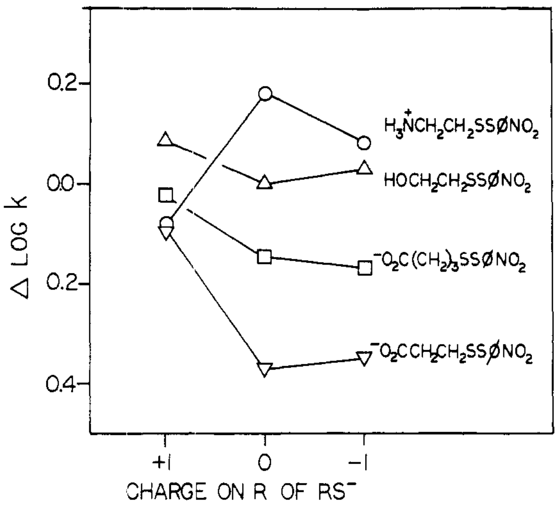
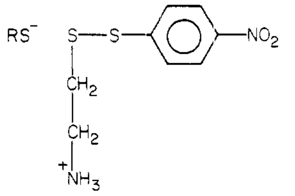
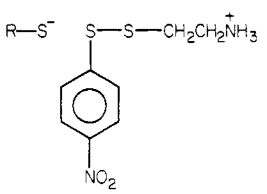


Figure 4. Plot of the calculated log *k* value minus the measured log *k* value vs. the charge on the R group of the attacking RS⁻.

sulfur atoms may be attacked by the nucleophilic thiol anion as shown in structures A and B. By use of the value of β_{CT} and that for the leaving group ($\beta_{LG} = -\beta_{nuc} = -0.5$) and by use of the fact that aryl thiol anions leave sixfold faster than alkyl thiol anions,[2] a calculation of the relative rates of attack at the two sites may be made. The ratio of rates of the desired reaction (A) to the undesired reaction (B) is calculated to be about 15 in the worst case. This small percentage of attack on the wrong sulfur has no effect on the rate if the entering and leaving thiol are identical or similar in pK_a. In the few cases where the small amount of new mixed disulfide would have differed substantially in rate from the starting mixed disulfide, semilog plots of the absorbance data were made. The linear plots found ensured that there was very little, if any, error in the measured rate due to initial attack at the wrong sulfur.


A


B

The points for the variously charged disulfides and thiols exhibit small but significant deviations from the Brønsted type plots found for the uncharged systems. The deviations are plotted in Figure 4 and show a pattern that indicates that pK_a values alone provide a good but not perfect index of how the charge will affect the stability of a transition state. The negative charges on R groups destabilize the calibrating ionization reaction of the thiols and the positive charges stabilize the same reaction. The fact that there are negative deviations for negative groups and positive deviations for positively charged groups implies that charge has a proportionally greater effect on transition-state energy than inductive effects when compared to the calibrating ionization reaction.

One interesting feature of Figure 4 is that the deviation from uncharged values is greatest when the charge is on the central group rather than on the attacking group and that increasing the distance from the reacting site diminishes the effect of the charge. Coulombic interactions are apparently also evident between attacking and central thiol R groups in the relatively low rates found when both are positively charged.

We conclude that predictions of rate constants for the thiol–disulfide interchange reaction in aqueous solution may be in error by as much as a factor of 2.5 when structure–reactivity correlations measured with uncharged substituents are used to predict the rates of those with charged substituents. The effect of these deviations can have a profound effect on the *β* value measured for a reaction. If a series of reactants is used in which the highest pK_a reactants are negatively charged and the lowest positively charged, there will be a tendency to tilt the slope of the plot. A total set of deviations of 0.6 log *k* unit over a range of 3 pK_a units would give a *β* value in error by 0.2 and thus give a much different estimate of the degree of bond formation than would be obtained with neutral substituent groups.

Acknowledgment. This work was supported by the National Science Foundation, Grant CHE-78-08723.

Registry No. $O_2NC_6H_4SH$, 1849-36-1; $(^-O_2CCH_2CH_2S)_2$, 58823-20-4; $(^+H_3NCH_2CH_2S)_2$, 58823-21-5; $(HOCH_2CH_2S)_2$, 111-48-8; $(^-O_2C(CH_2)_3S)_2$, 73873-03-7; $^+H_3NCH_2CH_2SSC_6H_4NO_2$, 73873-04-8; $HOCH_2CH_2SSC_6H_4NO_2$, 53595-97-4; $^-O_2CCH_2CH_2SSC_6H_4NO_2$, 73891-30-2; $^-O_2C(CH_2)_3SSC_6H_4NO_2$, 73891-31-3; $^+H_3NCH_2CH_2SH$, 40302-08-7; $HOCH_2CH_2SH$, 60-24-2; $^-O_2CCH_2CH_2SH$, 2365-49-3.

