Conformational Influence of Nonacyl Groups on Acyl Group Properties in N-Monosubstituted Amides and in Other Carboxylic Acid Derivatives: a 7-Position Proximity Effect[1]

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Abstract: NMR substituent chemical shifts (SCS) for the acyl methyl protons of 32 N-monosubstituted acetamides, CH_3CONHR', have been measured in CCl_4. The variation in SCS can be accounted for by steric effects from the R′ group, but not in terms of only the steric substituent constant E_s^c. That is, groups in the 7 position of R′ (from the carbonyl oxygen as position 1) exert an influence not accounted for by E_s^c. Reevaluation of reaction and nonreaction properties of carboxylic acid derivatives demonstrates that a 7-position proximity effect of general significance operates from the nonacyl on the acyl portion of these molecules and is thus a factor of importance in considering properties associated with the acyl portion. Data demonstrating the interinfluence of proximate groups in some selected noncarboxylic acid systems suggest that a 7-position proximity effect may be operating in those systems as well.

Studies of substituent proximity and steric effects and their influence on molecular properties have provided considerable information concerning the various contributory factors of substituents and many of these studies have produced quantitative relationships which account for the influence of these factors.[2,3] In the case of carboxylic acids and esters, Newman[4] has demonstrated that the 6-number of a substituent (i.e., the number of atoms in the 6 position from the carbonyl oxygen atom as atom number 1) makes a large contribution to the total steric effect of that substituent and is thus an important factor in considering the esterification of carboxylic acids and the saponification of the corresponding esters. In an attempt to refine the 6-number concept, Hancock and his co-workers[5] recognized that the steric 6-number effect was already included in the overall or total corrected[6] steric substituent constant E_s^c for a particular substituent when in the acyl portion of an ester (R of RCO_2R'); but was not necessarily correctly included in E_s^c for the same particular substituent when placed in the alkyl portion of the ester (R′ of RCO_2R'). The latter observation arises because in moving a particular substituent from the acyl to the alkyl portion of an ester the 6-number may, depending upon the structure of the substituent, increase, decrease, or remain the same. In order to account for this variability, Hancock and his co-workers[5] proposed and demonstrated that the change in 6-number, Δ6 (i.e., the 6-number of a substituent in the acyl portion of an ester minus the 6-number of the same substituent in the alkyl portion of the ester) provides the necessary steric 6-number correction to E_s^c when E_s^c is used for a substituent in the alkyl portion of an ester. Kan[7] and independently Hancock and his co-workers[8] have shown that various 6-number effects are also of importance when considering nonreaction properties such as NMR substituent chemical shifts (SCS) of the methyl protons for acetate esters (CH_3COOR'), and more recently the alkaline hydrolysis and NMR substituent chemical shifts (SCS) for thiolacetates (CH_3COSR') have been treated in a similar manner.[9] For the SCS data on both the oxygen and sulfur esters, the 6-number effect of the R′ group was found to be best represented in terms of the carbon 6-number (i.e., the number of carbon atoms in the 6 position). In these same cases, the 6-number, the Δ6 number, and the hydrogen 6-number were apparently not important. While these results are of interest and do provide further demonstrations of the ability of remote substituents to influence properties conformationally and/or sterically, no adequate indication of the nature of these effects for substituents in the nonacyl portion of a carboxylic acid derivative has been advanced. In particular, if the number of carbon atoms in the 6 position of the nonacyl portion of the molecule is an important factor in considering the SCS's for the acyl methyl protons in acetates and thiolacetates, it seems reasonable to assume that atoms directly attached to the 6 position might be influential also and in fact might be the primary factor responsible for the origin of the 6-number effect. In order to investigate these points and to provide data on another important class of carboxylic acid derivatives, which, in addition, serve as a simple model peptide bond system, we have prepared an extensive series of N-monosubstituted acetamides (CH_3CONHR') and have determined the NMR SCS's for the acyl methyl protons of these compounds. The present paper reports the results of this study, evaluates previously reported data on carboxylic acid derivatives in terms of these results, and provides an indication of the origin of 6-number effects from the nonacyl portion in carboxylic acid derivatives.

Results and Discussion

The chemical shifts in hertz for the acyl methyl protons of the N-monosubstituted acetamides were measured vs. Me_4Si at 37 °C in a 10% CCl_4 solution. These data are reported in Table I as substituent chemical shifts (SCS) where SCS = chemical shift of the acyl methyl protons of CH_3CONHR' minus the chemical shift of the acyl methyl protons of $CH_3CONHCH_3$. A positive SCS then represents a downfield shift from the acyl methyl protons of $CH_3CONHCH_3$, while a negative SCS indicates an upfield shift. Also reported in Table I are a number of substituent parameters for the R′ group of CH_3CONHR'.

