mittee for providing access to the National NMR Center (Director: Dr. Alan Jones). We are indebted to Professor R. D. Topsom for the infrared intensity measurements, and to Professor R. W. Taft and Dr. R. T. C. Brownlee for a copy of the DSP computer program.

Registry No. I (X = H), 23062-62-6; I (X = CH_2OH), 23760-80-7; I (X = CH_2Cl), 70631-55-9; I (X = CH_2CN), 70631-56-0; I (X = CH_2COOH), 70631-57-1; I (X = CH_2COOCH_3), 70631-58-2; I (X = $CH(CN)_2$), 70631-59-3; I (X = $C(CN)_3$), 70631-60-6; 1-fluoro-3-(bromomethyl)naphthalene, 34236-55-0; 1-fluoro-3-(cyanomethyl)-naphthalene, 70631-33-3; 1-fluoro-3-(tricyanomethyl)naphthalene, 70631-34-4; 1-fluoro-4-(bromomethyl)naphthalene, 6905-05-1; 1-fluoro-4-(cyanomethyl)naphthalene, 3832-87-9; 1-fluoro-4-(tricyanomethyl)naphthalene, 61653-16-5; 1-fluoro-5-(bromomethyl)-naphthalene, 70631-35-5; 1-fluoro-5-(cyanomethyl)naphthalene, 70631-36-6; 1-fluoro-5-(tricyanomethyl)naphthalene, 70631-37-7; 1-fluoro-6-(bromomethyl)naphthalene, 70631-38-8; 1-fluoro-6-(cyanomethyl)naphthalene, 70631-39-9; 1-fluoro-6-(tricyanomethyl)-naphthalene, 70631-40-2; 1-fluoro-7-(bromomethyl)naphthalene, 70631-41-3; 1-fluoro-7-(cyanomethyl)naphthalene, 70631-42-4; 1-fluoro-7-(tricyanomethyl)naphthalene, 70631-43-5; 2-fluoro-4-(bromomethyl)naphthalene, 70631-44-6; 2-fluoro-4-(cyanomethyl)-naphthalene, 70631-45-7; 2-fluoro-4-(tricyanomethyl)naphthalene, 70631-46-8; 2-fluoro-5-(bromomethyl)naphthalene, 70631-47-9; 2-fluoro-5-(cyanomethyl)naphthalene, 70631-48-0; 2-fluoro-5-(tricyanomethyl)naphthalene, 70631-49-1; 2-fluoro-6-(bromomethyl)-naphthalene, 581-72-6; 2-fluoro-6-(cyanomethyl)naphthalene, 66922-61-0; 2-fluoro-6-(tricyanomethyl)naphthalene, 61653-14-3; 2-fluoro-7-(bromomethyl)naphthalene, 64168-12-3; 2-fluoro-7-(cyanomethyl)naphthalene, 66922-65-4; 2-fluoro-2-(tricyanomethyl)-naphthalene, 61653-15-4; 2-fluoro-8-(bromomethyl)naphthalene, 70631-50-4; 2-fluoro-8-(cyanomethyl)naphthalene, 70631-51-5; 2-fluoro-8-(tricyanomethyl)naphthalene, 70631-52-6; (tricyanomethyl)benzene, 5247-17-6; 1-(tricyanomethyl)naphthalene, 5247-21-2; 2-(cyanomethyl)naphthalene, 7498-57-9; 2-(dicyanomethyl)-naphthalene, 32122-61-5; 2-(tricyanomethyl)naphthalene, 70631-53-7; *m*-fluoro(tricyanomethyl)benzene, 5247-19-8; 2-(dicyanomethyl)-6-fluoronaphthalene, 70631-54-8; 1-fluoro-3-ammonionaphthalene, 70631-61-7; 1-fluoro-4-ammonionaphthalene, 70631-62-8; 