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(23) In addition, the model proposed in ref 8 has the quinoxaline ring approximately at right angles to the carbonyl group. The anticipated partial double bond character of the C2–CO bond and the LIS results on quinoxaline carboxamide make the conformation shown in structure IV substantially more probable.

Heteronuclear Vicinal Coupling Constants and Site-Specific Isotopic Substitution in the Investigation of Rotational Isomerism in Leucine

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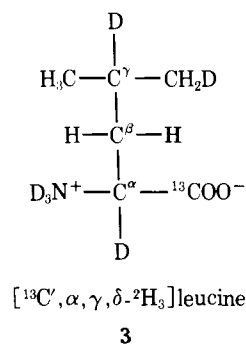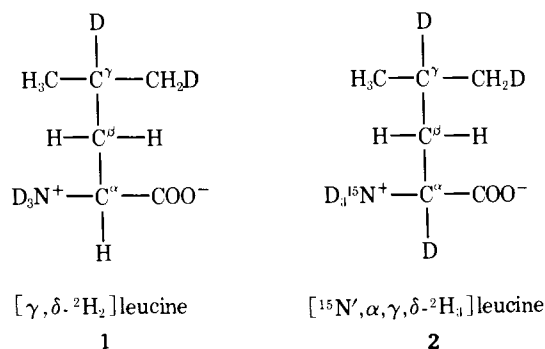Received June 17, 1977*

Abstract: Vicinal coupling constants about the C^α–C^β bond between combinations of ^1H, ^{13}C, and ^{15}N nuclei were measured in three isotopic isomers of leucine. The couplings found were used to calculate populations of staggered rotamers. These values, which are overdetermined by the several coupling constants, are found to be self-consistent for both anionic and cationic forms. The necessity for simplification of the spin system by substitution of deuterium for hydrogen is discussed. A statistical method of using the observed couplings to make stereochemical assignments is introduced.

It has been generally accepted that the conformational properties of amino acids, peptides, and proteins in solution can be described by determining the appropriate torsional angles, inasmuch as bond lengths and bond angles remain relatively constant in such molecules.[2] The torsional angles connected with the backbone of a peptide have received major attention, while it has often been assumed that the first torsional angle of the side chains in peptides is averaged by rapid rotation about the C^α–C^β bond. Vicinal coupling constants have been used to measure the rotamer populations about these bonds[2] in amino acids and a few peptides using standard assumptions.[3] Most studies have centered around the vicinal couplings between protons, but some of the other vicinal couplings have been employed or proposed, such as those between the amide ^{15}N and the β protons[4,5] and those between the carbonyl ^{13}C and the β protons.[6,7]

This report is concerned with NMR studies of a series of isotopic isomers of leucine (**1-3**), which were designed to determine as many of the vicinal coupling constants as possible, both homo- and heteronuclear, in a single compound; homonuclear H^α–H^β couplings for **1** have been previously reported and the equilibria between rotamers derived from these values have been discussed.[8] Syntheses of these isomers were performed by modifications of standard methods.

Experimental Section

Racemates were used throughout this work. In discussion of identities of rotamers, the L isomer only is considered (see Figure 1). The population states, I, II, III correspond to the torsional angles (−60,

[γ,δ-$^2H_2$]leucine
1

[$^{15}N',\alpha,\gamma,\delta$-$^2H_4$]leucine
2

[$^{13}C',\alpha,\gamma,\delta$-$^2H_3$]leucine
3

180, +60°) for the L isomer and (+60, 180, −60°) for the D isomer

Amino acid analyses were carried out on a Beckman MS amino acid

analyzer using a 0.9 × 30 cm column of Durrum DC-6A resin. The analyzer had been modified to perform automatically the two buffer changes that are required for a single column analysis. The Durrum picobuffer system II was employed.

The NMR spectra of the intermediates and products of synthesis were taken at 220 MHz at 19 °C; the solvent was D_2O unless otherwise noted. The internal reference was sodium $[2,2,3,3-^2H_4]$3-(trimethylsilyl)propionate (TSP) in D_2O and $(CH_3)_4Si$ in $(CD_3)_2SO$ and $CDCl_3$.