Inspection of these data indicates that the various upfield and downfield SCS's are not simple functions of just polar effects (as represented by σ^*) or steric effects (as represented by E_s^c) or steric "correction site" parameters (as represented by 6-no., Δ6, C-6no., or H-7no.). That is, for several of the isomeric alkyl group sets (no. 5–8; 9–14; 15–20; 21–24; 25–26) and for the polar group set (no. 27–32), the SCS's present an apparent scatter in order and magnitude. In an attempt to quantify these qualitative assessments and to understand the SCS's for these amides in terms of the variations in structure, we have followed the lead of previous investigators who have studied carboxylic acid derivatives and have subjected some of these SCS data to correlation analysis[3,10] via the extended

Table I. Substituent Chemical Shifts (SCS) and Substituent Constants for 32 N-Monosubstituted Acetamides, CH_3CONHR'

No.	R′ in CH_3CONHR'	SCS, Hz[a]	σ^*[b]	E_s^c[c]	6-no.[e]	$\Delta 6$[f]	C-6no.[g]	H-7no.[h]
1	Me	0	0	0	0	0	0	0
2	Et	−1.3	−0.100	−0.38	3	−3	0	0
3	*n*-Pr	−1.5	−0.115	−0.67	3	0	1	3
4	*i*-Pr	−2.1	−0.190	−1.08	6	−6	0	0
5	*n*-Bu	−1.3	−0.125	−0.70	3	0	1	2
6	*i*-Bu	−0.2	−0.130	−1.24	3	3	2	6
7	*s*-Bu	−1.6	−0.210	−1.74	6	−3	1	3
8	*t*-Bu	−4.1	−0.300	−2.46	9	−9	0	0
9	*n*-$BuCH_2$	−1.3	−0.13	−0.71	3	0	1	2
10	*i*-$BuCH_2$	−1.3	−0.13	−0.66	3	0	1	1
11	*s*-$BuCH_2$	0.2	−0.143		3	3	2	5
12	*t*-$BuCH_2$	1.7	−0.165	−2.05	3	6	3	9
13	*i*-PrCHMe	1.9	−0.230		6	0	2	6
14	$Et(Me)_2C$	−3.7	−0.315		9	−6	1	3
15	*t*-$Bu(CH_2)_2$	−1.7		−0.65[d]	3	0	1	0
16	*t*-BuCHMe	0.7	−0.265		6	3	3	9
17	*i*-$Pr(Me)_2C$	−4.8	−0.330		9	−3	2	6
18	*s*-BuCHMe	0.5	−0.243		6	0	2	5
19	*i*-BuCHMe	−1.5	−0.230		6	−3	1	1
20	$(Et)_2MeC$	−4.7	−0.330		9	−3	2	6
2	$(i\text{-Pr})_2CH$	−0.1	−0.260		6	6	4	12
22	*t*-$Bu(Me)_2C$	−4.3	−0.365	−4.82	9	0	3	9
23	*s*-$BuCH_2CHMe$	−1.1	−0.229		6	−3	1	1
24	*i*-$BuCH_2CHMe$	−1.6	−0.227		6	−3	1	2
25	(*n*-Bu)(Et)$CHCH_2$	−0.6	−0.150		3	3	2	4
26	*t*-$BuCH_2(Me)_2C$	−6.1	−0.334	−3.49[d]	9	−6	1	0
27	$(Me)_2NCH_2CH_2$	−1.8	0.079		3	−1	0	
28	$MeOCH_2CH_2$	−1.3	0.238		3	−2	0	
29	$ClCH_2CH_2$	−0.8	0.385		3	−3	0	
30	$H_2C{=}CHCH_2$	−0.1	(0.12–0.20)		2	0	1	2
31	$HSCH_2CH_2$	1.5	0.169		3	−2	0	1
32	$EtO(CH_2)_3$	−1.9			3	0	1	0

[a] SCS = chemical shift of the acyl methyl protons of CH_3CONHR' in 10% CCl_4 minus the chemical shift of the acyl methyl protons of $CH_3CONHCH_3$ in 10% CCl_4. Chemical shift of the acyl methyl protons of $CH_3CONHCH_3$ (10% CCl_4) vs. Me_4Si is 115.8 Hz. [b] From ref 2 or from P. R. Wells, "Linear Free Energy Relationships", Academic Press, New York, N.Y., 1968, Chapter 2, or calculated by Taft's additivity principle (see ref 2 and/or ref in footnote *d*, Table I, p 369). [c] See ref 2 and 6. [d] E_s from O. A. Reutov, "Fundamentals of Theoretical Organic Chemistry", Appleton-Century-Crofts, New York, N.Y., 1967, p 371. E_s^c calculated as described in ref 6. [e] See ref 4. [f] See ref 5. [g] Number of carbon atoms in the 6 position. [h] Number of hydrogen atoms in the 7 position.

Taft equation. The resulting equations, eq 1–4, represent correlations for 14 of the amides in Table I (1–10, 12, 15, 22, 26) for which both polar[2] (σ^*) and steric[6] (E_s^c) substituent constants were available. In each of these equations the additional parameter is a 6-number steric "correction site" constant, R^2 is the square of the correlation coefficient[11a] expressed as a percentage (provides an indication of percent variation in SCS accounted for by the particular relationship) and s[11a] is the standard deviation from regression. The numbers in parentheses below the various parameters are the significance levels as determined by "Student's" t test.[11b] This statistic, recommended earlier by other chemists,[12,13] has recently been suggested[14] as an appropriate goodness of fit criterion for expressing the confidence with which a regression coefficient is known. We endorse these recommendations and have used this statistic here for comparing the significance of the parameter combinations in the various correlation equations.[15]

$$\underset{(>0.500)}{\text{SCS} = 0.94 - 4.10\sigma^*} \underset{(0.500)}{- 0.24E_s^c} + \underset{(0.14)}{0.83\ (6\text{-no.})},\quad R^2 = 74.6\%,\ s = 1.18 \quad (1)$$