1-fluoro-5-ammonionaphthalene, 70631-63-9; 1-fluoro-6-ammonionaphthalene, 70631-64-0; 1-fluoro-7-ammonionaphthalene, 70631-65-1; 2-fluoro-4-ammonionaphthalene, 70631-66-2; 2-fluoro-5-ammonionaphthalene, 70631-67-3; 2-fluoro-6-ammonionaphthalene, 70631-68-4; 2-fluoro-7-ammonionaphthalene, 70631-69-5; 2-fluoro-8-ammonionaphthalene, 70631-70-8; 1-fluoro-3-methylnaphthalene, 319-15-3; 1-fluoro-4-methylnaphthalene, 315-50-4; 1-fluoro-5-methylnaphthalene, 51010-55-0; 1-fluoro-6-methylnaphthalene, 70631-71-9; 1-fluoro-7-methylnaphthalene, 59080-31-8; 2-fluoro-4-methylnaphthalene, 59079-88-8; 2-fluoro-5-methylnaphthalene, 59079-89-9; 2-fluoro-6-methylnaphthalene, 324-42-5; 2-fluoro-7-methylnaphthalene, 29885-92-5; 2-fluoro-8-methylnaphthalene, 70631-72-0; 1-fluoro-4-(dibromomethyl)naphthalene, 70631-73-1; 1-fluoro-7-(dibromomethyl)naphthalene, 70631-74-2; 2-fluoro-6-(dibromomethyl)-naphthalene, 70631-75-3; 2-fluoro-7-(dibromomethyl)naphthalene, 70631-76-4; 2-fluoro-7-(dicyanomethyl)naphthalene, 70631-77-5; 1-fluoro-4-(tribromomethyl)naphthalene, 70631-78-6; 2-fluoro-6-(tribromomethyl)naphthalene, 70631-79-7; 2-fluoro-7-(tribromomethyl)naphthalene, 70631-80-0; 1-fluoro-6-formylnaphthalene, 70631-81-1; 1-fluoro-6-aminonaphthalene, 13720-50-8; 1-fluoro-6-carboxynaphthalene, 70631-82-2; *p*-fluoro(tricyanomethyl)benzene, 5247-20-1; *m*-fluoroammoniobenzene, 28966-00-9; *p*-fluoroammoniobenzene, 29131-39-3; phenylacetone, 103-79-7; 3-methyl-4-phenylbutanoic acid, 7315-68-6; 3-methyl-1-tetralone, 14944-23-1; 3-methyl-1-tetralone oxime, 70631-83-3; 3-methyl-1-naphthylamine hydrochloride, 13615-39-9; 3-methyl-1-naphthyldiazonium hexafluorophosphate, 70631-85-5; 5-fluoro-1-naphthylmagnesium bromide, 70631-86-6; 3-methylbenzyl chloride, 620-19-9; 4-(*m*-tolyl)butanoic acid, 22156-45-2; 6-methyl-1-tetralone, 51015-29-3; 6-methyl-1-tetralone oxime, 70631-87-7; *o*-fluorobenzyl chloride, 345-35-7; 4,4-dimethoxybutan-2-one, 5436-21-5; β-(*m*-fluorophenyl)propionic acid, 458-45-7; 4-(*m*-fluorophenyl)butanoic acid, 70631-88-8; 6-fluoro-1-tetralone, 703-67-3; 6-fluoro-1-methyl-1-tetralol, 70631-89-9; 6-fluoro-1-methyl-3,4-dihydronaphthalene, 70631-90-2; 7-fluoro-1-tetralone, 2840-44-0; 4-phenyl-1-bicyclo[2.2.2]octylcarboxylic acid, 953-69-5; 4-phenyl-1-bicyclo[2.2.2]octylmalonamide, 70631-91-3; 2-(*o*-fluorobenzyl)-4,4-dimethoxy-2-butanol, 70631-92-4; methyl bromide, 74-83-9.

Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy. Natural-Abundance Nitrogen-15 Chemical Shifts of Alkyl- and Aryl-Substituted Ureas[1]

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^{15}N chemical shifts of urea and several alkyl- and arylureas have been determined at the natural-abundance level in DMF and Me_2SO. Dilution has very little effect on the chemical shifts. N-Methylation at nitrogen induces systematic upfield shifts which contrast with expected downfield shifts. Alkyl substitution at positions β, γ, and δ to the nitrogen induces shifts in the expected order based on aliphatic amines. Multiple regression analysis gives appropriate α, β, γ, and δ substituent parameters. The shifts of urea and the methylureas can be correlated with ionization potential differences between lone-pair molecular orbitals. Activation energy barriers for rotation around the C–N bond have been estimated using equations derived for substituted amides; the appropriateness of this method is discussed. ^{13}C chemical shifts of the ureas have also been determined.

As a class of compounds, ureas are chemically and pharmacologically important because they are effective protein denaturants and because the urea moiety is a structural element in biologically active compounds such as barbiturates and purine bases. To the extent that nitrogen nuclear magnetic resonance (NMR) spectroscopy is useful in probing the structures and interactions of these types of compounds, a knowledge of the factors influencing their chemical shifts is useful. Some early results using ^{14}N NMR have been reported,[2,3] but identification of resonances of unsymetrically substituted ureas is hampered by the inherently broad signals arising from ^{14}N quadrupolar relaxation. ^{15}N data for urea and tetramethylurea

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Table I. ^{15}N Chemical Shifts and Related Data for Methylureas

compd no.	δ_N, ppm[a] 4 M DMF[b]	2 M DMF[b]	4 M Me_2SO[b]	$\delta_{^{14}N}$, ppm[c]	$\delta_{C=O}$, ppm[d]	IP, π_1, eV[e]	IP, π_2, eV[e]
1a	75.00	74.94	77.59	75.0	161.1	10.22	10.78
1b	N_1, 69.07	68.71	70.04	71.2[g]			
	N_2, 72.94	72.70	75.49	71.1	159.8	9.21	10.23
1c	66.61	66.65	67.99	69.4[g]	159.5	9.23	9.73
1d	N_1, 65.57		60.8				
	N_2, 72.70		76.33		159.4	8.27	9.93
1e	N_1, 62.92		63.51		159.0	8.80	9.93
	N_2, 67.62		68.71				
1f	63.51	62.66	63.51	59.7[h]	164.8	8.64	8.98

[a] Measured with respect to external $CH_3{}^{15}NO_2$, converted to anhydrous ammonia scale (ref 13) via the relationship $\delta_{NH_3} = \delta_{CH_3NO_2} + 380.23$. [b] DMF = *N,N*-dimethylformamide; Me_2SO = dimethyl sulfoxide. [c] References 2 and 3; pure liquids except as noted. [d] Urea carbonyl chemical shift, measured as 2 M solution in Me_2SO, reported with respect to tetramethylsilane. [e] Photoelectron ionization potential, ref 10. [f] Concentration not known. [g] Aqueous solution. [h] Acetone solution.

Table II. ^{15}N and Carbonyl ^{13}C Chemical Shifts of Alkylureas

compd no.	δ_N, ppm[a] 4 M DMF[b]	2 M DMF[b]	4 M Me_2SO[b]	$\delta_{^{14}N}$, ppm[c]	$\delta_{C=O}$, ppm[d]
2a	N_1, 87.22	86.73	88.07	90.7[g]	
	N_2, 72.94	72.58	72.58	71.1	159.5
2b	N_1, 83.71	83.35	84.44		
	N_2, 72.94	72.46	75.12		159.3
2c	N_1, 100.65	100.77	101.77		
	N_2, 71.86	73.07	73.07		
2d	N_1, 83.83	83.59	84.68	90.7	
	N_2, 72.94	72.63	75.12	67.7	160.0
2e	N_1, 82.33	81.90			159.2
	N_2, 73.07	72.58			
2f	N_1, 103.91[e]	104.69	105.25[e]		158.4
	N_2, 74.15	73.79	76.33		
2g	N_1, 105.73	105.61	106.82	99.5[h]	156.6
	N_2, 77.54	77.06	79.54	69.0	
2h	N_1, 80.73	80.33	81.3		
	N_2, 73.31	72.94	75.6		159.3
3a	84.92	84.68	85.77	89.8	158.2
3b	82.41[f]	82.41	82.31[e]		158.3
3c	107.67[f]	107.67[f]	108.88[e]	104.3[h]	152.6

[a-h] Footnotes as in Table I.

have been reported,[4] but substituent effects have not been systematically elucidated. Consequently, we have carried out a systematic study of ureas 1–3 in order to evaluate

$(R_1)(R_2)N^1C(O)N^2(R_3)(R_4)$

1a, $R_1 = R_2 = R_3 = R_4 = H$
b, $R_1 = CH_3$, $R_2 = R_3 = R_4 = H$
c, $R_1 = R_3 = H$; $R_2 = R_4 = CH_3$
d, $R_1 = R_2 = CH_3$; $R_3 = R_4 = H$
e, $R_1 = R_2 = R_3 = CH_3$; $R_4 = H$
f, $R_1 = R_2 = R_3 = R_4 = CH_3$

$RN^1HC(O)N^2H_2$

2a, R = C_2H_5
b, R = *n*-C_3H_7
c, R = *i*-C_3H_7
d, R = *n*-C_4H_9
e, R = *i*-C_4H_9
f, R = *t*-C_4H_9
g, R = C_6H_5
h, R = $-CH_2CH=CH_2$

RNHC(O)NHR

3a, R = C_2H_5
b, R = *n*-C_4H_9
c, R = C_6H_5

substituent effects on ^{15}N chemical shifts and to assess the importance and influence of lone-pair delocalization on nitrogen shifts in these systems. In addition, using reported ^{15}N NMR methods for estimating activation energy barriers for rotation around the C–N bond in amides and derivatives,[5,6] we have attempted to estimate these barriers in ureas, which otherwise are not obtained easily by ^1H or ^{13}C NMR spectroscopy.[7-9]

Experimental Section

All ureas were commercially available. Solvents were dried over molecular sieves and distilled before use.