$[\gamma,\delta-^2H_2]$Leucine (1) was prepared by modification of the procedure of Albertson and Archer.[9] Ethyl 2-acetamido-2-carbethoxy-4-methyl-4-pentenoate (15 g) was dissolved in 100 mL of benzene, 500 mg of chlorotris(triphenylphosphine)rhodium was added, and the mixture was deuterated at 40 psi using a shaking Parr apparatus. The theoretical quantity of deuterium was absorbed in 2 h at room temperature. The resulting red solution was concentrated in vacuo, dissolved in 75 mL of 48% HBr in water, and heated at reflux for 24 h.

The hydrolysate was concentrated in vacuo, dissolved in 125 mL of water, decolorized with charcoal, adjusted to pH 6, and chilled overnight. The crystals were filtered, washed thoroughly with ethanol, and redissolved in a minimum amount of 3 M HCl. The solution was again adjusted to pH 6 and chilled. The resulting crystals were washed with water (twice) and ethanol (three times) and dried in vacuo: yield 6 g (73%); NMR δ 4.14 (q, 1 H), 1.82 (m, 2 H), 0.97 (d, 5 H); amino acid analysis, only leucine detected.

Anal. Calcd for $C_6H_{11}D_2O_2N$: C, 54.12; (H, D), 11.35; N, 10.51. Found: C, 54.07; (H, D), 11.31; N, 10.39.

$[^{15}N',\alpha,\gamma,\delta-^2H_3]$Leucine (2) was prepared by the reaction of potassium $[^{15}N]$phthalimide with the appropriate α-bromo methyl ester, prepared from β-methylallylmalonic acid diethyl ester[10] (4) as follows.

$[\gamma,\delta-^2H_2]$Isobutylmalonic Acid Diethyl Ester (5). Thirty grams of 4 was dissolved in 100 mL of benzene, 250 mg of chlorotris(triphenylphosphine)rhodium was added, and the mixture was deuterated at 40 psi using a shaking Parr apparatus. Deuteration for 20 h at room temperature (17 °C) gave only about 50% yield, but deuteration close to 100% was obtained in 2 h by warming the Parr apparatus to about 40 °C with a heat lamp. The resulting red solution was concentrated in vacuo and distilled at reduced pressure (105–107 °C at 7 Torr): yield 29 g (95%); NMR δ 4.17 (4 H), 3.39 (1 H), 1.74 (2 H), 1.22 (6 H), 0.91 (5 H).

Anal. Calcd for $C_{11}H_{18}D_2O_4$: C, 60.53; (H, D), 10.14. Found: C, 60.72; (H, D), 10.21.

$[\gamma,\delta-^2H_2]$Isobutylmalonic Acid (6). Twenty-five grams of 5 was added in a steady stream with vigorous stirring to a hot solution of KOH in water (25 g in 20 mL) in a 200-mL three-necked flask. The mixture was stirred and heated for 5 h and then transferred to a stirred beaker in an ice bath. When the temperature had dropped to 15 °C, concentrated HCl was added (at such a rate that the temperature did not exceed 20 °C) until the pH of the solution was 2. The resulting precipitate was extracted thoroughly with ether and dried over $CaCl_2$. The ether solution was then filtered and evaporated to dryness: yield 16.6 g (89%); NMR δ (($CD_3)_2SO$) 3.28 (1 H), 1.62 (2 H), 0.85 (5 H).

$[^2H'_2,\gamma,\delta-^2H_2]$Isobutylmalonic Acid (7). Twenty grams of 6 was dissolved in and recovered by evaporation of solvent from 20-g lots of D_2O until deuteration was effectively complete, and the solution was then extracted with ether and dried over $CaCl_2$ for 24 h. The ether solution was then filtered, evaporated to dryness, and stored in vacuo, yield 20 g (98.7%).

