry, Pittsburgh, Pa., Feb 1966.

(9) An equimolar quantity of MNQ and TFA in DMS-d_6 was prepared.

methyl-1-nitro-2-thiopseudourea. An analytically pure sample, mp 162 (lit.[10] mp 160.6–161°),[11] was obtained after several recrystallizations from ethanol.

Methylguanidinium Bromide.—Equimolecular quantities of aqueous methylamine (40%) and 2-benzyl-2-thiopseudourea hydrobromide were refluxed with 50 ml of H_2O for 2.5 hr. The mixture was cooled to 10° and extracted three times with 100-ml portions of ether to remove the benzyl mercaptan. The aqueous phase was evaporated to dryness and the white solid was recrystallized from absolute ethanol–ethyl acetate (mp 143–144°). *Anal.* Calcd for $C_2H_8N_3Br$: C, 21.42; H, 5.95; N, 25.00. Found: C, 21.82; H, 5.93; N, 24.47.

1,3-Dimethylguanidinium Bromide.—Equimolecular quantities of aqueous methylamine (40%) and 2-benzyl-1-methyl-2-thiopseudourea hydrobromide gave impure 1,3-dimethylguanidinium bromide, mp 138–139°. Several recrystallizations from ethanol–ethyl acetate gave an analytically pure sample, mp 144–145° (lit.[12] mp 144°).

(10) L. Fishbein and J. A. Gallaghan, *J. Am. Chem. Soc.*, **76**, 1877 (1954).
(11) All melting points were taken on a micro Kofler hot stage.
(12) J. O. Mold, J. M. Ladino, and E. J. Schantz, *J. Am. Chem. Soc.*, **75**, 6321 (1953).

1,2,3-Trimethylguanidinium Bromide.—The reaction of aqueous methylamine (40%) with 2-benzyl-1,3-dimethyl-2-thiopseudourea hydrobromide gave crude 1,2,3-trimethylguanidinium bromide, mp 342–346°. An analytical sample (mp 350°) was obtained by four recrystallizations from absolute ethanol–ethyl acetate. *Anal.* Calcd for $C_4H_{12}N_3Br$: C, 26.37; H, 6.59; N, 23.08. Found: C, 26.33; H, 6.45; N, 22.80.

Nuclear Magnetic Resonance Mesurements.—The measurements were performed with a Varian DP-60 spectrometer equipped with a superstabilizer and a Varian high-speed recorder. The separation of doublet peaks was measured (with a precision of ±0.05 cps) by placing side bands of the doublet 20 cps on both sides of the doublet. The side-band frequency was measured with a Hewlett-Packard Model 522-B electronic frequency counter. Temperature was kept constant to within ±0.2° by the use of a Leeds and Northrup Azar II recorder controller. The temperature was varied with dry nitrogen gas and the use of a Varian 4340 variable-temperature nmr probe assembly and a Model V-4331-THR spinning sample dewar probe insert.

Acknowledgment.—The authors acknowledge several helpful discussions with Dr. Elton Price of Howard University.

Kinetic *vs.* Thermodynamic Control in Addition Reactions of Dialkaliphenylacetamides with Benzophenone in Liquid Ammonia[1]

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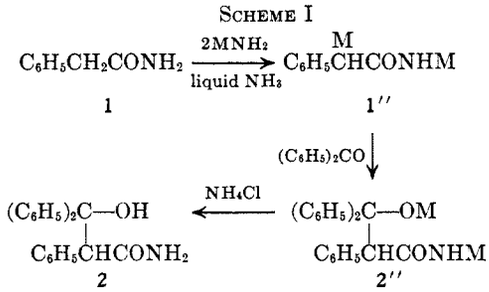
Received June 8, 1966

Disodio-, dipotassio-, and dilithiophenylacetamides underwent addition reactions with benzophenone to form, on inverse neutralization after a relatively short period, the corresponding adduct in good yields. However, only starting materials were recovered after longer periods. Evidently, the initial addition reaction is kinetically controlled, and this is followed by a thermodynamically controlled addition reaction between the alkali amide and the ketone present in equilibrium. The relative ease of the latter reaction as the metallic cation is varied decreased in the order K > Na > Li. Theoretical and synthetic aspects are considered.

Recently,[2] dipotassiophenylacetamide (1″, M = K) was reported not to undergo an addition reaction with benzophenone to form adduct 2 (Scheme I), and dilithiophenylacetamide (1″, M = Li) was found to do so in only 7% yield even though the reaction mixtures were neutralized inversely.[3] This seemed

SCHEME I



rather surprising since, not only had these dialkali salts 1″ been shown to undergo satisfactorily other types of condensations, *e.g.*, alkylation,[4] benzoylation,[2] and conjugate addition,[5] but the related disodio- or dilithiophenylacetate[6] and dipotassiobenzoylacetone[7] had been observed to exhibit carbonyl addition reactions with benzophenone in good yields under similar conditions.

We have now obtained adduct 2 in good yields from dialkali salts 1″ (M = Na, K, and Li) and benzophenone (Scheme I) by inverse neutralization of the reaction mixtures after relatively short periods; after more common condensation periods, only starting materials were recovered. In Table I are summarized the yields of adduct 2 and of recovered benzophenone obtained on adding the ketone to the dialkali salt 1″ during 5 min, and neutralizing the reaction mixture after an appropriate further condensation period. Phenylacetamide was recovered along with the ketone but its isolation was generally not attempted.

Table I shows that disodiophenylacetamide (1″, M = Na), which was studied the most thoroughly, afforded adduct 2 in 53% yield on inverse neutralization after 1 min (beyond the 5-min ketone-addition period), whereas none of 2 was isolated after 10–15 min (expt 1–3). When 2.2 molecular equiv of sodium amide was employed in the preparation of disodio salt 1″ instead of the required 2 equiv (see Scheme I), adduct 2 was obtained in yields of 64–86% on inverse neutralization after 1–15 min but none was isolated after 30 min (expt 4–8). In these experiments with

(1) (a) Supported by the Army Research Office (Durham) and by the National Science Foundation; (b) a preliminary report appeared as a communication, *Chem. Ind.* (London), 1299 (1965).
(2) S. D. Work, D. R. Bryant, and C. R. Hauser, *J. Org. Chem.*, **29**, 722 (1964).
(3) This method of neutralization, which involves pouring the reaction mixture into excess ammonium chloride, was employed to minimize possible reversion of this aldol-type condensation during work-up.
(4) R. B. Meyer and C. R. Hauser, *J. Org. Chem.*, **26**, 3696 (1961).
(5) R. B. Meyer and C. R. Hauser, *ibid.*, **26**, 3187 (1961).
(6) P. J. Hamrick, Jr., and C. R. Hauser, *J. Am. Chem. Soc.*, **82**, 1957 (1960).
(7) R. J. Light and C. R. Hauser, *J. Org. Chem.*, **26**, 1716 (1961).