Properties and Mechanisms for the Interconversion of the *E* and *Z* Isomers of Phenyl *N*-Methylacetimidates[1]

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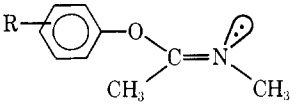
Abstract: The biphasic first-order kinetics for the hydrolysis and reactions with (excess) methylamine and bicarbonate of phenyl *N*-methylacetimidates arise from different reactivities of the *E* and *Z* forms of the imidate and the relatively slow interconversion of the isomers. The methylamine reaction provides a kinetic assay, consistent with nmr analysis, for the relative concentrations of the two isomers. The conjugate acid of the *E* form is three to ten times more reactive than its isomer and has a pK_a of 6.55, compared with 8.0 for the *Z* isomer. Since the conjugate acid is the reactive species even at high pH, the higher p*K* of the *Z* form causes this isomer to react more rapidly at higher pH values. Electron-withdrawing substituents on the phenyl ring increase the fraction in the *E* form at equilibrium and protonation favors conversion to the *Z* form. The *E*–*Z* isomerization is catalyzed by triethylenediamine through a mechanism that involves proton abstraction from the *C*-methyl group of the conjugate acid of the imidate; the existence of a concurrent nucleophilic mechanism of isomerization is not excluded. The uncatalyzed equilibration in carbon tetrachloride at 0° follows first-order kinetics (k = 0.023 min^{-1}). The absence of a rate increase in aqueous solution or upon protonation supports an inversion (lateral shift) mechanism of isomerization.

We describe here some properties of the *E* and *Z* isomers of substituted phenyl *N*-methylacetimidates and a study of the mechanisms for catalyzed and uncatalyzed interconversion of the isomers. The work was initiated in an effort to explain nonlinear first-order kinetics that were observed for the hydrolysis and other reactions of these compounds. The presence of comparable concentrations of the *E* and *Z* isomers in preparations of phenyl *N*-methylacetimidate and nonlinear kinetics for the hydrolysis of this compound were first reported by Kandel and Cordes.[2] The compounds examined are the *p*-tolyl, *p*-chlorophenyl, and *m*-nitrophenyl *N*-methylacetimidates II–IV.



II, R = *p*-CH_3
III, R = *p*-Cl
IV, R = *m*-NO_2

Experimental Section

Materials and methods were generally as described previously.[3] The hydrochloride salt of II_a, mp 186–188°, was prepared by refluxing 2.0 ml of II in 3.4 ml of dry acetonitrile for 15–60 min after conversion to the hydrochloride with gaseous hydrochloric acid. Crystallization was induced by the addition of ether and the product was recrystallized from acetonitrile. The kinetics of hydrolysis and nmr spectra (see below) showed that the product was >87% in the *Z* configuration.

Solvents for nmr were obtained from Stohler Isotope Chemicals, and deuterium oxide was obtained from BioRad Laboratories.

The kinetics of hydrolysis of II, III, and IV were followed spectrophotometrically at 277, 280, and 335 nm, respectively.[3]

Spectrophotometric titrations of the acetimidates were carried out by adding small aliquots of solutions of II or IIa hydrochloride in acetonitrile to a series of aqueous buffer solutions and measuring the absorption extrapolated to zero time. The initial absorption was corrected for any absorption of the buffer, and the results from different experiments were normalized to a constant absorbance of the protonated form at low pH before plotting against the pH. The solutions were buffered with 0.1 *M* methoxyacetic acid, acetic acid, N-substituted morpholines, or quinuclidinol buffers.

The composition of preparations of IIa hydrochloride was determined by nmr after extraction of the base form into carbon tetrachloride at low temperature. The hydrochloride (30 mg) was added to 1 ml of carbon tetrachloride and 3 ml of 0.2 *M* borate buffer (75% base) at 0° and the mixture was vigorously mixed for 20 sec with a Vortex mixer. The mixture was immediately cooled to −13° in a salt–ice bath and after separation of the layers an aliquot of the carbon tetrachloride layer was transferred successively to two chilled test tubes and to an nmr tube; the first nmr spectrum was taken within 4 min of the addition of the hydrochloride salt to the borate buffer.

The equilibration of the *E* and *Z* isomers was followed by measuring the change in the *C*-methyl nmr absorbance at −13 and 0° with a Varian A-60 spectrophotometer. The rate of equilibration of the *E* and *Z* forms was also measured by determining the concentrations of the fast and slow reacting forms in the presence of methylamine. Aliquots of the equilibrating solution in carbon tetrachloride were added to 4 ml of 0.01 *M* methoxyacetate buffer (50% base) and mixed for 15 sec with a Vortex mixer. An aliquot of 0.5 ml of the aqueous phase was immediately added to 2.0 ml of 0.025 *M* methylamine hydrochloride in 0.1 *M* borate buffer, 75% base, and the rate of *p*-cresol release was followed with a Gilford 2000 recording spectrophotometer.[3] The relative concentrations of the fast and slow reacting forms were determined from the intercepts of first-order plots extrapolated to zero time.

Results

Kinetics of Hydrolysis. The hydrolysis of the free base of II at pH 9 follows first-order kinetics (Figure 1, solid circles), but the hydrolysis of the conjugate acid of II at pH 3.4 follows a biphasic first-order course (Figure 2, solid circles). A preparation of the hydrochloride of II that has been refluxed in acetonitrile (II_a) follows the converse behavior, with apparently linear first-order hydrolysis of the conjugate acid at pH 3.4 and biphasic hydrolysis of the basic form at pH 9 (open circles, Figures 1 and 2). In each case the rate constant for the slower phase of the biphasic reaction is similar to that for the slow monophasic hydrolysis of the other form of the imidate. The intercept at zero time for the slow phase of the hydrolysis of IIa at high pH corresponds to 25% of the total absorbance change.

(1) Supported by grants from the National Science Foundation (GB 4648) and the National Institute of Child Health and Human Development of the National Institutes of Health (HD 01247). A. S. was a Predoctoral Fellow of the National Institutes of Health (GM 212).

