Additive Linear Free-Energy Relationships in Reaction Kinetics of Amino Groups with α,β-Unsaturated Compounds[1,2]

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Reaction rates of nucleophilic additions of amino groups in amino acids and peptides to α,β-unsaturated compounds were studied as functions of structural variations in both reactants. The observed wide variations in rates are correlated by a linear free-energy equation, which includes parameters associated with polar and steric factors of both reactants. This equation has theoretical significance and should be of value for the calculation of predicted polar and steric factors and reaction rates of a large number of compounds. Linear relationships were observed between reaction rates for a number of vinyl compounds and several physicochemical parameters inherent in structural features associated with these compounds. These relationships indicate that resonance stabilization of ground and transition states appears to be the main factor that governs relative electrophilic reactivities of α,β-unsaturated compounds.

This investigation was designed to determine whether an equation can be developed that describes, in terms of additive free-energy parameters, rates of a series of similar nucleophilic addition reactions where structural changes are simultaneously imposed on both reactants. Hammett–Taft and related linear free-energy relationships are used to correlate differences in reaction rates of numerous series of compounds to steric, polar, and resonance parameters for variations in structural features associated with only one of the reactants.[4] Hansson[5] developed an equation which relates differences in kinetics of reaction of several epoxides with a number of amines in terms of parameters associated with both reactants. However, he observed that certain compounds behaved as exceptions to this relationship. Limitations of the Hansson equation probably resulted not from theoretical barriers but from evaluation of insufficient parameters required to account for all the structural variations encountered in his systems. For example, Hall[6] has observed different linear correlations between pK_a values of primary, secondary, and tertiary amines and σ^* values which he ascribes as being due to differences in steric parameters in these compounds.

Selection of the addition reaction of primary amino compounds to vinyl derivatives for this study was based on the previously successful kinetic analysis of the reaction of primary amino groups in amino acids and peptides with acrylonitrile where the elucidation of the influence of structural changes in the amino component on rates of reaction was the main objective.[7] Reaction rates were shown to vary with pH of the medium and pK_2 values of amino groups, thereby establishing that amino acid anions are the reactive species which participate with acrylonitrile in the rate-determining step. A Hammett–Taft-type free-energy relationship was used to correlate the separate contributions of polar and steric parameters associated with the amino compounds to reactivities. Activation parameters for amino groups in a number of substances were related to structural features inherent in these compounds. The same relationship was applied to the kinetics of reaction of amino groups with ninhydrin.[8] In a subsequent study it was demonstrated that reaction rates of thiol groups in thiols and aminothiols could be correlated with those of amino groups by means of an analogous free-energy equation which contains an additional nucleophilicity factor to account for the greater reactivities of mercaptide ions as compared to amino groups.[2]

In the present study an analysis was made of structural features associated with both reactants in Michael-type nucleophilic additions of primary amino groups in amino acids and peptides to a series of α,β-unsaturated compounds. Both the nature of the electron-withdrawing functional group conjugated with the alkene moiety and the steric environment near the reactive site were varied. Based on the present and previous results a general additive linear free-energy relationship has been developed in terms of parameters that govern reactivities of both amino and vinyl compounds in this reaction series.[9] An attempt is also made to correlate reaction rates for several vinyl compounds with physicochemical parameters inherent in structural features of these compounds to enhance the significance and utility of the results.

Results and Discussion

Reaction Rates of Amino Groups with Vinyl Compounds.—The rates of reaction were followed by means of a ninhydrin colorimetric procedure, previously described,[7] which measures the amount of primary amino compound in the reaction mixture and gives negligible color with alkylated amino compounds. The fraction of starting material left unreacted is given as A_t/A_0, where A_t is the absorbance at 570 mμ at time t and A_0 is the initial absorbance (see Experimental Section).

When a sufficient excess of vinyl over amino compound was employed, the graph of log A_t/A_0 *vs.* time gave straight lines establishing that the reaction followed pseudo-first-order kinetics. The half-lives ($t_{1/2}$) were read directly from the graph and the pseudo-first-order rate constants (k_1) and second-order rate

(1) Presented at the Division of Organic Chemistry, 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965, Abstract, p 74S.

(2) Paper III of a series on reactions of amino acids, peptides, and proteins with α,β-unsaturated compounds. For paper II, see M. Friedman, J. F. Cavins, and J. S. Wall, *J. Am. Chem. Soc.*, **87**, 3672 (1965).

(3) This is a laboratory of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(4) For a review, see P. R. Wells, *Chem. Rev.*, **63**, 171 (1963).

(5) J. Hansson, *Svensk Kem. Tidskr.*, **66**, 351 (1954); **67**, 246 (1955).

(6) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **79**, 5441 (1957).

(7) M. Friedman and J. S. Wall, *ibid.*, **86**, 3735 (1964).

(8) M. Friedman and C. W. Sigel, *Biochemistry*, **5**, 478 (1966).

(9) For a relevant theoretical discussion on extrathermodynamic relationships, see J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963, Chapter 6.

constants (k_2) were calculated by means of the formulas $k_1 = 0.693/t_{1/2}$ and $k_2 = k_1/\text{concentration of vinyl compound}$. Second-order anion rate constants (k_{A^-}) were calculated by means of eq 1 where $[H^+]$ is the

$$k_{A^-} = k_2(1 + [H^+]/K_2) \quad (1)$$

hydrogen ion concentration of the reaction medium and K_2 is the acid–base equilibrium constant for the amino group. It was previously shown that eq 1 governs cyanoethylation rates of amino groups and that anion second-order rate constants are pH independent. These conclusions were assumed to be valid for alkylations of amino groups with α,β-unsaturated compounds other than acrylonitrile. It should be noted that any convenient pH value may be chosen on the alkaline side at which k_{A^-} may be determined.