$$\underset{(0.500)}{\text{SCS} = -0.20 + 10.84\sigma^*} + \underset{(0.016)}{1.01E_s^c} + \underset{(0.001)}{0.35(\Delta 6)},\quad R^2 = 84.3\%,\ s = 0.91 \quad (2)$$

$$\underset{(>0.500)}{\text{SCS} = 0.33 - 2.66\sigma^*} + \underset{(0.500)}{0.36E_s^c} - \underset{(0.025)}{0.58\ (\text{H-6no.})},\quad R^2 = 80.8\%,\ s = 1.02 \quad (3)$$

$$\underset{(0.260)}{\text{SCS} = -0.14 + 9.37\sigma^*} + \underset{(0.230)}{0.85E_s^c} + \underset{(0.006)}{1.23(\text{C-6no.})},\quad R^2 = 85.4\%,\ s = 0.89 \quad (4)$$

For example, in eq 1–4, the t test indicates that the least significant variable is σ^*. Rejecting this variable, eq 5–8 are obtained.

$$\underset{(0.400)}{\text{SCS} = 0.97 - 0.38E_s^c} - \underset{(0.003)}{0.74(\text{6-no.})},\quad R^2 = 73.4\%,\ s = 1.09 \quad (5)$$

$$\underset{(0.002)}{\text{SCS} = -0.25 + 0.77E_s^c} + \underset{(<0.001)}{0.32(\Delta 6)},\quad R^2 = 81.4\%,\ s = 0.91 \quad (6)$$

$$\underset{(0.400)}{\text{SCS} = 0.63 + 1.52E_s^c} - \underset{(0.001)}{0.51(\text{H-6no.})},\quad R^2 = 80.5\%,\ s = 0.98 \quad (7)$$

$$\underset{(<0.001)}{\text{SCS} = -1.07 + 1.54E_s^c} + \underset{(<0.001)}{1.44(\text{C-6no.})},\quad R^2 = 80.6\%,\ s = 0.93 \quad (8)$$

While none of these equations are highly significant, eq 8 involving the C-6no. parameter provides the best overall corre-

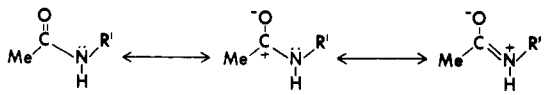
lation.[16] In general, this result was obtained by previous workers on studies of oxygen and sulfur esters.[8,9] That is, the number of 6-carbons appears to make some contribution to the total steric effect of a substituent and is not included in the E_s^c value for that substituent in the nonacyl portion of a carboxylic acid derivative. While previous workers have given little further attention to the nature of this effect, it seemed reasonable to us that if the 6-carbon is an important factor in these considerations that hydrogens attached to these carbons (i.e., 7-hydrogens) might also be influential. In order to assess this consideration, we have carried out an additional correlation using the hydrogen-7 number as a steric "correction site" parameter to obtain

$$\underset{}{\mathrm{SCS} = -0.37 + 4.80\sigma^* + 1.15E_s^c + 0.44(\text{H-7no.}),}$$
$$\underset{}{(>0.500)\quad (0.09)\quad (<0.001)}$$
$$R^2 = 90.8\%,\ s = 0.71 \quad (9)$$

As in eq 1-4, the t test indicates that σ^* is the least significant variable. Rejection of this variable yields

$$\underset{}{\mathrm{SCS} = -0.73 + 1.53E_s^c + 0.48(\text{H-7no.}),}$$
$$\underset{}{(<0.001)\quad <0.001)}$$
$$R^2 = 90.4\%,\ s = 0.66 \quad (10)$$

A comparison of eq 8 and 10 as well as application of an F test[11c,17] (analysis of variance) indicates that the hydrogen-7 number provides a significant improvement in the correlation and that it is the steric "correction site" parameter of primary importance in considering the SCS's for the N-monosubstituted acetamides. A more complete appreciation of this can be obtained by considering the various structural features of an N-monosubstituted acetamide. That is, N-monosubstituted acetamides exist predominantly in the trans conformation I[18,19] and are resonance hybrids with structures I, II, and III being



I II III

the main contributors. However, the relative importance of these contributing structures in any particular amide is a function of the steric and conformational effects of the R′ group, so that properties influenced by varying degrees of contribution from structures I, II, and III will be affected. In these terms, N-monosubstituted acetamide models indicate that 6-no. groups in the R′ portion of the molecule experience minimal conformational differences with respect to the carbonyl oxygen in contributing structures such as II and III. However, 7-no. groups in R′ are conformationally further removed from the carbonyl oxygen in a contributing structure such as II than they are in a structure such as III. In terms then of the number of hydrogens in the 7 position, the greater the H-7no. of R′, the greater is the contribution from a structure such as II, the greater then is the partial positive character of the carbonyl carbon and, therefore, the greater is the deshielding experienced by the acyl methyl protons. As a consequence, the downfield shift of the acyl methyl protons of an N-monosubstituted acetamide (from that of the parent compound *N*-methylacetamide) tends to increase as the H-7no. increases. In more general terms, this effect originates primarily from the 7 position, but is not limited to just hydrogens in that position. For example, for the first five compounds shown in Table II, the 7 position is occupied by unshared electron pairs or by π electrons. In these cases, the SCS of the acyl methyl protons tends to become more positive (representing a downfield shift) as the van der Waal's radius of the atom associated with the 7-position electrons increases and/or as the number of 7-position electron pairs increases. The order