(2) M. Kandel and E. H. Cordes, *J. Org. Chem.*, **32**, 3061 (1967).

(3) A. C. Satterthwait and W. P. Jencks, *J. Amer. Chem. Soc.*, **96**, 7031 (1974).

Table I. *N*-Methylacetimidate Nmr Spectra[a]

N-Methylacetimidate	Solvent	δ, *C*-methyl, ppm *Z*	δ, *C*-methyl, ppm *E*	δ, *N*-methyl, ppm *Z*	δ, *N*-methyl, ppm *E*	% *Z* at equilibrium	pK_a resident alcohol
Methyl *N*-methylacetimidate[b]	Carbon tetrachloride[c]	1.78		2.92		0	15.5
p-Tolyl *N*-methylacetimidate (II)	Carbon tetrachloride[d]	1.80	2.04	2.97	2.86	33	10.2
	Deuterated chloroform	1.88	2.07	3.08	2.96	33	
	Deuterated acetonitrile	*e*	2.00	2.97	2.84	20	
Phenyl *N*-methylacetimidate[f]	Carbon tetrachloride[g]	1.8	1.95	3.0	2.85	33	10.0
p-Chlorophenyl *N*-methylacetimidate (III)	Deuterated chloroform	1.9	2.1	3.1	3.0	20	9.35
m-Nitrophenyl *N*-methylacetimidate (IV)	Deuterated chloroform	1.9	2.1	3.1	3.0	10	8.35

[a] Nmr spectra were taken of 20–75 mg/ml of the acetimidates at ambient temperature unless otherwise noted. Chemical shifts are relative to tetramethylsilane. [b] R. M. Moriarty, C.-L. Yeh, K. C. Ramey, and P. W. Whitehurst, *J. Amer. Chem. Soc.*, **92**, 6360 (1970); C. O. Meese, W. Walter, and M. Berger, *J. Amer. Chem. Soc.*, **96**, 2259 (1974). [c] The solution was 15% acetimidate (w/v). [d] Spectra at 0 and −13°. [e] Interference from the solvent which was not completely deuterated. [f] Reference 2. [g] The solution was 1 *M* in acetimidate.

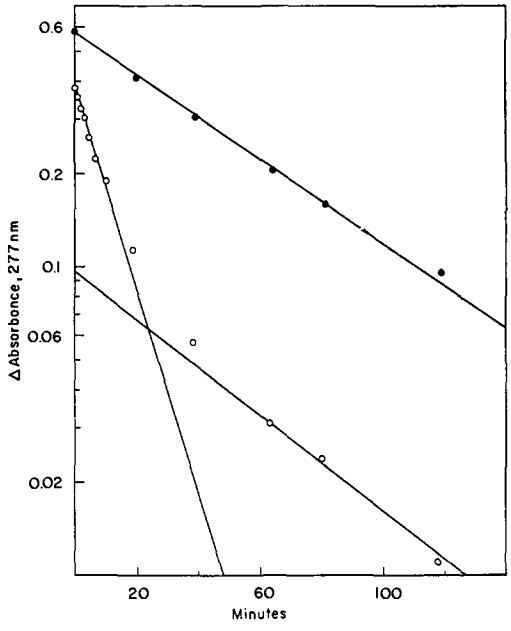


Figure 1. First-order plots for the hydrolysis of II (●) and II_a (○) in 0.03 *M* borate buffer, pH 9.0, 25°, ionic strength 1.0 (KCl).

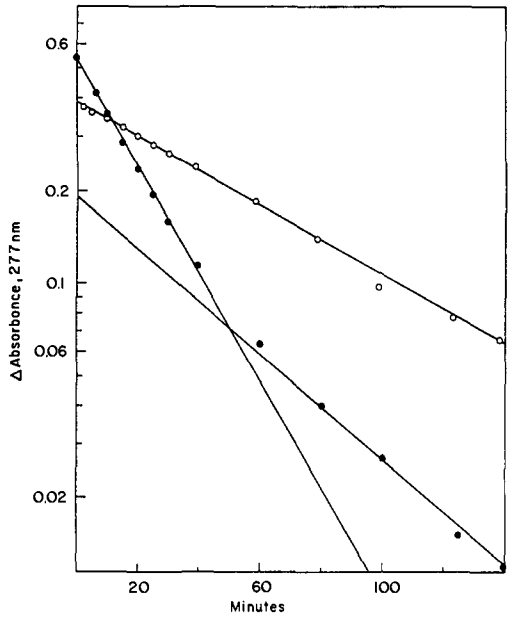


Figure 2. First-order plots for the hydrolysis of II (●) and II_a (○) in 0.05 *M* methoxyacetate buffer, pH 3.40, 25°, ionic strength 1.0 (KCl).

Since the hydrolysis of II_a at low pH follows monophasic first-order kinetics and nmr analysis shows that II_a is >87% homogeneous, this means that conversion of II_a to a slowly reacting form must occur during hydrolysis in aqueous solution at pH 9.0. A plot of the initial rate constants for the hydrolysis of II and IIa as a function of pH exhibits a crossover in the rates of hydrolysis of the two forms near neutral pH (Figure 3). The rates were shown to be independent of buffer concentration or were extrapolated to zero buffer concentration. These results show that II can exist as two isomers, II_s and II_a, that undergo hydrolysis at different rates and that interconvert slowly at a rate that is slower than the rate of hydrolysis of the rapidly hydrolyzing isomer but of a comparable magnitude to the rate of hydrolysis of the slowly reacting isomer. Imidates III and IV exhibit similar behavior, with biphasic hydrolysis at pH 2.0–3.4 and monophasic hydrolysis at pH 7–9.

