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Isoxazoles. 4. Hydrolysis of Sulfonamide Isoxazole Derivatives in Concentrated Sulfuric Acid Solutions. A New Treatment of the Medium Effects on Protonation Equilibria and Reaction Rates

Ruben H. Manzo* and María Martínez de Bertorello

Departamento de Farmacia, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, 5000 Córdoba, Argentina

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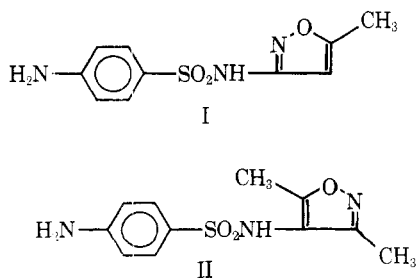
The acid hydrolysis of N^1 -(5-methyl-3-isoxazolyl)sulfanilamide (I) and N^1 -(3,5-dimethyl-4-isoxazolyl)sulfanilamide (II) to sulfanilic acid and their respective amino isoxazole derivatives in concentrated solutions of sulfuric acid was studied. An approach to correlate the medium effects on equilibria and reaction rates was made by introduction of a function, which represents the protonating ability of sulfuric acid solutions. The medium effects study has shown that I undergoes hydrolysis through protonation on the heterocyclic N atom, while II needs to be protonated on the sulfonamide group. The lower reactivity of II can be explained as mainly due to a more weakly basic site of protonation and a lower $\log(f_s/f_{\pm})$ response toward changes in acidity.

We have previously reported¹⁻³ that the acid-catalyzed degradation of N^1 -(3,4-dimethyl-5-isoxazolyl)sulfanilamide (III) in concentrated mineral acids occurs through two parallel pathways, one is the sulfonamide moiety hydrolysis and the other the isoxazole ring rupture. Both pathways can be associated with a preprotonation on the isoxazole N atom.

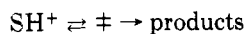
We here report a kinetic study of the hydrolysis of I and II in concentrated sulfuric acid solutions. Since Zuker and

Hammett works⁴ the study of medium effects on reaction rates in concentrated solutions of mineral acids has been focused by a method involving the correlation of rates with acidity functions^{5,6} ($H_x = -\log(a_{H^+}f_X/f_{XH^+})$) or related magnitudes.⁷ Such functions are built up from the measurements of the protonation equilibria of structurally related indicators and they involve the assumption that the ratio of activity coefficients of the acidic and basic forms of the indicators are the same within each set; however, this is not strictly true and few differences are found even within the set.

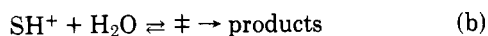
On the other hand, some efforts have been made in order to rationalize medium effects on reaction rates correlating them with representative magnitudes of some properties of the acid solutions, namely water activity⁸ (a_{H_2O}) and more recently sulfuric acid activity^{9,10} ($a_{H_2SO_4}$). However, there is no representative variable of some acid solution properties, with the exception of acidity functions, which can be applied in a wide concentration range. In this paper an alternative treatment is proposed.



Scheme I

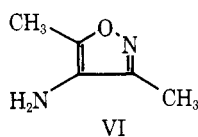
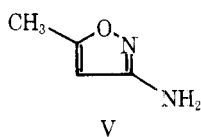
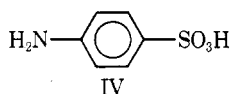


or



Results and Discussion

Under our reaction conditions I gives IV and V whereas II leads to IV and VI, both in quantitative yields. Both reactions



show first-order kinetics and are acid catalyzed. Consequently, the usual mechanism depicted in **Scheme I** can be used to explain the results.