$[\alpha,\gamma,\delta-^2H_3]$α-Bromoisocaproic Acid (8). Twenty grams of 7 was dissolved in ether (50 mL). A small quantity of bromine (0.5 mL) was initially added, and then an additional 5 mL was introduced drop by drop. D_2O was added (20 mL), the solution was shaken, the aqueous phase was replaced by 20 mL of 3 M DBr in D_2O, and the solution was shaken again. The organic phase was concentrated in vacuo, and the residual liquid was decarboxylated by refluxing (5 h, 130 °C). The bromo acid was distilled at reduced pressure (115–118 °C, 8 Torr): yield 16.6 g (68%); NMR δ 4.29 (0.1 H), 1.89 (q, 2 H), 0.93 (d, 5 H).

$[^{15}N',\alpha,\gamma,\delta-^2H_3]$Leucine (2). The conversion of 16 g of 8 to its methyl ester (9) used diazomethane,[11] yield 15.6 g (91.5%). The ester (1.3 g) was mixed with 1 g of potassium $[^{15}N]$phthalimide and cupric oxide (165 mg) and sealed in a thick-walled evacuated glass tube. The tube was placed in a 200 °C oven for 4 h. The product was worked up as

previously described[12] to yield 859 mg of 2. The crude product was dissolved in 200 mL of 0.01 M HCl and applied to a 2 × 20 cm column of BioRex AG50 WX8 (200–400 mesh) previously equilibrated with 0.01 M HCl. The column was washed with 250 mL of 0.01 M HCl, 400 mL of water, and 300 mL of 4 M aqueous ammonia. The ammonia fraction was concentrated to a small volume, adjusted to pH 6, and diluted with acetone. The resulting precipitate was washed with acetone (three times) and ether (three times) and dried overnight: yield 350 mg (48% from phthalimide); NMR δ 4.14 (0.16 H), 1.82 (m, 2 H), 0.97 (d, 5 H); amino acid analysis, only leucine detected.

$[^{13}C',\alpha,\gamma,\delta-^2H_3]$Leucine (3) was synthesized using the Strecker reaction on the appropriate aldehyde which had been prepared from $[\beta,\gamma-^2H_2]$3-methylbutanoic acid (9).

$[\beta,\gamma-^2H_2]$3-Methylbutanoic Acid (9). Forty grams of 3-methyl-3-butenoic acid[13] was dissolved in 100 mL of benzene, 500 mg of chlorotris(triphenylphosphine)rhodium was added, and the mixture was deuterated at 40 psi and 40 °C in a shaking Parr apparatus. The expected molar equivalent amount of deuterium was taken up after 10 h. The resulting red solution was extracted with aqueous sodium carbonate (60 g/200 mL). The alkaline extract was adjusted to pH 4 and reextracted with ether. The final product was obtained from the ether extract after drying over sodium carbonate, concentration to a small volume, and distillation at 175 °C: yield 35 g (84%); NMR $(CDCl_3)$ δ 11.72 (s, 1 H), 2.23 (s, 2 H), 0.96 (t, 5 H).

Conversion to the amino acid was accomplished by, first, the reduction of 9 to $[1,1,3,4-^2H_4]$3-methyl-1-butanol. (10) using lithium aluminum deuteride. 10 was then oxidized to $[1,3,4-^2H_3]$3-methylbutyraldehyde (11) by the procedure of Ratcliffe and Rodehorst.[14] Nine millimoles of 11 was treated with 9 mmol of $K^{13}CN$ and 10 mmol of ammonium chloride in the Strecker reaction using conditions described for the synthesis of valine:[15] yield (from 9) 40%; NMR (1 M DCl, D_2O) δ 1.90–1.71 (m, 2 H), 0.96 (d, 5 H).

$[^{13}C']$DL-leucine was purchased from Koch Isotopes.