Effect of Ionic Strength on Rates.—The Debye–Hückel theory predicts that the ionic strength of a medium should exert major effects on rates and equilibria when more than one ionic species react or are produced in a reaction.[10] Although the rate-determining step for the reaction of amino groups with acrylonitrile involves only one charged species on each side of the equation, the ionization equilibrium occurring before the rate-determining step produces two charged species (see mechanism below). Ionic strength might therefore influence the extent of ionization. To investigate such secondary salt effects,[11] rates of reaction of the amino group in α-alanine with acrylonitrile were determined as a function of ionic strength. The results, summarized in Table I, show that the rates at several ionic strengths all fall within the experimental error for this reaction. Ionic strength was maintained constant at the high value of 1.2 for all further rate studies because the buffering capacity of the buffers was better at this ionic strength.

Similar observations were previously made when the reaction of thiol groups with acrylonitrile was studied as a function of ionic strength.[2]

TABLE I

RATES OF REACTION OF THE AMINO GROUP IN DL-α-ALANINE WITH ACRYLONITRILE AT 30° AND pH 8.75 AS A FUNCTION OF IONIC STRENGTH

Ionic strength	$k_{A^-} \times 10^3$, l./mole/sec
0.15	3.50
0.30	3.52
0.60	3.40
1.2	3.42
1.2	3.53[a]
Av and std dev	3.47 ± 0.05

[a] This value was determined at pH 8.4.[7]

Rates as a Function of Electron-Withdrawing Functional Groups.—Second-order anion rate constants calculated by means of eq 1 for the reaction of amino groups with a series of α,β-unsaturated compounds of structure $CH_2{=}CHX$, where X is an electron-withdrawing functional group, are shown in Table II.

(10) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2d ed., John Wiley and Sons, Inc., New York, N. Y., 1961, Chapter 2.

(11) K. B. Wiberg, "Physical Organic Chemistry," part 3, John Wiley and Sons, Inc., New York, N. Y., 1964.

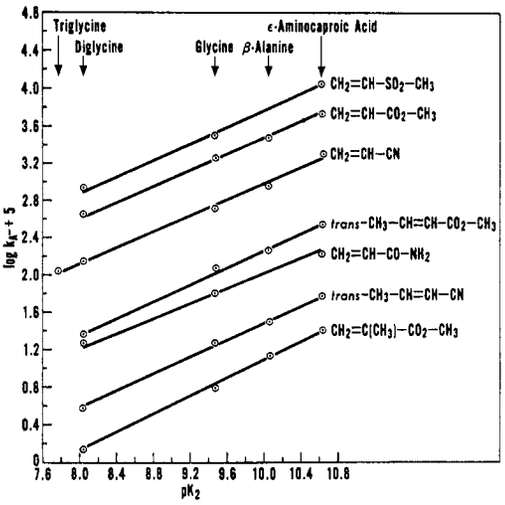


Figure 1. Plot of log k_{A^-} *vs.* pK_2 values for the reaction of amino acids and peptides of the following type with α,β-unsaturated compounds.

$$\begin{matrix} CH_2RCOOH \\ | \\ NH_2 \end{matrix}$$

In most of the reactions studied interfering side reactions would not be expected. However, because the carbonyl group in methyl vinyl ketone could, in principle, react with the amino group to form a Schiff base, a reaction was carried out with methyl ethyl ketone instead of the vinyl analog. Since no reaction occurred under the conditions of the kinetic study, it is concluded that this side reaction is negligible. Similarly, the amino groups could displace the chlorides in bis(β-chloroethyl) vinyl phosphonate. To determine whether this actually occurs with this vinyl compound, a kinetic experiment with glycine was carried out. Periodically aliquots were removed and tested with a few drops of 0.1 *N* $AgNO_3$ for chloride ion. Since no chloride ion was detected throughout the kinetic experiment, it is concluded that the possible side reaction does not take place under the conditions used.

Brønsted-type plots of log k_{A^-} *vs.* pK_2 values for the reaction of amino groups attached to primary carbon atoms with a number of vinyl compounds are shown in Figure 1. As shown previously,[7] plots for acrylonitrile follow a Hammett–Taft-type free-energy relationship

$$\log \frac{k_{A^-}(\text{any amino compound with } CH_2{=}CHCN)}{k_{A^-}(\text{glycine with } CH_2{=}CHCN)} = \rho\sigma^A + Esa \quad (2)$$

where ρ is the polar reaction parameter which measures sensitivities of rates to basicities of amino groups, σ^A is the polar substituent parameter equal to the difference between pK_2 values for any amino compound and for glycine, and *Esa* is the steric substituent constant associated with the amino component.

