A Nitrogen-15 NMR Study of the Barriers to Isomerization about Guanidinium and Guanidino Carbon–Nitrogen Bonds in L-Arginine[1]

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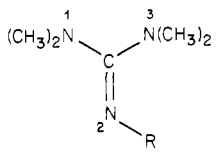
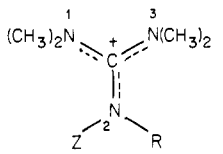
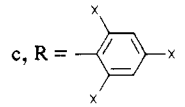
Abstract: ^{15}N nuclear magnetic resonance (NMR) spectroscopy has been employed to investigate barriers to isomerization about the C–N2 bond in guanidinium and guanidino groups of L-arginine by line-shape analyses of the N1 and N3 resonances in a 50% (v/v) dimethyl sulfoxide/water solution from −52 to 25 °C. The free energies of activation were found to be 12.9 and 10.4 kcal/mol, and the chemical-shift differences between the nonequivalent nitrogens, N1 and N3, were 2.4 and 42.3 ppm for the guanidinium and guanidino groups of L-arginine, respectively. For the guanidino form of L-arginine, the three possible tautomers with different arrangements of the guanidino protons are interconverted rapidly on the NMR time scale over the whole of the temperature range studied. Approximately one-third of the guanidino form is present as the R—N=C$(NH_2)_2$ tautomer. The results are compared with those previously reported for tetramethylguanidine derivatives.

While barriers to rotation about the carbon–nitrogen bond in amides have been extensively studied by NMR spectroscopy,[2] corresponding studies on guanidines have been mostly limited to ^1H NMR studies of tetramethylguanidine derivatives and their salts,[3-9] **1** and **2**.

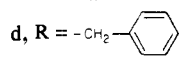




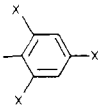
1a, R = H
b, R = $-CH_3$



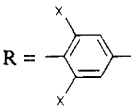
c, R =



d, R = $-CH_2-$



2a, Z = H; R =

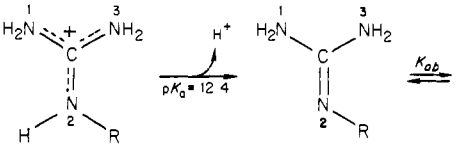


b, Z = $-CH_3$; R =

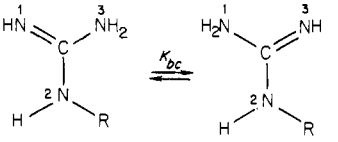
X = H, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$

Two mechanisms have been proposed for cis-trans isomerization about a carbon–nitrogen double bond: (i) rotation of the N substituent out of the plane of the molecule and (ii) an in-plane "lateral shift" or inversion.[10] In **2**, isomerization occurs by rotation,[5-7] but evidence in favor of inversion has been reported for **1b** and **1c**.[6,8]

For guanidinium ion itself, $C(NH_2)_3^+$, the chemical equivalence of the N–H protons precludes standard NMR studies using isotropic conditions, but studies in an anisotropic nematic solution indicate an upper bound for the free energy of activation, $\Delta G^{\ddagger} \leq 13$ kcal/mol, for rotation about each C–N bond.[11] For guanidinium ions and guanidines substituted on N2, such as in L-arginine (**3** and **4**), restricted rotation about the C–N2 bond is expected to cause nonequivalence of N1 and N3 protons.



3 4a



4b 4c

R = $-(CH_2)_3CH(COO^-)-NH_3^+$ for L-arginine (pH <9)

R = $-(CH_2)_3CH(COO^-)-NH_2$ for L-arginine (pH >9)

However, temperature-dependent quadrupole coupling between ^{14}N and its bonded hydrogens precludes meaningful analysis of ^1H NMR spectra of such systems.[12] In aqueous solution, additional dynamic processes such as the exchange of the guanidino protons with water and, in case of **4**, interconversion of tautomers **4a**, **4b**, and **4c** complicate the study of isomerization. Such groups occur in a number of biologically important molecules such as L-arginine, streptomycin, and tetradotoxin, and it is important to understand their isomerization behavior in aqueous solution.

^{15}N NMR spectroscopy has proven to be useful for studying dynamic processes such as the exchange rate of NH protons in systems that are not amenable to ^1H NMR studies.[13,14] It also offers potential for determining the barriers to isomerization about the C–N2 bond in **3** and **4** through line-shape analyses of N1 and N3 resonances at a series of temperatures. Because it was found that subzero temperatures were required for useful line-shape analysis, 50% (v/v) dimethyl sulfoxide/water was used as solvent.