Structure–Reactivity Relationships in Nucleophilic Reactions on Cinnamoyl Azide and Phenyl Cinnamates. Kinetic Stability of the Acyl Azide and Relative Leaving Ability of Nitrogen and Oxygen

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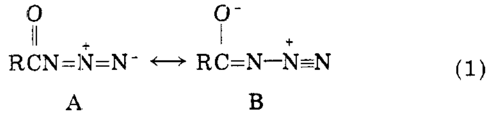
The alkaline hydrolysis and aminolysis of cinnamoyl azide and aryl-substituted phenyl cinnamates and the azidolysis of the phenyl cinnamates have been studied. The positions of the rate-determining steps in the reactions are identified by the structure–reactivity relationships. The enhanced affinity of azide ion for an acyl carbon compared with its basicity is proposed to account for the observed kinetic stability of cinnamoyl azide toward alkaline hydrolysis and aminolysis. Azide ion resists expulsion from the tetrahedral intermediate more than quinuclidine derivatives but less than phenolates. This is explained in terms of the electron withdrawal as well as electron donation by resonance.

Nucleophilic reactions on acyl derivatives, especially esters and amides, have been the subject of extensive studies. The existence of a tetrahedral intermediate with a finite lifetime, the nature of the rate-determining steps, the relative leaving ability of the leaving groups, and the changes in the effective charge on the nucleophilic elements are included among the actively investigated topics in the mechanistic studies of acyl transfer from esters or amides.[2-8]

A large number of studies on the aminolysis of esters have been performed.[2] In particular, ester aminolysis with tertiary amines[3,4] including imidazoles or pyridines[4-6] has been studied, so that possible ambiguities from proton transfer were avoided and the basicity of the leaving alkoxides was not much different from that of the attacking amines. From these studies, a comparison has been made of the leaving abilities of nitrogen and oxygen.[4] In reactions with esters, the nitrogen of the tertiary amine acquires a positive charge in the tetrahedral intermediate and destabilizes the resulting amide. Furthermore, the amines used are quite bulky, and the consequent steric effects must be considered.

The leaving nitrogen of an acyl azide contains no formal charge or bulky groups and, thus, is free from the electronic and steric complications. In addition, its basicity ($pK_{HN_3} = 4.73$) is not much different from that of the leaving groups of activated esters. Resonance stabilization and the consequent double bond character of the C–N bonds of acyl azides (eq 1) are expected to be significant. This



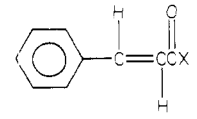
$$\underset{A}{R\overset{\overset{O}{\|}}{C}N{=}\overset{+}{N}{=}N^-} \longleftrightarrow \underset{B}{R\overset{\overset{O^-}{|}}{C}{=}N{-}\overset{+}{N}{\equiv}N} \qquad (1)$$

is because charge creation does not take place, and the negative charge moves to the more electronegative element, O, on going from A to B.[9] Thus, acyl azides can be useful as mechanistic probes of acyl-transfer reactions.

Kinetic studies on acyl transfer from acyl azides have rarely been reported because acyl azides usually undergo Curtius rearrangement (eq 2).[10] However, we have found

$$RC(O)N{=}N^+{=}N^- \xrightarrow{-N_2} RN{=}C{=}O \xrightarrow{H_2O} RNHCOOH \xrightarrow{-CO_2} RNH_2 \qquad (2)$$

that the derivatives of cinnamoyl azide (1) are quite stable toward Curtius rearrangement. Thus, we have performed kinetic studies on nucleophilic attack on 1. The kinetic studies have been directed toward elucidation of the kinetic stability of 1 compared with aryl-substituted phenyl cinnamates **2a–d** and the leaving ability from the tetrahedral intermediate of the azide ion relative to phenolates or aliphatic tertiary amines.