Natural abundance ^{13}C and ^{15}N spectra were determined at 25.03 and 10.09 MHz, respectively, by the pulsed Fourier transform method on a JEOL PS/PFT 100 NMR spectrometer equipped with the JEOL EC-100 data system. For ^{13}C spectra, a sweep width of 5.0 kHz over 8K data points was used, and 1000–2000 transients were collected for proton-noise-decoupled spectra. Pulse widths corresponding to tip angles of 20–25° and a repetition rate of 2.0 s were employed. The samples were run as 2 M solutions in Me_2SO. Chemical shifts were measured with respect to tetramethylsilane.

^{15}N spectra of mono- and 1,3-disubstituted ureas required 2000–2500 transients accumulated over a 5-kHz range using 8K words of memory. Pulse widths of 20–25° and a repetition rate of 2.0 s were used. With tri- and tetrasubstituted ureas, the spectra were accumulated overnight to get adequate signal intensities.

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The reference signal for the nitrogen spectra was derived from a concentric capillary of ca. 20% enriched nitromethane in deuterionitromethane, which provided the field-frequency lock.[13] Chromium tris(acetylacetonate) (ca. 10–20 mg) was added to solutions of ureas with tertiary nitrogens to shorten T_1 values.

Results

The ^{15}N chemical shifts of **1a–f** are given in Table I, which also includes some ^{14}N chemical shifts,[2,3] photoelectron vertical ionization potentials for methylureas,[10] and ^{13}C chemical shifts of the urea carbonyl carbons, some of which have been reported.[11,12] Similar data for **2–3** are reported in Table II. Spectra for unsymmetrical ureas were assigned on the basis of gated decoupling experiments. While the ^{15}N nuclei in $(CH_3)_2SO(Me_2SO)$ are slightly more deshielded than in dimethylformamide (DMF), trends displayed in each solvent are the same, and dilution to 2 M in DMF (the lowest practical limit for ureas with disubstituted nitrogen atoms) has no appreciable effect on the resonance positions.

It is useful at the outset to compare the nitrogen shifts of ureas with those of closely related amides. In general, the nitrogen nucleus of a urea is shielded compared with that of a corresponding amide. Thus, the ^{15}N resonance of formamide[13] is ca. 40 ppm downfield from that of urea. To the extent that lone-pair delocalization deshields nitrogen, this difference is consistent with reduced lone-pair delocalization in urea compared to the amide, presumably because of competitive cross-conjugation to the two nitrogens with the carbonyl group. This suggestion is also in accord with photoelectron spectroscopic results discussed below. The extent of lone-pair delocalization may be seen also in the ^{13}C chemical shifts of the urea carbonyls, whose nuclei are shielded more than those of the corresponding amides. Similarly, the low-field position of arylureas is ascribable to the same influence.

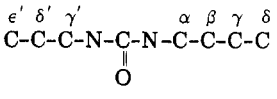
Alkyl substitution at amide and urea nitrogens results in similar trends, in that successive methylation at nitrogen in both urea and formamide shields the nitrogen. The direction of this change persists in the series urea → methylurea → tetramethylurea and in formamide → *N*-methylformamide → *N,N*-dimethylformamide.[13] Going from **1a** to **1b**, the substituted nitrogen is shielded by 6 ppm; further methylation of the substituted nitrogen (**1d**) leads to an additional but smaller shielding of 3.5 ppm. The effect of substitution levels off with additional methylation. These changes in resonance position on substitution contrast markedly to effects of substitution on the ^{13}C chemical shifts of structurally analogous alkyl ketones, where downfield shifts of 2.5 ppm are displayed.[14] Similarly, α substitution of aliphatic amines is reported to deshield nitrogen nuclei, although the magnitude of the shift (~9 ppm) was derived by multiple regression analysis of primary amine data rather than by direct measurement.[15] Several other examples of upfield α effects have been reported.[16–20] Thus, the nitrogen resonance of dimethylaniline lies ~12 ppm upfield from that of aniline.[16] Similarly, the nitrogen nucleus of *N*-methylpyrrolidone is shielded by 7.1 ppm compared with the unsubstituted compound.[17] The same applies to nitrogen nuclei of N-methylated barbituric acids.[19] As will be discussed below, these kinds of upfield shifts on α-methylation are common to (but not restricted to[20]) systems in which the nitrogen lone pair interacts conjugatively with an adjacent π system.