(1) Supported by the National Science Foundation, and by the U.S. Public Health Service, Grant No. GM-11072 from the Division of General Medical Sciences.

(2) Jackman, L. M.; Cotton, F. A. "Dynamic Nuclear Magnetic Resonance Spectroscopy"; Academic Press: New York, 1975; pp 203–252 and references cited therein.
(3) Bauer, V. J.; Fulmor, W.; Morton, G. O.; Safir, S. R. *J. Am. Chem. Soc.* **1968**, *90*, 6846–6847.
(4) Kessler, H. Leibfritz, D. *Tetrahedron Lett.* **1969**, *6*, 427–430.
(5) Kessler, H.; Leibfritz, D. *Tetrahedron* **1969**, *25*, 5127–5145.
(6) Kessler, H.; Leibfritz, D. *Tetrahedron* **1970**, *26*, 1805–1820.
(7) Kessler, H. *Angew Chem., Int. Ed. Engl.* **1970**, *9*, 219–235.
(8) Kalinowski, H.; Kessler, H. In "Topics in Stereochemistry"; Allinger, N. L., Eliel, E. L., Eds.; Interscience: New York, 1973; pp 295–383.
(9) Santo, A. V.; Mickevicius, G. *J. Org. Chem.* **1979**, *44*, 117–120.
(10) Curtin, D. Y.; Grubbs, E. J.; McCarty, C. G. *J. Am. Chem. Soc.* **1966**, *88*, 2775–2786.
(11) Bally, T.; Diehl, P.; Haselbach, E.; Tracey, A. S. *Helv. Chim. Acta* **1975**, *58*, 257–258.
(12) Hammons, G. S.; Newman, R. C. *J. Phys. Chem.* **1963**, *67*, 1655–1659.
(13) Nee, M.; Yu, C.; Squillacote, M. E.; Roberts, J. D. *Org. Magn. Reson.* **1982**, *18*, 125–127.
(14) Yu, C.; Yavari, I.; Roberts, J. D. *Org. Magn. Reson.* **1982**, *18*, 74–76.

0002-7863/83/1505-4698$01.50/0

Table I. Barriers to Isomerization about the C–N2 Bond in Guanidinium and Guanidino Groups of Arginine

	pH	solvent	$\Delta G^{\ddagger}$,[a] kcal/mol	$\Delta H^{\ddagger}$,[a] kcal/mol	$\Delta S^{\ddagger}$,[a] eu
guanidinium	7.0	H_2O	12.1 ± 0.05	21.7 ± 1.1	36 ± 4
	7.0	$(CH_3)_2SO/H_2O$[b]	12.9 ± 0.05	12.3 ± 1.5	−2 ± 5
guanidino	14.1	$(CH_3)_2SO/H_2O$[b]	10.4 ± 0.05	12.6 ± 0.5	9 ± 2

[a] With standard deviations. [b] 50% (v/v).

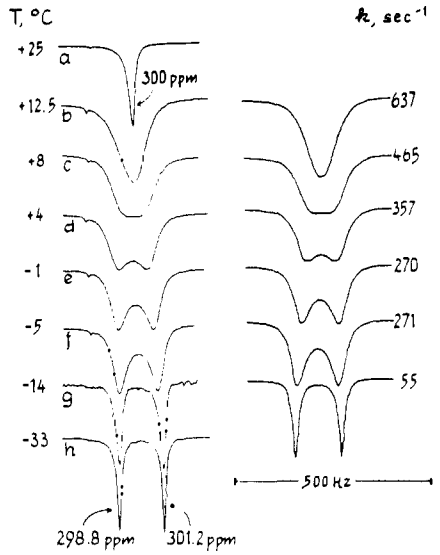


Figure 1. Temperature dependence of the proton-decoupled ^{15}N resonances of N1 and N3 of L-arginine in 50% (v/v) dimethyl sulfoxide/water at pH 7.0 and 50.65 MHz. Experimental spectra on the left and calculated on the right, with rate constants k.