Table II. Substituent Chemical Shifts (SCS) for Some N-Monosubstituted Acetamides of General Formula $CH_3CONHCH_2CH_2X$

SCS (Hz)[a]	X	$\sigma^*CH_2CH_2X$[b]	van der Waals radius of first atom in X, Å[c]
−0.5	NMe_2	0.079	1.55
0	OMe	0.238	1.52
0.5	Cl	0.385	1.75
1.2	$CH_2CH{=}CH_2$	0.12-0.20	(1.77)[d]
2.8	SH	0.169	1.80
−0.6	CH_2OEt		
−0.4	*t*-Bu		
−0.2	Me		

[a] SCS = chemical shift of the acyl methyl protons of $CH_3CONHCH_2CH_2X$ minus the chemical shift of the acyl methyl protons of $CH_3CONHCH_2CH_3$. [b] From references given in Table I. [c] A. Bondi, *J. Phys. Chem.*, **68**, 441 (1964). [d] Average half-width of aromatic ring.

of these SCS's is not in the direction which would be predicted by simple polar effects (as indicated by σ^*), but again reflects a 7-position effect which influences the relative importance of the various contributing structures of the resonance hybrid. Movement of the unshared electron pairs to the 8 position (X = CH_2OEt in Table II) or substitution of a large number of hydrogens at the 8 position (X = *t*-Bu in Table II has H-7no. = 0 and H-8no. = 9) show no effect comparable to such groups in the 7 position and exhibit acyl methyl proton SCS's on the order of that for *N*-*n*-propylacetamide (X = Me in Table II).

Other Applications of a 7-Position Proximity Effect from the Nonacyl Portion of Carboxylic Acid Derivatives. 1a. Alkaline Hydrolysis of Acetamides, Acetates, and Thiolacetates. All carboxylic acid derivatives are resonance hybrids and have the potential of drawing contribution to their overall structure from forms such as I, II, and III represented above for N-monosubstituted amides. For the alkaline hydrolysis of these acid derivatives, the rate-determining step in the reaction[20] involves coordination of hydroxide ion with the carbonyl carbon, so that this step should be fastest for those compounds which have the greatest contribution from a structure in which the carbonyl carbon has partial positive character (form II). For example, the alkaline hydrolysis rate constants shown in Table III for series of alkyl thiolacetates, alkyl acetates, and *N*-alkylacetamides are in an expected order based on the rel-

Table III. Alkaline Hydrolysis Rate Constants for Carboxylic Acid Derivatives, CH_3COGR'

	k, L mol^{-1} min^{-1}		
R′	G = -S-[a]	G = -O-[b]	G = -NH-[c]
Et	9.58	8.9	10.8×10^{-3}
n-Pr	7.40 (1.4)[d]	6.75 (−0.3)[d]	6.62×10^{-3}
n-Bu	6.30 (0.3)	5.38 (−0.8)	6.17×10^{-3}
i-Bu	6.23 (0.7)	3.95 (0)	3.85×10^{-3}
i-Pr	5.74 (−0.5)	1.84 (−2.5)	2.20×10^{-3}
s-Bu	4.14	0.954	
t-Bu	2.52	0.103	

[a] In 40% aqueous *p*-dioxane at 35 °C; ref. 9. [b] In 40% aqueous *p*-dioxane at 35 °C; ref 5 and 6. [c] In aqueous 1 N NaOH at 75 °C. T. Yamana, Y. Mizukami, A. Tsuji, Y. Yasuda, and K. Masuda, *Chem. Pharm. Bull.*, **20**, 881 (1972). [d] Numbers in parentheses are SCS values for the acyl methyl protons of the alkyl thiolacetates (ref 9) and alkyl acetates (ref 8).

ative contribution which forms such as I, II, and III make to the reactant molecules.[9,21-23] That is, thiolacetates, in which a form such as III has little contribution relative to that for an acetate, react faster under identical reaction conditions than do the corresponding acetates, while the *N*-alkylacetamides react considerably slower even at higher temperatures. The rate constants for the alkaline hydrolysis of the thiolacetates are represented fairly well by eq 11 with steric effects, as represented by E_s^c in eq 12, having the greater influence.

$$\log k = 1.14 + 0.66\sigma^* + 0.23E_s^c, \quad (0.010)\ (<0.001)$$
$$R^2 = 95.5\%,\ s = 0.061 \quad (11)$$

$$\log k = 1.15 + 0.31E_s^c,\ R^2 = 87.6\%,\ s = 0.094 \quad (12)\ (<0.001)$$

In addition, neither of these relationships is significantly improved by inclusion of a "correction site" parameter. The apparent absence of a general 7-position effect for the thiolacetates can be accounted for in terms of the geometry about the C-S-R′ portion of the molecule and because of the predominant influence of a form such as II relative to III. However, a 7-position effect is operative to the extent that the order and magnitude of the rate constants for certain of the compounds differ from what would be predicted. For example, the fact that the *i*-Bu substituted compound reacts faster than the *i*-Pr even though E_s^c for the *i*-Bu group is larger than that for the *i*-Pr can be accounted for in these terms. That is, the *i*-Bu group, with a H-7no. of 6, favorably (for the alkaline hydrolysis reaction) affects the relative importance of the various contributing structures for its resonance hybrid compared to the *i*-Pr group with a H-7no. of 0. Also, the *n*-Pr substituted compound (H-7no. = 3) reacts faster than the *n*-Bu compound (H-7no. = 2) in spite of the fact that the *n*-Pr and *n*-Bu groups have essentially identical E_s^c values. As indicated by the data in Table III, these same considerations apply to the corresponding alkyl acetates and *N*-alkylacetamides. In addition, for each of these series, the H-7no. is a variable of general significance in the quantitative structure-reactivity relationships represented by eq 13 for the alkyl acetates and eq 14 for the *N*-alkylacetamides.[24]