The steric substituent constants, *Esa*, calculated from eq 2, are free-energy parameters that give a direct measure of the steric factor associated with the amino component. This point is illustrated best by comparing the reactivities of glycine and α-alanine. When compared to glycine, the structure of α-alanine has one hydrogen on the carbon atom to which the amino group is attached replaced by a methyl group. This methyl group causes an increase in the pK_2 of

TABLE II

SECOND-ORDER ANION RATE CONSTANTS ($k_{A^-} \times 10^4$ IN L./MOLE/SEC) FOR THE REACTION OF AMINO GROUPS WITH α,β-CONJUGATED COMPOUNDS OF TYPE $CH_2{=}CHX$ AS A FUNCTION OF X AT pH 8.75 AND 30° (μ = 1.2)

	X						
Amino compd	$CONH_2$	$PO(OCH_2CH_2Cl)_2$		CO_2CH_3	CN	SO_2CH_3	$COCH_3$
Diglycine	2.00			46.0	13.7	90.0	
Glycine	6.30	20.9	42.0	182	50.0	306	4000
β-Alanine				284	89.2		
ϵ-Aminocaproic acid	16.9			528	203	1120	
L-α-Alanyl-L-α-alanine	0.730			24.7	7.85		
DL-Phenylalanine	2.22			64.0	17.6		
DL-Methionine				69.0	17.6		
DL-α-Alanine	3.50	10.7	25.0	111	35.3		2280
DL-Norleucine				130	34.9		
α-Aminoisobutyric acid				13.1	3.17		316

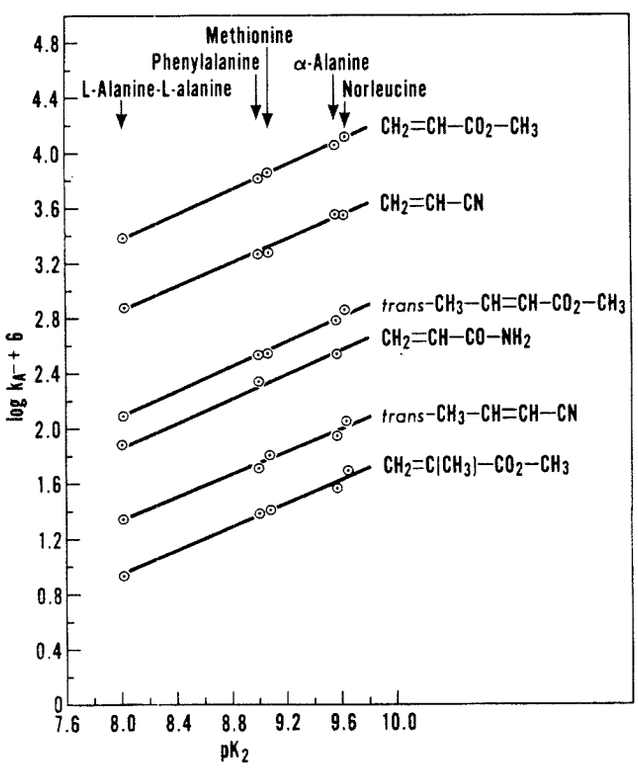


Figure 2. Plot of log k_{A^-} *vs.* pK_2 values for the reaction of amino acids and peptides of the following structure with α,β-unsaturated compounds.

$$\begin{array}{l} RCHRCOOH \\ | \\ NH_2 \end{array}$$

the amino group (polar factor) as well as a change in the steric environment near the amino group (steric factor). The effect of the polar factor resulting from the change in the pK_2 value on rates is quantitatively given by $\rho\sigma^A$ and that of the steric factor by *Esa*. Equation 2 permits calculating individual contributions of polar and steric factors associated with the amino compounds to relative reactivities.[7,8] This equation may be classified as an empirical linear free-energy relationship since a linear combination of polar and steric parameters may be used to calculate predicted rates.[9]

For the compounds having amino groups attached to primary carbon atoms, as in Figure 1, *Esa* is taken as zero. Since the slopes in Figure 1 are nearly parallel, sensitivities of rates to basicities of amino groups are the same for all the vinyl compounds shown. Differences in intercepts with the vertical axis indicate relative reactivities of the vinyl compounds shown with any of the amino acids. Quantitatively this difference may be expressed by the following equation

$$\log \frac{k_{A^-}\text{ (any amino compound with } CH_2{=}CHX)}{k_{A^-}\text{ (same amino compound with } CH_2{=}CHCN)} = Pv \quad (3)$$

where *Pv* may be defined as the polar reaction parameter associated with the vinyl compounds, which gives an indication of relative electron-withdrawing abilities of X and/or relative abilities of X to stabilize transition states, as compared to the cyano group.

The electron-withdrawing functional group activates the terminal carbon atom for nucleophilic addition *via* resonance, inductive, and field effects. The polar factor *Pv* measures relative abilities of functional groups to stabilize ground and transition states.

Brønsted-type plots for the reaction of amino groups attached to secondary carbon atoms with a number of vinyl derivatives are shown in Figure 2. The intercept of the curve with the vertical axis in Figure 2 for each vinyl compound is displaced from the corresponding intercept for the same vinyl compound in Figure 1 by a value equal to the average *Esa* value for amino groups attached to secondary carbon atoms. The average slope (ρ value) of the graphs in Figure 1 (0.438 ± 0.021) is similar to that in Figure 2 (0.429 ± 0.015). The average slope of the 13 graphs of both figures is 0.434 ± 0.018. The *Pv* values for vinyl compounds reacting with amino groups attached to secondary carbon atoms may be directly estimated as differences in intercepts with the vertical axis between the lines for any of the vinyl compounds shown and the corresponding intercept for acrylonitrile. *Pv* values obtained by this procedure from Figures 1 and 2 are of the same order of magnitude for each vinyl compound. *Pv* values for the reaction of any amino compound with any vinyl compound of type $CH_2{=}$CHX may be calculated by means of eq 3. Because *Pv* values for the reaction of sterically different amino compounds with the same vinyl compound are similar within experimental error, the steric arrangement near the amino group probably makes an independent contribution to the free energy of activation, which does not significantly influence that due to the nature of the vinyl compound.