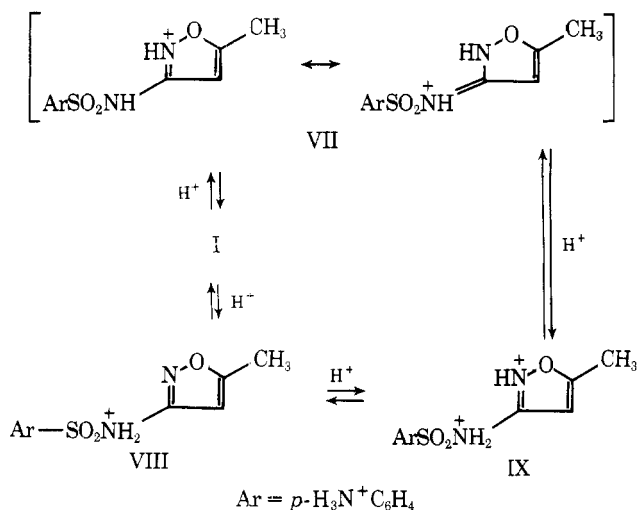
a. Protonation equilibria. The substrates under study carry three basic sites: one is the aromatic amine, which is almost completely protonated under our reaction conditions; the second is the nitrogen of the isoxazole ring, which in the case of I has a pK_a of -3.52 (l.f.e.r. method)¹ (the NMR study of II suggests an analogous behavior); and the third is the sulfonamide group which in the case of neutral alkyl¹¹ and aryl¹² sulfonamides have pK_a values around -5.5 and -6.6 and are protonated on nitrogen; however, its basicity in I and II is expected to be decreased by the electronic effects of the ammonium and the heterocyclic ring. In fact, UV and NMR analysis of II in sulfuric acid 96% shows no experimentally detectable changes.

The protonation equilibria involved can be described by Schemes II and III, I, VII, II, and X being the predominant species.

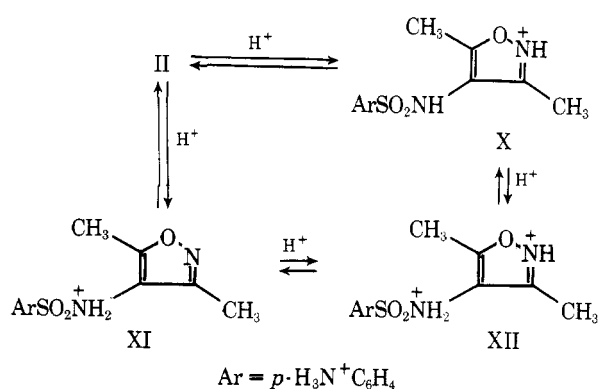
Species VII, VIII, and IX for I and X, XI, and XII for II can in principle be responsible for the acid catalysis observed. The following study of the medium influence on the reaction rates will permit the description of the major reaction pathways for each substrate.

b. An Approach to Correlate the Medium Effects on Equilibria and Reaction Rates. The protonating ability toward different kinds of bases is the chief property of aqueous

Scheme II

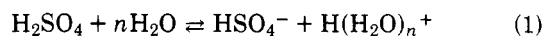


Scheme III



solutions of sulfuric acid. This property is mainly due to hydrogen ions with different degrees of solvation. This mixture manifests changes in its protonating ability upon changing the acid concentrations which are much greater than what could be attributed merely to the changes in hydrogen ion concentration. The major species in moderately concentrated solutions are $H(H_2O)_n^+$, HSO_4^- , H_2O , and in a minor degree SO_4^{2-} , while at higher acid concentrations of H_2SO_4 , $H_3SO_4^+$, and $H_2S_2O_7$ become important.^{6,10}

Several theoretical approaches were made in order to understand the concentration dependence of the acidity of aqueous strong acids considering the chemical hydration of hydrogen ion.¹³⁻¹⁷ Such approaches have been widely used to account for the fact that the increasing protonating ability of the medium is due largely to the decreasing water activity. However, an unambiguous definition of their acidity is not available owing to its complexity and because individual ion activities cannot be measured experimentally. Reaction 1 is considered the main one in moderately concentrated solutions



According to eq 2, it can be seen that there is a direct contribution from $a_{H_2SO_4}$ to $a_{H(H_2O)_n^+}$, while a_{H_2O} raised to an adequate power affords a more complex functional relationship with $a_{H(H_2O)_n^+}$ since n is also a function of the medium composition; however, as it was mentioned above, it has been largely recognized that the acidity and water activity are inversely related in concentrated mineral acid solutions. Similar considerations can be applied to other equilibria where solvated hydrogen ions are generated.