$$\log k = 1.31 + 1.10\sigma^* + 0.78E_s^c + 0.068(\text{H-7no.}), \quad (<0.001)\ (<0.001)\ (<0.001)$$
$$R^2 = 99.8\%,\ s = 0.044 \quad (13)$$

$$\log k = -1.67 + 0.90E_s^c + 0.056(\text{H-7no.}), \quad (<0.001)\ (0.008)$$
$$R^2 = 98.4\%,\ s = 0.056 \quad (14)$$

Descriptions similar to those given above for the alkaline hydrolysis data and for the SCS data on the N-monosubstituted acetamides can also be made for the acyl methyl group SCS's of the alkyl thiolacetates and the alkyl acetates. These data (numbers in parentheses in Table III) indicate a trend for SCS similar to that for the second-order alkaline hydrolysis rate constants. That is, the SCS's for *i*-Bu and *n*-Pr substituted compounds are more positive than those for the *i*-Pr and *n*-Bu substituted compounds, respectively, and again reflect a 7-position influence from the nonacyl portion of the compound.

1b. Alkaline Hydrolysis of Alkyl Lactates, $CH_3CHOHCO_2R'$, and of Alkyl Benzoates, $C_6H_5CO_2R'$. In his original paper[5] proposing Δ6 as a correction factor for E_s^c, Hancock showed that the alkaline hydrolysis rate constants in water at 10 °C for nine alkyl lactates[25] and in 60% aqueous *p*-dioxane at 35 °C for 11 alkyl benzoates[26] were represented more significantly by eq 15 (lactates) and 16 (benzoates)

$$\log k = 1.71 + 2.31\sigma^* + 0.37E_s^c + 0.067(\Delta 6), \quad (<0.001)\ (0.001)\ (0.002)$$
$$R^2 = 99.2\%,\ s = 0.084 \quad (15)$$

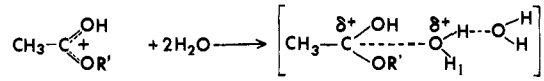
$$\log k = 0.14 + 1.15\sigma^* + 0.65E_s^c + 0.039(\Delta 6), \quad (0.004)\ (<0.001)\ (0.018)$$
$$R^2 = 98.4\%,\ s = 0.089 \quad (16)$$

than by relationships not involving Δ6. We now recognize that Δ6 is of importance in these correlations because of its relation to the number of 6-carbons and thus in turn to a 7-position effect in terms of the H-7no. Substitution of H-7no. for Δ6 in eq 15 and 16 give overall improved correlations for the lactates (eq 17) and benzoates (eq 18).

$$\log k = 1.67 + 2.65\sigma^* + 0.58E_s^c + 0.091(\text{H-7no.}), \quad (<0.001)\ (<0.001)\ (<0.001)$$
$$R^2 = 99.6\%,\ s = 0.065 \quad (17)$$

$$\log k = 0.12 + 1.46\sigma^* + 0.78E_s^c + 0.065(\text{H-7no.}), \quad (<0.001)\ (<0.001)\ (0.001)$$
$$R^2 = 99.0\%,\ s = 0.070 \quad (18)$$

2. Acid-Catalyzed Hydrolysis of Alkyl Acetates, CH_3COOR'. For the acid-catalyzed hydrolysis of several alkyl acetates, Yates and McClelland have reported[27] that reaction at low acidities occurs via an $A_{AC}2$ type of mechanism[28] in which a protonated ester molecule is attacked in the rate-determining step by two water molecules. They suggest a transition state (IV) involving one water molecule acting as

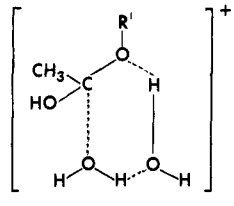


IV

a nucleophile with the second assisting in dispersing the positive charge developing on oxygen. While attack of the nucleophilic water molecule might be expected to be sterically hindered by R′ in a transition state such as IV, the order of hydrolysis (R′ = Me > *n*-Pr > Et > *s*-Bu > *i*-Pr) indicated by the data in Table IV is not that expected based on the E_s^c values of the various R′ groups. However, the observed order of reactivity is expected based on the H-7no. of the R′ group relative to the water molecule hydrogen H(1) in IV. This order of reactivity is predicted fairly well by

$$\log k = -1.78 - 0.042(\text{H-7no.}), \quad (0.012)$$
$$R^2 = 86.6\%,\ s = 0.046 \quad (19)$$

and would appear to give credence to a transition state such as IV relative to a cyclic structure such as V.[27]



V

3. Infrared N-H Stretching Frequencies of N-Monosubstituted Amides, RCONHR′. Recorded in Table V are the infrared N-H stretching frequencies determined in dilute CCl_4 and reported by Nyquist[29] for several series of N-alkyl-substituted α-substituted amides. The effect of the *N*-alkyl group on the N-H stretching frequency is general for these various amide series. That is, in each case the N-Me compound exhibits the highest ν_{NH}. The N-*i*-Bu compound's ν_{NH} is always next highest (7-11 cm^{-1} less than the N-Me), the N-Et, N-*n*-Pr, and N-*n*-Bu occur next as a group (12-21 cm^{-1} less than the N-Me), and the N-*i*-Pr, N-*s*-Bu, and N-*t*-Bu occur

