

- (23) H. Tanida and T. Tsushima, *J. Am. Chem. Soc.*, **92**, 3397 (1970).
 (24) H. C. Brown and K. Takeuchi, *J. Am. Chem. Soc.*, **90**, 2691 (1968).
 (25) P. D. Bartlett and T. T. Tidwell, *J. Am. Chem. Soc.*, **90**, 4421 (1968).
 (26) H. C. Brown, F. J. Chloupek, and M.-H. Rei, *J. Am. Chem. Soc.*, **86**, 1248 (1964); H. C. Brown, I. Rothberg, P. v. R. Schleyer, M. M. Donaldson, and J. J. Harper, *Proc. Natl. Acad. Sci. U.S.A.*, **56**, 1653 (1966).
 (27) H. C. Brown and K. Ichikawa, *Tetrahedron*, **1**, 221 (1957).
 (28) H. C. Brown, R. S. Fletcher, and R. B. Johannesen, *J. Am. Chem. Soc.*, **73**, 212 (1951).
 (29) J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 3176 (1951).
 (30) J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 5034 (1951).
 (31) S. Winstein, B. K. Morse, E. Grunwald, H. W. Jones, J. Corse, D. Trifan, and H. Marshall, *J. Am. Chem. Soc.*, **74**, 1127 (1952).
 (32) C. H. DePuy, L. G. Schnack, and J. W. Hausser, *J. Am. Chem. Soc.*, **88**, 3344 (1966). The value for ρ^+ at 25 °C had to be based on only two values, for *p*-Me and *p*-H, whose rate constants could be extrapolated to that standard temperature. We have instituted a study of the solvolysis of 1-aryl-1-cyclopropyl *p*-nitrobenzoates with activating substituents in order to realize an alternative determination of ρ^+ , utilizing derivatives which undergo solvolysis with insignificant rearrangement.
 (33) X. Creary, *J. Am. Chem. Soc.*, **98**, 6608 (1976).
 (34) H. C. Brown, "Boranes in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1972.
 (35) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

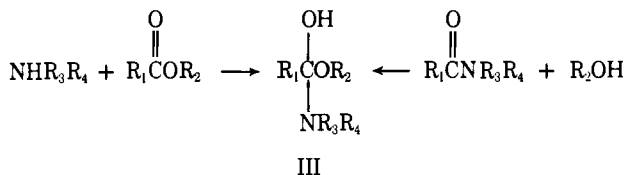
Aminolysis of Thionesters

Peter Campbell* and Barbara A. Lapinskas

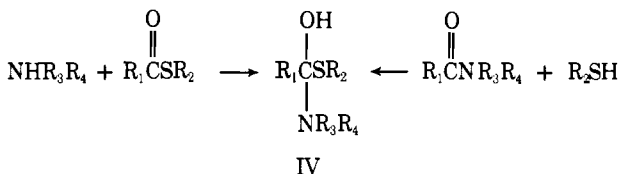
Contribution from the Department of Chemistry, New York University, New York, New York 10003. Received September 17, 1976

Abstract: Rates of reaction of *p*-nitrophenyl thionbenzoate (I) and *p*-nitrophenyl benzoate (II) with a series of primary amines and one secondary amine were measured. The pK_a 's of the conjugate acids of the amines studied range from 5.6 to 11. In contrast to the reaction of hydroxide ion, which is about equally reactive toward I and II, amines react up to 200 times faster with I than with II. Structure-reactivity correlations show a change in rate determining step in the aminolysis of I, consistent with rate limiting breakdown of a zwitterionic tetrahedral intermediate with moderately basic amines and rate limiting attack of highly basic amines. The break occurs with a less acidic leaving group than does the corresponding break in oxygen ester aminolysis and suggests that the tetrahedral intermediate formed from thionesters is more reactive than that formed from oxygen esters. This reactivity stems from the enhanced ability of sulfur to expel leaving groups.

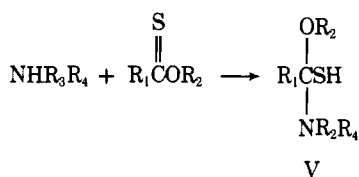
The mechanism of aminolysis of esters has recently received extensive attention.¹⁻⁴ This reaction is of special interest because one or more of the tetrasubstituted intermediates involved (III, its zwitterionic form, conjugate acid, and conjugate



base) are also formed in the acylation of chymotrypsin and other serine proteases by amides.³ A similar intermediate, IV,



is formed by the analogous acylation reaction of papain⁵ and other cysteine proteases,⁶ and is also generated in the aminolysis of thioesters.⁷ A closely related intermediate, V, is formally derived from the aminolysis of thionesters. We report here the first data on thionester aminolysis, which demonstrate the actual existence of V.