Analysis by Nmr. The two forms of II, III, and IV were shown to be the *E* and *Z* isomers by nmr (Figure 4A). The predominant form of the free base was assigned the *E* structure, in agreement with the assignment of Kandel and Cordes for phenyl *N*-methylacetimidate[2,4] (Table I). This structure is supported by the larger coupling constant of the *C*-methyl and *N*-methyl protons for the *Z* (J = 1.25 Hz) than for the *E* (J = 0.25 Hz) isomer,[2] which we have confirmed for II–IV and which is in agreement with the observed homoallylic coupling in *N*-methylimines,[5,6] and by dipole moment measurements on II and III, which

(4) The convention for the designation of syn and anti forms used by Kandel and Cordes[2] is opposite to that used by some other workers;[12] we have used the unambiguous *E*–*Z* nomenclature.

(5) D. A. Nelson and R. L. Atkins, *Tetrahedron Lett.*, 5197 (1967); E. P. Kyba, *ibid.*, 5117 (1973).

(6) K. Tori, M. Ohtsuru, and T. Kubota, *Bull. Chem. Soc. Jap.*, **39**, 1089 (1966).

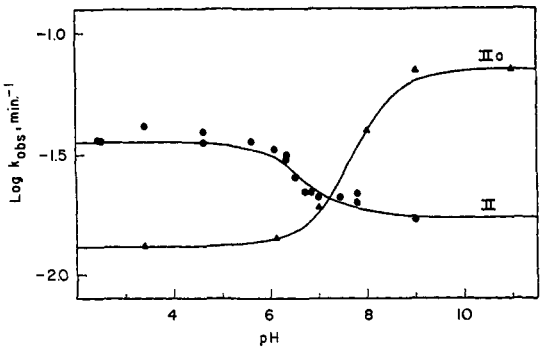
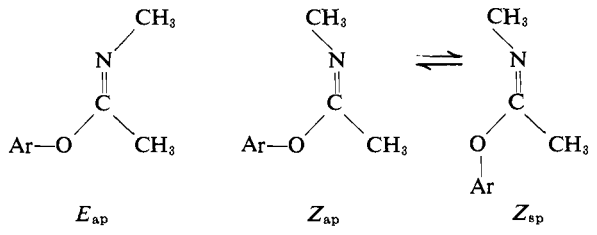


Figure 3. Dependence on pH of initial log k_{obsd} for the hydrolysis of II (●) and II_a (▲) at 25°, ionic strength 1.0 (KCl). Buffers were 0.05–0.10 *M* cyanoacetate, methoxyacetate, acetate, *N*-propargylmorpholine, *N*-allylmorpholine, *N*-methylmorpholine, borate, and quinuclidinol. The solid lines were calculated based on p*K* values of 6.55 and 8.00.

further suggest that the predominant isomer has the E_{ap} structure with the methyl and phenyl groups antiperiplanar about the C–O bond, as shown.[7] The E_{ap}



structure has been calculated to be the most stable form of formimidic acid, HOCH=NH.[8] Some uncertainty about this assignment is raised by the fact that the *C*-methyl protons are shifted to higher field and the *N*-methyl protons to lower field in the *Z* compared with the *E* isomers (Table I), whereas in most examples of >C=NR isomerism the chemical shifts are in the opposite direction.[5,9-10] However, these shifts are small, solvent dependent, and sometimes reversed in direction.[6,10] The observed shifts of the *C*-methyl protons in the phenyl imidates would be accounted for if nonbonded interactions of the *N*-methyl and phenyl groups caused a significant fraction of the *Z* isomer to exist in the sp form with the phenyl group syn to the *C*-methyl group; the shielding effect of the aromatic substituent in this position would be expected to cause an upfield shift of the adjacent *C*-methyl protons. Space-filling molecular models show crowding in the Z_{ap} isomer of the phenyl imidates, and the Z_{sp} isomer has been calculated to be more stable than the Z_{ap} isomer of formimidic acid.[8]

Electron-withdrawing substituents on the phenyl group increase the relative stability of the *E* isomer, as shown by the increase from 67 to 90% of the fraction of this isomer at equilibrium as the substituent is changed from the *p*-methyl group of II to the *m*-nitro group of IV (Table I). The methyl imidate exists as the *E* isomer,[11] contrary to an earlier report.[12] Thus, in contrast to the substituent effect within the phenyl series, substitution of the electron-withdrawing phenyl group for methyl stabilizes the *Z* relative to the *E* isomer; *i.e.*, the effect of polar substituents on the dipole moments of a single conformation of the *Z* and *E* isomers does not appear to provide a simple explanation for the relative stabilities of the isomers.

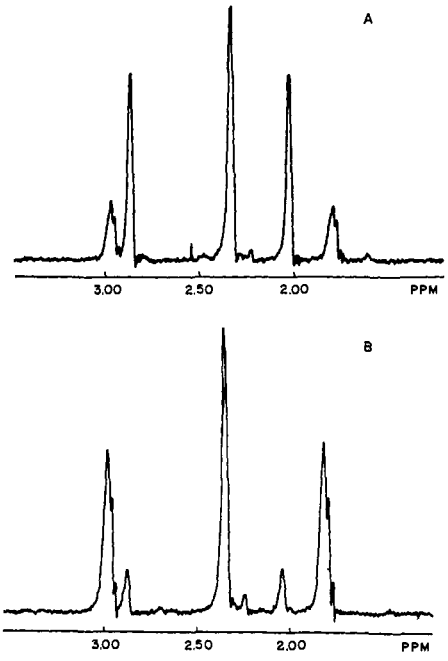
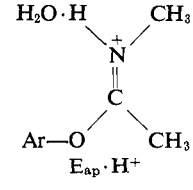


Figure 4. Nmr spectra of the methyl protons of II (A) and II_a (B) in carbon tetrachloride at −13°. The assignments of the *E* and *Z* isomers are given in Table I; the central peak is the *p*-methyl group on the phenyl ring.