1, X = N_3
2a, X = $3,4\text{-}(NO_2)_2PhO$
b, X = $4\text{-}NO_2PhO$
c, X = $3\text{-}NO_2PhO$
d, X = ClPhO

Table I. Rate Data for the Alkaline Hydrolysis of Cinnamoyl Azide and Phenyl Cinnamates[a]

compd	pK_a of conjugate acid of leaving group[b]	k_{OH^-}, M^{-1} s^{-1}
1	4.73	0.992 ± 0.009
2a	5.45	2.56 ± 0.12
2b	7.15	0.421 ± 0.011
2c	8.40	0.262 ± 0.006

[a] Measured in 1:1 (v/v) acetone-water at 25 °C and an ionic strength of 1.0. [b] The pK_a values were taken from the literature.[16]

Experimental Section

Materials. Cinnamoyl azide (1) was prepared according to the literature;[11] mp 85–86 °C (lit.[11] mp 86 °C). Phenyl cinnamates were prepared by heating cinnamoyl chloride with the corresponding phenol[12] or by coupling cinnamic acid and the corresponding phenol with dicyclohexylcarbodiimide in acetone. Esters obtained were as follows: 3,4-dinitrophenyl cinnamate (**2a**); *p*-nitrophenyl cinnamate (**2b**), mp 146–147 °C (lit.[13] mp 146.5–147.5 °C); *m*-nitrophenyl cinnamate (**2c**), mp 113–114 °C (lit.[13] mp 114–115 °C); *p*-chlorophenyl cinnamate (**2d**), mp 104–105 °C (lit.[14] mp 105 °C). When analyzed by TLC and visible spectroscopy, **2a** was found to be contaminated by several molar percent of 3,4-dinitrophenol. The contaminant was not removed by repeated recrystallization from dry ether, probably due to the low stability of **2a**. However, kinetic measurements in the presence of various amounts of initially added 3,4-dinitrophenol indicated that the phenol did not exert detectable effects on the kinetic results.

Sodium azide was used after recrystallization from water–ethanol. The normality of sodium hydroxide was checked by titration against potassium biphthalate. Water was redistilled and deionized and acetone purified according to the literature[15] before being used in the kinetic studies. Quinuclidine (**3a**), 3-quinuclidinol (**3b**), 3-chloroquinuclidine hydrochloride (**3c**·HCl), and 3-quinuclidinone hydrochloride (**3d**·HCl) were purchased from Aldrich and used after recrystallization. The hydrochloride salts of **3c** and **3d** were converted to the corresponding neutral species by adding 0.9 equiv of sodium hydroxide when the respective reaction mixtures were prepared.

Miscellaneous. Kinetic measurements were carried out with a thermojacketed Beckman Model 25 spectrophotometer. The temperature was controlled to within ± 0.1 °C with a Haake E 52 circulator. pH measurements were performed with a Chemtrix Type 60 A pH meter. Ionic strength was maintained with sodium chloride. In the kinetic studies, evaporation of acetone from 1:1 (v/v) acetone–water mixtures was prevented by sealing the cuvettes tightly with serum caps while the reaction solutions were thermally equilibrated and the reaction rates were measured.

The pseudo-first-order rate constants were calculated from the plots of ln ($OD_i - OD_\infty$) against time. In these cases, first-order kinetics were manifested at least up to 80% completion of the reactions. However, in the azidolysis of slowly reacting esters, the rate data were obtained by the Guggenheim method or by initial-rate measurements as indicated in Table III.

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(1) An undergraduate research participant.

(2) J. F. Kirsch and A. J. Kline, *J. Am. Chem. Soc.*, **91**, 1841 (1969), and references therein.

(3) M. J. Gresser and W. P. Jencks, *J. Am. Chem. Soc.*, **99**, 6963 (1977).

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(7) N. Gravitz and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 489, 499, 507 (1974).

(8) P. Y. Bruice and T. C. Bruice, *J. Am. Chem. Soc.*, **96**, 5533 (1974).

(9) Recent ab initio MO calculations on formyl azide, formyl amide, and vinyl formate (private communication, D. J. Pasto) revealed that the C–N bonds in the azide and the amide contain 30 and 29% double bond character, respectively. The corresponding C–N bond lengths were 1.382 and 1.400 Å. On the other hand, the double bond character in the etheral C–O bond of the ester was 16%. One can expect that the double bond character in the etheral C–O bond is smaller than that in the phenyl esters because of the electron-withdrawing nature of the phenyl groups [J. F. Kirsch, W. Clewell, and A. Simon, *J. Org. Chem.*, **33**, 127 (1968)].

