

[CONTRIBUTION FROM THE OLIN MATHIESON CHEMICAL CORPORATION, ENERGY DIVISION]

The Effect of Structure on the Reactivity of Oximes with Acyl Halides^{1a,b}

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RECEIVED AUGUST 26, 1958

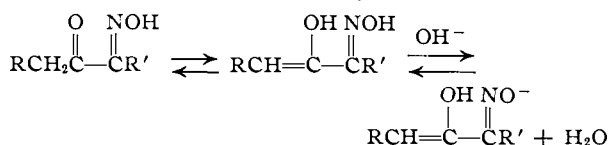
A study of the kinetics of the reactions of oximes with acyl halides in 95% aqueous acetone revealed that ordinary oximes, such as those derived from cyclohexanone and pinacolin, react as the neutral oximes whereas the reactive species α -oximo ketones are the oximate ions.

Introduction

Molecules containing both nucleophilic and electrophilic groups in the proper steric configuration take part in many chemical reactions at rates which exceed the combined activities of the individual groups.² This phenomenon has recently been confirmed in the reactions of catechol with acid halides.³ Catechol reacts with acid halides by a displacement reaction involving the monocatecholate ion.^{3,4}

It was of interest to determine whether other substances containing both electrophilic and nucleophilic groups in approximately the same steric configuration as is found in the monocatecholate ion would react similarly.

An example of substances closely allied to the catechols in that they contain both nucleophilic and electrophilic substituents in the same molecule are enolizable α -aldehydes and ketoximes.



This paper deals with the kinetics of the reaction of various oximes with propionyl fluoride, benzoyl fluoride and benzoyl chloride.

Experimental

The chemicals used in these studies were prepared in these laboratories, or were available commercially.

Isonitrosoacetone was prepared by the method of Meyer and Zublin.⁵ Isonitrosoacetyl acetone was prepared by the method of Wolf.⁶ Diisonitrosoacetone was prepared by the method of Koessler and Hanke.⁷

β -Benzil monoxime was prepared from the α -isomer by the method of Taylor and Lavington.⁸ Other oximes were prepared by the method of Shriner and Fuson.⁹

Propionyl fluoride and benzoyl fluoride were synthesized by the method of Mashentsev.¹⁰

Kinetic Studies.—The rates of reaction of acid halides with oximes were studied in a 5% (by volume) water in acetone solution at 25°. The experiments were conducted at constant pH employing a Beckman model K Automatic

Titrimeter with glass and calomel electrodes. The reaction temperature was regulated to ± 0.1 by the use of a jacketed reaction flask through which constant temperature water was circulated.

Procedure.—The oxime (5–10 meq. representing at least a fivefold excess) was dissolved in 200 ml. of solvent (95% acetone–water). A sufficient quantity of base was added to give the desired pH.¹¹ About 1 meq. of acid halide was added to the reaction mixture at time zero. The rate of addition of base by the titrimeter at constant pH was used as a measure of the rate of reaction. Reaction rate constants were obtained by the conventional graphical method for pseudo-first-order reactions. Second-order constants were obtained by dividing the first-order constants by the oxime or oximate ion concentration.¹² The results are summarized in Table I. Inasmuch as the rates of reaction with oximes under the investigated conditions were at least 100-fold faster than the self-hydrolysis reactions of propionyl fluoride and benzoyl fluoride, no correction for the hydrolysis was necessary. In the case of benzoyl chloride a correction was necessary and was made.¹³ The kinetic effect of the change in water concentration as a result of titration was negligible as indicated by the linearity of the pseudo-first-order plots up to about 50% reaction.

At the termination of the reaction a large volume of water was added to the reaction mixture. Considerable amounts of additional acid were released upon the addition of the water. The reaction liberated one equivalent of acid titratable in 95% acetone.

Tables I and II summarize the experimental results. The calculated second-order rate constants in Table I are based upon the total oxime concentration. The reaction rate constants in Table II are selected constants based upon the oximate ion concentration for those oximes whose rates of reaction vary with pH. The pK_a 's of the oximes were determined in the solvent medium used in this study.