Based on the following premises, (a) the acidity of aqueous sulfuric acid solutions lies essentially on solvated hydrogen ions, (b) due to the complexity of the system it is not possible to give an explicit definition of the acidity as a function of ionic specie activities, and (c) a_{H_2O} and $a_{H_2SO_4}$ are both a measure of the "free" specie concentrations in the solution¹⁶ (a representative function of the protonating ability of the solution (a_S) is defined on the grounds of the "nonionic portion" of the system).

The "molar activity fractions" of sulfuric acid ($A_{H_2SO_4}$) and water (A_{H_2O}) can be calculated as in eq 3.

$$A_{H_2SO_4} = a_{H_2SO_4} / (a_{H_2SO_4} + a_{H_2O}) \text{ and } A_{H_2O} = a_{H_2O} / (a_{H_2SO_4} + a_{H_2O}) \quad (3)$$

The reference states used are $a_{H_2O} = 1$ for pure water ($N_{H_2O} = 1$) and $a_{H_2SO_4} = 1$ for pure sulfuric acid ($N_{H_2SO_4} = 1$), where N represents the respective stoichiometric molar fractions.

The protonating ability a_S is defined as directly proportional to $A_{H_2SO_4}$ and inversely proportional to A_{H_2O} , eq 4,

Table I. Reaction Rates at Various Sulfuric Acid Concentrations

H ₂ SO ₄ (wt %)	I ^a				II ^b log <i>k</i> _ψ
	log <i>a</i> _S ^c	log <i>k</i> _ψ	log ([SH ⁺] ^d /[S])	log (<i>k</i> _ψ [S] _{st} /[SH ⁺])	
34.72	-8.505	-4.618	-1.627	-2.981	-4.971
46.52	-6.747	-3.745	-0.670	-2.990	-4.506
58.90	-4.598	-3.146	0.499	-3.026	-4.058
62.98	-3.777	-3.088	0.945	-3.041	
67.87	-2.698	-3.049	1.532	-3.036	
72.04	-1.689	-3.113	2.081	-3.107	-3.390
78.77	+0.0236	-3.142	3.013	-3.142	-2.917

^a Reaction at 100 °C. ^b Reaction at 135 °C. ^c Log *a*_S values were obtained by interpolation of log *a*_S vs. (wt %).² ^d Calculated from log ([SH⁺]/[S]) = 0.544 log *a*_S + 3.00.

Table II. Acidity Functions Against Log *a*_S in Aqueous Sulfuric Acid^a

	-H ₀ ^b	-H ^{'''} ^b	-H ₁ ^b	-H _R ^c	-H _A ^b
Slope	0.595	0.738	0.784	1.175	0.328
Intercept	7.09	9.11	9.50	13.99	4.50
δ Points	0.057	0.113	0.040	0.122	0.045
δ Slope	0.003	0.006	0.004	0.012	0.003
<i>r</i>	0.9997	0.9994	0.9997	0.9993	0.9994
Range, wt %	10-90	10-90	10-70 ^d	10-70 ^e	20-90 ^d
No. of points	17	17	13	13	15