Upon refluxing in acetonitrile the hydrochloride of II is converted to the *Z* isomer; *i.e.*, the *E* isomer is the more stable form of the base but the *Z* isomer of the conjugate acid is more stable. An nmr spectrum of IIa that was prepared by rapid neutralization of the hydrochloride and extraction of the base into carbon tetrachloride shows 87% *Z* isomer (Figure 4B), but this represents a lower limit since some conversion to the *E* form takes place during the procedure. This isomerization is in the same direction as that for methyl *N*-methylacetimidate in sulfuric acid, based on the recent assignment of structure for this compound.[11,12] Inspection of molecular models suggests that the hydrophobic phenyl group provides an unfavorable environment for the solvated N–H^+ group of $E_{ap}\cdot H^+$ and thereby shifts the equilibrium toward the protonated *Z* isomer.



The approach to equilibrium of a solution of IIa in carbon tetrachloride at 0° follows first-order kinetics

(7) O. Exner and O. Schindler, *Helv. Chim. Acta*, **55**, 1921 (1972).
(8) L. Radom, W. J. Hehre, and J. A. Pople, *J. Amer. Chem. Soc.*, **93**, 289 (1971).
(9) D. Wurmb-Gerlich, F. Vögtle, A. Mannschreck, and H. A. Staab, *Justis Liebigs Ann. Chem.*, **708**, 36 (1967).
(10) G. J. Karabatsos and N. Hsi, *Tetrahedron*, **23**, 1079 (1967), and references therein; R. M. Moriarty, C.-L. Yeh, E. Liaus, and K. Ramey, *Tetrahedron Lett.*, **26**, 2655 (1972).
(11) C. O. Meese, W. Walter, and M. Berger, *J. Amer. Chem. Soc.*, **96**, 2259 (1974).
(12) R. M. Moriarty, C.-L. Yeh, K. C. Ramey, and P. W. Whitehurst, *J. Amer. Chem. Soc.*, **92**, 6360 (1970).

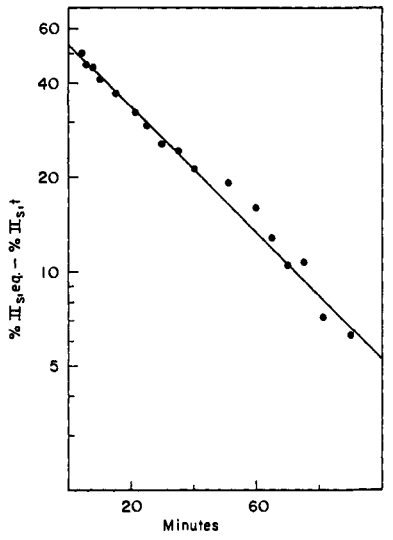


Figure 5. First-order plot for the approach to equilibrium of 0.15 M II_a in carbon tetrachloride at 0°, followed by nmr.

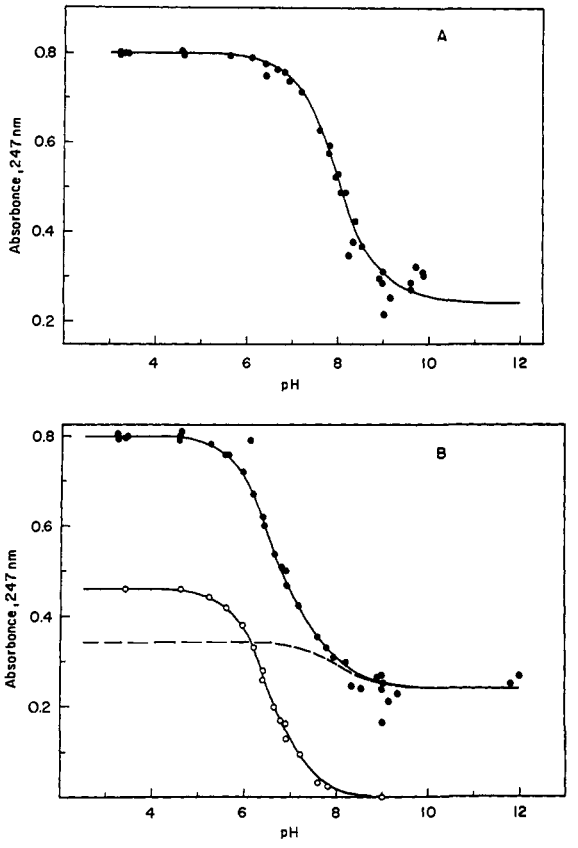


Figure 6. Spectrophotometric titration curves for II_a (A) and II (B) at 25°, ionic strength 1.0 (KCl). The lower curve in B is for II_s after correction of the observed upper curve (for II) for the presence of 20% of the Z isomer in the acetonitrile stock solution. The correction is shown by the dashed line. The solid lines are calculated for pK 8.00 (A), 6.55 (B, lower curve), and a mixture of 20% II_a and 80% II_s (B, upper curve).

with k_{obsd} = 0.023 min^{-1} (Figure 5). For the approach to equilibrium (eq 1), $K^0 = k_s/k_a$ = 2.0 and $k_{obsd} = k_s + k_a$, so that k_a = 0.0077 min^{-1} and k_s = 0.015 min^{-1}. One experiment at −13° gave values of k_{obsd} = 0.0061 min^{-1}, k_a = 0.0020 min^{-1}, and k_s = 0.0041 min^{-1}. Approximate values of k_{obsd} = 0.14 min^{-1},

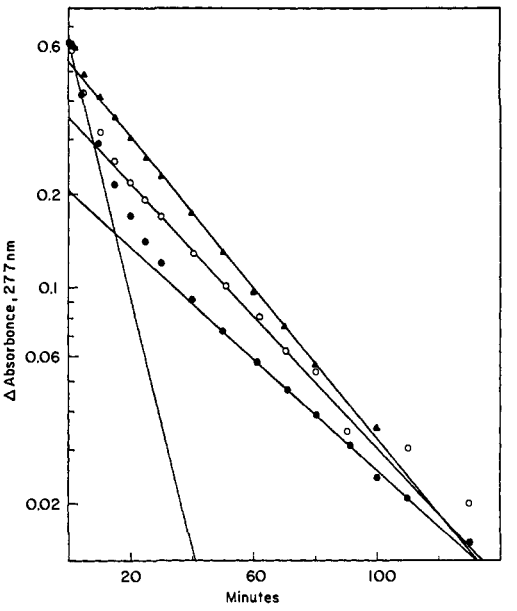


Figure 7. The effect of triethylenediamine buffers on first-order plots for the hydrolysis of II_a at 25°, ionic strength 1.0: borate buffer, 0.1 M, pH 9.0 (●); triethylenediamine buffer, 0.03 M, pH 9.7 (○); triethylenediamine buffer, 0.20 M, pH 9.8 (▲).