Table III. Substituent Parameters for Alkylureas[b]

position	substituent parameter, ppm[a]	no. of points used
α	−4.64 ± 0.40	13
β	16.61 ± 0.56	7
γ	−1.81 ± 0.53	4
δ	−0.67 ± 0.92	2
γ'	−0.99 ± 0.37	12
δ'	0.51 ± 0.58	8
ϵ'	−0.36 ± 0.87	4

[a] Positive values denote shifts to lower field. [b] Constant value = 72.61 ppm. Standard deviation 0.96 ppm.

Alkyl substitution at sites β, γ, and δ to nitrogen in urea leads to shifts expected on the basis of results in saturated amines: substitution β to nitrogen leads to a large downfield shift similar to nitrogen shifts in amides[6] and alkylamines,[15] while γ and δ substitution lead to small upfield shifts. Following the method of Grant and Paul,[21,22] substituent parameters defined below may be derived for the nitrogen chemical shifts. The parameters obtained from the regression analysis are listed in Table III and display a multiple correlation coefficient r = 0.995. Because of the limited number of data points, no attempt was made to account for possible effects of branching in the regression analysis. Furthermore, the value for *tert*-butylurea, which deviates considerably from the regression line, was not included in the analysis.



Examination of Table III shows that, except for α substitution, ^{15}N chemical shifts substantially parallel the ^{13}C shifts of alkanes. The values in Table III also show that the chemical shifts of unsubstituted nitrogens are not greatly affected by substitution on the other nitrogen. Comparison of the ^{14}N[2,3] and ^{15}N chemical shifts shows the same trends, but a few of the ^{14}N shifts differ from ours. This is a consequence of the less precise ^{14}N values, which also accounts for the earlier conclusion that methyl substitution has no effect on the chemical shifts.

Inspection of Table I shows that the carbonyl ^{13}C chemical shifts for the ureas do not vary much on alkyl substitution at nitrogen. This behavior resembles that exhibited by amide carbonyls in a similar environment.[6] On the expectation that the urea carbonyl and urea nitrogens would be influenced in a similar manner by lone-pair delocalization, a correlation between these two sets of data was sought, but none seems to exist.

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Discussion

The shielding of the methylurea nitrogen nuclei is consistent with inhibition of lone-pair delocalization. This in turn can increase the nitrogen electron density as well as decrease the C–N π bond character. Within the qualitative Karplus–Pople treatment of chemical shifts a decrease in the latter parameter is expected to decrease the paramagnetic term of the chemical shift and shield the nitrogen.[23] An argument of this type has been used to rationalize the nitrogen shifts of both methyl-substituted[16] and conjugatively substituted anilines.[24-26]

The upfield shifts on α-methylation of aniline have been rationalized with the help of photoelectron spectroscopy. This approach suggests that α-methylation inhibits p–π interaction between the nitrogen lone pair and the adjacent π system, possibly by increasing the energy difference between the nonperturbed orbitals. The argument also applies to other conjugated systems. For example, ^{15}N chemical shifts of methyl-substituted formamides[6a] and acetamides[6a] correlate separately (r = 0.988 and 0.980, respectively) and together (r = 0.92) with the photoelectron ionization potentials of the highest occupied π orbitals of these compounds.[27a] Calculations suggest that this orbital is rather highly localized on nitrogen.[27a,b] At the same time, microwave data indicate that the amide N–C bonds in formamides remain torsionally undistorted as a result of N-methyl substitution.[27c] Hence, the additional shielding

	δ_N^{29}	IP (π)	δ_N^{29}	IP (π)
R = H, H	112.4	10.52	110.5	10.32
R = H, CH_3	109.6	9.87	106.3	9.68
R = CH_3, CH_3	104.8	9.25	98.3	9.09

and lower ionization potentials resulting from these structural changes are probably attributable to the same sources suggested for the N-methylated anilines.[16]