NMR Spectroscopy. ^1H spectra were measured on a Varian HR/Nicolet Technology Corp. TT-220 spectrometer. Spectra were accumulated by pulse and fast Fourier transform techniques. Concentration of each sample was 0.5 M. An exponential decay equivalent to 0.2 Hz in the frequency domain was applied prior to the transformation of the free-induction decay (the sum of between 4 and 64 transients) in order to increase the signal to noise ratio at the expense of a slight loss in resolution. After Fourier transformation, the 1500-Hz spectral width occupied 4096 memory locations. To compensate partially for the limited number of computer memory locations, peak positions were calculated from a three-point interpolation of a Lorentzian function. The pD of each sample was checked by an electrode equilibrated in D_2O at 25 °C and calibrated with deuterated standards.[16] Analysis and simulation of spectra were performed by an implementation of LAOCN3.[17] ^{13}C NMR spectra were measured on a modified Bruker HX-90 spectrometer at 22.63 MHz. The $^{13}C'$ region of the spectrum was observed using a Nyquist frequency of 500 Hz. Either no ^1H decoupling was employed, or slight nuclear Overhauser enhancement was obtained by the following sequence: 20-μs ^{13}C 90° pulse, 4.1-s data acquisition, 1.5-s ^1H broad-band decouple

Side-Chain Rotamers about the $C^\alpha-C^\beta$ Bond of L-Amino Acids with Two β Protons ABX Systems

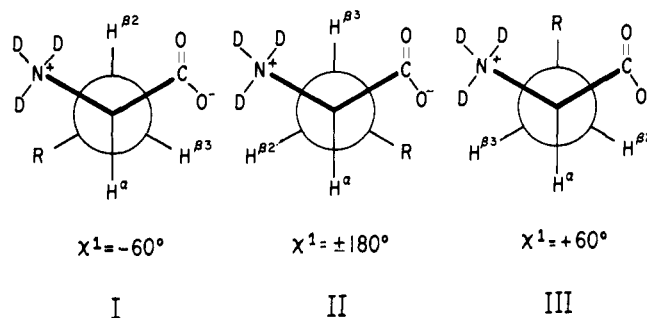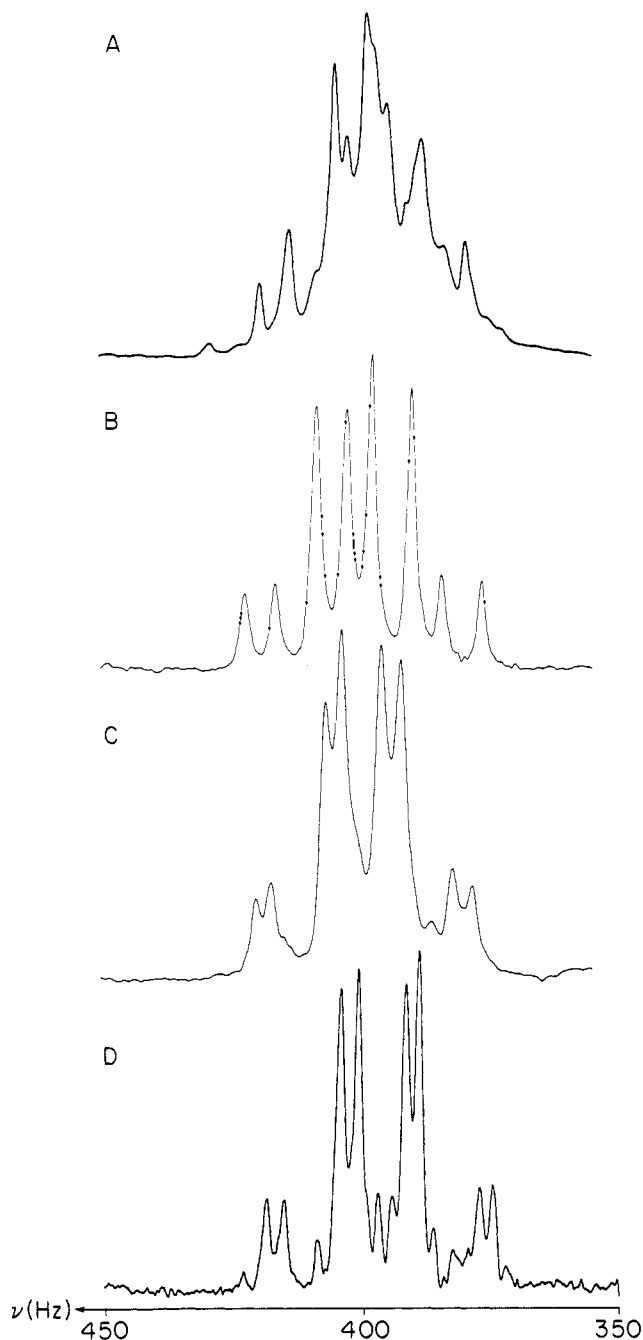**Figure 1.** The staggered rotamers about the $C^\alpha-C^\beta$ bond of L-leucine zwitterion in D_2O. R denotes the isopropyl group.