Results and Discussion

The reactions between oximes and acyl halides in 95% aqueous acetone appear to follow two courses. In the case of the oximes such as those of pinacolin (I) and cyclohexanone (II) the rate constants were independent of the pH. In these cases a large variation in the (H⁺) did not change the rate of reaction (see Table I). These oximes are very weak acids and the concentrations of anion present

(11) The meaning of pH in a 95% acetone solution may be ambiguous. It is used in this paper to signify a reproducible value which is given by the measuring instrument. Titration curves of acetic and hydrofluoric acids in 95% acetone with 0.1 N aqueous sodium hydroxide were determined. The curves are normal in shape and the titrations have sharp end-points. The pK_a of the acid is displaced to the basic side by about 2–3 units. The apparent pK_a 's of hydrofluoric acid in 95 and 50% acetone solution are 6.0 and 4.6, respectively. The pK_a 's of several oximes were determined from the half-neutralization points. The values are given in Table II.

(12) These equations were used for the calculations:

$$k_1 = \frac{-2.3}{t} \log \frac{a}{a-x}; \quad k_2' = \frac{k_1}{(\text{Ox}^0)}; \quad k_2 = \frac{k_1}{(\text{Ox}^-)}$$

Where, k_1 is the pseudo-first-order constant, k_2' is the second-order constant based upon total oxime concentration in moles per liter (Ox⁰), k_2 is the second-order constant based upon oximate ion concentration in moles per liter (Ox⁻), a is the initial acid halide concentration, and x is the amount reacted at time t (in seconds).

(13) The self-hydrolysis constants for propionyl fluoride, benzoyl fluoride and benzoyl chloride are: $<4.2 \times 10^{-6}$ sec.⁻¹, $<4.2 \times 10^{-4}$ sec.⁻¹ and 2×10^{-4} sec.⁻¹, respectively, over the pH range studied.

(1) (a) This document is based upon work performed under Contract No. DA-18-108-CML-5635 for the Chemical Corps, Department of the Army. (b) Presented before the 133rd Meeting of the American Chemical Society, San Francisco, Calif., April, 1958.

(2) C. C. Swain and J. F. Brown, *THIS JOURNAL*, **74**, 2538 (1952).

(3) J. W. Churchill, M. Lapkin, F. Martinez and J. A. Zaslowsky, *ibid.*, **80**, 1944 (1958).

(4) B. J. Jandorf, T. Wagner-Jauregg, J. J. O'Neill and M. Stolberg, *ibid.*, **74**, 1521 (1952); J. Epstein, D. H. Rosenblatt and M. M. Demek, *ibid.*, **78**, 341 (1956).

(5) V. Meyer and J. Zublin, *Ber.*, **11**, 695 (1878).

(6) L. Wolf, *et al.*, *Ann.*, **325**, 139 (1902).

(7) K. K. Koessler and M. T. Hanke, *THIS JOURNAL*, **40**, 1717 (1918).

(8) T. W. J. Taylor and E. M. W. Lavington, *J. Chem. Soc.*, 1439 (1933).

(9) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948.

(10) A. I. Mashentsev, *J. Gen. Chem.*, (USSR), **15**, 915 (1915).

TABLE I
SPECIFIC RATE CONSTANTS OF OXIMES WITH ACID HALIDES AT 25° (95% ACETONE) BASED UPON TOTAL OXIME CONCENTRATION

Reactants		"pH"	Specific rate constant k_2' liters mole ⁻¹ sec. ⁻¹ × 10 ²	k_2' (H ⁺) × 10 ³
Oxime ^a	Acid halide ^b			
Cyclohexanone oxime	Propionyl fluoride	5.0, 6.5, 7.4	1.8	No pH dependence
Cyclohexanone oxime	Benzoyl chloride	6.0	78.0	No pH dependence
Cyclohexanone oxime	Benzoyl chloride	6.6	80.3	No pH dependence
α -Benzil monoxime	Propionyl fluoride	7.4	9.3 ± 0.8	3.73
α -Benzil monoxime	Propionyl fluoride	5.4, 5.8	No reaction ^c	..
α -Benzil monoxime	Benzoyl fluoride	7.0	4.07 ± 0.17	4.07
β -Benzil monoxime	Benzoyl fluoride	7.0	0.45	0.45
β -Benzil monoxime	Benzoyl fluoride	8.0	5.42 ± 0.8	0.542
Salicylaldehyde oxime	Benzoyl fluoride	7.0	1.6	1.6
Salicylaldehyde oxime	Benzoyl fluoride	7.4	3.66	1.47
Salicylaldehyde oxime	Benzoyl fluoride	8.0	17.0	1.7
Isonitrosoacetone	Propionyl fluoride	5.0	No reaction ^c	..
Isonitrosoacetone	Propionyl fluoride	7.4	90	36.0
Isonitrosoacetone	Benzoyl fluoride	5.6	No reaction ^c	..
Isonitrosoacetone	Benzoyl fluoride	7.0	7.68	7.67
Isonitrosoacetone	Benzoyl fluoride	7.2	11.03	7.0
Isonitrosoacetone	Benzoyl fluoride	7.4	16.7	6.67
Isonitrosoacetylacetone	Propionyl fluoride	7.4	666	267
Pinacoloneoxime	Benzoyl fluoride	6.5, 8.4	0.50	No pH dependence
Diisonitrosoacetone	Propionyl fluoride	7.4	>700 ^c	>280 ^c