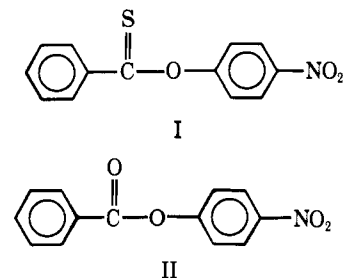


Aminolysis reactions of thionesters show extensive mechanistic similarity to the corresponding reactions of oxygen esters, but with differences which lend insight into the role of the

carbonyl heteroatom in acyl transfer and thionacyl transfer reactions.

Results

p-Nitrophenyl thionbenzoate (I), a thionester with a highly



acidic leaving group, undergoes reaction with amines and with hydroxide ion with liberation of *p*-nitrophenol or *p*-nitrophenoxide ion. Because I is sparingly soluble in water, reaction products and rates were determined in a mixed solvent containing 20% acetonitrile and 80% water by volume. Aminolysis and hydrolysis reactions of the corresponding oxygen ester, *p*-nitrophenyl benzoate (II), were studied, for the purposes of comparison, in the same mixed solvent.

The pseudo-first-order rate constants for the hydrolysis of I were identical when measured spectrophotometrically at either 288 (destruction of the $-\text{C}(=\text{S})\text{O}-$ chromophore⁸) or 400 nm (production of *p*-nitrophenoxide). From the rate constants shown in Figure 1 it can be seen that the reaction obeys the simple rate law

$$k_{\text{obsd}} = k_1 [\text{OH}^-] + k_0 \quad (1)$$

For comparison, rate constants for the hydrolysis of II under identical conditions are also included in Figure 1. For neither ester was buffer catalysis observed. The rates of uncatalyzed, or water, reactions (k_0) were too slow to be measured accurately at the pH values studied.

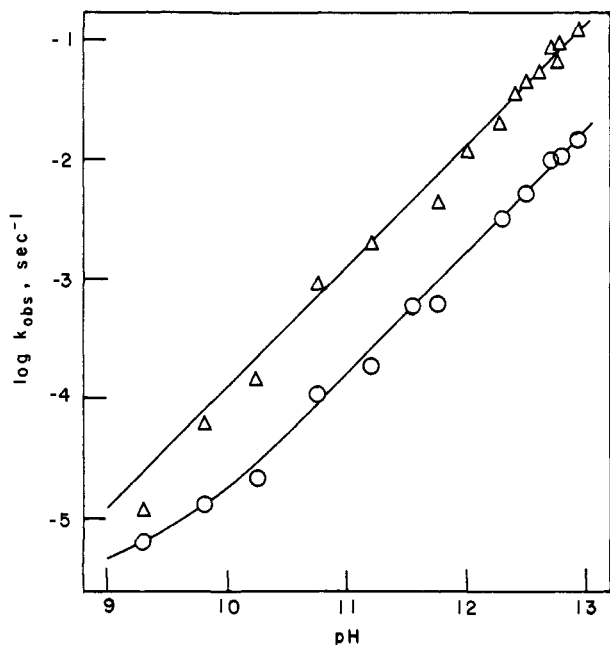


Figure 1. pH-rate profile for the hydrolysis of I (O) and II (Δ) at 25 °C, 20% CH₃CN, $\mu = 0.24$. The solid lines are calculated using eq 1, the rate constants of Table I, and an approximation of $2.3 \times 10^{-6} \text{ s}^{-1}$ for k_0 for I.

Table I. Second-Order Rate Constants for the Reaction of Hydroxide Ion and Amines with I and II^a

Nucleophile	pK_a^b	$k_1, \text{ M}^{-1} \text{ s}^{-1}$	
		I	II
Hydroxide	15.7 ^c	0.172	1.45
Diethylamine	10.9	0.695	0.0402
Ethylamine	10.8	2.56	0.990
Glycine	9.7	2.33	0.144
Benzylamine	9.4	1.86	0.0965
Glycylglycine	8.2	0.459	0.00547
Glycine ethyl ester	7.8	0.404	0.00330
Trifluoroethylamine	5.7	0.00992	

^a 25 °C, $\mu = 0.1$, 20% v/v CH₃CN. ^b Of conjugate acid. Determined under reaction conditions, except as indicated. ^c In water.