A similar approach may be useful with the ureas if the nitrogen shifts can be correlated with appropriate ionization potentials. In order to assess this possibility, we have made use of the detailed analysis of the photoelectron spectra of methylureas recently reported by McGlynn et al.[10] These authors were able to identify π-type orbitals associated with each nitrogen and estimate the influence of alkyl substitution on lone-pair interaction. The reduced nitrogen delocalization suggested above in ureas, relative to correspondingly substituted amides, may be apparent from the photoelectron data, in that the urea nitrogen ionization potentials for π_1 are smaller than those of the appropriate amides. For example, the value for urea is 0.27 eV less than that for formamide.[27b,28] Furthermore, using the published data,[10] it is possible to approximate the effect of substitution on each nitrogen separately. This is done on the assumption that the ionization potential which

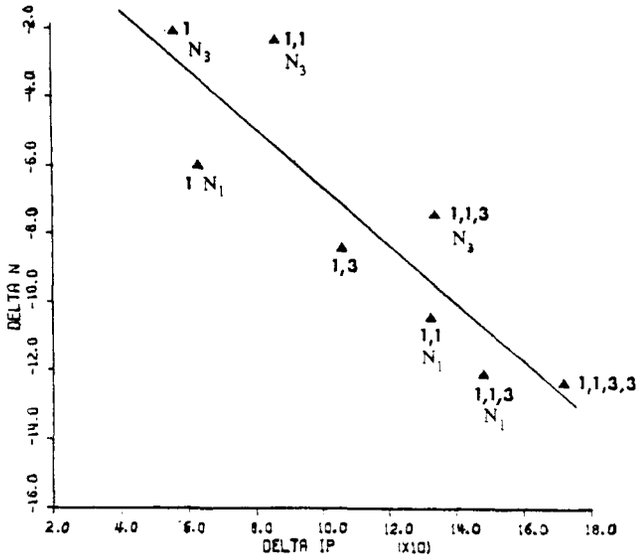
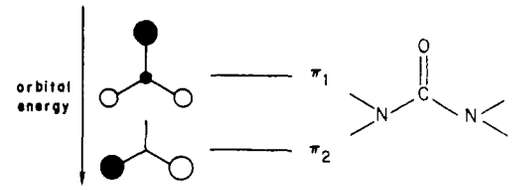


Figure 1. Plot of methylurea ^{15}N chemical shifts vs. photoelectron ionization potentials (see Discussion). The straight line has no statistical significance.

changes more on substitution can be attributed largely to the substituted nitrogen. The relevant orbitals as derived by McGlynn et al. are shown below. While in all cases



the lower lying π_2, with the larger electron density at nitrogen, is more strongly affected by substitution, both ionization potentials decrease. The corresponding destabilization of these levels by methyl substitution parallels that displayed by the corresponding levels in the methylanilines.[16] Furthermore, π_1 displays a "saturation" effect when nitrogen is completely substituted, while π_2 continues to decrease on further substitution (e.g., **1d** → **1e**, **1f**). Presumably, electron density in π_1 is more heavily localized at the fully substituted nitrogen, hence further substitution occurs at a site where electron density is low. Thus, for a given ionization potential difference, a larger change occurs for a nitrogen which undergoes further substitution, and this is the basis for our assumption above.

From the reported data, ionization potential differences were derived as follows: For unsymmetrical ureas, the π_1 and π_2 ionization potentials were assigned to the more and less highly substituted nitrogens, respectively. The difference between each of these and the corresponding values for urea itself gives ΔIP for each nitrogen. For symmetrical ureas, ΔIP is the difference between the *average* ionization potential of the substituted urea and the *average* value for urea itself, 10.53 eV. These values are given in Table I and are plotted against the nitrogen chemical shift differences with respect to urea (Figure 1). Although there is considerable scatter, a definite trend may be discerned, so that the nitrogen shifts and the ionization potentials may be related reasonably to lone-pair delocalization.

The scatter in Figure 1 may arise because of steric effects in the more highly substituted ureas, which conceivably could inhibit delocalization in a manner reflected differently by the two methods. This could be especially so for tetramethylurea. Although no structural data have been reported for this compound, tetramethylthiourea is known to be nonplanar in the crystalline state.[30] The single

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nitrogen resonance observed could be a time-averaged value between conjugated and nonconjugated nitrogen nuclei or it could reflect a single species in which conjugation of both nitrogens is partially inhibited to the same extent. We have no way of independently assessing these factors, although the low rotational barrier (see below) supports the former suggestion. Nonetheless, the effect of torsional distortion is expected to influence both types of experimental data in the same direction.