^a Values of log *a*_S were calculated from *a*_{H₂O} and *a*_{H₂SO₄} data reported by M. Liler;⁶ the latter were only available between 40 and 100 wt %; therefore, we have widened the data up to 10 wt % in the same way he described it (by Gibbs-Duhem equation). The log *a*_S values obtained are: -11.47, -10.88, -10.19, -9.745, -9.128, and -8.464 for 10, 15, 20, 25, 30, and 35 wt %, respectively. ^b Acidity function values were taken from ref 22. ^c Values from ref 6. ^d There are no data at concentrations higher than 70 wt % for *H*₁ and lower than 16 wt % for *H*_A. ^e Deviations of linearity were observed at concentrations higher than 70 wt %.

$$a_S = A_{H_2SO_4}/A_{H_2O} \quad (4)$$

and taking logarithms

$$\log a_S = \log (A_{H_2SO_4}/A_{H_2O}) = \log (a_{H_2SO_4}/a_{H_2O}) \quad (5)$$

A plot (not shown) of log *a*_S against *N*_{H₂SO₄} shows a steady increase with the acid concentration. Below *N*_{H₂SO₄} = 0.35 the increase is mainly due to *A*_{H₂SO₄}, whereas above this point *A*_{H₂O} is the major contributor.

The fact that *a*_S gives a satisfactory account of the protonating ability of concentrated aqueous sulfuric acid is demonstrated by the linear relationships found between log *a*_S and acidity functions (Figure 1, Table II) or the logarithms of the ionization ratios of weak bases, within a wide range of acidity.¹⁸ The definition of *a*_S (eq 4) implies that all hydrogen ions are supplied by sulfuric acid; therefore, in very diluted solutions where the autoprotolysis of water generates significant quantities of protons, eq 4 is no longer valid. However, in the concentration range used in the present paper hydrogen ions supplied by water are only a very small fraction of total hydrogen ions and consequently can be neglected. Therefore, log *a*_S will be used here as a variable to discuss the medium effects on protonation equilibria and reaction rates. The usual equations⁵⁻⁷ for the phenomenological and theoretical interpretation of the equilibrium and kinetic processes described in Scheme I can be expressed as linear functions of log *a*_S (eq 6-9).

$$\log ([SH^+]/[S]) = pK_{SH^+} + \log (a_{H^+}/f_{SH^+}) = G_e \log a_S + D_e \quad (6)$$

$$\log k_\psi - \log ([SH^+]/[S]_{st}) = \log k + \log (f_{SH^+}/f_\pm) = G_r \log a_S + D_r \quad (7)$$

$$\log k_\psi + \log ([SH^+]/[S]) - \log (SH^+/S_{st}) = \log (ka_{H^+}/K_{SH^+}f_\pm) = (G_e + G_r) \log a_S + (D_e + D_r) \quad (8)$$

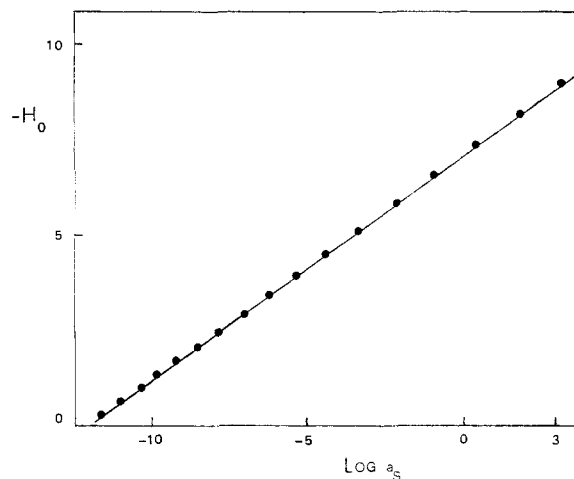


Figure 1.