The rate constants for the reactions of I and II with various amines were determined under pseudo-first-order conditions, with the amine in large stoichiometric excess over ester or thionester. In all cases the production of *p*-nitrophenoxide or *p*-nitrophenol, monitored spectrophotometrically at 400 or 320 nm, respectively, obeyed first-order kinetics. The observed first-order rate constants can be described by the simple equation

$$k_{\text{obsd}} = k_1[\text{R}_1\text{R}_2\text{NH}] \quad (2)$$

Plots of k_{obsd} vs. total amine (free amine + ammonium ion) concentration passed through the origin, indicating that the contribution of terms for lyate-catalyzed and uncatalyzed reactions is negligible under the conditions studied. This is consistent with the rate constants for the hydroxide-catalyzed and uncatalyzed hydrolysis of I and II. The linearity of these plots indicates the absence of any higher order terms in eq 2. A typical plot is shown in Figure 2. The slopes of these plots may be replotted vs. the fraction of total amine in the basic form. Again the plots are linear and pass through the origin (Figure 3), showing that general acid catalysis is absent and leaving the single term in eq 2 as an accurate description of the rate law.

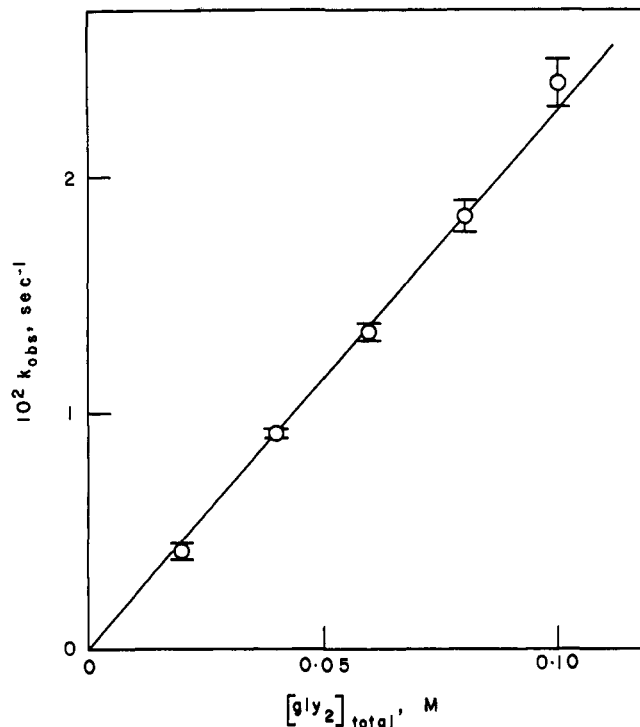


Figure 2. Typical plot of k_{obsd} for an aminolysis reaction of I as a function of total amine concentration.

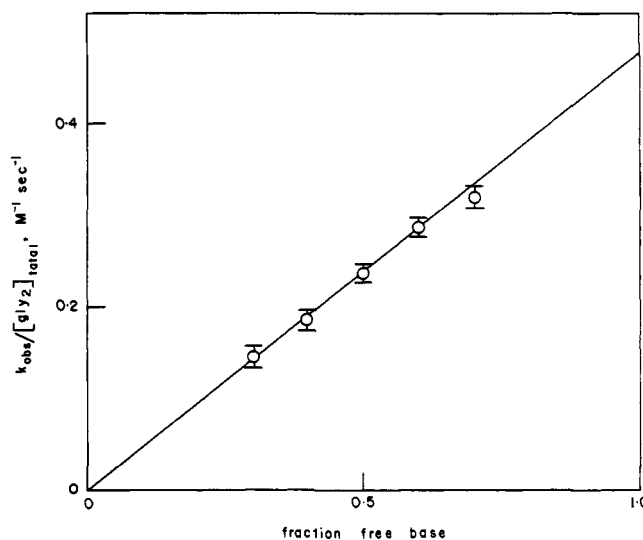


Figure 3. Typical plot of slopes from graphs such as Figure 2 as a function of fraction of total amine in the free base form.

The second-order rate constants, k_1 , for the reactions of I and II with hydroxide ion and with a series of amines are listed in Table I. A Brønsted plot of these rate constants as a function of the basicity of the amine is shown in Figure 4.