k_a = 0.05 min^{-1}, and k_s = 0.09 min^{-1} at 25° were obtained by extrapolation of a plot of log k against $1/T$. The isomerization of phenyl N-methylacetimidate has been observed as a coalescence of the nmr bands of the E and Z isomers at elevated temperatures in carbon tetrachloride and o-dichlorobenzene.[2,11]

$$II_a \underset{k_a}{\overset{k_s}{\rightleftharpoons}} II_s \qquad (1)$$

Titration of the E and Z Isomers. The pK_a of the conjugate acid of II_a was found to be 8.0 by spectrophotometric titration (Figure 6A). The pK_a of II_s was found to be 6.55 (Figure 6B, lower curve) by correcting the observed titration curve of II for the contribution of 20% II_a (Figure 6B, upper curves). The concentration of II_a was determined by nmr analysis of the stock solution of II in acetonitrile. The difference in ionization constants must correspond to the difference in the equilibrium constants for the E–Z interconversion of the free and protonated forms of the imidate (eq 2)

$$\begin{array}{ccc} II_aH^+ & \overset{K^+}{\rightleftharpoons} & II_sH^+ \\ K_Z \big\uparrow\downarrow \pm H^+ & & K_E \big\uparrow\downarrow \pm H^+ \\ II_a & \underset{K^0}{\rightleftharpoons} & II_s \end{array} \qquad (2)$$

according to the relationship $K_E/K_Z = K^0/K^+$ = 28. Thus, protonation shifts the equilibrium toward the Z conformation by a factor of 28.

The calculated solid lines in the pH–rate profile for the hydrolysis of II_a and II_s (Figure 3) are based upon the above pK_a values for the two isomers and show a satisfactory fit to the data. The rate constants for the hydrolysis of II_a and II_s are 0.069 and 0.017 min^{-1} for the base forms and 0.013 and 0.038 min^{-1} for the conjugate acids, respectively.

Reactions with Buffers and Nucleophiles. In the presence of increasing concentrations of triethylenediamine buffers the biphasic kinetics for the hydrolysis of II_a progressively disappear (Figure 7). As the

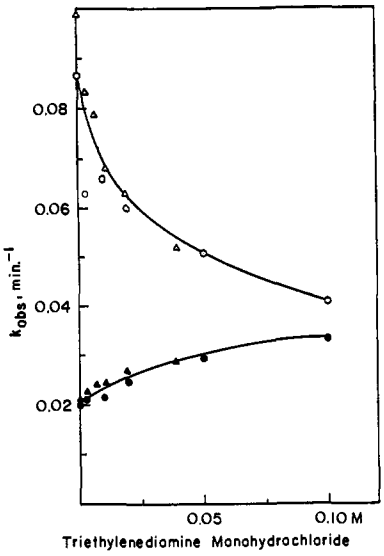


Figure 8. The effect of triethylenediamine buffers on the initial rates (open symbols) and final rates (closed symbols) for the hydrolysis of II_a at 25°, ionic strength 1.0 (KCl). The buffers were 20% (triangles) and 50% (circles) triethylenediamine hydrochloride.

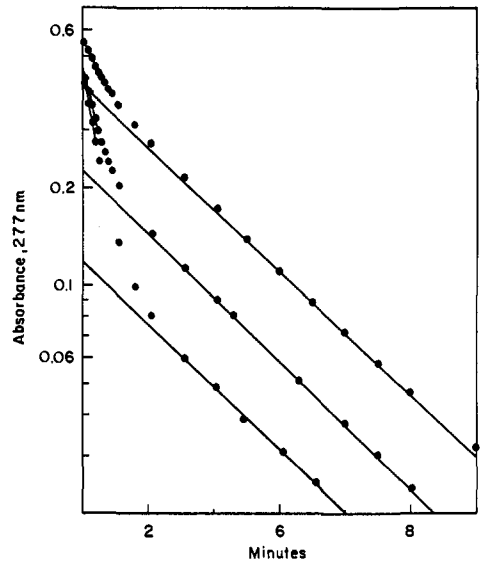


Figure 10. First-order plots for the reactions of mixtures of II_a and II_s with 0.025 *M* methylamine hydrochloride in 0.10 *M* borate buffer, 75% base, at 25°, and ionic strength 1.0 (KCl).

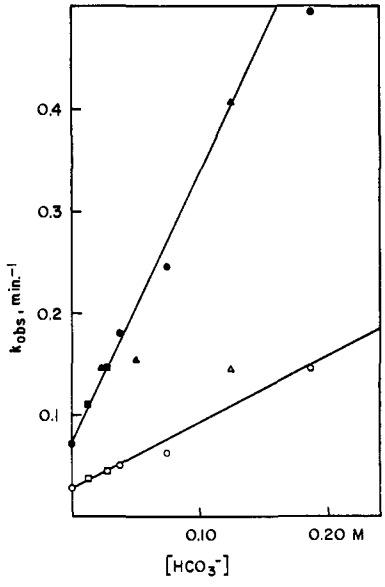


Figure 9. The effect of carbonate buffers on the initial rates (closed symbols) and final rates (open symbols) for the hydrolysis of II_a at 25°, ionic strength 1.0 (KCl). The buffers contained 25% (squares), 50% (triangles), and 75% (circles) bicarbonate.