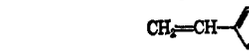
TABLE III

SECOND-ORDER ANION RATE CONSTANTS (k_A^- × 10^5 IN L./MOLE/SEC) FOR REACTION OF AMINO GROUPS WITH METHYL SUBSTITUTED α,β-UNSATURATED COMPOUNDS AT pH 8.75 AND 30° (μ = 1.2)

Amino compd	*trans*-$CH_3CH{=}CHCONH_2$	$CH_2{=}C(CH_3)CO_2CH_3$	*trans*-$CH_3CH{=}CHCN$	*cis*-$CH_3CH{=}CHCN$	*trans*-$CH_3CH{=}CHCO_2CH_3$
Diglycine	0.60	1.35	3.64		22.0
Glycine	3.00	5.80	20.0	24.3	120
β-Alanine		13.7	31.0		176
ϵ-Aminocaproic acid		26.0	59.4		332
L-α-Alanyl-L-α-alanine		0.84	2.23		10.8
DL-Phenylalanine		2.48	5.10		33.1
DL-Methionine		2.93	6.30		33.6
DL-α-Alanine	1.40	3.64	6.90	10.7	58.5
DL-Norleucine		5.04	11.3		73.5

TABLE IV

POLAR (*Pv*) AND STERIC (*Esv*) SUBSTITUENT CONSTANTS FOR α,β-UNSATURATED COMPOUNDS

α,β-Unsaturated compd	*Pv*	*Esv*	Rel anion rates with glycine
$CH_2{=}CHCN$	0.0	0.0	1.00
$CH_2{=}CHCONH_2$ (6)[a]	−0.975 ± 0.090[b,c]	0.0	0.126
$CH_2{=}CHPO(OCH_2CH_2Cl)_2$ (2)	−0.482 ± 0.030[c]	0.0	0.418
 (2)	−0.114 ± 0.035[c]	0.0	0.840
$CH_2{=}CHCO_2CH_3$ (10)	+0.534 ± 0.057[c]	0.0	3.64
$CH_2{=}CHSO_2CH_3$ (3)	+0.779 ± 0.031[c]	0.0	6.12
$CH_2{=}CHCOCH_3$ (3)	+1.90 ± 0.100[c]	0.0	80.0
$CH_2{=}C(CH_3)CO_2CH_3$ (9)	+0.566 ± 0.060[d]	−2.43 ± 0.07[e]	0.0116
trans-$CH_3CH{=}CHCN$ (9)	+0.003[d]	−1.51 ± 0.07[e]	0.0400
cis-$CH_3CH{=}CHCN$ (2)	0.000[d]	−1.41 ± 0.10[e]	0.0486
trans-$CH_3CH{=}CHCONH_2$ (3)	+0.887 ± 0.085[d]	−1.40 ± 0.07[e]	0.00600
trans-$CH_3CH{=}CHCO_2CH_3$ (9)	+0.576 ± 0.074[d]	−1.30 ± 0.08[e]	0.240

[a] Numbers in parentheses indicate the number of values (Tables II and III) used to calculate average *Pv* and *Esv* values and standard deviations. [b] Standard deviations were calculated by the formula: $s = n\Sigma x^2 - (\Sigma x)^2/n(n-1)$. [c] Calculated by means of eq 3. [d] Calculated by means of eq 5. [e] Calculated by means of eq 4.

Rates as a Function of Methyl Substitution in the Vinyl Compound.—Second-order anion rate constants for the reaction of amino groups with crotono and methacrylo derivatives are given in Table III.

A comparison of Tables II and III indicates that the introduction of methyl substituents near the reactive site of vinyl compounds reduces their reactivities. Presumably this reduction in reactivities is due mainly to the steric factors associated with the methyl groups. A steric substituent constant (*Esv*) for crotono and methacrylo derivatives is defined as follows (eq 4).

$$\log \frac{k_A^-\text{ (any amino compound with } CH_3{-}CH{=}CHX \text{ or } CH_2{=}C(CH_3)X)}{k_A^-\text{ (same amino compound with } CH_2{=}CHX)} = Esv \quad (4)$$

The *Esv* values may be directly estimated from Figures 1 and 2 as differences in intercepts between $CH_3CH{=}CHX$ or $CH_2{=}C(CH_3)X$ and $CH_2{=}CHX$.

Additive Linear Free-Energy Relationship.—Since the experimental data indicate that the polar and steric factors associated with the vinyl and amino components make independent contributions to observed reactivities, eq 2, 3, and 4 may be combined in a general empirical linear free-energy relationship, which encompasses reactivities of both amino and vinyl components.

$$\log \frac{k_A^-\text{ (any amino with any vinyl compound)}}{k_A^-\text{ (glycine with acrylonitrile)}} = \rho\sigma^A + Esa + Pv + Esv \quad (5)$$

Glycine was chosen as the standard for the amino component because it is the simplest amino acid and acrylonitrile was chosen as the standard for the vinyl component because the largest number of rate constants was available for the reaction of amino and thiol groups with this vinyl compound.