Figure 2. 220-MHz ^{1}H NMR spectra of the β protons of the cations at 25 °C of (A) unsubstituted leucine; (B) [γ,δ-^{2}H$_2$]leucine (**1**); (C) [^{15}N',α,γ,δ-^{2}H$_3$]leucine (**2**); (D) [^{13}C',α,γ,δ-^{2}H$_3$]leucine (**3**).

at a power of approximately 10 W. All spectra were measured at 25 °C.

Calculation of Populations and Standard Coupling Constants. Populations (p) were calculated from vicinal coupling constants (^3J) by standard methods.[3] From H$^\alpha$–H$^\beta$ couplings, $p_{\rm I} = \{^3J({\rm H}^\alpha{\rm -H}^{\beta2}) - {}^3J_g({\rm HH})\}/\Delta^3J({\rm HH})$, $p_{\rm II} = \{^3J({\rm H}^\alpha{\rm -H}^{\beta3}) - {}^3J_g({\rm HH})\}/\Delta^3J({\rm HH})$, and $p_{\rm III} = 1 - p_{\rm I} - p_{\rm II}$; from ^{15}N'–H$^\beta$ couplings, $p_{\rm I} = \{^3J({}^{15}{\rm N'-H}^{\beta3}) - {}^3J_g({\rm NH})\}/\Delta^3J({\rm NH})$, $p_{\rm II} = 1 - p_{\rm I} - p_{\rm III}$, and $p_{\rm III} = \{^3J({}^{15}{\rm N'-H}^{\beta2}) - {}^3J_g({\rm NH})\}/\Delta^3J({\rm NH})$; from ^{13}C'–H couplings, $p_{\rm I} = 1 - p_{\rm II} - p_{\rm III}$, $p_{\rm II} = \{^3J({}^{13}{\rm C'-H}^{\beta2}) - {}^3J_g({\rm CH})\}/\Delta^3J({\rm CH})$, and $p_{\rm III} = \{^3J({}^{13}{\rm C'-H}^{\beta3}) - {}^3J_g({\rm CH})\}/\Delta^3J({\rm CH})$; $\Delta^3J({\rm XH}) \equiv {}^3J_t({\rm X-H}^\beta) - {}^3J_g({\rm X-H}^\beta)$ where X is H$^\alpha$, ^{15}N' or ^{13}C'.

The following respective values of gauche (^3J_g) and trans (^3J_t) couplings were used: (a) for H$^\alpha$–H$^\beta$ couplings, 2.60 and 13.56 Hz;[18] (b) for ^{15}N'–H$^\beta$ couplings, −1.8 and −4.8 Hz;[5] (c) for ^{13}C'–H$^\beta$ couplings, 1.3 and 9.8 Hz.[7]

Standard gauche and trans coupling constants were calculated by $^3J_g({\rm NH}) = \{p_{\rm I}{}^3J({}^{15}{\rm N'-H}^{\beta2}) - p_{\rm III} {}^3J({}^{15}{\rm N'-H}^{\beta3})\}/(p_{\rm I} - p_{\rm III})$ and

$^3J_t({\rm NH}) = \{(1 - p_{\rm III})^3J({}^{15}{\rm N'-H}^{\beta3}) - (1 - p_{\rm I})^3J({}^{15}{\rm N'-H}^{\beta2})\}/(p_{\rm I} - p_{\rm III})$. We have assumed that all vicinal coupling constants between ^{15}N' and H$^\beta$ are negative.[19]

