[CONTRIBUTION FROM THE CHEMOTHERAPY BRANCH, CHEMICAL WARFARE LABORATORIES, AND THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF DELAWARE]

Rates of Reaction of Vicinally Substituted Hydroxamic Acids with Isopropyl Methylphosphonofluoridate (Sarin)[1]

BY MARVIN A. STOLBERG[2] AND WILLIAM A. MOSHER

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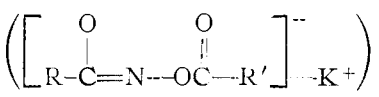
The half-time of hydrolysis, pseudo-monomolecular rate constants and the specific rate constants for the reaction of certain *o*-substituted benzohydroxamic and vicinal dihydroxamic acids with isopropyl methylphosphonofluoridate (Sarin) are reported. A plot of the $\log_{10}$ of the specific rate constants *versus* the pK_a's of the hydroxamic acids coincided with the line previously established for the *p*-substituted benzohydroxamic acids. Thus, there is no marked change of the rates of reaction of hydroxamic acids with Sarin due to vicinal substitution and no alteration in the nature of the reacting group by these substituents. The most probable reactive form of the hydroxamate ion is postulated.

An exhaustive investigation of the Lossen rearrangement of acylated hydroxamic acids has been reported by Hauser and associates.[3] It was shown that the rates of decomposition of the potassium salts of a series of dibenzohydroxamates



in which R is phenyl and R′ is phenyl, containing certain *o*-, *m*- and *p*-substituents, are, with the exception of the *o*-methoxy derivative, directly related to the ionization constants of the acids corresponding to R′COOH. In a series of dibenzohydroxamates studied, where R′ is phenyl and R is phenyl, containing certain *m*- and *p*-substituents, an inverse relationship exists between the rate constants and the ionization constants. However, the rate constants of the *o*-substituted phenyl derivatives are more than 100 times greater than would be predicted.

The peculiar effects of a substituent in the *o*-position have been attributed to an *ortho* or proximity effect[4]; however, it has not been possible to estimate the relative importance of electrical effects and specific *ortho* effects for a strongly polar substituent. Generally, these effects have been attributed to steric inhibition of resonance, F strain and hydrogen bonding. The enhancement in rates of reactions by vicinal groups has been reported frequently in the literature.[5]

In the investigation of candidate drugs for the destruction of the "nerve gas" isopropyl methylphosphonofluoridate (Sarin), Hackley, *et al.*,[6] and Swidler, *et al.*,[7] have observed the rapid reaction rates of certain *p*-substituted benzohydroxamic acids with this compound. In a search for more efficacious prophylactic compounds, it was important to determine whether these reactions could be markedly accelerated by placing substituents in the *o*-position. In the accompanying paper[8] the synthesis of certain *o*-substituted benzohydroxamic and vicinal dihydroxamic acids is described.

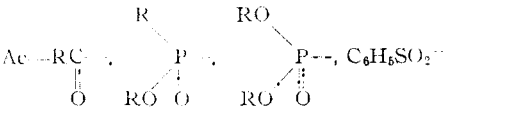
The half-times of hydrolysis of Sarin in the presence of various hydroxamic acids are reported in Table I. To assure first-order kinetics the reactions were carried out with a tenfold molar excess of hydroxamic acid over Sarin. The values were obtained by measuring the rate of addition of standard alkali consumed by the reaction mixture when maintained at a fixed *p*H by a Beckman autotitrator. A detailed discussion of the use of this instrument for studying the kinetics of the reaction of benzohydroxamic acid with Sarin was reported by Swidler and Steinberg.[9] They confirmed the validity of the use of acid production as a measure of the destruction of Sarin as well as the mechanism postulated for the reaction between hydroxamic acids and phosphoryl halides,[6] sulfonyl halides[10] or acyl halides[10a] in alkaline aqueous or inert solvents. These reactions proceed by the initial acylation of the hydroxamate ion followed by a Lossen rearrangement according to the scheme

