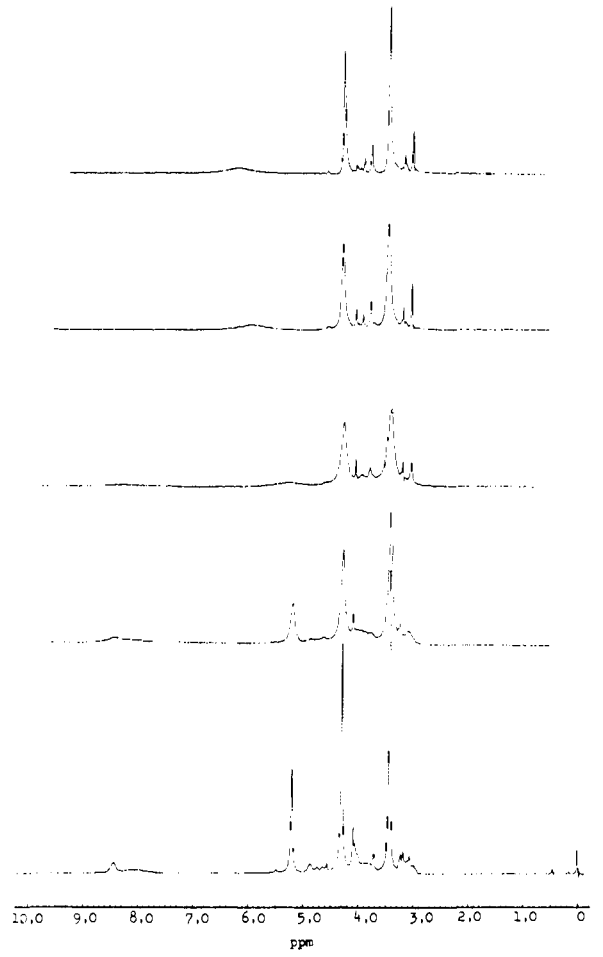
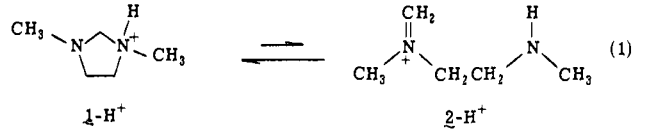


Figure 1. The 60-MHz ^1H spectrum of 1,3-dimethyltetrahydroimidazole (**1**) in CF_3CO_2H as a function of temperature (bottom to top: 40, 60, 80, 100, and 120 °C).



1-H^+ **2**-H^+ (1)

CH_2=N protons, just as the C=O double bond deshields aldehyde (CH=O) protons. We corroborated these assignments by the preparation of 1,3-dimethyl-1,3-diazolidine-*2,2-d*$_2$, whose ^1H spectrum lacked not only the NCH_2N resonance of **1**-H^+ at δ 5.2 but also the CH_2=N resonance of **2**-H^+ at 8.4. Taken in CF_3CO_2D, the spectrum of the *2,2-d*$_2$ variant exhibits only the two sharp singlets at δ 3.4 and 4.3. Some of the small peaks in the δ 3.0–5.0 region are from the remaining protons in **2**, but specific assignments could not be made. In addition, there are some impurities. Integration of the δ 5.2 and 8.4 peaks indicates that the ring form (**1**) is present at equilibrium to the extent of 82 ± 2%.[5] Our evidence does not prove conclusively that the less abundant species is **2**, but this form is consistent with all evidence to date.

The temperature dependence of the ^1H spectrum (Figure 1) demonstrates a dynamic interconversion of the ring (**1**-H^+) and chain (**2**-H^+) forms,[5] as best seen from the dramatic alterations of the NCH_2N resonance at δ 5.2. This peak begins to broaden above 40 °C and all but disappears by 80 °C. The CH_2=N peak at δ 8.4 also broadens and disappears, and the pair of peaks is replaced above 120 °C by an average singlet at about δ 6.3 (the fast exchange extreme was not fully attained). That the NCH_2N protons of the ring form and the CH_2=N protons of the chain form were indeed undergoing mutual exchange was confirmed by Forsén–Hoffman-type double resonance experiments[6] in the range 40–80 °C, whereby irradiation of either peak brought about considerable reduction in the intensity of the other peak. The NCH_2CH_2N and NCH_3 resonances also undergo alterations due to exchange, but less obviously. In both the undeuterated and the deuterated (*2,2-d*$_2$) forms, these peaks simply broaden at 60 °C and resharpen above 100 °C (Figure 1). The changes are less dramatic than for the NCH_2N resonances because the chemical shift differences between the ring and chain resonances are much smaller. All the temperature effects are fully reversible.

The coalescence temperature for ring–chain tautomerism in protonated 1,3-dimethyl-1,3-diazolidine (**1**) is ~90 °C, and the free energy of activation ($\Delta G^{\ddagger}$) at this temperature is 16.9 ± 0.3 kcal mol^{-1}. This reaction is an example of the normally disfavored 5-endo-trigonal ring closure (**2** → **1**).[7] Its relatively rapid rate may result from the strongly electrophilic nature of the iminium carbon in **2**-H^+ or from a variety of other possibilities. The DNMR method promises to be an extremely useful approach to studying this heterocyclic phenomenon. Our current work explores the effect of ring size and heteroatom identity on ring–chain tautomerism.