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(16) W. P. Jencks and J. Regenstein in "Handbook of Biochemistry", 2nd ed., CRC Press, Cleveland, OH, 1970, p J-187.

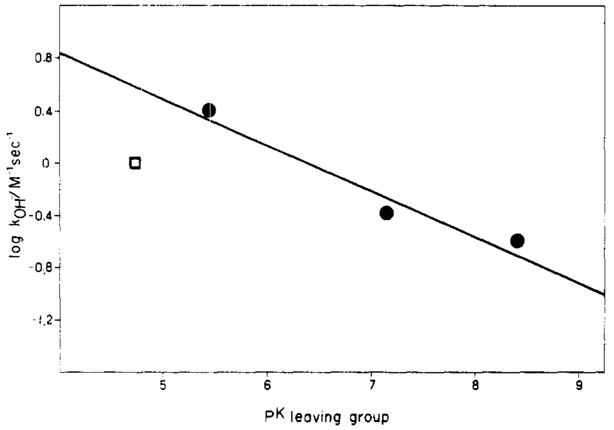


Figure 1. Plot of log K_{OH^-} against the pK_a of the conjugate acid of the leaving group for the alkaline hydrolysis of 1 and 2a–c. The straight line is drawn for the data points of 2a–c (●). For the pK_a values, see Table I.

Table II. Rate Data for the Aminolysis of Cinnamoyl Azide and Phenyl Cinnamates[a]

compd	amine[b]	k_{am}, M^{-1} s^{-1}
1	3a	3.94 ± 0.09
1	3b	0.310 ± 0.010
1	3c	(6.50 ± 0.20) × 10^{-3}
2a	3a	316 ± 10
2a	3b	49.0 ± 1.4
2a	3c	2.51 ± 0.04
2a	3d	0.224 ± 0.001
2b	3a	(3.53 ± 0.19) × 10^{-1}
2b	3b	(4.69 ± 0.30) × 10^{-2}
2b	3c	(3.21 ± 0.19) × 10^{-3}
2c	3a	(2.45 ± 0.14) × 10^{-2}
2c	3b	(3.96 ± 0.08) × 10^{-3}
2c	3c	(1.81 ± 0.18) × 10^{-4}

[a] Measured in 1:1 (v/v) acetone-water at 25 °C and an ionic strength 1.0. [b] The reported values of the pK_a of the conjugate acids of the amines are 11.45 for 3a, 10.02 for 3b, 9.03 for 3c, and 7.53 for 3d.[3]

Results

Alkaline Hydrolysis of Cinnamoyl Azide and Phenyl Cinnamates. Although acyl azides undergo Curtius rearrangement (eq 2), hydrolysis was the only reaction observed with 1 in alkaline media ([OH$^-$] > 1 mM) as evidenced by the product spectra. The alkaline hydrolysis of 1 and 2a–c was carried out in 1:1 (v/v) acetone–water mixtures at 25 °C and at an ionic strength of 1.0. The hydrolysis of 2d was not studied because the spectral measurement of the release of *p*-chlorophenolate was not possible due to the large absorbance of acetone. The rates of the alkaline hydrolysis were proportional to the concentration of hydroxide ion, indicating that the rates of the water path were negligible. Second-order rate constants (k_{OH^-}) are summarized in Table I. In Figure 1, a plot of log k_{OH^-} against the pK_a of the conjugate acid of the leaving group for 1 and 2a–c is illustrated.

Aminolysis of Cinnamoyl Azide and Phenyl Cinnamates. The aminolysis of 1 and 2a–c by quinuclidine derivatives (3a–d) was studied in 1:1 (v/v) acetone–water at 25 °C at an ionic strength of 1.0. The aminolysis of 1 was not accompanied by rearrangement. The aminolysis rates were proportional to the amine concentration, and second-order rate constants, k_{am}, are summarized in Table II. Plots of log k_{am} against the pK_a of the conjugate acid of the amine for 1 and 2a–c are illustrated in Figure 2. The pK_a values employed in the plots are those measured in water at 25 °C at an ionic strength of 1.0.[3] Although the pK_a values of the conjugate acids of the amines are expected to be different in the solutions of the present study, the good linear correlation seen in Figure 2 indicates that the affinity of the amines for protons in water is a good measure of the nucleophilicity of the amines toward acyl carbons in 1:1 (v/v) acetone–water. Plots of log k_{am} against the pK_a of the conjugate acid of the leaving group for each of the amines are illustrated in Figure 3.

