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

I		II	
Temp, °C	$k_\psi \times 10^4$, s^{-1}	Temp, °C	$k_\psi \times 10^4$, 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 H_2SO_4 at 32 wt % to 2.37 and 2.50 in H_2SO_4 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 Amides[1]

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 ^{15}N chemical shifts of 17 *N*-alkyl- and *N*-arylethanamides have been determined at the natural-abundance level of ^{15}N 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 ^{15}N shifts in dipeptides. The sensitivity of the ^{15}N shift of *N*-arylethanamides to electronic effects, as reflected in the Hammett ρ constant, is less than that of the ^{15}N shift in para-substituted benzenamines.

Peptides contain many fewer nitrogen atoms than carbon or hydrogen atoms and it might be expected that ^{15}N NMR spectroscopy would be useful for structural studies of peptides in solution. The well-known difficulties in observing the NMR signals of ^{15}N, 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 ^{15}N 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 $CH_3CONHC_\alpha H_2R$, which could provide a measure of the substituent effect of R on the chemical shift of peptide nitrogen. A number of ^{14}N shifts of secondary amides have been determined,[7-9] but the generally broad signals obtained with this nucleus can introduce shift uncertainties. The ^{15}N spectra of *N*-methylethanamide[10] and *N*-methylmethanamide[11] 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 ^{15}N 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 ^{15}N 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 ^{15}N 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

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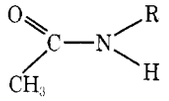
Table I. ^{15}N Chemical Shifts in *N*-Alkyl- and *N*-Arylethanamide[a]



R	Registry no.	$\delta_{^{15}N}$, ppm
H	60-35-5	270.6[b]
CH_3	79-16-3	268.2
CH_3CH_2	625-50-3	249.2
$(CH_3)_2CH$	1118-69-0	237.9
$(CH_3)_3C$	762-84-5	235.6
$CH_3CH_2CH_2$	5331-48-6	254.2
$(CH_3)_2CHCH_2$	1540-94-9	256.2
$CH_3CH_2CH_2CH_2$	1119-49-9	254.3
$CH_3CH_2CH_2CH_2CH_2$	2524-60-9	254.0
$CH_3CH_2(CH_3)CH$	1189-05-5	240.3
$CH_3CH_2(CH_3)_2C$	15501-38-9	239.3
$C_6H_5CH_2CH_2$	877-95-2	256.1
p-$CH_3OC_6H_4$	51-66-1	242.9[c]
p-$CH_3C_6H_4$	103-89-9	241.6[c]
C_6H_5	103-84-4	240.8[c]
p-ClC_6H_4	539-03-7	242.0[c]
p-$NO_2C_6H_4$		

[a] Upfield from external $D^{15}NO_3$. Chemical shifts measured with 36-44 mol % solutions in chloroform. [b] 4 mol % solution in chloroform. [c] 10-16 mol % solutions in dimethyl sulfoxide.

mode operation. Each spectrum was obtained using a repetition rate of 4.5 s, an acquisition time of 0.819 s, and a total accumulation of 2000 transients. The pulse angle was 20° (20-μs pulse width), and 4 W of proton decoupling power was used. The chemical shifts are reported in parts per million upfield from external 1.0 M $H^{15}NO_3$ in D_2O contained in a coaxial 5-mm o.d. tube.

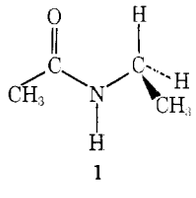
Results and Discussion

The ^{15}N chemical shifts for *N*-alkylethanamides are given in Table I. The shift for ethanamide, also included here, was measured at a lower concentration than the secondary amides. The ^{14}N chemical shift of ethanamide has already been reported, but with respect to a different reference.[7]

The results in Table I show that ^{15}N shift differences for secondary amides are quite large and are susceptible to the same kinds of electronic and steric influences as ^{13}C shifts[14] and ^{15}N shifts in aliphatic amines.[15] Thus, there are deshielding α and β effects, as well as a shielding, presumably sterically induced, γ effect. The δ and ε effects appear to be almost negligible.