References and Notes

(1) We thank the National Science Foundation (Grant No. CHE77-08384) and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.
(2) L. M. Jackman and F. A. Cotton, Eds., "Dynamic Nuclear Magnetic Resonance Spectroscopy", Academic Press, New York, 1975.
(3) A. R. Katritzky and J. M. Lagowski, "The Principles of Heterocyclic Chemistry", Methuen, London, 1967, p 158; R. J. Ferm, J. L. Riebsomer, E. L. Martin, and G. H. Daub, *J. Org. Chem.*, **18**, 643 (1953).
(4) Ring–chain tautomerization of a diazolidine system occurs in the reactions of the enzyme cofactor N^5,N^{10}-methylenetetrahydrofolic acid. A recent model study observed the ring–chain process by stopped-flow techniques as the first step in the hydrolysis of 2-*tert*-butyl-1,3-dimethyl-1,3-imidazolidine to pivaldehyde and 1,3-dimethylethylenediamine. See T. H. Fife, J. E. C. Hutchins, and A. M. Pellino, *J. Am. Chem. Soc.*, **100**, 6455 (1978).
(5) The open-chain tautomer **2**-H^+ may protonate again at the amine nitrogen to become diprotonated (**2**-$2H^+$), but we cannot tell from the spectrum.
(6) S. Forsén and R. A. Hoffman, *J. Chem. Phys.*, **39**, 2892 (1963).
(7) J. E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman, and R. C. Thomas, *J. Chem. Soc., Chem. Commun.*, 736 (1976).
(8) On leave of absence from the Institute of Drug Research, Pharmaceutical Faculty of the Medical Academy, Łódź, Poland; Petroleum Research Fund Postdoctoral Fellow, 1977–1978.

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Racemization of Isovaline by γ-Radiation. Cosmological Implications

Sir:

Isovaline (α-amino-α-methylbutyric acid) is of considerable cosmological interest since (1) it is one of the 12 nonprotein amino acids isolated and identified from the Murchison carbonaceous chondrite[1] and (2) it has no α hydrogen at its asymmetric center and has been shown[2] to be incapable of racemization by the mechanisms accounting for the racemization of ordinary α-amino acids. It had previously been suggested[3] that the enantiomeric composition of the Murchison isovaline should represent that prevailing at the time of its original synthesis in the meteorite, thus giving a clue as to the primordial enantiomeric composition of the other amino acids in the meteorite regardless of their present composition. Recently we reported[4-6] that ionizing radiation could cause "radioracemization" of α-amino acids both in the solid state and in solution, along with their well-known radiolysis.[7] We now have found that such radiation is capable of racemizing isovaline as well.

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Table I. γ-Radiolysis and Radioracemization of Crystalline Isovaline and Leucine

amino acid	dose, rads × 10^{-8}	decompn, %	racemizn, %
D-Ival	9.0	79.6	4.9
L-Ival	9.0	78.0	4.7
D-Leu	8.1	67.9	5.6
L-Leu	8.1	68.0	5.0

Crystalline samples of D- and L-isovaline (shown to be optically pure by gas chromatographic (GC) analyses of their diastereomeric *N*-TFA-isovalylleucine isopropyl ester derivatives[8] (I)) were irradiated in a 3000-Ci ^{60}Co γ-ray source with radiation doses selected to cause significant but not complete radiolysis. Each irradiated sample was quantitatively divided and the separate portions were converted to the appropriate I derivative and examined by GC for racemization and degradation (using the "enantiomeric marker" technique[9]). All GC analyses were performed in replicate with the previously obtained precision[10] using 50-m capillary columns coated with enantiomeric phases[11] consisting of *N*-docosanoyl-D- (or L-) valine *tert*-butylamide. GC conditions were such that the GC peaks of the unidentified radiolysis products in no way interfered with the peaks of the residual isovaline during the GC analyses. A comparison of the radiolysis and radioracemization of isovaline with those previously found[5,6] for leucine is shown in Table I.

Table I shows that the percent radioracemization (i.e., 2 × percent of opposite antipode produced) accompanying the γ-radiolysis of D- and L-isovaline is roughly comparable with that noted[5,6] for the common aliphatic α-amino acids D- and L-leucine. While the enantiomeric composition of the isovaline in the Murchison meteorite was found[2] to be *approximately* 50:50 D:L, the presently observed radioracemization of isovaline suggests the desirability of reevaluating the earlier conclusion[2,3] that the primordial enantiomeric composition of isovaline and the other amino acids in the Murchison meteorite must therefore have been racemic. While the "cosmic ray exposure age" of the Murchison chondrite (i.e., the time since its parent body fragmented) is only 1.2×10^6 years,[12] resulting in a cosmic ray radiation dose of $\sim 0.3 \times 10^8$ rads during this period (based on 10^8 rads during 3.5×10^6 years for the Orgueil meteorite[13,14]), natural radioactivity in the parent body has provided an integrated dose of some 5×10^8 rads during the 4.5×10^9 years of its existence.[14,15] Thus the isovaline in the Murchison has received a total dose of $\sim 5.3 \times 10^8$ rads, some 60% of the radiation dose in Table I which caused 4.8% racemization of crystalline isovaline. While it is not known how such radioracemization might be altered by the mineral matrix of the metorite, it is clear that significant racemization of any nonracemic amino acids indigenous to meteorite parent bodies might be expected during the 4.5×10^9 years since their primeval origin. While the above data carry no implications whatsoever that the racemic amino acids in meteorites were originally optically active, the phenomenon or radioracemization nevertheless, in principle, makes the question of the primordial enantiomeric composition of amino acids in meteorites an indeterminate one.