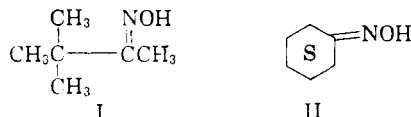
^a Oxime concentration, 2.5 to 5.0 × 10⁻² mole/liter. ^b 5 × 10⁻³ mole/liter. ^c Could not be measured accurately under the experimental conditions used with the other oximes.

TABLE II
SPECIFIC REACTION RATE CONSTANTS OF OXIMES WITH ACYL HALIDE BASED UPON THE OXIMATE ION CONCENTRATION

Reactants		"pKa" of ^a oxime	"pH"	k_2 , liters mole ⁻¹ sec. ⁻¹
Oxime	Acyl halide			
Isonitrosoacetone	Propionyl fluoride	10.95	7.4	3.17 × 10 ³
Isonitrosoacetone	Benzoyl fluoride	10.95	7.0	6.85 × 10 ²
			7.2	6.17 × 10 ²
			7.4	6.0 × 10 ²
Isonitrosoacetyl- acetone	Propionyl fluoride	10.05	7.4	3.0 × 10 ³

^a See footnote 10.

at the pH values employed in this study are very low. The neutral oxime is the reactive specie; its reactivity is sufficient to give a measurable rate of reaction with acid halides.

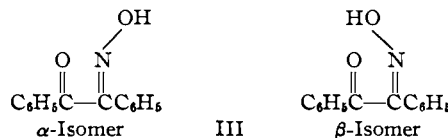


In contrast to the above the presence of an α -carbonyl substituent in the oxime leads to rates of reaction which vary with pH. For example, the specific reaction rate constant for the reaction of propionyl fluoride with isonitrosoacetone at a pH of 7.4 is 9 × 10⁻¹ liter mole⁻¹ sec.⁻¹; the comparable reaction rate constant with cyclohexanone oxime is 1.8 × 10⁻² liters mole⁻¹ sec.⁻¹. However, at pH 5 isonitrosoacetone reacts very slowly with propionyl fluoride while the reactivity of cyclohexanone oxime remains constant. These data indicate that ordinary oximes do not participate in the acylation reaction by the same mechanism as the oximino ketones.

The reaction of α -oximino ketones with acid halides leads to unidentified products with the libera-

tion of one equivalent of acid completely titrated in 95% acetone. The relative rates of reaction at constant pH of the α -oximinoketones with acid halides were in the following order: diisonitrosoacetone > isonitrosoacetylacetone > isonitrosoacetone > α -benzil monoxime > β -benzil monoximes.

Enolization of the oximinoketones does not explain the pH dependency of the reaction rates. Although oximes such as isonitrosoacetone can enolize, the benzil oximes (III) are incapable of such tautomerism.¹⁴



Inasmuch as enolization can be excluded in the case of the benzil oximes, a concerted displacement mechanism is not indicated despite the observed variation of the rate of reaction with pH.

A reasonable explanation of the role of the α -carbonyl substituent is that it prevents the undissociated oximino group from participating in the normal oxime reaction by virtue of its known inductive effect. This effect is manifested by the enhanced acidity of α -oximinoketones. It is apparent that the carbonyl oxygen is decreasing the electron density of the oximino oxygen. The anion of any oxime is a much stronger nucleophilic agent than the neutral oxime. The stronger the acid strength of the oxime the weaker would be the reactivity of the neutral oxime and the greater would be the concentration of oximate ion at any pH. In the pH range studied it would be expected that pH dependency would be noted with oximino ketones and no such dependency would be noted with ordinary oximes. The data presented

(14) Sidgwick's "Organic Chemistry of Nitrogen," T. W. J. Taylor and W. Baker, Oxford University Press, London, 1942, pp. 181-186.

in Table I and Table II support the above conclusions. Thus, isonitrosoacetyl acetone (pK_a 10.05) reacts about eight times faster at pH 7.4, with propionyl fluoride than isonitrosoacetone (pK_a 10.95).¹⁵