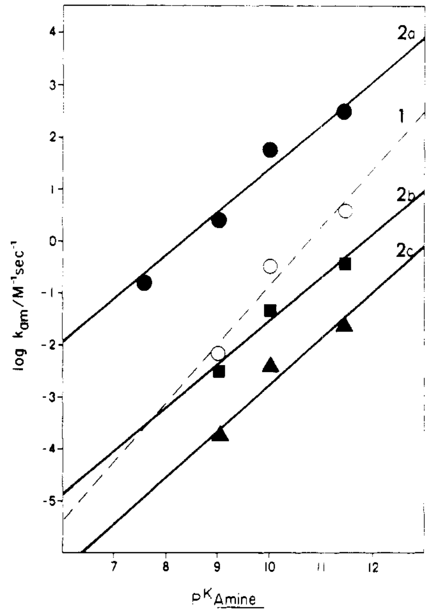


Figure 2. Plot of log k_{am} against the pK_a of the conjugate acid of the quinuclidine derivative for the aminolysis of 1 (○), 2a (●), 2b (■), and 2c (▲). For the pK_a values of the amines, see footnote *b* of Table II.

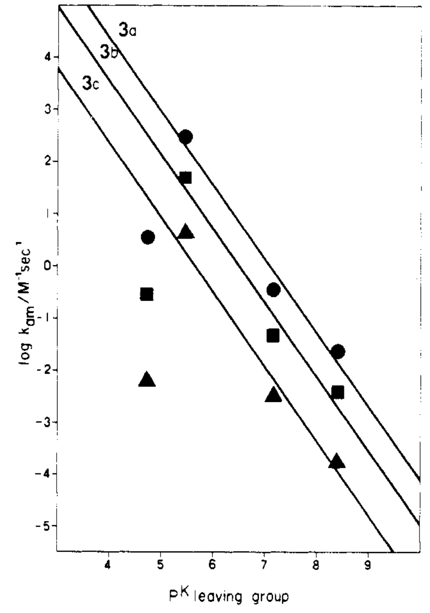


Figure 3. Plot of log k_{am} against the pK_a of the conjugate acid of the leaving group for the aminolysis of 1 and 2a–c by 3a (●), 3b (■), and 3c (▲). For the pK_a values, see Table I.

Azidolysis of Phenyl Cinnamates. The azidolysis of 2a–d was studied in 1:1 (v/v) acetone–water mixtures at 25 °C at an ionic strength of 1.0. The nucleophilic nature of the reaction was established by the spectral observation of the formation of 1. Under the conditions of the azidolysis, 1 was stable enough to permit correct spectrophotometric rate measurements of the azidolysis. The rates of the azidolysis were proportional to the concentration of azide ion. Second-order rate constants, $k_{N_3^-}$, are summarized in Table III. A plot of log $k_{N_3^-}$ against the pK_a

Table III. Rate Data for the Azidolysis of Phenyl Cinnamates[a]

compd[b]	$k_{N_3^-}$, M^{-1} s^{-1}
2a	$(7.50 \pm 0.10) \times 10^{-2}$
2b	$(1.17 \pm 0.01) \times 10^{-3}$
2c	$(1.86 \pm 0.11) \times 10^{-4}$ [c]
2d	$(9.71 \pm 0.16) \times 10^{-6}$ [d]

[a] Measured in 1:1 (v/v) acetone-water at 25 °C and an ionic strength of 1.0 in the presence of 0.3-0.9 M sodium azide. Under these conditions, 1 was stable over the period of time needed for the kinetic measurements. [b] For the pK_a values of the conjugate acids of the leaving groups, see Table I. The pK_a value for 2d is 9.40.[16] [c] Pseudo-first-order rate constants were calculated by the Guggenheim method. [d] Initial rates of the formation of 1 were measured because the reactions were very slow.