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References and Notes

(1) Kvenvolden, K. A.; Lawless, J. G.; Ponnamperuma, C. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 486.
(2) Pollock, G. E.; Cheng, C. N.; Cronin, S. E.; Kvenvolden, K. A. *Geochim. Cosmochim. Acta* **1975**, *39*, 1571.
(3) Lawless, J. G. *Geochim. Cosmochim. Acta* **1973**, *37*, 2207.
(4) Bonner, W. A.; Van Dort, M. A.; Yearian, M. R.; Zeman, H. D.; Li, G. C. *Isr. J. Chem.* **1976/77**, *15*, 89.
(5) Bonner, W. A.; Lemmon, R. M. *J. Mol. Evol.* **1978**, *11*, 95.
(6) Bonner, W. A.; Lemmon, R. M. *Bioorg. Chem.* **1978**, *7*, 175.
(7) Garrison, W. M. *Radiat. Res. Rev.* **1972**, *3*, 305.
(8) Flores, J. J.; Bonner, W. A.; Van Dort, M. A. *J. Chromatogr.* **1977**, *132*, 152.
(9) Bonner, W. A. *J. Chromatogr. Sci.* **1973**, *11*, 101.
(10) Bonner, W. A.; Van Dort, M. A.; Flores, J. J. *Anal. Chem.* **1974**, *46*, 2104.
(11) Bonner, W. A.; Blair, N. E. *J. Chromatogr.*, in press.
(12) Cressy, Jr., P. J.; Bogard, D. D. *Geochim. Cosmochim. Acta* **1976**, *40*, 749.
(13) Nagy, B. "Carbonaceous Meteorites", Elsevier: Amsterdam, 1975; p 357.
(14) Studier, M. H.; Hayatsu, R.; Anders, E. *Science* **1965**, *149*, 1455.
(15) Anders, E. *Ann. N.Y. Acad. Sci.* **1961**, *93*, 651.

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Raman Scattering from Glucagon–Dimyristoyllecithin[1] Complexes. A Model System for Serum Lipoproteins

Sir:

Raman spectroscopic studies of intact biological membranes are difficult since the fluorescent emission from trace components obscures the weaker Raman signal from the lipid and protein moities. The technique is well suited for studies of lipid–protein interaction in reconstituted systems since conformational changes in both components can be monitored and fluorescent entities can be excluded. The polypeptide hormone glucagon interacts with dimyristoyllecithin (DMPC) when the latter is in its gel state (below 23 °C) to produce a soluble complex which has features similar to those found in serum lipoproteins.[2] We have found that the glucagon-DMPC complex can be concentrated sufficiently in solution to yield high quality Raman spectra. Detailed information as to the effect of protein on lipid conformation has thereby been obtained. The spectra arise from the DMPC component in the complex since that component is present in large molar excess (30:1).

Complexes were formed as described by Epand et al.[2a] and prepared for Raman spectroscopy by (i) removal of the ammonium acetate buffer by dialysis and (ii) concentration by partial lyophilization to a concentration of 50 mg/mL. Typical Raman spectra are shown in Figure 1 for two spectral regions (2700–3100 and 900–1200 cm^{-1}) of the complex and two control systems: DMPC in multibilayer form and DMPC in small unilamellar vesicles. The C–C stretching region (1050–1150 cm^{-1}) is sensitive to trans–gauche isomerization in the DMPC hydrocarbon chains. The intensity ratio $I(1130/1100)$ has been correlated with the number of CH_2 groups in the all-trans conformation.[3] The temperature dependence of $I(1130/1100)$ is shown in Figure 2 for the three systems studied. A sigmoid-shaped variation is observed for DMPC in both sonicated and multibilayer form, with the sharp discontinuity at 23 °C reflecting the gel–liquid crystal phase transition.[4,5] The change in $I(1130/1100)$ during melting indicates the cooperative loss of four–five trans bonds in the DMPC hydrocarbon chains (as calculated by the method of Gaber and Peticolas[3]). Also evident is the noncooperative formation of two–three gauche rotamers prior to the main chain melt. The DMPC–glucagon complex exhibits significant differences from the control systems in the 7–20 °C range. At 7 °C, $I(1130/1100)$ is reduced by 25–30% from the control systems, indicating an additional two–three gauche rotations

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