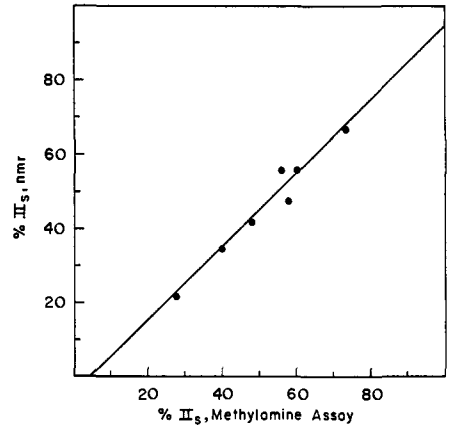


Figure 11. Comparison of analyses of the *E* and *Z* isomers of II in carbon tetrachloride by nmr (ordinate) and by the methylamine assay after extraction of aliquots (abscissa). The total concentration of II was initially 0.15 *M*.

buffer concentration is increased the initial rate of hydrolysis decreases and the final rate increases, approaching a constant value (Figure 8). Experiments carried out at two base ratios (50 and 80% base) show that these effects are dependent on the fraction of the buffer in the protonated form. These results suggest that this buffer acts as a catalyst to increase the rate of *E*–*Z* interconversion and that at high buffer concentrations a situation is approached in which the observed first-order hydrolysis represents the hydrolysis of a rapidly equilibrating mixture of the *E* and *Z* isomers.

In contrast, methylamine and bicarbonate cause an increase in the rate of *p*-cresol appearance from both isomers of the imidate but have little effect on the ratio of the rate constants for the fast and slow phases of the reaction. The rate increase of both phases of the reaction is proportional to the concentration of bicarbonate ion at three buffer ratios (Figure 9) and gives second-order rate constants of 2.7 and 0.7 M^{-1} min^{-1} for the fast and slow reactions, respectively. The corresponding rate constants for methylammonium ion are 70 and 7 M^{-1} min^{-1}, respectively. Borate buffers, 0.1–0.2 *M*, were found to have no effect on the rate.

Since the methylamine reaction is faster than isomerization, it provides a convenient assay for the concentrations of the two isomers. The intercepts at zero time of the first-order plots for the fast and slow phases of the reaction provide a measure of the relative concentrations of the isomers (Figure 10). A plot of per cent II_s obtained by this method against the same quantity measured by nmr is linear (Figure 11) but has an abscissa intercept of 4% that is probably caused by a small amount of isomerization during extraction or of hydrolysis of II_a before the first readings were obtained. Assays of aliquots by this method gave the same rate constant for the isomerization of 0.15 *M* II_a in carbon

Table II. Rate Constants for Base Catalyzed Alcohol Release from Acetimidate Cations at 25°, Ionic Strength 1.0 (KCl)

Base	pK_a	Rate constants, k_N[a] Phenyl *N*-methylacetimidate[b] (M^{-1} min^{-1})	II_s (M^{-1} min^{-1})	II_a (M^{-1} min^{-1})	*p*-Tolyl *N,N*-dimethylacetimidate[c] (M^{-1} min^{-1})
H_2O	−1.75	1.2×10^{-3}	7.3×10^{-4}	2.4×10^{-4}	1.3×10^{-4}
CH_3COO^-	4.60				2×10^{-2}
HPO_4^{2-}	6.50	11.6			
$(CF_3)_2C(OH)O^-$	6.45				2.7×10^{-2}
CO_3^{2-}	9.90		1.16×10^3	1.2×10^2	
CH_3NH_2	10.7	1.5×10^5	1.3×10^5	3.2×10^4	
HO^-	15.75	6.3×10^5	5.6×10^5	8×10^4	1.2×10^5

[a] For reaction with the protonated or cationic imidate (eq 4). [b] Reference 2. [c] Reference 3.

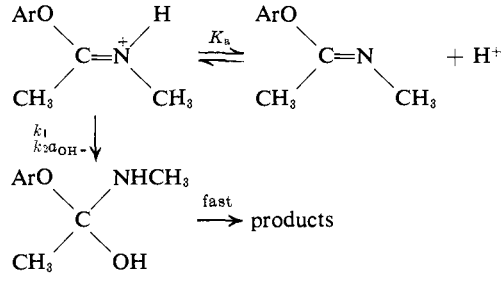
tetrachloride as direct measurement by nmr. The same rate constant was also obtained with the methylamine assay for 0.015 *M* II_a, showing that the rate of isomerization is not dependent on the concentration of imidate.

Deuterium Exchange. The hydrolysis of 0.005 *M* II in 0.01 *M* borate buffer, pD 9.9 in deuterium oxide, occurs without incorporation of deuterium into the *C*-methyl group of the *N*-methylacetamide product as measured by nmr.[3] More than 80% exchange into the *C*-methyl group of the product was found, however, when 0.25 *M* II was hydrolyzed in deuterium oxide in 0.05 *M* borate buffer (50% base) or in 0.1 *M* triethylenediamine buffer (50% base). In 0.23 *M* NaOD the hydrolysis of 0.25 *M* II gave <20% exchange. The exchange of deuterium into the *C*-methyl group of initially added II_a was found to be almost complete (>80%) 20 min after the addition of 0.005 *M* II_a to 0.05 *M* triethylenediamine (50% base) in 0.2 *M* borate buffer (50% base) in deuterium oxide.

Discussion

The nonlinear first-order hydrolysis of *p*-tolyl *N*-methylacetimidate is caused by the different rates of hydrolysis of slowly equilibrating *E* and *Z* isomers, which were identified by nmr spectroscopy. During the hydrolysis at pH 9 of the *Z* form, prepared by refluxing the hydrochloride salt of II in acetonitrile, there is significant isomerization to the more slowly hydrolyzing *E* form. The rate of isomerization in water was not measured directly, but the value of k_s was estimated to be in the range 0.023–0.070 min^{-1} from the observations that the hydrolysis of II_a shows no apparent deviation from first-order kinetics for the first 10 min and that 25% of II_s, the slowly hydrolyzing form at pH 9.0, has been formed at 60 min (Figure 1). However, it is possible that the isomerization is catalyzed by the reaction product, *p*-cresol. Consequently, this range represents an upper limit for the rate constant for the uncatalyzed isomerization; it is slightly smaller than the extrapolated rate constant of $k_s \sim 0.09$ min^{-1} for isomerization in carbon tetrachloride at 25°.