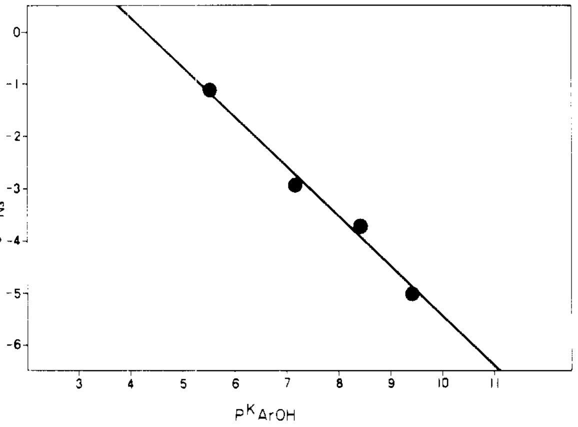


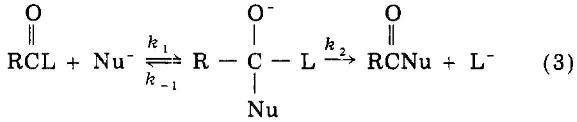
Figure 4. Plot of log $k_{N_3^-}$ against the pK_a of the leaving phenol for the azidolysis of **2a–d**. For the pK_a values, see footnote *b* of Table III.

of the phenol is illustrated in Figure 4.

In Table IV, the slopes of the straight lines drawn in Figures 1–4 are summarized.

Discussion

Rate-Determining Steps. When nucleophilic substitution on the cinnamoyl derivatives proceeds through the formation of the tetrahedral intermediate (eq 3), the



$$\overset{\displaystyle O}{\overset{\|}{\mathrm{RCL}}} + \mathrm{Nu}^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{R}-\underset{\underset{\displaystyle \mathrm{Nu}}{|}}{\overset{\overset{\displaystyle O^-}{|}}{\mathrm{C}}}-\mathrm{L} \xrightarrow{k_2} \overset{\displaystyle O}{\overset{\|}{\mathrm{RCNu}}} + \mathrm{L}^- \qquad (3)$$

overall rate constant is expressed as $k_1k_2/(k_{-1} + k_2)$. Thus, the relative magnitude of k_{-1} (expulsion of the attacking nucleophile) and k_2 (expulsion of the leaving group) determines the position of the rate-determining step. The possibility that the reaction proceeds without any discrete addition intermediate, however, is not excluded.

A slope (β_{lg}) of −0.35 was obtained for the plot of log k_{OH^-} against the pK_a of the phenol for the alkaline hydrolysis of **2a–c**. Similar values of β_{lg} have been observed in similar reactions in which the formation of the tetrahedral intermediate was rate determining.[3,5] In the alkaline hydrolysis of 1 and **2a–c**, the expulsion of hydroxide ion (k_{-1}) is likely much slower than that of the leaving groups (k_2), and the rate-determining step is the formation of the tetrahedral intermediate.

A value of $\beta = 1.1$ is obtained from the Brønsted-type plot of log k_{am} against pK_{am} for 1 (Figure 2). The same plots for **2a–c** give values of $\beta = 0.8$–0.9. Similar values (0.9 ± 0.1)[3,5] have been obtained for the aminolysis of esters where the breakdown of the tetrahedral intermediate was rate determining. The values of β_{lg} obtained from the plots of log k_{am} against the pK_a of the phenol (Figure 3) are about −1.4. Similar values (−1.2 ± 0.2) have been obtained in the aminolysis of phenyl esters where the breakdown of the tetrahedral intermediate was rate determining.[3] The structure–reactivity relationships illustrated in Figures 2 and 3, therefore, indicate that the rate-determining step in the aminolysis of 1 and **2a–c** by quinuclidines is the breakdown of the tetrahedral intermediate. The absence of a break in these plots indicates that the breakdown of the intermediate is rate determining even for the attack by the most basic amine and for the attack on the most labile ester.[3,5,17]

For the azidolysis of **2a–d**, a β_{lg} value of −0.95 is obtained (Figure 4). This value corresponds to those of the rate-determining aryl oxide expulsion as discussed above. Thus, the rate-determining step in the azidolysis of the esters is the breakdown of the tetrahedral intermediate.

Reactivity of Cinnamoyl Azide Compared with the Reactivities of Phenyl Cinnamates. Good linear free-energy relationships are obtained for the alkaline hydrolysis and aminolysis of the esters as illustrated in Figures 1 and 3. In these figures, comparison of the reactivities of 1 and **2a–c** toward alkaline hydrolysis or aminolysis is made. For alkaline hydrolysis, the pK_a of the leaving phenol for the hypothetical ester whose rate is equal to the rate of 1 is greater by 1.7 pK units than that of hydrazoic acid (HN_3). When aminolysis is considered, the pK_a difference is 2–2.5 pK units.