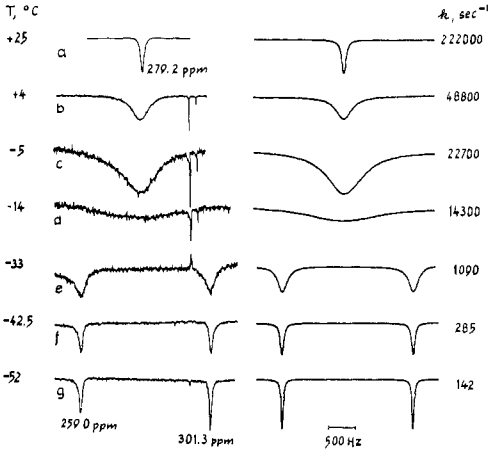


Figure 2. Temperature dependence of the proton-decoupled ^{15}N resonances of N1 and N3 of L-arginine in 50% (v/v) dimethyl sulfoxide/water at pH 14.1 and 50.65 MHz. Experimental spectra on the left and calculated on the right, with rate constants k. The sharp peaks at 295 and 297.5 ppm in (b), (c), and (d) arise from impurities in the sample.

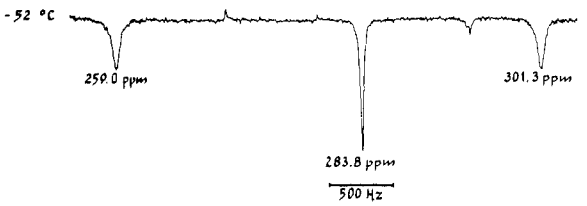


Figure 3. Proton-decoupled ^{15}N resonances of N1, N2, and N3 of L-arginine in 50% (v/v) dimethyl sulfoxide/water at pH 14.1 and 50.65 MHz.

Experimental Section

L-Arginine hydrochloride, 99% enriched in ^{15}N at N1 and N3, was purchased from KOR isotopes. Uniformly ^{15}N-labeled L-arginine was isolated from *Neurospora crassa* grown on $^{15}NH_4Cl$ medium as described previously.[15] The NMR samples of guanidinium and guanidino forms of L-arginine were prepared by dissolution of 200 mg of [^{15}N]L-arginine in 1.5 mL of water, adjustment of the pH with potassium hydroxide solution to 7 and 14.1, respectively, and finally, addition of an equal volume of dimethyl sulfoxide.

The ^{15}N NMR spectra were obtained with a Bruker WM-500 spectrometer operating at 50.65 MHz. The operating conditions employed 36-μs pulses (90° flip angle), 4-s delays, and broad-band proton decoupling. The ^{15}N chemical shifts are reported in ppm upfield from 1 M $H^{15}NO_3$. Because of radiofrequency heating of the sample when broad-band proton decoupling is used, sample temperatures can differ from the probe temperature. The sample temperatures were therefore measured by simulating the conditions of spectral acquisition on an arginine sample in which a thermometer was immersed and reading the temperature immediately after each simulated run. The temperature readings were found to be reproducible to within ±1 °C.

Theoretical line shapes were calculated by procedures used previously.[16] An initial fit was made by comparing calculated and experimental line widths and, when two peaks could be observed, the line separations and saddle heights were also considered. A final check involved comparison of plotted and experimental curves. Because of uncertainties in the natural (or spectrometer limited) line widths, only spectra in the intermediate range with line widths of 25 Hz or more could be used to give reaction rates.

Results

Figures 1 and 2 show the temperature dependence of broad-band proton-decoupled ^{15}N spectra obtained at 50.65 MHz of N1 and N3 resonances of L-arginine in 50% (v/v) dimethyl sulfoxide/water at pH 7.0 and 14.1, respectively. In both the guanidinium and guanidino forms of L-arginine, rotation about the C–N2 bond is rapid at room temperature so that a single averaged peak for N1 and N3 is observed (Figures 1a and 2a). At lowered temperatures, isomerization is slowed and separate N1 and N3 resonances appear (Figures 1h and 2 g).

For the guanidino form of L-arginine (pH 14.1), corresponding spectra were obtained for arginine enriched in ^{15}N at N2 as well. In the spectrum at −52 °C (Figure 3), three peaks are observed. The peak at 283.8 ppm arises from N2, and those at 259.0 and 301.3 ppm arise from N1 and N3. Which is cis and which trans to R is not known. That a single peak is observed for each nitrogen is clear evidence for rapid base-catalyzed interconversions of **4a**, **4b**, and **4c** on the NMR time scale, even at −52 °C. The resonance of N2 was sharp ($\nu_{1/2}$ = 16 Hz) from −52 to 25 °C. The fact that the N2 resonance is narrower than those of N1 and N3 (36–41 Hz) at −52 °C shows that rotation is still significantly influencing the line widths at −52 °C.