The polar and steric parameters associated with changes in structure of the vinyl compounds were calculated by means of eq 3–5 (Table IV).

Substitution into eq 5 of the appropriate parameters, listed in Table IV and in a previous communication,[7] enables the calculation of predicted rates for any new amino acid or peptide, whose pK_2 is known, with any of the vinyl derivatives shown in Tables II and III and for any new vinyl compound whose *Pv* and *Esv* values have been determined. No kinetic study is required to calculate predicted rates for any new amino compound. To calculate predicted rates for any new vinyl derivative, all that is necessary is a determination of its rate constant with glycine. Equation 5 is valid for all amino compounds listed in Tables II and III. For example, the equation simplifies for the reactions of glycine to eq 6 since σ^A and *Esa* values are zero for this amino acid.

$$\log \frac{k_A^-\text{ (glycine with any vinyl compound)}}{k_A^-\text{ (glycine with acrylonitrile)}} = Pv + Esv \quad (6)$$

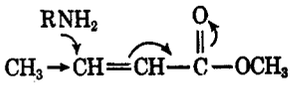
The *Pv* values for methyl methacrylate, *trans*- and *cis*-crotononitrile, *trans*-crotonamide, and *trans*-methyl crotonate were calculated from eq 5 with the data listed in Tables II–IV, the average slope ρ in Figures 1 and 2 of 0.434, pK_2, σ^A, and *Esa* values given for the amino compounds.[7]

The *Pv* values for the same electron-withdrawing functional group associated with different α,β-unsaturated compounds are similar in magnitude and within experimental error if standard deviations are taken into account. Standard deviations give an indication of the precision to be expected when eq 5 is used to calculate predicted rates. In defining *Pv*, CH_2=CHCN served as a reference to CH_2=CHX and, in defining *Esv*, CH_2=CHX served as a reference to CH_3—CH=CHX and CH_2=C(CH_3)X.

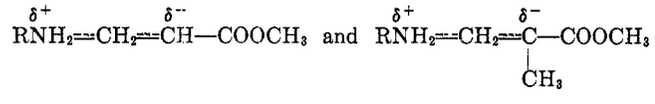
Two reasons might account why *Pv* values for the same electron-withdrawing functional group are not exactly identical: the nature of the definitions themselves and the difference in number of determinations made to obtain an average value. For example, *Pv* values for methyl substituted vinyl compounds were calculated by eq 5, whereas *Pv* values for unsubstituted vinyl compounds, by eq 3. Note that in eq 5 *Esv* values are used but not in eq 3.

The fourth column in Table IV gives a relative reactivity scale for the various α,β-unsaturated compounds used in the correlations. The range in reactivities between the slowest vinyl compound (*trans*-crotonamide) and the fastest (methyl vinyl ketone) is around 1.3×10^4.

The *Esv* values determined by eq 4 are probably not a true measure of the steric parameter of the vinyl component in the activation step. The lower rate of methyl crotonate as compared to methyl acrylate must be due to the additional steric requirement of the methyl group in methyl crotonate, as well as to the inductive electron-releasing effect which results in an altered electron density at the reactive site, as illustrated.



Similarly, the large rate decrease in going from methyl acrylate to methyl methacrylate is probably due to both the additional steric requirements of the α-methyl group and to differences in stabilities of the respective transition states. The transition state of methyl acrylate involves a secondary carbanion, whereas the carbanion for methyl methacrylate is tertiary.



Since tertiary carbanions are known to be less stable than secondary ones, the rate with methyl methacrylate would be expected to be slower than the corresponding rate with methyl acrylate on purely electronic grounds. Indeed, model studies show that the steric factor in methyl methacrylate is smaller than in methyl crotonate. The slower rate of the former must therefore come primarily from the electronic effect.

Model studies of transition states with *cis*- and *trans*-crotononitrile indicate that the amino group has to approach both from the top, and since the steric factors appear to be similar, rates for the two geometric isomers should be the same. However, *cis*-crotononitrile has a higher ground-state strain energy than the *trans* isomers,[12] and, because of greater relief of steric hindrance in the transition state for the *cis* isomer, it should react at a faster rate. Actually, data in Table III show that the *cis* isomer reacts only about 20% faster than the *trans*.

Reactivities of Conjugated Acids.—Reaction rates of several conjugated acids were studied to determine the influence of negative charges on carboxyl groups on reactivities. The extent of reaction of glycine with acrylic, maleic, and fumaric acids was negligible after about a week at pH 8.75, and the k_A- values for the reaction of triglycine or diglycine with acetylene dicarboxylic acid were quite low (10.7×10^{-7} and 9.3×10^{-7} l./mole/sec, respectively). Apparently, negative charges on carboxyl groups of conjugated acids electrostatically repel the incoming nucleophile, which is also a carboxylic acid anion, and reduce the conjugative interaction of the carbonyl group with the double bond. Elving and co-workers[13] observed that α-halo esters are polarographically reduced at a potential of *ca.* 0.15 v lower than that required for corresponding neutral acids, which are in turn reduced by a potential of *ca.* 1 v lower than that required for the corresponding acid anion. Their observation support the explanation given above for the slow reactivities of conjugated acids since the mechanisms of nucleophilic additions to conjugated systems and polarographic reduction of the same compounds are similar (see below).