The rate constant for the very slow reaction of II with trifluoroethylamine was not determined accurately. A rough estimate of the half-life of this reaction (several days) is consistent with the extrapolation of the Brønsted line for II to the pK_a of trifluoroethylamine. Trifluoroethylaminolysis of substituted phenyl acetates is known to be well behaved, with its rate constant falling near the Brønsted line for these esters.¹

Reaction products were determined for hydrolysis and ethylaminolysis reactions of I after acidification and extraction of the reaction mixture. Gas chromatographic analysis showed thiobenzoic acid and *p*-nitrophenol, identified by comparison of retention times to those of authentic samples, as the only

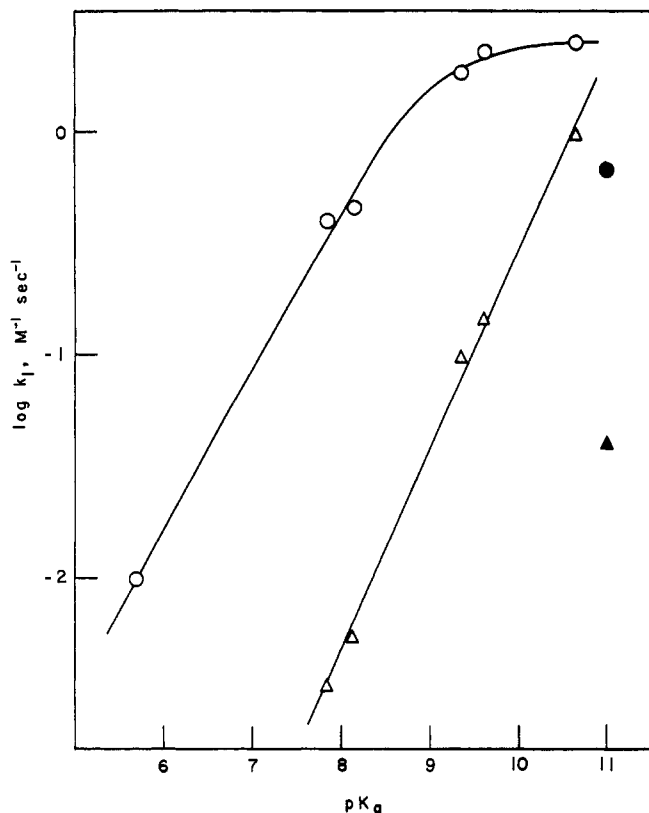
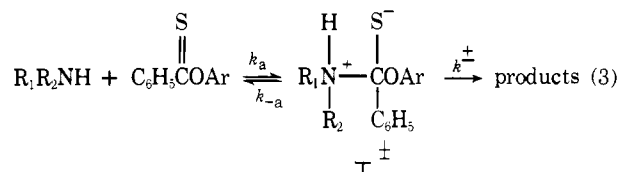


Figure 4. Brønsted plot of second-order rate constants for the reactions of amines with I (O) and II (Δ). Open symbols represent primary amines, solid symbols diethylamine.

products of the hydrolysis reaction. No benzoic acid was detected. Similarly, *p*-nitrophenol and *N*-ethylthiobenzamide were the only products of the ethylaminolysis reaction.

Discussion

A mechanism for the aminolysis of I is presented in eq 3.



This mechanism is identical with that proposed by Satterthwait and Jencks³ for the uncatalyzed aminolysis of phenyl oxygen esters. The mechanism of aminolysis of these reactive esters is relatively simple, involving only one tetrahedral intermediate, and being uncomplicated by any of the several proton transfer steps which may become rate determining in the aminolysis of esters with poorer leaving groups. For most phenyl oxygen esters, attack of amine is rapid and reversible, and expulsion of phenoxide rate determining. A transition to rate-limiting attack is observed with basic amines and highly reactive esters such as 2,4-dinitrophenyl acetate (DNPA) and *N*-acetoxy-4-methoxypyridinium ion (AMPP).¹

This mechanism is sufficient to explain our results on the aminolysis of I. The most striking feature of the aminolysis reaction is that, in contrast to hydroxide ion catalyzed hydrolysis, where rates are about equal for esters and thionesters,⁹ thionester I is as much as 200 times as reactive than its oxygen analogue II. This is not unreasonable if different steps of the mechanism are rate determining in the reactions of different nucleophiles. In the reaction of hydroxide with either ester or thionester the symmetry of the reaction pathway dictates that the formation of the tetrahedral intermediate be rate limiting when the leaving group is acidic, as in I and II. Thus the rela-

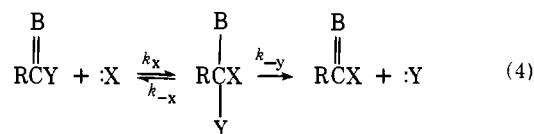
tive rates of hydrolysis of I and II depend primarily on the relative abilities of oxygen and sulfur to stabilize the negative charge which develops on the heteroatom as nucleophile attacks. On the other hand, in aminolysis the observed rate will depend on both the stability of the intermediate and the ability of $-O^-$ and $-S^-$ to expel the leaving group. Since it is not expected that the intermediates formed from the aminolysis of I and II will differ greatly in free energy,¹⁰ one reaches the tentative conclusion that the unshared electrons on sulfur can provide a significantly greater driving force for the expulsion of *p*-nitrophenoxide than can those on oxygen. This conclusion is supported by two other arguments which are discussed below.