The shifts for secondary amides in Table I are downfield of the shift for ethanamides. As noted previously,[7] N-methylation of ethanamides causes only a slight downfield shift in the nitrogen chemical shift (2.4 ppm). However, a much larger shift of 19.0 ppm is observed in going from the *N*-methyl to the *N*-ethyl derivative. The β effect of a methyl substituent on the ^{15}N shift of a primary amine is approximately the same magnitude (18.2 ppm).[15]

In contrast to the results for primary amines, the β effects in secondary amides diminish substantially as the degree of substitution of the *N*-methyl group increases. In the change from *N*-ethyl to *N*-isopropyl, a downfield shift for the ^{15}N nucleus of 11.3 ppm is observed. Substitution of a third methyl group on the *N*-methyl carbon moves the ^{15}N shift downfield a further 2.3 ppm. Corresponding β effects derived from comparison of the ^{15}N shifts for *N*-propyl-, *N*-(1-methylpropyl)-, and *N*-(1,1-dimethylpropyl)ethanamides show β effects of 13.9 and 1.0 ppm, in fair agreement with the values above. The dependence of the β effect on the extent of substitution at the *N*-methyl carbon may be the result of steric effects. Thus, for *N*-ethylethanamide, the α-methyl group can avoid steric interactions with the carbonyl group by assuming conformation **1**. As the α hydrogens in **1** are replaced by methyl groups, the contribution of conformers like **2**, where a methyl group is eclipsed by the carbonyl group, are expected to increase and the resulting steric interactions could significantly affect the ^{15}N shifts.



1

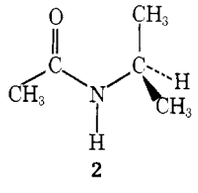


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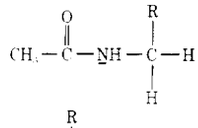
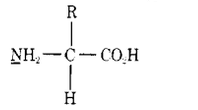
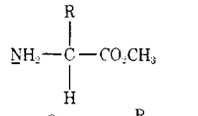
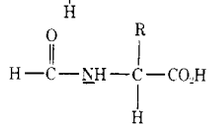
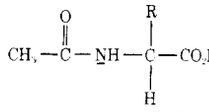
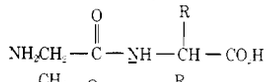
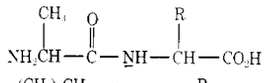
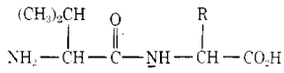
Table II. Substituent Effects on the ^{15}N Shifts of Secondary Amides, Amino Acids and their Derivatives, and Dipeptides[a]

Substituent group (R)	CH_3	$(CH_3)_2CH$	$C_6H_5CH_2$
	19.0	12.0	12.1
	13.0[b]	6.1[b]	9.1[c]
	13.2[d]	8.3[d]	10.4[d]
	15.0[f]	8.0[f]	10.7[f]
	15.0[g]	8.6[g]	11.5[g]
	14.5[e]	8.2[e]	
	14.3[e]	8.2[e]	
	13.2[e]	8.0[e]	

[a] In ppm relative to R = H in all series. Downfield shifts are positive. [b] Reference 3c, in 6 N HCl. [c] Reference 3c, in H_2O. [d] Reference 4, 5-9 M aqueous solution with pH values in the range 0.5-2.0. [e] Reference 5, 0.2 M aqueous solutions in pH range 5.0-6.2. [f] Reference 2, 3-4 M in dimethyl sulfoxide. [g] Reference 2; 1 M in dimethyl sulfoxide.

While the signs of the alkyl-substituent shift parameters parallel those observed for ^{13}C spectra, the magnitudes differ considerably; α_N is somewhat smaller than α_C (−9.1 ppm) while β_N is almost twice as large as β_C (−9.40 ppm).[14]

Contrary to reports from earlier ^{14}N studies,[7] the γ effects of methyl groups are upfield (Table I) in accord with ^{13}C spectra.[14] Changing from *N*-ethyl to *N*-propyl makes an upfield shift for the ^{15}N nucleus of 5.0 ppm. The γ effect of a second methyl substituent on the ^{15}N shift (i.e., *N*-(2-methylpropyl)ethanamide) is 2.0-ppm upfield.