Linear Correlations.—To increase our understanding of the factors that govern reactivities in the vinyl compounds and to enhance the usefulness of the kinetic results, a number of correlations were attempted between reaction rates of several vinyl compounds with the same amino acid and physicochemical parameters associated with electron-withdrawing substituents which are conjugated with the double bond or with the vinyl compounds themselves.

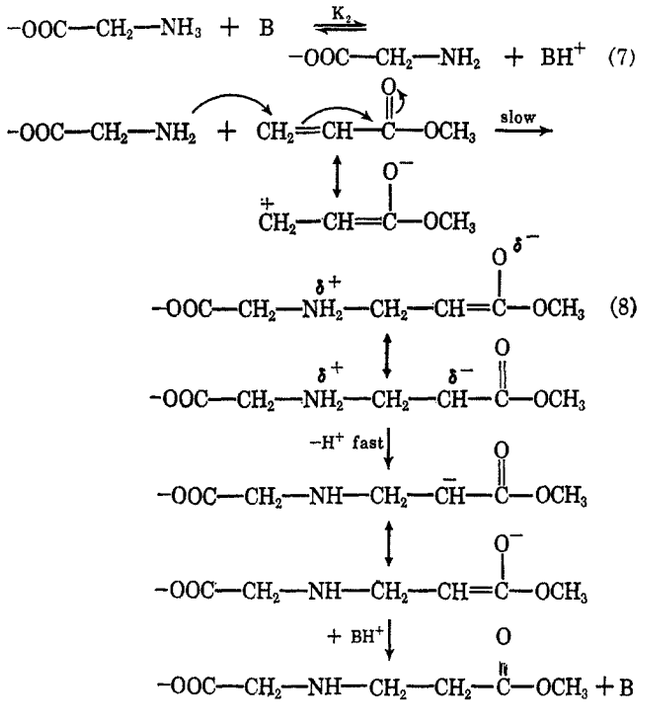
Nearly linear relationships between log k_A- and several physicochemical parameters measuring resonance effects were observed. In Figure 3 are plots of log k_A- for the reaction of three sterically different amino acids with a number of vinyl compounds of type CH_2=CHX against ultraviolet absorption maxima of XArOH and XAr,[14] polarographic half-wave potentials of CH_2=CHX,[15] $\sigma - \sigma^0$ values (defined as ArY resonance effects),[16] and σ_R values (defined as resonance effects of X for the ionization of XArCOOH).[17] Note that the scale on the abscissa for four of five of the parameters was adjusted to the one representing ultraviolet absorption maxima of phenols (light circles). Therefore, circles one and four represent all five parameters on the abscissa associated with acrylonitrile and methyl vinyl ketone. Since absorption maxima of aromatic compounds are governed by resonance stabilization of excited quinoid states[18] and

(12) J. N. Butler and R. D. McAlpine, *Can. J. Chem.*, **41**, 2487 (1963).
(13) (a) I. Rosenthal, C. S. Tang, and P. J. Elving, *J. Am. Chem. Soc.*, **74**, 6112 (1952); (b) P. J. Elving, I. Rosenthal, and A. J. Martin, *ibid.*, **77**, 5218 (1955).
(14) L. A. Cohen and W. M. Jones, *ibid.*, **85**, 3397, 3402 (1963).
(15) T. Fueno, K. Asada, K. Morokuma, and J. Furukawa, *J. Polymer Sci.*, **40**, 511 (1959).
(16) R. W. Taft, Jr., *J. Phys. Chem.*, **64**, 1805 (1960).
(17) R. W. Taft, Jr., N. C. Deno, and P. S. Skell, in "Annual Reviews of Physical Chemistry," H. Eyring, Ed., Annual Reviews, Palo Alto, Calif., 1958, p 287.
(18) G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1955, Chapter 6.

since both $\sigma - \sigma^0$ and σ_R values measure resonance effects in aromatic systems, the observed linear correlations indicate that resonance stabilization of transition states by electron-withdrawing functional groups appears to be the major factor which determines relative reactivities of the α,β-unsaturated compounds.

The spread in $\sigma - \sigma^0$ and σ_R values used in these correlations is quite narrow and may be within experimental error. Another parameter used to measure resonance effects in aromatic systems is $\sigma^- - \sigma^0$.[19] Only a qualitative correlation was noted between reaction rates and $\sigma^- - \sigma^0$ values for the ionization of $XArNH_3^+$ in water at 25°. These values for the electron-withdrawing functional groups of interest are CH_3CO, +0.58; CH_3SO_2, +0.49; CH_3CO_2, +0.41; and CN, +0.41. Note that the last two values are the same.

The preequilibrium (7) and a number of resonance forms involved in the slow and fast steps of the reaction (8) are illustrated below.