In the linear free-energy relationships for nucleophilic reactions on acyl derivatives, a better correlation would be obtained with the affinity of the leaving group for the acyl carbon (K_{AC}) than with that for proton (K_b). Among the phenyl cinnamates, where only small structural variation is involved, a good linear correlation between log k and pK_a is expected because the pK_a in turn would be linearly related to pK_{AC}. When 1 is compared with the esters, the linear relationship between pK_a and pK_{AC} would not hold due to the large structural difference between the azide ion and the phenolates. Thus, the deviation of the points for 1 from the lines drawn for **2a–c** in Figures 1 and 3 can be accounted for by assuming that the ratio of K_{AC}/K_b is greater for azide ion than for the phenolates.

Bond distances in azide ion agree with equal contribution of resonance structures C–F.[18] But bond lengths in

$${}^{-}\!:\!\ddot{\mathrm{N}}{=}\mathrm{N}^{+}{=}\underset{\cdot\cdot}{\mathrm{N}}\!:^{-} \qquad {}^{2-}\!:\!\underset{\cdot\cdot}{\ddot{\mathrm{N}}}{-}\mathrm{N}^{+}{\equiv}\mathrm{N}\!:$$
$$\mathrm{C} \qquad\qquad\qquad \mathrm{E}$$
$${}^{-}\!:\!\underset{\cdot\cdot}{\mathrm{N}}{=}\mathrm{N}^{+}{=}\ddot{\mathrm{N}}\!:^{-} \qquad :\mathrm{N}{\equiv}\mathrm{N}^{+}{-}\underset{\cdot\cdot}{\ddot{\mathrm{N}}}\!:^{2-}$$
$$\mathrm{D} \qquad\qquad\qquad \mathrm{F}$$

hydrazoic acid agree with equal resonance between G and H.[18] Thus, resonance in hydrazoic acid is likely much less

$$\mathrm{H}{-}\ddot{\mathrm{N}}{=}\mathrm{N}^{+}{=}\underset{\cdot\cdot}{\mathrm{N}}\!:^{-} \qquad \mathrm{H}{-}{}^{-}\underset{\cdot\cdot}{\ddot{\mathrm{N}}}{-}\mathrm{N}^{+}{\equiv}\mathrm{N}\!:$$
$$\mathrm{G} \qquad\qquad\qquad \mathrm{H}$$

extensive than that in azide ion while that in acyl azide (eq 1) is expected[9] to be significant. Consequently, loss of the resonance stabilization of azide ion could be smaller upon acylation than upon protonation. This can lead to the greater affinity of azide ion for an acyl carbon than

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(17) The absence of breaks in the Brønsted-type plots for the aminolysis of the esters may be taken to be contradictory to the results of ref 3. However, the breaks in the linear lines are obvious only for the most labile leaving group (2,4-dinitrophenolate) in ref 3 and this leaving group is not included in the present study. The absence of breaks in Figures 2 and 3, thus, does not conflict with the results of ref 3.

(18) L. Pauling, "The Chemical Bonding", 3rd ed., Cornell University Press, Ithaca, NY, 1960, pp 158–159.

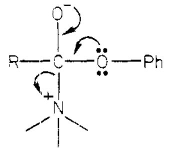
Table IV. Slopes of Plots of log k against pK_a

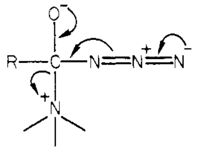
reaction	compd	pK_a plotted	slope	corrln coeff	figure no.
alkaline hydrolysis	2a–c	phenols	-0.35 ± 0.06	0.97	1
aminolysis by 3a–c	1	amines	1.11 ± 0.18	0.97	2
aminolysis by 3a–d	2a	amines	0.83 ± 0.06	0.99	2
aminolysis by 3a–c	2b	amines	0.83 ± 0.05	0.98	2
aminolysis by 3a–c	2c	amines	0.86 ± 0.11	0.97	2
aminolysis by 3a	2a–c	phenols	-1.42 ± 0.15	0.99	3
aminolysis by 3b	2a–c	phenols	-1.41 ± 0.17	0.98	3
aminolysis by 3c	2a–c	phenols	-1.42 ± 0.13	0.99	3
azidolysis	2a–d	phenols	-0.95 ± 0.05	0.99	4

expected from its basicity. The enhanced affinity of azide ion for an acyl carbon is further supported by its reactivity in attack on *p*-nitrophenyl acetate which is greater than expected from its basicity by about 2 pK units.[19,20]