For the reaction of the less basic primary amines with I and of all primary amines with II, linear Brønsted correlations are observed between rate constant and amine basicity (Figure 4). The slope of this plot, β_{nuc} , is 0.90 for the oxygen ester II. This is in excellent agreement with $\beta_{nuc} = 0.9 \pm 0.1$, observed for aminolysis of substituted phenyl acetates and AMPP.^{1,3} It is consistent with rate determining breakdown of T^\ddagger , in which nitrogen bears nearly a full positive charge in the transition state. β_{nuc} for the aminolysis of I is 0.71, significantly¹² smaller. This implies a less completely formed C-N bond in the transition state, and consequently less positive charge developed on nitrogen. One concludes that $-S^-$ (or $-S^{\delta-}$) is able to expel the leaving group with less than full assistance from the σ electrons of the C-N bond. Oxygen's more stringent requirements support the argument that sulfur can provide greater driving force for leaving group expulsion.

That an intermediate must exist in the aminolysis of thionesters is demonstrated by the break in the structure-reactivity plot of Figure 4. This break is consistent with a change in rate determining step with highly basic amines, where k_{-a} finally becomes slower than k^\ddagger . A similar break is observed in aminolysis of the highly reactive oxygen esters DNPA and AMPP, but not in the aminolysis of *p*-nitrophenyl acetate,¹ nor, as shown in Figure 4, of *p*-nitrophenyl benzoate. The reaction of highly basic amines with I involves an early transition state with very little C-N bond formation, as evidenced by the small value of β_{nuc} for this part of the Brønsted plot. An early transition state is also consistent with the diminished steric effect shown in the reaction of I with diethylamine. While the rate of diethylaminolysis of II is 60 times less than that expected on the basis of basicity, the same reaction of I is less than four times slower than its expected value. Clearly, steric hindrance is much more apparent in the transition state formed from the oxygen ester, where C-N bond formation is nearly complete.

The change between rate determining attack and breakdown of T^\ddagger derived from I occurs as the pK_a of the nucleophile reaches ~ 9.2 . The intermediate formed from I and such an amine breaks down with equally likely expulsion of amine and *p*-nitrophenoxide. Since the pK_a of *p*-nitrophenol is 7.1, one may conclude that amines are approximately 100 times better leaving groups from thionester tetrahedral intermediates than oxygen anions of comparable basicity. An analogous ratio of leaving group abilities from the corresponding oxygen ester tetrahedral intermediates has been determined, both from the break in the structure-reactivity correlation for the aminolysis of AMPP,¹ and from the direct study of the addition compounds formed from the *N,O*-trimethylenephthalimidinium cation.¹³ This ratio is 10^5 - 10^6 , showing that the sulfur-containing tetrahedral intermediate is less selective in its choice of leaving group, although nitrogen is still clearly preferred. Such reduced selectivity is generally interpreted¹¹ as indicating a more exergonic reaction step, and thus constitutes a final piece of evidence for the relative instability of the sulfur-containing tetrahedral intermediate, and therefore for the increased driving force for its breakdown.

Ritchie⁴ has correlated a large collection of rate constants for reactions of nucleophiles with oxygen esters and with cations, using a key assumption that the rate constants for breakdown of the tetrahedral intermediate formed from attack on an ester are independent of the identity of the ester. In other words, in eq 4 k_{-x} is independent of k_{-y} . He argues that the



quality of the correlations observed support the validity of the assumption. In contrast, Jencks¹³ has argued that the rates of expulsion of a leaving group are also determined partly by the driving force provided by the other group. Our data show that the alteration of the heteroatom B in eq 4 can change the relative values of k_{-x} and k_{-y} by 10^3 , and seem in better accord with the latter argument. Furthermore, the difference in β_{nuc} between oxygen esters and thionesters indicates that the amount of assistance rendered by X may vary as the structure of the intermediate changes. The simple assumption of independence of leaving group abilities, which holds well for a given family of tetrahedral intermediates where R and B are fixed, breaks down as the structure of the intermediate undergoes significant change.