The evidence here (Figure 3) that the tautomers **4a–c** are rapidly interconverted, even at −52 °C, has analogy in tetramethylguanidine (**1a**) for which separate cis-trans methyl proton resonances are not detectable down to −77 °C because of water-catalyzed exchange of the imine proton, although such resonances are clearly observable for pentamethylguanidine (**1b**) at room temperature.[6]

The rates obtained by matching theoretical (right) and observed spectra (left) in Figures 1 and 2 gave free energies of activation, $\Delta G^{\ddagger}$, for isomerization about the C–N2 bond which are shown in Table I. In 50% (v/v) dimethyl sulfoxide/water, $\Delta G^{\ddagger}$ is 10.4 kcal/mol for the guanidine species (pH 14.1), which is considerably lower than the $\Delta G^{\ddagger}$ of 12.9 kcal/mol for the guanidinium

(15) Kanamori, K.; Legerton, T. L.; Weiss, R. L.; Roberts, J. D. *Biochemistry* **1982**, *21*, 4916–4920.

(16) Cf.: Sutherland, I. O. "Annual Reports on Nuclear Magnetic Resonance Spectroscopy"; Mooney, E. F., Ed.; Academic Press: New York, 1971; Vol. 4, pp 76–84.

Table II. ^{15}N Chemical Shifts of the Guanidinium and Guanidino Nitrogens of L-Arginine and of Tetramethylguanidine Derivatives

no.	compound	solvent	pH	T, °C	δ ^{15}N, ppm N2	δ ^{15}N, ppm N1, N3	$\Delta\nu$, ppm = |δ N3 − δ N1|	ref
3	arginine (guanidinium)	$(CH_3)_2SO/H_2O$[a]	7.0	25		300.0		
				−33		298.8 301.2	2.4	
4	arginine (guanidino)		14.1	25		279.2		
				−52		259.0 301.3	42.3	
		H_2O		25	286.6	288.7		19
1a	tetramethylguanidine	neat		30	203.4	329.0		18
1b	pentamethylguanidine			30	182.6	329.6		18
1c	X = H	$CDCl_3$			172.1	319.6 320.0	0.4	17
	X = CH_3				170.7	313.5 323.5	10.0	17
	X = C_2H_5				170.9	308.5 323.3	14.8	17
1d		$CDCl_3$			180.1	317.5 335.3	17.8	17

[a] 50% (v/v).

species (pH 7.0). For the latter, $\Delta G^{\ddagger}$ was also obtained in H_2O and found to be reasonably close (12.1 kcal/mol). Comparisons of the relative $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values listed in Table I are not likely to be significant because of the shortness of the temperature range over which the spectra are compared in Figure 1. Qualitatively, these appear to be different enough to warrant further investigation.

The ^{15}N chemical shifts of these nitrogens in the regions of fast and slow isomerization are listed in Table II. It is interesting that the chemical-shift differences between the two nonequivalent nitrogens, N1 and N3, is only 2.4 ppm for the guanidinium group of L-arginine but is 42.3 ppm for the corresponding guanidino group. The latter is the largest so far reported for two nonequivalent nitrogens in guanidine derivatives. Thus, for tetramethylguanidine derivatives, the shift differences are <18 ppm[17] (Table II).