Relative Leaving Ability. In the nucleophilic reactions described by eq 3, the relative leaving ability (k_{-1} and k_2) of the two ligands in the tetrahedral intermediate, L$^-$ and Nu$^-$, can be determined by locating the position of the rate-determining step. Several factors affecting the relative leaving ability have been previously discussed.[4,7]

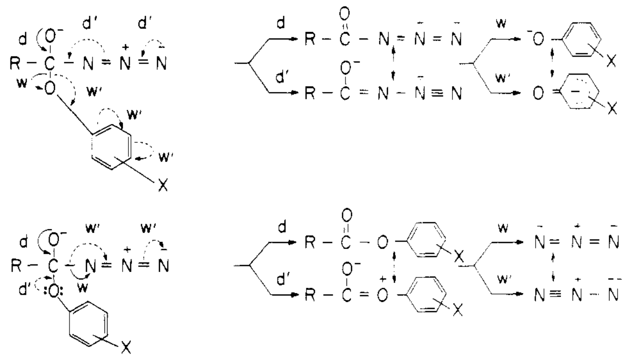
As discussed in the earlier section, the rate-determining step in the aminolysis of the esters and acyl azide by quinuclidines is the breakdown of the tetrahedral intermediate. Thus, azide ion and phenolates resist expulsion from the tetrahedral intermediate more strongly than the amines although they are much less basic than the amines. It is noteworthy that the leaving ability of azide ion is smaller than that of **3a** which is 5 × 10^6 times more basic than azide ion. The faster expulsion of quinuclidines compared with phenolates has been previously reported.[3,4,7] A "push" by electron donation from the ether oxygen (see structure I) was suggested[4] to contribute to the faster expulsion of the quinuclidines from the tetrahedral intermediate. A similar "push" can be drawn for the azide (see structure J), and this may be responsible for the relative leaving abilities of azide ion and quinuclidines.


I


J

In order to compare the leaving abilities of the azide ion and the phenolates, we have studied the azidolysis of **2a–c**. As discussed previously, the rate-determining step in this reaction is the breakdown of the tetrahedral intermediate. Thus, azide ion is expelled faster than the phenolates. This stands in contrast with the slower rates for the alkaline hydrolysis and aminolysis of **1** compared with those of **2a–c**. The results, however, do not indicate at which pK_a of the phenol the rates of the expulsion of phenolate and azide ion become equal and the change in the rate-determining step takes place. But they do indicate that 3,4-dinitrophenolate, which is only 5 times more basic than azide ion, leaves less readily than azide ion.

Scheme I



When electron donation can be provided by both of the leaving groups of the tetrahedral intermediate as in the azidolysis of esters, the "pull" by the leaving groups may be important in deciding the relative leaving ability. When tertiary amines are the nucleophiles, the positive charge acquired by the amine nitrogen in the tetrahedral intermediate can provide the "pull".[21] On the other hand, such a positive charge is not present in the phenolate and azide leaving groups. Instead, another type of electron withdrawal is possible for them as illustrated by Scheme I. In this scheme, the electron donation from the azide or the phenolates is indicated by d′, and the electron withdrawal to the remote parts of the leaving groups is denoted by w′. The electron withdrawal (w′) by azide and the phenolates is related to the resonance in the respective anions as the electron donation by azide, phenolate, imidazole, and pyridine leaving groups is related[4] to the resonance in the respective acyl derivatives. In view of the resonance structures (C–F) of the azide ion, the electron withdrawal by azide may be significant. Therefore, the balance between the electron donation and withdrawal by phenolates and azide can be responsible for the greater resistance of the phenolates against repulsion from the tetrahedral intermediate.

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Registry No. 1, 26829-64-1; **2a**, 73789-33-0; **2b**, 18736-43-1; **2c**, 62222-44-0; **2d**, 73789-34-1; **3a**, 100-76-5; **3b**, 1619-34-7; **3c**, 42332-45-6; **3d**, 3731-38-2.

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(19) W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, 1969, p 91.

(20) The enhanced thermodynamic and kinetic affinity of azide ion for acyl carbons can be compared with the "α-effect" compounds (ref 19, pp 107–111) although the unshared pair of electrons is located on the atom β instead of α to the nucleophilic atom in azide ion and the "α effect" is not easily accounted for by the direct-resonance effect alone in many cases.

(21) Some imidazole and pyridine derivatives are expelled from the tetrahedral intermediate more readily than the phenolates although they also provide electron donation by resonance.[4,6] This can be explained in terms of the electron withdrawal by the positive charges on the leaving nitrogens.