When [S] ≫ [SH⁺] the left member of eq 8 reduces to log *k*_ψ, then

$$\log k_\psi = \log (ka_{H^+}/K_{SH^+}f_\pm) = G_t \log a_S + D_t \quad (9)$$

Equation 6 states that there is a linear relationship between log (*a*_{H⁺}/*f*_{SH⁺}) and log *a*_S, with a proportionality constant *G*_e, which is a measure of the sensitivity of the activity coefficient ratio (*f*_S/*f*_{SH⁺}) toward changes in protonating ability of the solution and allows the characterization of step a in Scheme I. In the same way, eq 7 describes the relationship between log (*f*_{SH⁺}/*f*_±) and log *a*_S; therefore, the proportionality constant *G*_r is a measure of the sensitivity of this ratio to the changes in the medium giving information about step b (Scheme I). Finally, eq 9 can be applied when only a small fraction of the total substrate is protonated, thus *G*_t = *G*_e + *G*_r measures the overall medium effects on steps a and b.

c. Medium Effect Correlations. For the protonation

Table III. Activation and Medium Effect Parameters

Compd	G_e	D_e	G_r	D_r	G_t	D_t	E_a , kcal/mol ^a	ΔS^\ddagger , eu ^b
I	0.544	3.00	-0.019	-3.12	0.525	-0.12	29.6	4.6
II					0.236	-2.95	28.4	-6.9

^a Calculated with values of Table IV by Arrhenius plots. ^b Calculated according to ref 23.

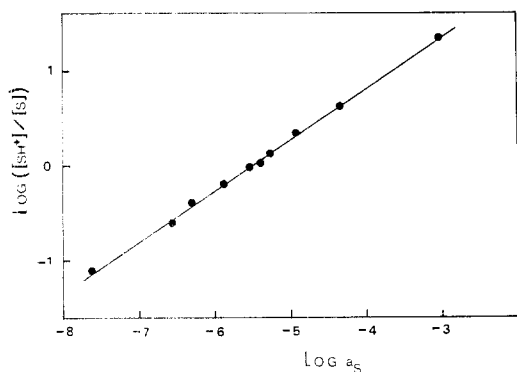


Figure 2.

equilibrium I \rightleftharpoons VII (Scheme II) the logarithms of the ionization ratios, from ref 1, were correlated by eq 6 (Figure 2). From the regression line, G_e and D_e parameters were calculated and are quoted in Table III.

The reaction rates of I increase up to ca. 68% sulfuric acid and then level off. The leveling off region coincides with the almost complete conversion of I into VII, thus, the data can be adequately correlated by eq 7. G_r obtained has a value near zero (-0.019) (Figure 3, Table III) indicating a similar response of f_{SH+} and f_{\pm} to medium changes; since f_{SH+} pertains to compound VII, the transition state of the reaction must be very closely related to it and we can infer that the decomposition of VII is a monomolecular step. Besides, the dependence of the rate on acidity allows the elimination of VIII and IX as possible intermediates.

The rate of II increases with the acid concentration in the whole range studied (34.7–78.8%). Figure 3 shows that the data are nicely correlated with $\log a_S$ through eq 9 which indicates that the reactive specie is only a very small fraction of the total substrate, thus XI and XII appear the most likely intermediates. The linear relationship found also indicates that both species react at similar rates since XI prevails at low and XII at high acidity. Since G_r expresses the overall medium dependence of the reaction and equilibrium parameters for the protonation of II and X (Scheme III) are unknown, the mechanism of step b cannot be elucidated.

Table III also includes activation parameters for both reactions. By comparison of their activation energy values, it can be seen that they are quite similar, and this is also true for what has been reported for the hydrolysis of III in hydrochloric acid¹⁹ ($E_a = 25.4$ kcal/mol).

It is clear now that the lower sensitivity to acid-catalyzed hydrolysis of II compared with I (and with III) can be explained as mainly due to differences in the mechanism of the reaction of I and II. The impossibility of resonance interaction between the protonated nitrogen of X and the amide nitrogen renders this specie inefficient to form the transition state for the hydrolysis of II, leaving XI and XII as alternatives. The high acidity of the latter two species and the weaker response of $\log (f_S/f_{\pm})$ toward changes in acidity for II as compared with I (G_t of I > G_t of II) make compound II less reactive than I.