The pH-independent hydrolysis at low pH may be formulated as rate-determining attack of water on the conjugate acid of the imidate and the pH-independent hydrolysis at high pH as the attack of hydroxide ion on the conjugate acid of the imidate (eq 3).[2,3,13,14] If breakdown of the addition intermediate to products were rate determining, the rapid reversion of the intermediate to starting materials would cause isomerization and biphasic kinetics would not be observed; there is other evidence that the attack step is rate determining.[3] Similar biphasic kinetics are observed in the faster reactions with methylamine and bicarbonate buffers and the methylamine reaction provides a convenient kinetic assay for determining the relative amounts of the *E* and *Z* isomers in a given sample of II (Figures 10 and 11). This shows that the biphasic reactions do not represent the fast reaction of only one of the two isomers and a rate-determining isomerization of the other isomer to the rapidly reacting species. As in the case of the pH-independent hydrolysis at high pH, the rates of the reactions with nucleophiles at high pH are proportional to the fraction of the nucleophile present as the conjugate acid but actually represent the kinetically equivalent reaction of the basic form of the nucleophile, N, with the conjugate acid of the imidate, ImH^+ (eq 4, in which K_{NH^+} is the dissociation



(3)

$$\text{rate} = k_{NH^+}[Im][NH^+] = k_{NH^+}\frac{K_a}{K_{NH^+}}[ImH^+][N] = k_N[ImH^+][N] \quad (4)$$

constant of NH^+).[2,14] The rate constants for the reactions with water and hydroxide ion, expressed as k_N for the reaction of the free nucleophile with the protonated imidate, are similar to those for the reactions of the same nucleophiles with *p*-tolyl *N,N*-dimethylacetimidate,[3] which can only exist in the cationic form (Table II). Although the rate constants for the two phases of the biphasic hydrolysis are perturbed by the concomitant isomerization reaction, they are close to the true rate constants for the hydrolysis of the two isomers. The ratios of the rate constants for the reactions of the *E* and *Z* isomers with different nucleophiles are similar; for water and methylamine the ratios are 3.0 and 4.0, and for the anionic nucleophiles carbonate and hydroxide ions they are 10.0 and 7.0, respectively (Table II).

The crossover in the relative rates of hydrolysis of the *E* and *Z* forms near neutral pH is caused by the

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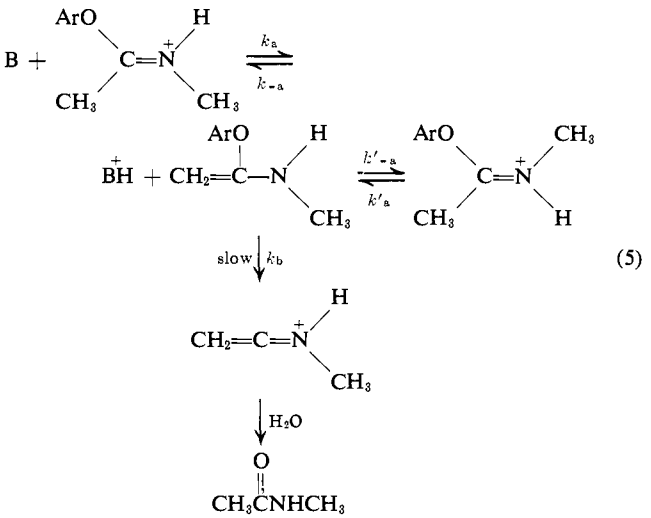
larger reactivity and larger dissociation constant of the protonated *E* isomer. At low pH the protonated *E* isomer reacts faster than the more stable protonated *Z* isomer, but at high pH the 28-fold smaller basicity of the *E* isomer causes a reduction in the concentration of the reactive, protonated form that more than compensates for the sevenfold difference in reactivity with hydroxide ion, so that the observed hydrolysis of the *E* isomer is fourfold slower than the *Z* isomer. Thus, increased kinetic reactivity is correlated with decreased thermodynamic stability for the two isomers, although the differences are smaller for the rate than for the equilibrium constants.

Isomerization. Four mechanisms may contribute to the *E*–*Z* isomerization of acetimidates.

(1) Bases may remove a proton from the *C*-methyl group of the protonated acetimidate to form an enamine that undergoes reprotonation to give imidate more rapidly than it expels alcoholate ion (eq 5). In



(5)

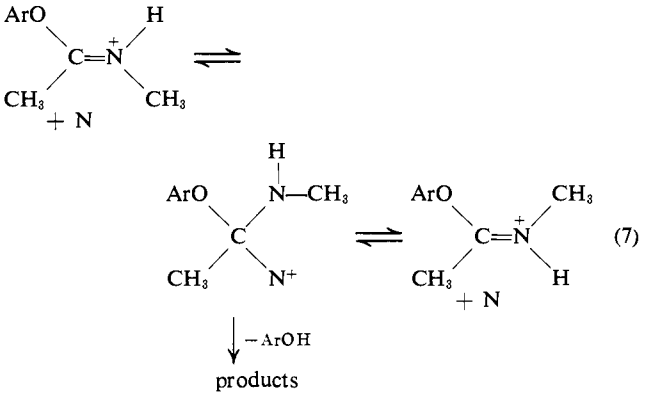
contrast to nucleophilic reagents such as methylamine and carbonate that cause increases in the rates of both the fast and slow phases of the reaction with increasing concentration, triethylenediamine buffers decrease the rate of the fast phase and increase the rate of the slow phase of the reaction. This shows that triethylenediamine buffers catalyze the equilibration of the two isomers. At high buffer concentrations the rate approaches a simple first-order hydrolysis of a rapidly equilibrating mixture of the two isomers (Figure 7 and 8). The observed rate constant for the hydrolysis of an equilibrating mixture is the weighted average of the rate constants for hydrolysis of the two isomers according to eq 6, in which k_S and k_A are pH-independent rate