Calculation of Probability of Correct Assignment. In this study, a set of observed values, **O** (vicinal coupling constants), is used with a set of fixed parameters, **A** (^3J_g and ^3J_t), presumed to be valid for a large set of observations and compounds, and with a set of formulas, f, to calculate the molecular properties, **V** (populations), i.e., **V** = $f($**O**,**A**$)$. Another set of formulas, g, may then be used to calculate a set, **C**, that corresponds to **O**, i.e., **C** = $g($**V**,**A**$)$, and an agreement factor, R, can be calculated from the elements of **O** and **C** by

$$\left(\frac{\sum[({\rm O}_i - {\rm C}_i)^2 w_i]}{\sum({\rm O}_i{}^2 w_i)}\right)^{1/2}$$

where w_i's are weighting factors.

An R factor can be calculated for each of the two sets of stereochemical assignments of the β protons. These two R factors can be compared and used in a statistical test, which has been extensively described by Hamilton.[20] The statistical inferences that can be drawn from these tests are limited. It is usually possible to determine whether or not a significant improvement in the fit has been made by changing some part of the data reduction, e.g., in this case, the values of the fixed parameters ^3J_g and ^3J_t or the assignment of the β protons, but it is not possible to test the overall applicibility of the model used in the fit.

In our application, the hypothesis tested is that the one set of assignments produces a fit from the observed values of ^3J as well as those from the other set of assignments. The rejection of this hypothesis implies that the set of assignments producing the smaller R factor is correct, given that the assumptions used in the method of calculation are correct. Reference 20 shows the methods of calculating the probabilities involved.

It is possible to choose the weights, w_i, in various ways. Using weights proportional to $|{\rm O}_i|^s$ where s ranges from 0 to 2, it was found that the calculations described here were not markedly sensitive to the value of s. In this report, results for an s value of 1.5 are used. The use of R factors has been proposed in studies of lanthanide-induced shifts.[21]

Results and Discussion

From ^{1}H and ^{13}C NMR spectra, six of the possible nine vicinal coupling constants about the C$^\alpha$–C$^\beta$ bond have been measured in various isotopic isomers of leucine (**1–3**).[22] Figure 2 show typical observed spectra, and Table I summarizes the observed couplings and the derived populations of the staggered rotamers using the standard values obtained previously from other amino acids. These values are remarkably consistent, particularly those calculated from H$^\alpha$–H$^\beta$ and ^{13}C'–H$^\beta$. Figure 2 also includes the spectrum of the β protons of unsubstituted leucine (A) illustrating the necessity for simplification.

In each line of Table I one of the populations is unequivocally derived, while the identity of the other two populations is not directly assignable. In each case the one unequivocally identified population is that in which the substituent on C$^\alpha$ vicinally coupled to the β protons is in a gauche relationship to each of the β protons, while the other two populations possess both a gauche and a trans relationship between these nuclei. The sums of the unequivocally identified populations are 1.11 for the anion and 0.95 for the cation. The difference between these experimental values and the value expected if only the three staggered rotamers are populated, 1.00, is small, and this suggests that the accuracy of any single value of a population is approximately ±0.1. As an alternative to examining the sum of these elements, a more general test of correct assignments can be made by averaging the three sets of three observed populations, calculating the expected coupling constants, and obtaining an R factor for the two possible assignments, as described in the Experimental Section. The R factors for the assignments in Table I are 0.026 (anion) and 0.017 (cation), while the reversed assignments yield R factors of 0.156 and 0.157, respectively. The ratios of R factors are 6.00 (anion) and 9.16 (cation). These ratios are sufficiently large that the possibility that the assignments cannot be distinguished can

Table I. Vicinal Coupling Constants and Derived Populations of Rotamers about the $C^\alpha-C^\beta$ Bond for Leucine Cation and Anion

Ionic state	Nucleus coupled to β protons	Coupling constant[a] at 25 °C to		Compd used	Populations[b]		
		β^2	β^3		I	II	III
Anion	H^α	8.76	5.94	1	0.56	0.30	0.13[c]
	$^{15}N'$	−2.15[e]	−3.15[e]	2	0.45	0.43[c]	0.12
	$^{13}C'$	4.06	2.36	3	0.55[c]	0.32	0.12
Cation	H^α	8.42	5.98	1	0.53	0.31	0.16[c]
	$^{15}N'$	−2.47[e]	−3.47[e]	2	0.56	0.22[c]	0.22
	$^{13}C'$	3.75	2.92	3[d]	0.52[c]	0.29	0.19