Experimental Section

Proton magnetic resonance spectra at 60 MHz were recorded on a Perkin-Elmer R20 spectrometer; infrared spectra on a Perkin-Elmer 700 spectrometer; ultraviolet and visible spectra on a Cary 15 spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

***p*-Nitrophenyl Thionbenzoate (I).** Thiobenzoyl chloride¹⁴ (1.05 g, 6.71 mmol) and 1.20 g (7.41 mmol) of sodium *p*-nitrophenoxide were added to 40 mL of diethyl ether and heated at reflux for 2 h. The reaction mixture was extracted with water, dried, and solvent removed, leaving an oil which crystallized upon standing. This material could be recrystallized from ethanol, but proved to be a mixture of two compounds. No significant purification could be achieved by repeated crystallization, but preparative thin layer chromatography (Anasil GF⁻ silica gel, 10% calcium sulfate binder, 1-mm thickness) could be used to resolve the mixture. Elution with a 1:9 (v/v) chloroform-cyclohexane solution produced the thionester at R_f 0.44, the impurity at R_f 0.27. The resolution is highly sensitive to the composition of eluent. Yield of the crude mixture was 1.07 g (62% as thionester); about 45% of the material subjected to thin layer chromatography could be recovered as pure thionester. *p*-Nitrophenoxide (1.03 ± 0.05 mol), by spectrophotometric determination at 400 nm, was produced upon hydrolysis per mole of thionester. The impurity produced no 400-nm chromophore upon treatment with concentrated sodium hydroxide: mp 98–101 °C; NMR (CDCl₃) 6.6–7.4 (m, 7), 8.02 (d, J = 9 Hz, 2); IR (KBr) 1590, 1510, 1340, 1270, 1200, 1150; UV (CH₃CN) 288 nm, 17 400 M⁻¹ cm⁻¹. Anal. (C₁₃H₉NO₃S) C, H, N, S.

Ethylamine, diethylamine, glycine, and glycine ethyl ester were obtained as the hydrochloride salts from Eastman Chemical Co. Glycylglycine hydrochloride and 2,2,2-trifluoroethylamine hydrochloride were obtained from Aldrich Chemical Co. Benzylamine, from Aldrich Chemical Co., was distilled under nitrogen and converted to the hydrochloride by adding concentrated HCl to an ethanol solution of the amine until no further crystals were produced. The hydrochloride salts were recrystallized from various solvents to constant melting points (Table II). As a further test of purity, rate constants measured in solutions prepared from amine hydrochlorides were always compared to those measured in solutions prepared from hydrochlorides which had been recrystallized at least one more time. Rate constants were always equal within experimental error.

p-Nitrophenyl benzoate was prepared by the method of Kirsch et al.¹⁵ Sodium *p*-phenoxide was prepared by combining nearly saturated solutions of *p*-nitrophenol and sodium hydroxide in methanol. The resulting precipitate was recrystallized from methanol before use. *N*-Ethylthiobenzamide¹⁶ was prepared from the corresponding amide

Table II. Properties of Amine Hydrochlorides

Hydrochloride	pK _a ^a	pK _a ^b	Crystallization solvent	Mp, °C	Lit. ^c
Diethylamine	10.98	10.9	Et ₂ O	227–228	227–230
Ethylamine	10.63	10.8	2-Propanol	109–111	110
Glycine	9.6	9.7	Acetone	180–182	182
Benzylamine	9.34	9.4	CHCl ₃	159–166	156–158
Glycylglycine	8.13	8.2	EtOH	140–142	142
Glycine ethyl ester	7.83	7.8	EtOH	143–144	144
Trifluoroethylamine	5.7	5.7	2-Propanol	220–222	>200 ^d

^a In water, from W. P. Jencks and J. Regenstein in "Handbook of Biochemistry", 2nd ed, H. A. Sober, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1970, pp J-198–204. ^b Determined under reaction conditions: 20% CH₃CN, μ = 0.1. ^c From "Handbook of Chemistry and Physics", 56th ed, R. C. Weast, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1975, except as noted. ^d E. R. Bissel and M. Finger, *J. Org. Chem.*, **24**, 1256 (1959).

by the method of Voss and Walter.¹⁷ Acetonitrile was distilled from calcium hydride. Water was redistilled in glass vessels. All other materials were commercially available and were used without further purification.

Kinetic measurements were carried out spectrophotometrically using a Gilford Model 222 spectrophotometer. Initial concentrations of ester or thionester were typically about 2×10^{-5} M. All solutions contained 20% v/v acetonitrile. For hydrolysis reactions bicarbonate-carbonate buffers were used up to pH 11; at higher pH values sodium hydroxide was used. pH values reported are glass electrode readings obtained from the water-acetonitrile solutions with no attempt made to correct for the change in solvent composition. At high pH values meter readings corresponded with hydroxide concentrations determined by titration.

Solutions for aminolysis reactions were prepared by adding a calculated amount of a titrated solution of NaOH in 20% acetonitrile to a weighed amount of amine hydrochloride and diluting to the required volume with the same solvent. Less concentrated amine solutions of the same acid-base ratio were prepared by diluting with a solution of NaCl in 20% acetonitrile, to maintain both constant ionic strength and constant solvent composition.