For the guanidine group of L-arginine, the rate of rotation about the C–N2 bond is expected to depend on its average double-bond character, which, in turn, will depend on the populations of tautomers **4a–c**. The equilibrium constant, K, for **4a** ⇄ [**4b**, **4c**] can be estimated from the observed ^{15}N shifts for N1, N2, and N3, which represent weighted averages of the shifts of the tautomers, and ^{15}N shifts of individual tautomers estimated from reasonable model compounds such as tetramethyl- and pentamethylguanidines (**1a** and **1b**) for which ^{14}N shifts have been obtained by Witanowski et al.[18] (Table II). The observed ^{15}N shifts are 286.6 ppm for N2 and 288.7 ppm for the averaged N1 and N3 resonances for L-arginine in aqueous solution at pH 14.1 (25 °C).[19] The shift of N2 of **4a** must surely be close to that of N2 of pentamethylguanidine (**1b**) (182.6 ppm), while N1 of **4b** or N3 of **4c** should have a shift close to N2 of tetramethylguanidine (**1a**) (203.4 ppm). Inferring the expected shifts of N1 and N3 of **4a** and of N2 and N3 of **4b** or N1 and N2 of **4c** from N1 of **1b** (329.6 ppm) and N3 of **1a** (329.0 ppm) is more difficult because replacement of hydrogen by methyl will surely be expected to have a substantial influence on the nitrogen shifts. One technique for solving that problem[20] is to let x be the combined influence of two CH_3 groups on the shift of N1 or N3 of **1a**. Taking F_a as the fraction of **4a** in the mixture **4a** and **4b–c**, we can write 288.7 (the observed shift of N1) = $F_a(329.6 + x) + (1 - F_a)(182.6 + 329.6 + x)/2$. A similar equation can be derived for the observed shift of N2 (286.6 ppm) although now we need to correct for a change from two methyls to a single alkyl substituent for **4b** or **4c**. If we assume that this change would produce a shift of $x/2$, we can write $286.6 = F_a(203.4) + (1 - F_a)(329.0 + x/2)$. Equating the two equations for F_a affords the very reasonable values for x of 9 ppm and $F_a = 0.36$. It is interesting that, in contrast to arylguanidines in which the preferred tautomer is **4a**, with the C=N2 bond conjugated with the aryl group,[21] there appears to be no marked preference for L-arginine to exist as **4a** over **4b–c**.

Discussion

The value of $\Delta G^{\ddagger}$ of 10.4 kcal/mol for isomerization of the guanidino group of L-arginine, **4**, is very much smaller than the 18.8 kcal/mol reported for pentamethylguanidine (**1b**).[6] If isomerization occurs by rotation, the lower barrier in **4** can most simply be explained by a lesser double-bond character of C–N2 in **4**, compared to **1b**, as the result of the tautomeric equilibrium between **4a**, **4b**, and **4c**. On the other hand, Kessler et al.[6,8] have reported evidence in favor of the inversion mechanism for **1b** and **1c**. Of the tautomers of **4**, inversion at the C–N2 bond is possible only for **4a**, and the inversion barrier for this substance is expected to be comparable to that reported for **1b** and thus much higher than the *average* barrier of 10.4 kcal/mol observed for **4**. The average barrier will include the contributions to the rate from **4b** and **4c**, which should have lower barriers for rotation about the C–N2 bond. Also, quantum-mechanical calculations have indicated that for unsubstituted guanidine, rotation is energetically more favorable than inversion.[22]

The $\Delta G^{\ddagger}$ of 12.9 kcal/mol obtained for isomerization of the guanidinium form of L-arginine, **3**, is very close to the upper bound of $\Delta G^{\ddagger} = 13.0$ kcal/mol deduced for unsubstituted guanidinium ion.[11] It is also close to $\Delta G^{\ddagger}$ of 12.5 kcal/mol for **2a** (X = H),[5] the closest structural analogue for which a precise value of $\Delta G^{\ddagger}$ has been reported.

An important question in the cis–trans isomerization of **3** is whether or not **3** is isomerized by, first deprotonation to **4**, then isomerization, and finally reprotonation. At first glance, this seems like a very viable mechanism, because the overall average double-bond character of the C–N2 bond in the tautomers of **4** is likely to be substantially less than for **3**, and this should facilitate isomerization. However, qualitative experiments show that the isomerization rate in solutions of **3** is not significantly less at pH 3 than at pH 7. Furthermore, the ratio of arginine isomerization rates at pH 14 and 7 is about 100. With the known guanidinium pK_a of 12.4 of arginine, the ratio of the sums of the concentrations of the tautomers **4a–c** in solution at pH 14 and 7 can be calculated to be about 2.5×10^5. Clearly, there is too little **4a–c** present at pH 7 to account for the observed isomerization rate at this pH.

Quantum-mechanical calculations based on the Hartree–Fock approximation have suggested a $\Delta G^{\ddagger}$ of 16.8 kcal/mol for the barrier to rotation about the C–N2 bond in methylguanidinium ion.[23] This value is considerably larger than the experimentally determined $\Delta G^{\ddagger}$ values for guanidinium groups cited above.