[a] Atomic nomenclature follows IUPAC-IUB Tentative Rules: *J. Mol. Biol.*, **52**, 1 (1970). Nomenclature for coupling constants follows rules proposed by R. Grinter, *Spec. Period. Rep.: Nucl. Magn. Reson.*, **4**, 67–68 (1976). [b] The rotameric states I, II, and III are illustrated in Figure 1. [c] The assignment of this population is unequivocal for this combination of nuclei. [d] The proximity of chemical shifts of the β and γ protons prevented the extraction of individual coupling constants from the ^{13}C NMR spectrum of [$^{13}C'$]leucine. The sum of these individual couplings could be obtained, however, from this ^{13}C spectrum. The value of the sum of couplings (6.32 Hz) can yield only a single population (p_1). ^1H NMR of compound **3** was necessary to derive the individual values for the cation. [e] These couplings are assumed to be negative.

be rejected at approximately the 0.005 level of significance (99.5% probability).[23] Although the data presented here are such that a similar conclusion could be made by inspection alone, it would be expected that other cases might require such calculation and comparison. If, for example, each individual population were approximately 0.33, or if only a limited number of the couplings could be measured, then assignment of the states would be much more difficult.

The observed coupling constants in Table I are quite precisely determined, certainly better than ±0.1 Hz in all the cases in which ^1H spectra were analyzed. The differences between the populations calculated from these coupling constants appear to be much greater than expected, however, for imprecisions in experimental determination. There are several possible causes of such differences; either the method of calculation may be imprecise or the choices of coupling constants for gauche and trans states may be incorrect. The values of J_g and J_t for $^{15}N'-H^\beta$ coupling used here are expected to be less precise than those for $H^\alpha-H^\beta$ and $^{13}C'-H^\beta$ because only a limited number of suitable model compounds have been examined. As an alternative to using independently the values of the various measured coupling constants, populations can be calculated using only the $H^\alpha-H^\beta$ couplings in Table I, and from these populations independent gauche and trans values for $^{15}N'-H^\beta$ couplings may be derived. The respective values obtained, −1.84 and −4.18 Hz (for the anion) and −2.04 and −4.74 Hz (for the cation), are slightly different from those reported previously, −1.8 and −4.8 Hz.[4,5] In these earlier reports the effect of changing the ionic state on the derived values of the coupling constants had not been considered.

The methods of calculation may be imprecise for reasons that have been extensively discussed elsewhere.[24-28] A significant cause of imprecision probably arises from the assumption of the equality of coupling constants for gauche states.[25-28] Corrections for the orientational dependence of substituent electronegativity have been suggested.[26-29] Other deviations may arise because of slight changes in bond angles, in bond lengths, or in the apparently averaged torsional angles of the rotamers between the model compounds and those under investigation. Nonetheless, it is generally accepted that improvements from using two standard values for the gauche states are of only modest value[25,26] and that the major difficulty in conformational analyses of the kind considered here has been that of correct assignment.[27]

This study demonstrates experimentally that vicinal heteronuclear coupling constants can be obtained in an amino acid possessing a complex spin system if an isotopic isomer with the appropriate simplifying substitution of deuterons for protons is used. It has previously been shown that γ-deuteration is an effective technique for the measurement of homonuclear

coupling constants in leucine,[8] and as can be seen from Figure 2, α-deuteration is most useful in obtaining easily interpretable ^1H spectra from which heteronuclear vicinal couplings can be obtained.