Table IV. Acid-Catalyzed Hydrolysis Rate Constants in 14.1% H_2SO_4 at 25 °C for Alkyl Acetates, CH_3COOR'

R′	10^2k^a	10^2k^b	E_s^c	H-7no.[c]
Me	1.50	1.66	0	0
Et	1.39	1.24	−0.38	3
n-Pr	1.47	1.37	−0.67	2
i-Pr	0.890	0.927	−1.08	6
s-Bu	0.964	1.02	−1.74	5

[a] Pseudo-first-order rate constants in L mol^{-1} min^{-1} from ref. 27. [b] Calculated from eq 19. [c] Number of hydrogen atoms in 7 position of R′ from H(1) hydrogen of water molecule in structure IV as atom 1.

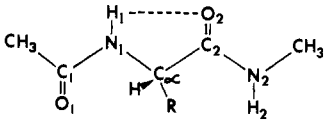
Table V. Infrared N-H Stretching Frequency Shifts ($\Delta\nu_{NH}$, cm^{-1}) for N-Monosubstituted Amides, $RCONHR'$[a]

	$\Delta\nu_{NN}$, cm^{-1} [b]				
R′	R = Me	R = CCl_3	R = $CHBr_2$	R = *p*-ClPh	R = *p*-OMe-Ph
Me	0	0	0	0	0
Et	−16	−13	−11	−21	−18
n-Pr	−17	−14	−12	−21	−17
n-Bu	−18	−17	−13	−18	−17
i-Bu	− 7	−11	−10	−12	−12
i-Pr	−27	−23	−23	−31	−25
s-Bu	−28	−24	−28	−30	−30
t-Bu	−25	−27	−25	−30	−29

[a] Reference 29. [b] $\Delta\nu_{NH}$ = ν_{NH} of substituted compound minus ν_{NH} of N-Me compound.

as a group at the lowest frequency (23–31 cm^{-1} less than the N-Me). With the exception of the ν_{NH} for the N-*i*-Bu compounds, these results can be rationalized fairly well in terms of the ability of R′ to inductively stabilize a contributing structure such as III (a form favoring a lower frequency ν_{NH}) relative to a structure such as II. However, for the N-*i*-Bu compounds, the inductive stabilization of III is offset by 7-position destabilization. That is, as described earlier for N-monosubstituted amides, the importance of III relative to II decreases as the H-7no. of the N-substituent increases. For the ν_{NH} data shown in Table V, the *i*-Bu group has the largest H-7no. and thus the N-*i*-Bu compounds exhibit the largest effect. A similar result is observed for the acyl methyl group SCS data reported in Table I for N-monosubstituted acetamides.

4. Conformational Analysis of Model Dipeptides, α-Substituted Monomethylamides of *N*-Acetyl-α-amino Acids, $CH_3CONHCHRCONHCH_3$. Marraud and Neel and coworkers have reported a number of spectroscopic studies in dilute CCl_4 dealing with the conformational possibilities of dipeptides[30–32] and model dipeptides[33–36] and for those model systems derived from *N*-acetyl-α-amino acids have postulated the existence of the conformation shown in VI. Such a form



VI

implies intramolecular interaction between H(1) and O(2) so that these two atoms along with C_α are involved in a five-membered ring. Marraud and Neel further suggest that because of the possibility of repulsive interactions between R and O(1) that the H(1)–O(2) interaction should become progressively weaker and the five-membered ring conformation progressively distorted out of planarity as R becomes increasingly more bulky. These assessments are fairly well confirmed by the data shown in Table VI for the bonded vs. nonbonded $\nu_{N(1)H(1)}$ absorptions[35] and for the estimated angles of rotation (ϕ)[35] about the N(1)–C_α bond, since ϕ tends to increase as the frequency shift $\Delta\nu_{N(1)H(1)}$ (bonded $\nu_{N(1)H(1)}$ minus nonbonded $\nu_{N(1)H(1)}$) decreases. However, ϕ is approximately the same for both R = Et and R = *n*-Bu even though E_s^c for *n*-Bu is twice that of Et and ϕ is larger for R = *i*-Pr relative to R = *i*-Bu even though E_s^c for *i*-Pr is smaller than that of *i*-Bu. Additional considerations of the effect of R on O(1) and thus on ϕ in terms of a 7-position effect account very well for the observed order of ϕ. That is, the effect of Et and *i*-Pr relative to *n*-Bu and *i*-Bu, respectively, is greater than expected based only on the E_s^c values because of the correspondingly greater H-7no.'s for Et and *i*-Pr. As indicated by

Table VI. Rotation Angle (ϕ^0, N(1)–C_α) and Frequency Shift ($\Delta\nu_{N(1)H(1)}$, cm^{-1}) for α-Substituted Monomethylamides of *N*-Acetyl-α-amino Acids, $CH_3CONHCHRCONHCH_3$ (VI)[a]

R	ϕ^{0b}	$\Delta\nu_{N(1)H(1)}$, cm^{-1c}	E_s^c	H-7no.[d]
Me	20	31	0	0
Et	23	28	−0.38	3
n-Bu	24	20	−0.70	2
i-Pr	28	15	−1.08	6
i-Bu	26	17	−1.24	1