The observed correlation between rates and half-wave potentials for the three vinyl derivatives suggests that the orientation of conjugated molecules at the surface of the electrode during polarographic reductions may be washed out and that adsorption contributions to half-wave potentials for these compounds may be neglected. Half-wave potentials of conjugated compounds, therefore, measure the electron density at the reactive sites, and the mechanism of polarographic reductions involving 1,4 addition of electrons to conjugated compounds is similar to that for nucleophilic addition of amino groups.[20,21]

The linear correlations given in Figure 3 suggest that the *Pv* value represents a molecular property of general significance. If broader correlations of this nature could be established, then *Pv* values would be useful to predict resonance effects of electron-withdrawing functional groups in aromatic systems and other physical phenomena involving α,β-unsaturated compounds. Deviations from these correlations may result when inductive and other factors, such as electrostatic and field effects and hydrogen bonding, largely determine relative electrophilic reactivities of an α,β-unsaturated compound.

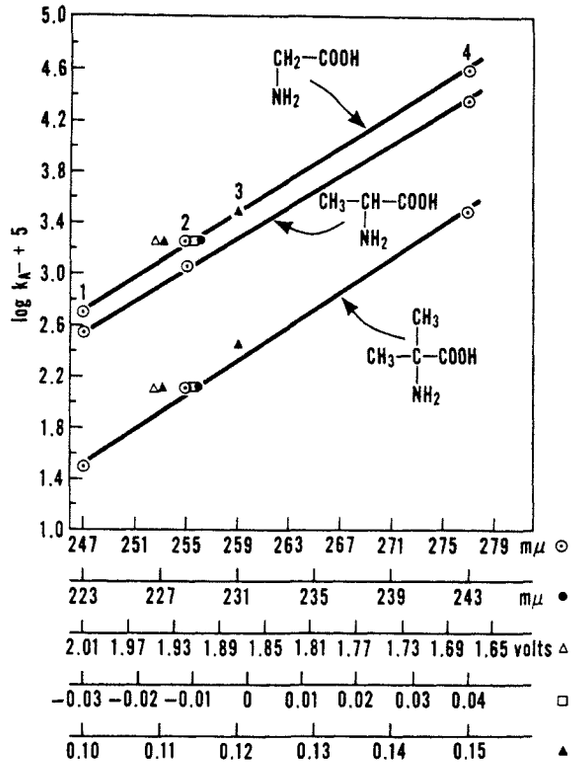


Figure 3. Plot of log k_A- for the reaction of amino groups with CH_2=CHX, where X for 1 is CN; for 2, CO_2CH_3; for 3, SO_2CH_3; and for 4, $COCH_3$, against ultraviolet maxima of XArOH (⊙) and XAr (●), $E_{1/2}$ (△), $\sigma - \sigma^0$ (□), and σ_R (▲) values. See text.

Conclusions

Reaction rates of amino groups of α,β-unsaturated compounds have been correlated by means of a four-parameter free-energy equation. This suggests that the over-all reactivity is due to a combination of polar and steric factors associated with each of the reactants.

Furthermore, these polar and steric parameters may be independently determined and appear not to be influenced by each other to any large degree. Equations which attempt to correlate multiple variation of substituents have been derived by Miller[22] and by Wells.[4] These contain cross-product terms or environmental factors. Such cross-product terms are negligible in the reaction of primary amino groups with vinyl compounds because the slopes of the graphs in Figures 1 and 2 are similar. Individual free-energy parameters associated with polar and steric factors of both reactants appear to be sufficient to describe rates of Michael-type nucleophilic additions. Whether or not the equations derived for this system are generally applicable to other nucleophilic addition and displacement reactions requires further study. In this

(19) (a) H. H. Jaffe, *Chem. Rev.*, **53**, 191 (1953); (b) J. Hine, "Physical Organic Chemistry," 2d ed, McGraw Hill Book Co., Inc., New York, N. Y., 1962, Chapter 3.

(20) P. J. Elving and B. Pullman, "Mechanisms of Organic Electrode Reactions," in "Advances in Chemical Physics," I. Prigogine, Ed., Vol. III, Interscience Publishers, Inc., New York, N. Y., 1961, pp 1–31.

(21) We thank Professor P. J. Elving for stimulating discussions on this point.

(22) S. Miller, *J. Am. Chem. Soc.*, **81**, 101 (1959).

connection, data reported in the previous paper of this series[2] indicate that the equations derived in this report may be applied to analogous reactions of thiols with α,β-unsaturated systems by inclusion of a nucleophilicity factor N, which corrects for the greater reactivity of mercaptide ions as compared to amino groups.

A future publication will be concerned with relative inductive effects of electron-withdrawing functional groups.

Experimental Section

Source of Materials.—The amino acids and peptides were the best commercial grades available. Acrylamide, acrylonitrile, and methyl vinyl ketone were obtained from Matheson[23]; methyl acrylate and methyl methacrylate from Rohm and Haas; bis-(β-chloroethyl) vinyl phosphonate from Stauffer; 4-vinylpyridine from Riley; crotononitrile from Aldrich; *trans*-crotononitrile, *trans*-methyl crotonate, and methyl vinyl sulfone from K and K Laboratories. The compounds were usually distilled before use although similar rate constants were generally obtained even when distillation was not done.

Separation of Crotononitrile into *cis* and *trans* Isomers.—Crotononitrile was separated into *cis* and *trans* isomers *via* gas chromatography on a preparative scale by means of an Autoprep A-7000 on a 10-ft, 0.25-in. column packed with 10% dinonyl phthalate on Celite. Crotononitrile separates into two major peaks.[24] After 100-μl portions were injected, the two peaks were monitored on a recorder and collected separately with cooling.