Values of ΔS^\ddagger for I and II are 4.3 and -6.9 eu, respectively, but at the acid concentration used in the activation parameter determinations, I is practically completely in its protonated

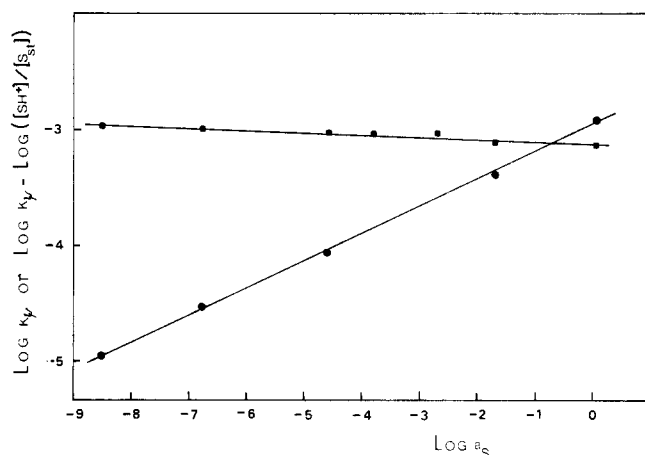


Figure 3.

form, then $k_{\psi} \approx k$ and ΔS^\ddagger has a maximum value for this reaction, whereas II exists mainly in its unprotonated form, therefore $k_{\psi} < k$ and consequently the ΔS^\ddagger obtained must increase when reaction conditions reach those of I. These values are consistent with those typically reported for hydrolysis reactions that proceed by the A-1 mechanism,²⁰ whereas A-2 hydrolysis has considerable more negative values.²⁰

Experimental Section

Materials and Apparatus. Sulfuric acid analytical reagent grade Carlo Erba G.R. was used; H_3PO_4 , NaH_2PO_4 , and NaOH were all analytical reagent grade; I was a commercial NF product purified according to ref 1; and II was prepared in the same way as it has been previously reported.²¹

Spectrophotometric readings and UV absorption spectra were taken in a Beckman DB-G spectrophotometer. NMR spectra were recorded on a Varian T-60, and chemical shifts are quoted in ppm downfield from tetramethylsilane.

Reactions. The hydrolysis reactions were carried out in sealed ampules of 5-mL capacity containing approximately 3 mL of solution which was prepared quantitatively by transferring 0.250 g of I or II to a volumetric flask of 100 mL capacity and adding the appropriate sulfuric acid solution until the volume was completed. The same procedure was followed with each acid solution.

The ampules were immersed in a constant temperature oil bath at 100.0 ± 0.2 °C for I and at 135.0 ± 0.2 °C for II; they were then withdrawn at appropriate intervals and quickly cooled in an ice bath for analysis at a later time.

Identification of Hydrolysis Products. Both I and II give a unique product with aromatic amino group, which was identified by TLC as IV using the procedure described earlier ref 2. V and VI, products from I and II, respectively, were both separated from reaction mixtures previously alkalized with 20% NaOH by ether extractions. The ethereal extracts were dried (Na_2SO_4) and evaporation of the solvent yielded the respective amino derivatives, which were purified and identified by its mp and mixture mp with those of known pure samples.

Quantitative Determinations and Kinetic Study. One milliliter of each one of the reaction mixtures was put into volumetric flasks of 50-mL capacity and neutralized by addition of an adequate volume of 1 N NaOH solution, and the flask was filled to the mark with 0.1 M phosphate buffer of pH 2.3. Two milliliters of these solutions was again diluted to 10 mL with the same buffer solution.