[a] Reference 35. [b] Rotational angle about the N(1)–C_α bond in structure VI. ϕ for R = H is zero. [c] Bonded $\nu_{N(1)H(1)}$ minus nonbonded $\nu_{N(1)H(1)}$. $\Delta\nu_{N(1)H(1)}$ for R = H is 43 cm^{-1}. [d] Number of hydrogens in the R group in structure VI relative to O(1) as atom number 1.

$$\phi = 20.4 - \underset{(0.011)}{5.59}E_s^c,\ R^2 = 87.2\%,\ s = 1.25 \quad (20)$$

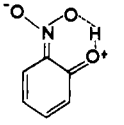
$$\phi = 19.9 - \underset{(<0.001)}{4.52}E_s^c + \underset{(<0.001)}{0.52}(\text{H-7no.}),$$

$$R^2 = 99.8\%,\ s = 0.17 \quad (21)$$

quantitative assessment of the effect of R on ϕ leads to a markedly improved correlation when H-7no. is included.

5. Application of a 7-Position Proximity Effect to Systems Other Than Carboxylic Acid Derivatives. The conformational influence of 7-position groups in the nonacyl portion of a carboxylic acid derivative and the resultant effect on the properties of these compounds has been adequately illustrated by the above discussion. However, such an effect, in terms of 7-position interaction between proximate groups, may also be of importance in considering certain properties or characteristics of other systems. Three selected examples are indicated below:

a. The strongest type of intramolecular hydrogen bond[37,38] is one usually associated with formation of a six-atom ring such as that shown in VII. This formation can in effect be viewed



VII

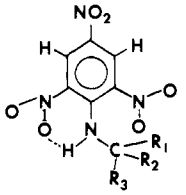
as a 7-position interaction between the unshared electron pairs of the atom serving as the basic site and the hydrogen of the subsequent hydrogen bond.

Table VII. Physical Properties for Eight N-Monosubstituted Acetamides, CH_3CONHR'[a]

R′	Bp (mm) or mp, °C
i-PrCHMe	99 (3.5)
$Et(Me)_2C$	95 (0.2)
$EtO(CH_2)_3$[b]	99 (0.8)
s-BuCHMe[c]	112 (0.9)
t-$Bu(CH_2)_2$[d]	86 (0.3)
s-$BuCH_2CHMe$[e]	119 (1.1)
i-$BuCH_2CHMe$	116 (1.5)
$(i\text{-Pr})_2CH$[f]	93–96

[a] Combustion analytical data for C, H, and N were within ±0.3% of theory except where noted as calculated/found. [b] H 10.41/10.85. [c] N 9.78/9.30. [d] H 11.96/11.52. [e] C 68.74/68.28. [f] C 68.74/68.30.

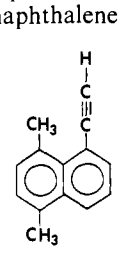
b. In N-monosubstituted-2,4,6-trinitroanilines, the 3 and 5 ring protons become nonequivalent at low temperatures.[39] It has been suggested[39] that this nonequivalence is due to different orientations of the 2- and 6-nitro groups as indicated by an increase in the difference between the chemical shifts of the ring protons as the size of the N-monosubstituent increases. In terms of structure VIII, these differences can be viewed as



VIII

a 7-position interaction between the oxygen of the 2-NO_2 and the R groups of the N-monosubstituent. That is, if $R_1 = R_2 =$ H, the chemical shift differences for the ring protons remain essentially constant regardless of the size or nature of R_3 (where R_3 = *n*-alkyl groups with 1–18 carbons, $CH_2C_6H_5$, or CH_2CH_2COOH). However, if the first atom of R_1 and/or $R_2 \neq$ H, the 7-position interaction increases and the chemical shift differences for the ring protons increases. That is, the effect of $R_1 = H, R_2 = R_3 = Me < R_1 = H, R_2 = R_3 = CH_2$ of cyclohexyl $< R_1 = H, R_2 = Me, R_3 = Et$ is approximately the same as $R_1 = R_2 = R_3 = Me$.

c. A recent report[40] concerning the magnetic deshielding effect by a triple bond on proximate protons provides another potential example of a 7-position interaction. For example, in 5-ethynyl-1,4-dimethylnaphthalene (IX), the 4-methyl group



IX

protons occur some 0.45-ppm downfield from those for the 1-methyl group. While the 1-methyl group protons are extremely remote from the triple bond, the 4-methyl group protons are in a 7 position relative to the center of the triple bond as position 1. We are currently conducting a study aimed at determining the distance-deshielding effect of a proximate proton–triple bond interaction. Preliminary results[41] on *o*- and *p*-alkyl substituted phenylacetylenes indicate that ortho group protons in a 7 position relative to the center of the triple bond are shifted downfield relative to either ortho group protons in a 6 position or para group protons.

Experimental Section

The N-monosubstituted acetamides which were not commercially available were prepared either by reaction of an amine with acetyl chloride or by reaction of an alcohol with acetonitrile–concentrated sulfuric acid. The properties of those amides prepared previously by other workers agreed with the values reported in the literature. The amides reported in Table VII have not been prepared previously.