Furthermore, this study shows that the values of the heteronuclear and homonuclear couplings related to conformation about the $C^\alpha-C^\beta$ bond of leucine and reported in Table I can be reasonably interpreted in terms of rotational isomerism among the three staggered conformations, provided that the published values of ^3J_g and ^3J_t for the various pairs of nuclei are accepted. The determination of the coupling constants from all three atoms attached to C^α and to C^β should permit the unequivocal determination of rotamer populations in systems having only a single β proton (such as isoleucine and valine) or when, in peptides, the chemical shifts of the two β protons of a residue are fortuitously equal. In principle the distribution of conformers among the three staggered rotamers is overdetermined by measurement of six distinct vicinal couplings, and it may be possible in the future to describe the distribution without resort to the usual assumption of the exclusive presence of these three rotamers. Conformational analysis of peptides containing isotopic isomers of amino acids of the kinds described in this report is now being actively pursued in our laboratory.[30]

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Ground States of Molecules. 40. MNDO Results for Molecules Containing Fluorine

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Abstract: Heats of formation, molecular geometries, first ionization potentials, and dipole moments are calculated by the MNDO method for a wide range of compounds containing fluorine. Major improvement, in comparison with MINDO/3, is obtained for most properties. The relative energies of conformational and geometrical isomers are in agreement with experiment and in some cases the results are superior to those obtained by ab initio methods. The calculated properties of the polyfluoromethane radical cations agree well with the observed stabilities. Good agreement is also obtained for higher vertical ionization energies, and particularly for species such as F_2, where the highest occupied molecular orbitals are correctly predicted to be of π_g, π_u, and Σ_g^+ symmetry, respectively. Calculated proton and electron affinities agree well with experimental values. Singlet–triplet separations for fluorocarbenes and fluoronitrene are discussed.

Introduction

Previous papers[1-3] of this series have described a new semiempirical SCF MO procedure (MNDO), based on the NDDO approximation, and its application to a wide variety of molecules derived from the elements H, B, C, N, and O. The results were almost uniformly much better than those from MINDO/3,[4] particularly for compounds containing pairs of adjacent heteroatoms. This was not unexpected because the INDO approximation (on which MINDO/3 was based) fails in such cases as a result of the neglect of one-center differential overlap.[4a] Similar problems also arose in attempts[4c] to extend MINDO/3 to compounds of fluorine, as again might have been expected since fluorine contains three pairs of unshared electrons. Here we report an extension of MNDO to fluorine and the results of calculations for a wide range of fluorine compounds.

Parametrization

The method previously described[1] was used in obtaining the fluorine parameters given in Table I. Initial estimates, obtained by linear extrapolation of the C, N, and O parameters,[1] were refined by fitting 50 selected properties of 12 fluorine molecules (marked * in the tables of results). The previously optimized atomic parameters for H, B, C, N, and O[1,3] were held constant during this procedure. The final fluorine parameters were close to the extrapolated values, which suggests that the MNDO method as a whole is suitably self-consistent. It is also interesting to note that optimized orbital exponents are regularly about 0.3 greater than Clementi's values[5] and that the one-

Table I. Optimized MNDO Parameters for Fluorine

Parameter	Value	Derived parameters	Value
U_{ss}, eV	−131.071548	ΔH_f^A, kcal mol^{-1}	18.860
U_{pp}, eV	−105.782137	E_{el}^A, eV	−476.683781
ζ, au	2.848487	D_1, Å	0.2681377
β_s, eV	−48.29046	D_2, Å	0.2275224
β_p, eV	−36.50854	ρ_0, Å	0.425492
α, Å^{-1}	3.419661	ρ_1, Å	0.243849
		ρ_2, Å	0.255793

Table II. Mean Absolute Errors $\Delta(\Delta H_f^\circ)$ in the Heats of Formation of Fluorine Compounds

Class of compd	No.	$\Delta\Delta H_f^\circ$, kcal mol^{-1} MNDO	MINDO/3
All compounds	71	9.80	24.8
Only CHF^a	23	7.1	6.4
Only CHFO	8	8.8	16.6
Only CHNF	6	11.8	58.2
CHBNOF	11	12.5	40.1
Carbenes	2	14.5	30.5
Cations	9	8.0	24.9
Anions	3	14.3	39.5
Radicals	6	14.3	30.5
Radical cations	3	8.0	19.1^b

^{a} Closed shell neutral compounds, not including carbenes. ^{b} 1 SCF calculation on the MNDO optimized geometry.