The sequence of ^{15}N shifts observed for *N*-propyl-, *N*-butyl-, and *N*-pentylethanamides indicates that the δ and ε effects of methyl substituents on ^{15}N shifts in secondary amides are not experimentally significant (−0.1 and 0.3 ppm, respectively). The effect of substituting a phenyl group on the β carbon of *N*-ethylethanamide is a 6.9-ppm upfield ^{15}N shift.

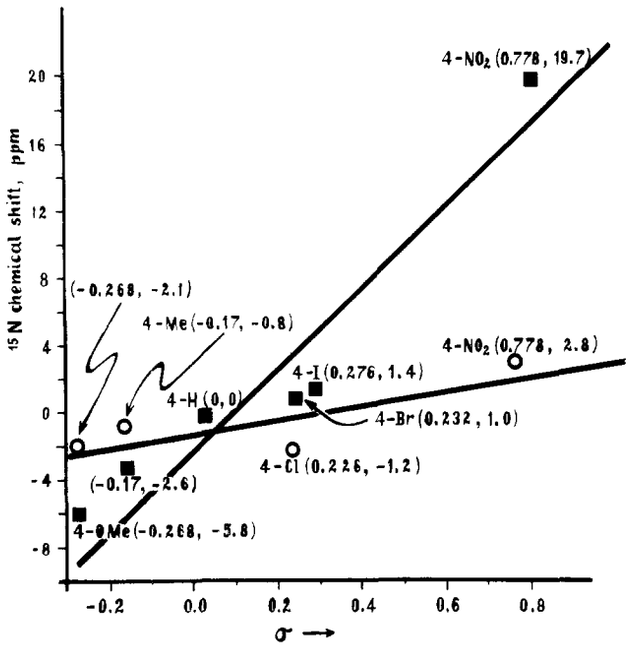


Figure 1. Correlation of ^{15}N chemical shifts for para-substituted benzenamines (■) and para-substituted *N*-phenylethanamides (○) with Hammett substituent constants (σ).

A number of β effects for N-substituted ethanamides are given in the top line of Table II. Only those N-substituted ethanamides of Table I which have R groups corresponding structurally to naturally occurring amino acid residues are included in Table II. Lines 2–8 of Table II are β effects for various R groups in amino acids as well as dipeptides. The numbers in Table II provide a test of the suitability of the secondary amides (line 1) as models for peptide linkages. It will be seen that the available data indicate that the β effects in line 1 are rather consistently larger than the corresponding effects for the same substituents in amino acids, dipeptides, etc. A possible explanation is that the shifts in line 1 of Table II were obtained in different solvents at different concentrations and different pH values than for the other substances. However, it is more likely that a systematic error is introduced by making comparisons on the basis of R = H as the standard substance for secondary amides, because the smaller the shifts are, the higher the degree of substitution at the α carbon. About all one can say is that there is a degree of parallelism between the ^{15}N shifts of various kinds of substances with a given change in the R group.

To determine the sensitivity of ^{15}N resonances in secondary amides to electronic effects, the ^{15}N shifts of *N*-phenylethanamide and several of its para-substituted derivatives were measured for 10–16 mol % solutions in dimethyl sulfoxide (Table I). Substitution of a directly bound phenyl group on nitrogen changes the shift of ethanamide 26.6 ppm downfield. Electron-donating groups in the para position of the phenyl ring cause upfield shifts, while electron-withdrawing para substituents produce the opposite effect. The range of chemical shifts between the *p*-nitro and *p*-methoxy substituents is only 4.9 ppm compared with the 25.5-ppm difference between the same substituents for benzenamines.[12] The ^{15}N shift of amide nitrogens are thus much less sensitive to electron withdrawal and donation than the ^{15}N shifts of amines, although both give reasonable trends with the Hammett substituent constants (Figure 1). The smaller change in shift for para-substituted amides compared with benzenamines is expected because of the strong conjugation of the amide nitrogen lone-pair electrons with the carbonyl groups, which compete for conjugation with the π system of the benzene ring. The downfield shift produced by electronegative para substituents in *N*-phenylethanamide (acetanilide) can be attributed to p–π interaction between the amide nitrogen lone pair and the aromatic ring, thus causing decreased π-electron density at the nitrogen with concomitant deshielding.

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