(17) Levy, G. C.; Lichter, R. L. "Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy"; Wiley: New York 1979; pp 68–69 [Franzen-Sieveking, M.; Leibfritz, D.; Lichter, R. L., unpublished results].

(18) Witanowski, M.; Stefaniak, L.; Szymanski, S.; Webb, G. A. *Tetrahedron* **1976**, *32*, 2127–2129.

(19) Kanamori, K.; Cain, A. H.; Roberts, J. D. *J. Am. Chem. Soc.* **1978**, *100*, 4979–4981.

(20) Gonnella, N. C.; Nakanishi, H.; Holtwick, J. B.; Horowitz, D.; Kanamori, K.; Leonard, N. J.; Roberts, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2050–2055.

(21) Botto, R. E.; Schwartz, J. H.; Roberts, J. D. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 23–25.

(22) Raban, M. *Chem. Commun.* **1970**, 1415–1416.

(23) Herzig, L.; Massa, L. J.; Santoro, A. *J. Org. Chem.* **1981**, *46*, 2330–2333.

The large chemical-shift difference of 42.3 ppm between N1 and N3 of the guanidino group of arginine at −52 °C reflects the average shift difference between the two nitrogens that are cis and trans, respectively, in the mixture of tautomers **4a–c**. In our view, the size of this shift difference, compared to those of other guanidines,[17] almost surely represents a preference for **4b** over **4c** or the reverse. The assignments of the 259.0-ppm and 301.3-ppm peaks to cis or trans nitrogen relative to R must await further study.

Most ^{15}N NMR spectra of free arginine in aqueous solution, or arginyl residues in proteins, or of intracellular arginine in microorganisms have been taken at or above room temperature and at ^{15}N resonance frequencies of less than 18 MHz.[24-26] Under such conditions, the resonances of N1 and N3 will be observed as a single peak, because $k_{ex} \gg \pi\Delta\nu$, where k_{ex} is the rate of isomerization and $\Delta\nu$ is the chemical-shift difference in hertz between the nitrogens in the absence of isomerization. However, at 50 MHz (^1H resonance frequency of 500 MHz), the N1–N3 peak is considerably broadened and has a $\nu_{1/2}$ of 30 Hz at 4 °C in neutral aqueous solution. Such line broadening resulting from slow isomerization should be taken into account in ^{15}N NMR studies of arginine and arginyl residues in enzymes at high magnetic fields.

The guanidinium group of arginine clearly plays an important role in binding anionic substrates and cofactors at the active sites of a number of enzymes.[27] Valuable information on enzyme–substrate complexes and transient intermediates can be obtained by "trapping" them at subzero temperatures in mixed aqueous organic solvents.[28] Applications of NMR for "low-temperature" enzymology are just emerging[29,30] and the nonequivalence of N1 and N3 resonances of arginine at subzero temperatures may be useful in this connection.

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Registry No. L-Arginine, 74-79-3.

(24) Levy, G. C.; Lichter, R. L. "Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy"; Wiley: New York, 1979.
(25) Witanowski, M.; Stefaniak, L.; Webb, G. A. In "Annual Reports on NMR Spectroscopy"; Webb, G. A. Ed; Academic Press: New York, 1981; Vol. 11B.
(26) Kanamori, K.; Roberts, J. D. *Acc. Chem. Res.* **1983**, *16*, 35–41.
(27) Patty, L.; Smith, E. L. *J. Biol. Chem.* **1975**, *250*, 565–569.
(28) Douzou, P. *Q. Rev. Biophys.* **1979**, *12*, 521–569.
(29) Markley, J. L.; Neves, D. E.; Westler, W. M.; Ibanez, I. B.; Porubcan, M. A.; Baillargeon, M. W. In "Frontiers in Protein Chemistry"; Liu, T. Y., Manuya, G., Yasunobu, K. T., Eds.; Elsevier/North-Holland: New York, 1980; pp 31–61.
(30) Malthouse, J. P. G.; Gamcsik, M. P.; Boyd, A. S. F.; Mackenzie, N. E.; and Scott, A. I. *J. Am. Chem. Soc.* 1982, **104**, 6811–6813.