$$(C_6H_5CONHO)^- + AcX \longrightarrow C_6H_5CONHOAc + X^-$$

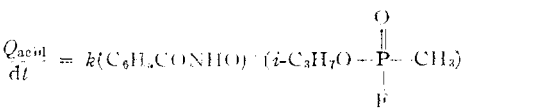
$$C_6H_5CONHOAc + OH^- \longrightarrow (C_6H_5CONOAc)^- + H_2O$$

$$(C_6H_5CONOAc)^- \longrightarrow C_6H_5NCO + Ac^-$$

$$C_6H_5NCO + (C_6H_5CONHO)^- \longrightarrow C_6H_5CONHOCONHC_6H_5$$



The rate of the reaction was found to be dependent on the concentration of the hydroxamate ion and the rate equation for the reaction was established as



Since the amount of hydroxamate ion used up in the course of the reaction is negligible in comparison

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(3) C. R. Hauser and W. B. Renfrow, THIS JOURNAL, **59**, 2308 (1937); R. D. Bright and C. R. Hauser, *ibid.*, **61**, 618 (1939).

(4) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 204.

(5) *Cf.* (a) C. G. Swain and J. F. Brown, Jr., THIS JOURNAL, **74**, 2538 (1952); (b) D. E. Pearson and W. E. Cole, *J. Org. Chem.*, **20**, 488 (1955).

(6) B. E. Hackley, Jr., R. Plapinger, M. A. Stolberg and T. Wagner-Jauregg, THIS JOURNAL, **77**, 3651 (1955).

(7) R. Swidler, R. Plapinger and G. M. Steinberg, to be published shortly.

(8) M. A. Stolberg, W. A. Mosher and T. Wagner-Jauregg, THIS JOURNAL, **79**, 2615 (1957).

(9) R. Swidler and G. M. Steinberg, *ibid.*, **78**, 3594 (1956).

(10) (a) M. A. Stolberg, R. C. Tweit, G. M. Steinberg and T. Wagner-Jauregg, *ibid.*, **77**, 765 (1955); (b) C. D. Hurd and L. Bauer, *ibid.*, **76**, 2791 (1954).

TABLE I

RATES OF REACTION OF SARIN (1×10^{-4} *M*) WITH *o*-SUBSTITUTED BENZOHYDROXAMIC AND VICINAL DIHYDROXAMIC ACIDS (1×10^{-3} *M*) AT *p*H 7.6 AND 30.5 ± 0.20°

Hydroxamic acid	pK_a	Anion $\times 10^4$ *M*	Half-time of hydrolysis, min.	k^a_{obs} $\times 10^3$, sec.$^{-1}$	k,[b] l. mole^{-1} sec.$^{-1}$
C_6H_5–	8.8	0.592	7.5	1.54	26.1
o-HOC_6H_4–	7.8	3.86	6.5	1.78	4.6
o-$NO_2C_6H_4$–	8.2	2.04	7.8	1.45	7.4
o-$CH_3OC_6H_4$–	8.9	0.476	11.5	1.00	21.1
o-$NH_2C_6H_4$–	9.0	0.382	8.8	1.32	35.3
o-$(CH_3)_2NC_6H_4$–	9.05	0.342	9.0	1.28	37.5
$C_8H_{12}O_5N_2$[c]	9.3	0.200	14.0	0.83	41.7
$C_8H_{14}O_4N_2$[d]	9.75	0.070	9.8	1.17	168

[a] k_{obs} = pseudomonomolecular rate constant = k-$(RCONHO)^-$. [b] k = specific rate constant. [c] *exo-cis*-3,6-Endoxohexahydrophthalohydroxamic acid. [d] *cis*-Hexahydrophthalohydroxamic acid.

with the total, the velocity equation takes the form

$$\frac{dQ_{acid}}{dt} = k_{obs}(i\text{-}C_3H_7O\text{—}\overset{\overset{O}{\|}}{\underset{\underset{F}{|}}{P}}\text{—}CH_3)$$

where $k_{obs} = k(C_6H_5CONHO^-)$.