The chemical shifts in hertz for the acyl methyl protons of the N-monosubstituted acetamides were measured on a Varian T-60 spectrometer vs. Me_4Si at 37 °C in a 10% CCl_4 solution. The values used to calculate the substituent chemical shifts (SCS) reported in Table I were the average of at least three determinations. The maximum deviation from the mean of replicate chemical shift values did not exceed 0.25% for any of the compounds studied.

The multiple and linear regression analyses were performed on an IBM 360-75 computer using the Ohio State University interactive regression program MULREG. Correlation coefficients, standard deviations, "Student's" *t* test values, *F* values, and parameter coefficients are all provided by the MULREG program.

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(15) For example, to say that the "Student's" *t* test shows that a parameter is significant at the 0.001 level means that the probability of finding a more significant value for this parameter is less than 0.001. In comparison, another parameter significant at a 0.005 level has a greater probability of having a more significant value, etc.
(16) Rejection of either E_s^c or the 6-number parameter from eq 5–8 leads to significantly poorer correlations. For example, the linear regression of SCS on E_s^c yields SCS = $-0.49 + 0.92E_s^c$, $R^2 = 42.0\%$, $s = 1.61$, and of SCS on C-6no. yields SCS = $-2.12 + 0.30$(C-6no.), $R^2 = 2.4\%$, $s = 2.09$.
(17) *F* value for eq 8 is 23.00 and for eq 10 is 51.84. In addition, neither C-6no. nor H-7no. cross correlate individually with E_s^c.
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The Site of Protonation in Aniline

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Abstract: We have applied experimental pulsed ion cyclotron resonance spectroscopy and ab initio molecular orbital theory to the problem of the identification of the preferred site of protonation in aniline. Our analysis concludes that, in the gas phase, (1) aniline is a nitrogen base and (2) that protonation on the aromatic ring is some 1–3 kcal/mol less favorable than protonation at nitrogen. The small magnitude of this difference indicates that both substituent and solvent effects should be capable of bringing about observable shifts in the order of nitrogen and carbon basicities of anilines.

The question of the preferred site of protonation of substituted aromatics in the gas phase has been the subject of numerous recent publications.[2] The techniques of high pressure mass spectrometry[3] and ion cyclotron resonance (ICR) spectroscopy[4] make possible the accurate determination of the relative stabilities of ions in the gas phase. However, such methods provide no direct information as to the geometrical structures of the species under scrutiny since the concentrations of ions present are too small to permit their absorption spectra to be obtained.[5,6] It has been necessary, therefore, to turn to a variety of indirect approaches in order to extract structural information from the gas-phase experiments. These have included the detailed comparison of experimental and theoretical relative ion stability data[2c,d] and the employment of isotopic labels as tracers to the course of reaction.[2a,b,d] Another approach, in which substituent effects are used to distinguish between ring and substituted protonation, is illustrated by the study presented herein.

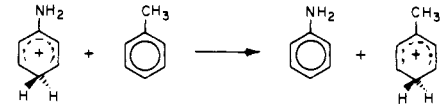
Theoretical and Experimental Methods, Results and Discussion

The enthalpy of nitrogen protonation in aniline may be estimated theoretically[7] by combining the calculated energy for the *isodesmic*[11] processes (eq 1) with the experimental proton

(1)

$\Delta E = -2.5$ kcal/mol

affinity of methylamine (211.2 kcal/mol[12]). The value which results, 208.7 kcal/mol, is in good agreement with the experimental proton affinity of aniline, 208.8 kcal/mol.[12,13] Consider, however, the possibility for aniline to protonate at a site other than on the nitrogen, in particular, on the aromatic ring para to the NH_2 substituent. An estimate for this quantity may be obtained by biasing ΔE for the *isodesmic* reaction 2 by the experimental proton affinity of toluene (188.7 kcal/mol).[12] The resultant affinity is 208.5 kcal/mol, which, well within the limits of confidence of the theory, is identical to both the cal-

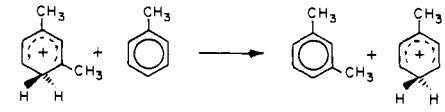


(2)

$\Delta E = 19.9$ kcal/mol

culated nitrogen affinity and to the experimentally determined quantity.[14] It is apparent, therefore, that the calculated ring and nitrogen proton affinities of aniline are too close to enable the theory to cleanly assign which, in fact, is the higher.

If the theoretical prediction regarding the closeness in stabilities of ring and substituent protonated aniline is correct, then it should be possible to shift the energetic balance to either side by the use of substituents. For example, we might expect that the ring methyl substituent present in *m*-toluidine would lead to only a very small increase in the affinity of aniline to protonate at nitrogen. Thus, the difference in the observed proton affinities of *N,N*-dimethyl, *m*-toluidine, and *N,N*-dimethylaniline[15] (both of which are, of course, nitrogen bases) is only 1 kcal/mol. On the other hand it is likely that the effect of the methyl group on the energy of protonation on the aromatic ring would be much more substantial. For example, we have found that the proton affinity of *m*-xylene is 6.1 kcal/mol greater than that for toluene, indicating a significant level of stabilization to the ion because of the second "ortho" Methyl group.[16] The observed difference in the proton affinities of



(3)

$\Delta H°(\text{ICR}) = 6.1$ kcal/mol[16]

m-toluidine (211.6 kcal/mol) and aniline is, however, only 2.8 kcal/mol, far smaller than that expected on the basis of comparison of the relative proton affinities of *m*-xylene and toluene,