Heats of Formation and Ionization Potentials of Some α-Aminoalkyl Radicals[1]

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Contribution from the Division of Chemistry, National Research Council of Canada, Ottawa, Ontario, Canada K1A 0R6, and the Department of Chemistry, University of Ottawa, Ottawa, Ontario, Canada K1N 6N5. *Received December 6, 1982*

Abstract: Heats of formation and ionization potentials of α-aminoalkyl radicals, $R_2NCR'_2$, were derived from measurements of the appearance energies for the fragmentations of a series of ethylenediamines. Stabilization energies, E_s, are high and increase with increasing C- or N-alkylation; the converse applies to ionization potentials, IP. For example, in the case of $H_2NC(Me)_2$, E_s = 17 kcal mol^{-1} and IP = 5.4 eV.

The stabilization energies,[3] E_s, of free radicals, R·, can be increased by appropriate substitution at the radical center (eq 1 and 2). When alkyl groups are adjacent to the unpaired electron

$$BDE(R\text{–}H) = \Delta H_f(R\cdot) + \Delta H_f(H\cdot) - \Delta H_f(R\text{–}H) \quad (1)$$

$$E_s = BDE(CH_3\text{–}H) - BDE(R\text{–}H) \quad (2)$$

the stabilizing effect is relatively small; e.g., the stabilization energies for $CH_3\dot{C}H_2$, $(CH_3)_2\dot{C}H$, and $(CH_3)_3\dot{C}$ are 4, 8, and 10 kcal mol^{-1}, respectively.[4] More pronounced effects are obtained when conjugation with π bonds or electron lone pairs is possible. It is well-known, for example, that allyl,[3,5,6] benzyl,[3,6] and (*E*,*Z*)-pentadienyl[3,7] radicals are highly stabilized with E_s = 18, 16, and 28 kcal mol^{-1}, respectively. Lone pairs of electrons on oxygen have a similar effect since for $\dot{C}H_2OH$[8] and $\dot{C}H_2OCH_3$[9] E_s = 8 and 11 kcal mol^{-1}, respectively. However, the stabilizing effect due to a nitrogen lone pair has not been thoroughly investigated.

In a preliminary report of this work,[10] we showed that the stabilization energies for α-aminoalkyl radicals were large and that they showed a rather dramatic dependence on the extent of N-alkylation. We now describe a detailed investigation of this subject.

Experimental Section

Apparatus. The apparatus used in this work has been described in detail elsewhere.[11,12] Briefly, ions were generated in the gas phase by impact of an energy-resolved electron beam from an electrostatic electron monochromator.[11] They were detected by using a quadrupole mass spectrometer coupled with a minicomputer data system.[12] The appearance energy, AE, of a given ion was determined by detecting the threshold for an ion current at the appropriate mass as the energy of the

(1) Issued as NRCC Publication No. 20968.
(2) University of Ottawa.
(3) Stabilization energies are referred to BDE(CH_3–H) as the standard; see: Dewar, M. J. S.; Fox, M. A.; Nelson, D. J. *J. Organomet. Chem.* **1980**, *185*, 157. Literature values[5-7] have been corrected to conform to the definition expressed in eq 2.
(4) Castelhano, A. L.; Griller, D. *J. Am. Chem. Soc.* **1982**, *104*, 3655.
(5) Rossi, M.; King, K. D.; Golden, D. M. *J. Am. Chem. Soc.* **1979**, *101*, 1223. Korth, H. G.; Trill, H.; Sustman, R. *Ibid.* **1981**, *103*, 4483.
(6) Rossi, M.; Golden, D. M. *J. Am. Chem. Soc.* **1979**, *101*, 1230. DeFrees, D. J.; McIver, R. T., Jr.; Hehre, W. J. *Ibid.* **1980**, *102*, 3334 and references cited therein.
(7) Davies, A. G.; Griller, D.; Ingold, K. U.; Lindsay, D. A.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1981**, 633.
(8) Cruickshank, F. R.; Benson, S. W. *J. Phys. Chem.* **1969**, *73*, 733.
(9) Cruickshank, F. R.; Benson, S. W. *Int. J. Chem. Kinet.* **1969**, *1*, 381.
(10) Griller, D.; Lossing, F. P. *J. Am. Chem. Soc.* **1981**, *103*, 1586.
(11) Maeda, K.; Semeluk, G. P.; Lossing, F. P. *Int. J. Mass. Spectrom. Ion Phys.* **1968**, *1*, 395.
(12) Lossing, F. P.; Traeger, J. C. *Int. J. Mass. Spectrom. Ion Phys.* **1976**, *19*, 9.

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