Swidler, Plapinger and Steinberg[7] have studied the reactions of *p*-substituted benzohydroxamic acids with Sarin and have come to the following conclusions: 1. A conventional Hammett plot of log k/k_0 *vs.* σ established a ρ of -0.77 ± 0.05. This value was reported to be consistent with a gross mechanism involving the attack of an anion upon a neutral molecule and inconsistent with a rate step involving Lossen rearrangement which yielded larger negative ρ-values (ρ *ca.* -2.6).[11] The excellence of the fit of compounds over a rather wide range of σ-values attested to the apparent mechanistic unity throughout the series and the practical utility of determining the comparative reactivities of the hydroxamic acids toward Sarin by following the rate of acid production.

2. A conventional Brönsted plot of log k *vs.* pK_a of *para* substituted benzohydroxamic acids yielded a β of $+0.78$, whereas the comparable value for the line upon which the hydroxide ion lies was *ca.* $+0.5$. It was therefore postulated that the inordinate reactivity of the hydroxamic acids most probably is due to a stereospecific attack upon the Sarin molecule.

3. The hydroxamic acids could be considered as polyfunctional catalysts and react with Sarin in a manner similar to catechol.[12]

The pseudo-monomolecular rate constant (k_{obs}) and specific rate constant (k) for the reaction of Sarin with each of the *o*-substituted benzohydroxamic and vicinal dihydroxamic acids are reported in Table I. Values of log k *versus* pK_a for these compounds fell, within experimental error, on the line established for *p*-substituted benzohydroxamic acids (Fig. 1). It is obvious that a vicinal group

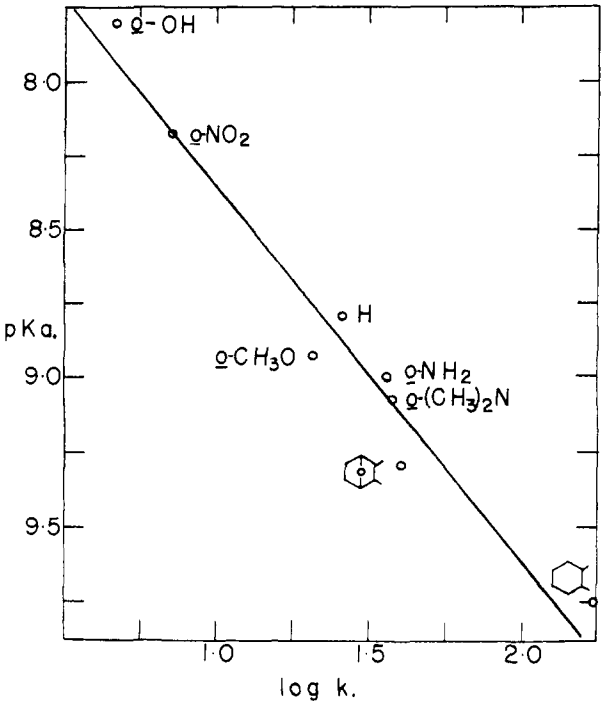


Fig. 1.—Relationship between pK_a values of certain *o*-substituted benzohydroxamic and vicinal dihydroxamic acids and log k for their reaction with Sarin. The equation for the line was obtained from a least squares plot of *p*-substituted benzohydroxamic acids.

produces no marked acceleration in the rate of reaction of a hydroxamic acid with Sarin. Changes in the rate of reaction were dependent only on the ionization constant of the hydroxamic acid. Since these derivatives adhere to a Brönsted relationship, it follows that there is no alteration of the reacting group by vicinal substituents.