The ionic strength of all solutions was 0.1, maintained by addition of NaCl. Solutions were stable, in the sense of giving reproducible rate constants, over the period of their use, generally a few days. No irregular behavior which might have resulted from acetonitrile hydrolysis or aminolysis was observed.

pK_a's of amines in 20% acetonitrile, μ = 0.1, were determined by measuring with a glass electrode a_{H+} of solutions containing equal amounts of amine and amine hydrochloride. The pK_a's so determined were independent of total amine concentration in the range 0.005–0.10 M, in which all rate constants were measured. These pK_a's are listed in Table II, along with the literature values for the same constants determined in aqueous solution.

Hydrolysis reactions were monitored by measuring *p*-nitrophenoxide production at 400 nm from I and II, or with II, by measuring disappearance of thionester at 288 nm. Identical rate constants were obtained at the two wavelengths. Aminolysis reactions were monitored by measuring *p*-nitrophenoxide production at 400 nm, except for the trifluoroethylaminolysis of I, which was monitored by measuring *p*-nitrophenol production at 320 nm. Measurements were made near the pK_a of the amine used, so that the amine served as its own buffer. Total amine concentrations were generally varied from 0.01 to 0.05 M, acid-base ratios from 1:4 to 4:1. All reactions showed clean first-order behavior through at least three half-lives. Stable infinity absorbances were observed, and plots of $\log(A_{\infty} - A)$ were used to calculate the observed first-order rate constants.

Plots of k_{obsd} vs. [amine]_{total} were analyzed by an unweighted least-squares fit to the equation $y = a_0 + a_1x$. In all cases a Student's *t* test at 95% probability showed no evidence that the intercept a_0 was different from zero. Similarly a plot of $k_{\text{obsd}}/[\text{amine}]_{\text{total}}$ vs. [amine]_{total} gave no evidence for a quadratic term in the rate law. The

data were then refit by unweighted least squares to the equation $y = a_1x$, and the calculated value of a_1 was taken as the second-order rate constant k_1 .

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the New York University Committee on Institutional Grants, for partial support of this research.

References and Notes

- (1) W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **90**, 2622 (1968).
- (2) G. M. Blackburn and W. P. Jencks, *J. Am. Chem. Soc.*, **90**, 2638 (1968); A. R. Fersht and W. P. Jencks, *ibid.*, **92**, 5442 (1970); C. B. Sawyer and J. F. Kirsch, *ibid.*, **95**, 7375 (1973); V. F. Smith, Jr., and G. L. Schmir, *ibid.*, **97**, 3171 (1975).
- (3) A. C. Satterthwait and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 7018 (1974).
- (4) C. D. Ritchie, *J. Am. Chem. Soc.*, **97**, 1170 (1975).
- (5) L. Polgar, *FEBS Lett.*, **47**, 15 (1974).
- (6) M. Shipton, M. P. J. Kierstan, J. P. G. Malthouse, T. Stuchbury, and K. Brocklehurst, *FEBS Lett.*, **50**, 365 (1975).
- (7) R. Barnett and W. P. Jencks, *J. Am. Chem. Soc.*, **90**, 4199 (1968); **91**, 2358 (1969); R. K. Chaturvedi and G. L. Schmir, *ibid.*, **91**, 737 (1969); G. M. Blackburn, *Chem. Commun.*, 249 (1970).
- (8) H. Viola, S. Schelthauer, and R. Mayer, *Chem. Ber.*, **101**, 3517 (1968).
- (9) This work shows ester II more reactive toward hydroxide by a factor of 8. Data for alkyl ester-thionester pairs show factors of 2 and 0.7. P. Y. Bruice and H. G. Mautner, *J. Am. Chem. Soc.*, **95**, 1582 (1973).
- (10) (a) For example, the rate constants for hydroxide ion catalyzed hydrolysis of ethyl acetate and ethyl thioacetate are essentially identical;^{10b} data on nucleophilic reactivity of thiolate anions and oxygen anions with *p*-nitrophenyl acetate indicate transition states differing in free energy by only about a kilocalorie for nucleophiles of corresponding structure.^{1, 10c} We will argue below that the intermediates do differ somewhat in free energy, reflecting as expected¹¹ differences in rates of reactions passing through these intermediates. (b) P. N. Rylander and D. S. Tarbell, *J. Am. Chem. Soc.*, **72**, 3021 (1950); B. K. Morse and D. S. Tarbell, *ibid.*, **74**, 416 (1952); (c) J. W. Ogilvie, J. T. Tildon, and B. S. Strauch, *Biochemistry*, **3**, 754 (1964).
- (11) J. E. Leffler, *Science*, **117**, 340 (1953); G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).
- (12) Because only three points of the Brønsted plot for I fall on the steep part of the plot, β_{nuc} is not known to high precision. Application of Student's *t* test shows a 70% probability that β_{nuc} for I is significantly smaller than that for II.
- (13) N. Gravitz and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 499 (1974).
- (14) R. Mayer and S. Schelthauer, *Chem. Ber.*, **98**, 829 (1965).
- (15) J. F. Kirsch, W. Clewell, and A. Simon, *J. Org. Chem.*, **33**, 127 (1968).
- (16) B. Böttcher and F. Bauer, *Justus Liebig's Ann. Chem.*, **568**, 218 (1950).
- (17) J. Voss and W. Walter, *Justus Liebig's Ann. Chem.*, **716**, 209 (1968).