Higher alkyl substitution needs little comment. It is interesting to note that the γ' parameter is smaller than the γ parameter, although both have the same sign. Conceivably, electronic differences in the intervening bonds as well as conformational differences may play an important role. It is not apparent why the resonance position for **2f** deviates so greatly.

Activation Energy Barriers

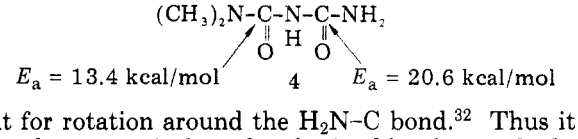
Although ^{1}H and ^{13}C NMR have been valuable in determining rotational barriers in simple amides, these techniques have been less widely applied in the study of ureas. A few scattered data on the barriers are in the literature.[5,9,31,32] Thus, an E_a value of 11.7 kcal/mol was derived from total line shape analysis of the temperature-dependent urea ^{1}H spectrum.[31a] From $T_{1\rho}$ measurements, the rotational barrier for tetramethylurea (**1f**) was estimated to be 6.4 kcal/mol.[31b] The drawback with ^{1}H NMR lies in the fact that the protons on the alkyl substituent frequently show no magnetic nonequivalence even at low temperatures.[8,33]

Very recently, ^{15}N chemical shift determinations have been suggested to be useful in evaluating activation energy barriers for C–N bond rotation in amides and derivatives.[5,6a] The rationale for this approach lies in the untested assumption that factors influencing both chemical shifts and rotational barriers have a common origin, namely, extent of nitrogen lone-pair delocalization in the ground state. Despite its highly empirical nature, this method appeared to yield qualitatively reasonable results for amide rotational barriers whose values span a fairly large range.[6a] In order to test its validity, we applied eq 1 and 2 (for methyl ureas and other alkyl-substituted ureas,

$$E_a \text{ (kcal mol}^{-1}) = -2.1 + 0.21\delta_N \quad (1)$$

$$E_a \text{ (kcal mol}^{-1}) = -7.8 + 0.208\delta_N \quad (2)$$

respectively), which had been derived for amides, to estimate rotational barriers for the alkylureas in Table I.[34] Direct substitution of the chemical shifts into the equations gives values for **1a** and **1f** which deviate substantially from the measured values.[31a,b] Very recently, Anet and Ghiaci confirmed the rotational barrier for **1f** by low-temperature dynamic NMR and pointed out that eq 1 and 2 may still apply if appropriately modified.[6b] They suggested that the value obtained when a urea shift is substituted directly into eq 1 first must be doubled, to account for the fact that each nitrogen displays only half the effect it would were it not cross-conjugated. From the value so obtained, Anet and Ghiaci subtract the rotational barrier arising from residual amide conjugation which remains when one nitrogen is twisted. On this basis, a value of $E_a = 2(11.2) - 17.3 = 5.1$ kcal/mol may be calculated for **1f**, which approximates the experimental value moderately well. It should be noted that in this calculation a variation of 0.5 ppm in ^{15}N shift produces a change of 1 kcal/mol in E_a. Straightforward application to symmetrical ureas, taking advantage of the near constancy of amide rotational barriers, gives results for **1a**, **1e**, **1f**, **3a**, and **3b** reported in Table IV. The last two values were derived from eq 2, whose constant term corrects for the substituent effects on the ^{15}N shifts which are expected to be independent of effects on the rotational barriers. Although eq 1 gives values ~10 kcal/mol higher for **3a** and **3b**, its use is inappropriate because it was derived from data for *N*-methyl-substituted compounds only. The values for the first three compounds lie in a reasonable region, but those for **3a** and **3b** are much too low. For example, the rotational barrier for *N*,*N*-diethylacetamide (18.0 kcal/mol)[35] compares with that for *N*,*N*-dimethylacetamide (17.3 kcal/mol), although the ^{15}N shifts differ markedly.[6a] Furthermore, in the series formamide → *N*-methylformamide → *N*,*N*-dimethylformamide, E_a is found by direct measurement to increase.[6a] This contrasts with the results for these compounds obtained from eq 1. By contrast, E_a for rotation around the $(CH_3)_2N$–C bond of *N*,*N*-dimethylbiuret (**4**) is less than



that for rotation around the H_2N–C bond.[32] Thus it is clear that numerical results obtained by this method are likely to be unreliable.