$$k_{obsd} = k_S[\text{fr II}_s] + k_A[\text{fr II}_a] \qquad (6)$$

constants for the hydrolysis of II_s and II_a, respectively, and fr is the fraction of total imidate in the indicated form. From the limiting rate constant of $k_{obsd} = 0.035$ min^{-1} in Figure 8, the value of $K^0 = (\text{fr II}_s)/(\text{fr II}_a)$ was estimated to be approximately 2.0, the same as the value that was measured directly in carbon tetrachloride. From this equilibrium constant and eq 2, the equilibrium constant for the isomerization of the conjugate acids of the imidate in aqueous solution, $K^+ = [II_s \cdot H^+]/[II_a \cdot H^+]$, is approximately 0.07. This value provides further evidence for the decreased stability of the protonated *E* isomer. Since the isomerization reaction involves the basic form of the catalyst and the conjugate acid of the imidate, the observed rate follows eq 4 and is proportional to the fraction of the amine in the protonated form, as observed (Figure 8).

The observation that triethylenediamine catalyzes the incorporation of deuterium from deuterium oxide into the *C*-methyl group of unreacted imidate shows that this base catalyzes *E* and *Z* isomerization by the mechanism of eq 5. The observed incorporation of deuterium into the *C*-methyl group of the *N*-methylacetamide product when concentrated, but not dilute, solutions of II undergo hydrolysis in deuterium oxide suggests that the other reaction product, *p*-cresol, also catalyzes deuterium exchange and isomerization. As in the case of triethylenediamine, the rate of exchange is expected to be proportional to the fraction of the cresol in the protonated form and little or no deuterium incorporation is observed in 0.23 *M* NaOD. Added *p*-cresol, 10^{-3} *M*, was also observed to increase the fraction of the slowly hydrolyzing form of II_a at pH 9 from 0.3 to 0.5, suggesting that catalysis of isomerization is significant even in dilute solution. It has been shown by Lienhard and Wang that the base catalyzed abstraction of a proton from the *C*-methyl group of ethyl *N*,*N*-dimethylthioacetimidate cation is more rapid than hydrolysis and the isomerization of acetone *N*-methyl-*N*-phenylhydrazone occurs through a mechanism involving hydrogen exchange that is induced by chlorinated solvents or impurities in the solvents.[15] A slow deuterium exchange at the acyl carbon atom has been observed by nmr spectroscopy for methyl *N*-methylacetimidate and *O*-ethylvalerolactam in CD_3OD solution.[11,16]

(2) A nucleophilic reagent, N, may catalyze isomerization by reversible addition to the double bond of the protonated imidate (eq 7) and evidence for nucleophilic catalysis by methoxide ion of the isomerization of *O*-methylbenzohydroximoyl chlorides has been reported.[17] Nucleophilic catalysis will be significant whenever the tetrahedral addition intermediate expels the attacking nucleophile and reverts to starting material more rapidly than it expels the leaving group to give products, provided that the rate of rotation, in-



(7)

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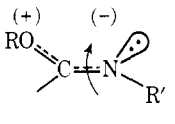
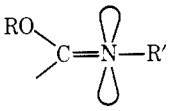
version, or protonation of the amine is fast relative to the lifetime of the addition intermediate. It is possible, but not proved, that this mechanism contributes to the observed catalysis of isomerization by triethylenediamine. The absence of significant nucleophilic catalysis of isomerization by methylamine and bicarbonate is not unexpected, in view of the good leaving ability of the phenoxide ion. Tetrahedral addition intermediates formed from ethyl imidates expel the attacking amine more rapidly than alcohol at pH values below the maximum in the pH rate profile[14a] so that the nucleophilic mechanism of isomerization should become significant for ethyl and methyl imidates under these conditions.

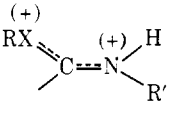
(3) The uncatalyzed isomerization of imidates may occur by rotation about the C–N bond (V) or by an inversion (lateral shift) mechanism (VI). The transition



V



VI



VII

state for rotation will be stabilized by electron donation from oxygen that increases the single bond character of the C–N bond (V) whereas the transition state for nitrogen inversion will be almost linear and will have less charge separation than that for rotation (VI).[18] There is evidence supporting a rotation mechanism for a few related compounds.[19] Cations of this class of compound, in which the electron pair on nitrogen is bound to a proton or Lewis acid, cannot undergo inversion[20,21] so that isomerization of the cationic species, when it is observed, must take place by rotation.[12,22] The rotation mechanism will be facilitated by protonation, which increases the single bond character of the C–N bond (VII), and the fact that there is no large increase in the rate of isomerization of *p*-tolyl *N*-methylacetimidate upon protonation suggests that isomerization of the basic form does not proceed through a rotation mechanism; this conclusion is supported by the very slow isomerization of methyl *N*-methylacetimidate in 100% sulfuric acid.[12] It is not certain whether the observed isomerization of the hydrochloride salt of II involves rotation of the cation or the inversion of a small concentration of base that is in equilibrium with the cation.[20]

(4) The inversion mechanism (VI) has been firmly established as the predominant pathway for *E*–*Z* isomerization about the free carbon–nitrogen double bond.[23,24] The simplest and perhaps the strongest evidence for the inversion mechanism is an insensitivity of the rate to solvent polarity, reflecting the relatively low polarity of the transition state for inversion; a small decrease in rate is observed in hydroxylic solvents that hydrogen bond to the free electron pair of nitrogen.[21,23] The observation that the isomerization of *p*-tolyl *N*-methylacetimidate is no faster in water than in carbon tetrachloride supports the conclusion that the mechanism for isomerization of this compound is nitrogen inversion.

Acknowledgments. We are grateful to Robert Suva and Dennis Haggerty for analysis of III and IV and to John Mieyal for his help with the nmr measurements.

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