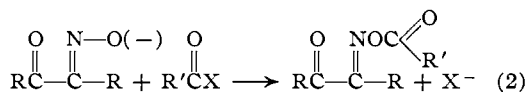
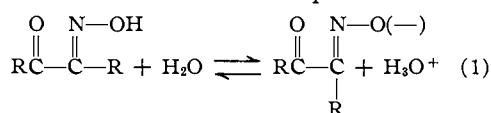
It is to be noted that the oximate ion concentration is given by the equation

$$(\text{Ox}^-) = (\text{Ox}^0) \frac{K_a}{(\text{H}^+) + K_a}$$

where (Ox^0) = total oxime + oximate ion concentration and (Ox^-) = oximate ion concentration.

When (K_a) is small relative to (H^+) (as is the case in these studies) the concentration of anion varies inversely with (H^+) . The data in Table I indicate that a variation of one pH unit changes the rate of reaction by a factor of approximately 10. Similarly other changes in pH follow the above equation. This is shown in the last column of Table I where k_2 (H^+) is shown to be relatively constant for each system.

The reaction mechanism in the case of oximino-ketones involves a nucleophilic attack on the substrate with the liberation of an equivalent amount

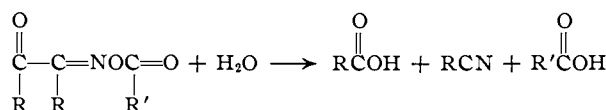


of acid. It is important to note that the oximate ion is consumed in step 2 and the acid is generated in step 1. The rate of reaction is thus determined directly by the rate of acid liberation at constant pH if the oximate ion concentration is very low. At the pH values of these experiments no appreciable quantity of the anion is present.

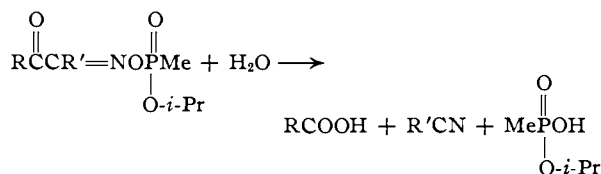
Although the initial product of the reaction is the acyl derivative of the oxime the addition of a large quantity of water slowly liberated acid from the reaction product. This is probably due to the hydrolysis of the keto and aldo-oxime propionates or benzoates.¹⁶

(15) This indicates that if a Brønsted free energy relationship of the form $k = gKB^\gamma$ existed, γ would have a value of 0.02.

(16) An alternate explanation involves the regeneration of oxime and the liberation of the carboxylic acid. This has been rejected on the basis of the amount of acid formed upon the addition of water. Although no quantitative measure of this acid was made it was in all cases more than expected from hydrolysis to the oxime.

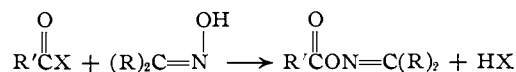


Green and Saville¹⁷ reported an analogous hydrolytic decomposition for oximino-ketone and oximino-aldehyde derivatives of isopropylmethylphosphonic acid.



The rate of formation of the initial product of the reaction of phosphonic acid halides with α -carbonyl oximes was found, in agreement with the results described in this paper, to be a function of the oximate ion concentration.

In the case of simple oximes the reaction proceeds as



The reaction occurs by the direct nucleophilic attack of the oxime oxygen on the carbonyl carbon. The faster rates of reaction reported in Table I for cyclohexanone oxime relative to pinacol oxime are as expected on the basis of steric consideration.

The rates of reaction of acid halides with α -benzil monoxime are about 10 times greater (at a fixed pH) than with the β -isomer. This is attributed to the greater acidity of the α -isomer because of hydrogen bonding in the β -isomer. The greater solubility of the β -benzil monoxime in organic solvents as compared to the α -derivative is strong evidence for chelation in the β -isomer.¹⁸

The rate of reaction of salicylaldehydeoxime with benzoyl fluoride was measured at pH 7.0, 7.4 and 8.0. The second-order specific reaction rate constant was directly proportional to the oximate ion concentration. The pH dependency is probably due to the decreased activity of the oximino groups owing to hydrogen bonding by the phenolic hydroxyl group; however, the possibility of a concerted mechanism cannot be ruled out.

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(17) A. L. Green and B. Saville, *J. Chem. Soc.*, 3887 (1956).

(18) L. Hunter, *Ann. Reports Progr. Chem.*, **43**, 141 (1946).