Application of eq 1 and 2 to unsymmetrical ureas is problematic. Following the above method, one must apply appropriate correction values for residual amide rotational barriers. For example, estimation of the barrier for *N* – 1 of **1b** requires that the result obtained from eq 1 (12.4 kcal/mol) first be doubled then be reduced by the rotational barrier for the most appropriate isosteric amide (propionamide). However, values for alkylamides are roughly comparable at ~16–18 kcal/mol[35] and depend

Table IV. Calculated Activation Energies of Alkylureas[a]

compd no.	$E_a(N_1)$, kcal/mol	$E_a(N_2)$, kcal/mol
1a	10.6	
1b	8.1	8.4
1c	5.6	
1d	6.6	9.0
1e	4.2	6.9
1f	5.1	
2a	4.0	8.4
2b	2.5	8.4
2c	9.5	7.0
2d	2.6	8.4
2e	1.9	8.5
2f	9.9	8.9
3a	1.7	
3b	0.7	

[a] Activation energies for **1a-f** and for the NH_2 group of **2a-h** were calculated using eq 1. Remaining values were derived from eq 2.

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markedly on solvent. To reduce the complexity of these highly approximate calculations, we have taken the value for acetamide (16.7 kcal/mol) as the correction value for substituted urea nitrogens and that for *N*-ethylacetamide (18.0 kcal/mol) as the corresponding value for unsubstituted nitrogens. The results are included in Table IV, and clearly the choice of correction values is hardly critical. Rotational barriers for **2a–e** appear to be much too low, and increasing the size of the N-alkyl substituent (**2a** → **2c** → **2f**) apparently increases E_a. In light of the relative constancy of the amide values, this result appears anomalous.

Thus, while ^{15}N chemical shifts may in fact be related to rotational barriers, quantitative evaluations are questionable at best. Direct determination still remains the most reliable method for evaluating rotational barriers.

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Registry No. 1a, 57-13-6; **1b**, 598-50-5; **1c**, 96-31-1; **1d**, 598-94-7; **1e**, 632-14-4; **1f**, 632-22-4; **2a**, 625-52-5; **2b**, 627-06-5; **2c**, 691-60-1; **2d**, 592-31-4; **2e**, 592-17-6; **2f**, 1118-12-3; **2g**, 64-10-8; **2h**, 557-11-9; **3a**, 623-76-7; **3b**, 1792-17-2; **3c**, 102-07-8.

Electrophilic Additions to Acetylenes. 7.[1] Relative Reactivity of Double and Triple Bonds toward Carbenium Ions

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The relative reactivity of pairs of phenyl-substituted alkynes and alkenes toward diphenylmethyl- and 1-phenylethylcarbenium ions, generated in situ by the interaction of the corresponding chlorides with anhydrous zinc chloride in dichloromethane, has been determined by a competition method. Reactivity ratios alkyne/alkene ranging from 0.2 to 3.5 have been found, with the reactions involving *cis*-stilbene as the only exception. This behavior is similar to that previously found for alkyne–alkene pairs in hydration reactions but differs considerably from that of halogenation reactions, where alkenes are more reactive than alkynes by factors of 10^3–10^7. The results are discussed in terms of relative stability of saturated and unsaturated cationic intermediates with respect to the ground-state stability of substrates and, in a broader sense, in terms of relative ability of the various electrophiles to form open or bridged intermediates. The low reactivity of *cis*-stilbene is ascribed to steric factors.

In the previous papers of this series[1-5] we have shown that phenyl- and alkyl-substituted acetylenes may react with alkyl halides under Friedel–Crafts conditions to give 1:1 addition or cyclization products. These reactions were shown to occur via addition of a carbenium ion, generated by interaction of the alkyl halide with a Lewis acid, to the triple bond of the substrate to give a vinyl cation, which in a subsequent fast step is captured either by an external nucleophile present in the reaction medium, e.g., a halide ion, thus leading to the product of 1:1 addition, or by an internal nucleophile, e.g., a phenyl ring in an appropriate position, to give a product of cyclization by an intramolecular Friedel–Crafts reaction. Similar reactions are known or can easily be postulated to occur also with alkenes. We have decided therefore to use these reactions in order to obtain information on the relative reactivity of the two unsaturated systems toward the addition of carbenium ions.

As a matter of fact, the question of the relative reactivity of double and triple bonds toward electrophilic reagents is still open,[6-13] for with electrophiles like the halogens, alkenes are 10^3–10^7 times more reactive than alkynes bearing the same substituents,[9,10,13-17] whereas in hydration (or acid addition) reactions rate ratios close to unity were observed for the two systems.[8,9,18] This clearly indicates

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