Rearrangements of Nitrones to *O*-Alkyl Oximes via Geometrically Isomerizing Iminoxy Radicals¹

Thomas S. Dobashi, David R. Parker, and Edward J. Grubbs*

Contribution from the Department of Chemistry, San Diego State University, San Diego, California 92182. Received November 29, 1976

Abstract: The isomeric *N*-benzhydryl- α -phenyl- α -*p*-tolyl nitrones ((*E*)-1 and (*Z*)-1) have been prepared and separated. The stereochemical courses of their thermal rearrangements to the *O*-benzhydryl *p*-methylbenzophenone oximes ((*E*)-4 and (*Z*)-4) have been determined in *tert*-butyl alcohol. Initial rates of the N to O rearrangements have been measured in the same solvent. Using these data, the rates of interconversion of the intermediate *E* and *Z* iminoxy radicals have been estimated. Rates and activation parameters for the geometric isomerization of (*E*)- and (*Z*)-sodium *p*-methylbenzophenone oximate in methanol are reported. These data are discussed in terms of mechanisms for the N to O rearrangement and syn-anti isomerizations.

N-Benzhydryl- α , α -diarylnitrones are known to undergo thermal isomerization to corresponding *O*-benzhydryl oximes (*O*-ethers).^{2,3} However, the decomposition of these nitrones is more complicated than earlier envisioned. The available evidence⁴⁻⁷ now indicates that the decomposition involves the formation of iminoxy and benzhydryl radicals. Among several options available to these geminately formed radicals is the recombination at oxygen to form the *O*-ethers both intra- and intermolecularly.⁶

In the present study, the geometric courses of the N to O rearrangements of the syn and anti nitrones, (*Z*)-1 and (*E*)-1, have been determined. The results of this study lead to an estimate of the rates of geometric isomerization of the intermediate iminoxy radicals (*Z*)-2 and (*E*)-2. A striking contrast is observed between these rate constants and those for the geometric isomerizations of the corresponding oxime anions (*Z*)-5 and (*E*)-5. These data are discussed in terms of possible mechanisms of these isomerizations.

Results

Syntheses of the Nitrones and *O*-Benzhydryl Oximes and Geometric Assignments. A mixture of the nitrones (*Z*)-1 and (*E*)-1 was prepared by the reaction of *p*-tolylphenylketimine with *N*-benzhydrylhydroxylamine by a procedure similar to that described previously.³ The isomers were resolved by

fractional crystallization. Geometric assignments were made by a ¹H NMR method based upon the multiplicity characteristics of the ortho protons of the α -aryl ring cis to the oxygen atom.^{8,9} Thus (*Z*)-1 exhibits a low-field two-proton doublet at δ 7.99 which can be attributed to the ortho protons on an α -aryl ring which is (a) substituted in the para position and (b) cis to the oxygen atom. The doublet is presumably half of the AA'BB' signal involving coupling of the ortho protons to the meta protons which are obscured in the remaining complex aromatic multiplet at higher field. By contrast the two-proton absorption for (*E*)-1 in the region δ 8.14-7.43 is a complex multiplet.

The two *O*-benzhydryl oximes, (*Z*)-4 and (*E*)-4, were prepared by the alkylations of the geometrically pure oxime anions employing benzhydryl bromide in acetone. The geometric assignments were based upon the assumption that geometric retention of configuration was maintained during the alkylations.¹⁰ This is also consistent with the observed configurational stability of these oxime anions described below. Further support for these assignments comes from the composition of the *O*-ethers obtained from thermolyses (interrupted at early stages of the decompositions) of isomerically pure¹² nitrones.

Thermal Decompositions of Nitrones. *O*-Ether Product Composition as a Function of Percent Nitron Decomposition.