Preparation of *trans*-Crotononamide.—To 2 g (30 mmoles) of redistilled *trans*-crotononitrile was added 1.6 ml of concentrated H_2SO_4 dropwise with stirring and cooling. After stirring the reaction mixture for 2 days, it solidified to a transparent mass. The product was taken up in 25 ml of water and neutralized with 4 *N* NaOH. The aqueous solution was extracted with four 75-ml portions of ether. Most of the ether was evaporated off on an aspirator, and fluffy white needles crystallized from the remainder: yield 1 g (15 mmoles, 50%); mp 159°, lit.[25] mp 159–160°.

Kinetic Measurements.—A tightly stoppered flask of amino compound in a pH 8.75 borate buffer containing the vinyl compound was placed in a 30° constant-temperature bath together with blank solutions as previously described.[7] When feasible, the vinyl derivative was used in excess to obtain pseudo-first-order kinetics. The concentration of the amino component was 0.01 *M* and that of the vinyl compound ranged from 0.08 to 0.17 in most runs depending on its solubility. Several rate determinations were carried out with more dilute concentrations of both reactants for the fastest reacting vinyl compounds, methyl vinyl ketone and methyl vinyl sulfone, to obtain a convenient reaction time. Rates were carried out for at least four half-lives with all vinyl compounds except methyl crotonate and methyl methacrylate. With the former, rates were run to about 50% reaction and with the latter, to about 20%, to minimize the possibility of hydrolysis of these esters under the reaction conditions. The pseudo-first-order linear plots for these vinyl compounds were extrapolated to complete reaction. The pH of the medium was measured before and after reaction. Where any noticeable change was observed, an intermediate pH value was used to calculate the anion rate constants. The accuracy of the rate determinations is estimated to be ±5%; that of the pH of the medium during reaction, ±0.05 pH units; and that of the pK_2 values of amino groups, ±0.03 pK_2 units. The progress of reaction was followed as previously described.[7]

Acknowledgment.—We wish to acknowledge the assistance of Miss Judith A. Romersberger and Mr. Gary V. Kaiser with the rate determinations.

(23) The mention of firm names or trade products does not imply that they are recommended by the Department of Agriculture over other firms or similar products not mentioned.

(24) (a) G. S. Reddy, J. H. Goldstein, and L. Mandell, *J. Am. Chem. Soc.*, **83**, 1300 (1961); (b) D. E. McGreer, *J. Org. Chem.*, **25**, 852 (1960).

(25) P. Bruylants and A. Castille, *Bull. Classe Sci., Acad. Roy Belg.*, (5) **13**, 767 (1927); *Chem. Zentr.*, 1644 (1928).

The Preparation and Unusual Reactions of Dimethyldodecylphosphinimine

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N-Trimethylsilyldimethyldodecylphosphinimine (III) was prepared and treated with acidic methanol at −35° in an attempt to obtain dimethyldodecylphosphinimine (IV). Although IV was most likely formed, it reacted further to give bis(dimethyldodecylphosphoranylidene)ammonium methoxide (V) and/or dimethyldodecylphosphine oxide depending on the concentration of the reactants in the medium. It was demonstrated that V is also unstable to methanol and that there are two competing pathways by which the phosphine oxide can ultimately be formed from the methanolysis of IV (and hence III). Dimethyldodecylphosphinimine (IV) can be prepared in good yield from the reaction of aminodimethyldodecylphosphonium chloride and *n*-butyllithium. A lithium chloride complex of IV is initially formed which can be destroyed by distillation to give free IV and then reformed by addition of lithium chloride.

Since the work of Staudinger in 1921,[1] very few reports have appeared in the literature concerning the chemistry of phosphinimines in which all of the substituents on phosphorus are aliphatic. Recently, however, the preparation of N-trimethylsilyltrialkylphosphinimines and their subsequent acid-catalyzed methanolysis to the corresponding unsubstituted trialkylphosphinimines was reported by Birkofer.[2] Using this method he prepared the triethyl, tripropyl, and tributyl compounds (IIa–c, respectively) in yields of 85–90%, and these are the only reported examples of unsubstituted trialkylphosphinimines. As part of an investigation of the chemistry of alkyldimethylphosphinimines, we attempted to apply Birkofer's procedure to N-trimethylsilyldimethyldodecylphosphinimine (III)

$$R_3P{=}NSiMe_3 \xrightarrow[-20^\circ]{MeOH\text{–}H_2SO_4} R_3P{=}NH + MeOSiMe_3$$

Ia, R = Et; b, R = *n*-Pr; c, R = *n*-Bu — IIa, R = Et; b, R = *n*-Pr; c, R = *n*-Bu

$$C_{12}H_{25}P(Me_2){=}NSiMe_3 \qquad C_{12}H_{25}P(Me_2){=}NH$$

III IV

in order to prepare dimethyldodecylphosphinimine (IV). Although the desired product apparently was formed, it could not be isolated, and this paper deals with the interesting subsequent reactions that prevented

(1) H. Staudinger and E. Hauser, *Helv. Chem. Acta*, **4**, 861 (1921); *Chem. Abstr.*, **16**, 1074 (1922).

(2) (a) L. Birkofer and S. M. Kim, *Ber.*, **97**, 2100 (1964); (b) this type of reaction has also been used to prepare triphenylphosphinimine, $(C_6H_5)_3P{=}NH$ [L. Birkofer, A. Ritter, and S. M. Kim, *ibid.*, **96**, 3099 (1963)].