The relative concentrations of the reactants and products were

Table IV. Reaction Rates at Several Temperatures in Sulfuric Acid (70 wt %)

I		II	
Temp, °C	$k_{\psi} \times 10^4, \text{s}^{-1}$	Temp, °C	$k_{\psi} \times 10^4, \text{s}^{-1}$
79.0	0.802	115.0	0.751
88.5	2.32	124.0	1.77
99.0	6.89	134.0	3.84
109.0	21.6	144.2	10.2

determined by UV spectrophotometric analysis using for both I and II reaction light of 268 nm as the analytical wavelength; this one corresponds to a maximum in the absorption spectra for both reactants. Each kinetic experience was carried out using 10 ampules, which were processed as described above, and their absorbances were regarded. From plots of $\ln(A_t - A_{\infty}/A_0 - A_{\infty})$ vs. time (sec) were obtained straight lines as habitually are found in first-order kinetics. The slopes obtained from regression lines were considered as pseudo-first-order constants k_{ψ} .

Medium and Temperature Effects on Reaction Rates. Tables I and IV report the results obtained when I and II hydrolyses were carried out at several different acid concentrations and at several temperatures, respectively.

NMR in Sulfuric Acid. For II, methyl signals change from 1.98 and 2.05 in H₂SO₄ at 32 wt % to 2.37 and 2.50 in H₂SO₄ at 70 wt %.

Registry No.—I, 723-46-6; II, 64682-95-7; sulfuric acid, 7664-93-9.

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Nitrogen-15 Magnetic Resonance Spectroscopy. Natural-Abundance Spectra of Secondary Amides¹

Philip W. Westerman and John D. Roberts*

Contribution No. 5673, Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California 91125

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The ¹⁵N chemical shifts of 17 *N*-alkyl- and *N*-arylethanamides have been determined at the natural-abundance level of ¹⁵N using Fourier-transform methods. The shift effects produced by several substituent groups are compared with corresponding substituent effects in amino acids, amino acid derivatives, and dipeptides. The results show that *N*-alkylethanamides are not especially good models for predicting ¹⁵N shifts in dipeptides. The sensitivity of the ¹⁵N shift of *N*-arylethanamides to electronic effects, as reflected in the Hammett ρ constant, is less than that of the ¹⁵N shift in para-substituted benzenamines.

Peptides contain many fewer nitrogen atoms than carbon or hydrogen atoms and it might be expected that ¹⁵N NMR spectroscopy would be useful for structural studies of peptides in solution. The well-known difficulties in observing the NMR signals of ¹⁵N, with its low natural abundance and often long relaxation times, have been partially overcome by the use of large samples, high magnetic-field strengths, quadrature detection, and Fourier-transform techniques.

Assignments of signals in the ¹⁵N spectra of peptides have been aided by chemical shifts of model systems.²⁻⁶ Further help may possibly be expected from secondary amides of the type CH₃CONHC _{α} H₂R, which could provide a measure of the substituent effect of R on the chemical shift of peptide nitrogen. A number of ¹⁴N shifts of secondary amides have been determined,⁷⁻⁹ but the generally broad signals obtained with this nucleus can introduce shift uncertainties. The ¹⁵N spectra of *N*-methylethanamide¹⁰ and *N*-methylmethanamide¹¹ have been reported, but there appears to be no other systematic

study of substituent effects in secondary amides. As a result, we have determined the ¹⁵N chemical shifts at the natural-abundance level of a series of secondary amides with R groups generally chosen to correspond structurally to peptide groupings of naturally occurring amino acids.

The sensitivity of ¹⁵N NMR shifts to electronic factors, as reflected in Hammett ρ constants, has been determined for several para-substituted *N*-phenylethanamides and the results have been compared with similar studies on para-substituted benzenamines.¹²

Experimental Section

Primary aliphatic and aromatic amines were obtained commercially and acetylated by standard procedures. The physical properties of the products were consistent with reported values.¹³

Proton-noise decoupled ¹⁵N spectra were recorded at the natural-abundance level with a Bruker WH-180 NMR spectrometer operating at 18.25 MHz. Measurements were made with 15-22-mL samples in 25-mm o.d. tubes, using quadrature detection and Fourier-transform