The tautomeric structures of hydroxamic acids are

$$R\text{—}\overset{\overset{OH}{|}}{C}\text{=}N\text{—}OH \rightleftharpoons R\text{—}\overset{\overset{O\ H}{|\ |}}{C}\text{—}N\text{—}OH$$

The abstraction of a proton with base could thus provide

$$R\text{—}\overset{\overset{OH}{|}}{C}\text{=}N\text{—}O^- \qquad R\text{—}\overset{\overset{O\ H}{\|\ |}}{C}\text{—}N\text{—}O^-$$
A B

$$R\text{—}\overset{\overset{O^-}{|}}{C}\text{=}N\text{—}OH \leftrightarrow R\text{—}\overset{\overset{O}{\|}}{C}\text{—}\bar{N}\text{—}OH$$
C

Although absolute evidence as to which anion (A, B or C) is the reactive species cannot be provided, the *o*-derivatives yield information that enables one to postulate the most probable reactive form.

Examination of data in Table II reveals that a comparable relationship exists between the acidities of the benzohydroxamic acid and phenylpropiolic acid series, but they are quite different from the benzoic acid series. In the benzoic acid series the *ortho* isomer is markedly stronger than the *para* regardless of substituent, whereas in the former

(11) H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

(12) (a) W. A. Mosher and R. Denison, Annual Progress Report of Research for Chem. Corps, June 15, 1952; (b) J. Esptein, D. H. Rosenblatt and M. M. Demek, THIS JOURNAL, **78**, 341 (1956); (c) T. Wagner-Jauregg, *Arzneimittel-Forsch.*, **6**, 194 (1956).

cases the *ortho* is weaker than the *para* for the nitro group and stronger than the *para* for the methoxy group. This suggests that structure C would not be the predominant form in the ionization, since this form would be expected to be influenced by *o*-substituents.

TABLE II

pK_a'S OF *o*- AND *p*-SUBSTITUTED BENZOHYDROXAMIC, PHENYLPROPIOLIC AND BENZOIC ACIDS

Substituent	pK_a RCON-HOH	pK_a RC≡C—COOH[a]	pK_a RC≡C—COOH[b]	pK_a RCOOH[c]
C_6H_5–	8.8	3.58	3.24	4.20
o-$NO_2C_6H_4$–	8.2	3.39	2.83	2.17
p-$NO_2C_6H_4$–	8.0	3.26	2.57	3.42
o-$CH_3OC_6H_4$–	8.9	..	3.37	4.09
p-$CH_3OC_6H_4$–	9.0	..	3.44	4.47
o-ClC_6H_4–	..	3.51	3.08	2.92
p-ClC_6H_4–	8.6	3.47	3.07	3.98

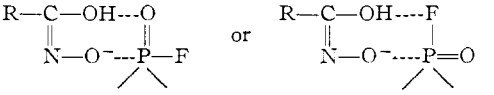
[a] Apparent pK_a's in 50% ethanol–50% water (by volume); Roberts and Carboni.[13] [b] Apparent pK_a's in 35% dioxane–65% water (by weight); Newman and Merrill.[14] [c] pK_a's in water; J. F. Dippy and J. E. Page, *J. Chem. Soc.*, 357, (1938). All pK_a's at 25°.

A linear relationship exists between the logarithms of the ionization constants and reaction rates of *o*-, *m*- and *p*-substituted phenylpropiolic acids with diphenyldiazomethane,[13] whereas ester saponification[13] and acid-catalyzed esterification[14] of *o*-substituted phenylpropiolic acids were faster than would be expected from the relationship between the rates and ionization of the *m*,*p*-substituted acids. This effect was ascribed to a decrease in the reaction site–ring distance, since both esterification and hydrolysis of esters involve attack of a nucleophilic agent at the carbonyl carbon.[13]

Since a linear relationship does exist between the logarithms of the ionization constants and the reaction rates of *o*-, *m*- and *p*-substituted benzohydroxamic acids with Sarin, it seems improbable that structure C is the reactive form because the *o*-substituents do not produce a deviation from linearity that would be expected if reaction occurred close to the ring.

Thus, tautomers A and/or B would appear to be the reactive forms of the anion in both ionization and reaction with electrophilic reagents, since both would take place at a site which is at a maximum distance from the *o*-substituent. However, if the inordinate reactivity of the hydroxamate ion (when compared to simple bases, *i.e.*, OH^-) is due to a concerted attack upon the Sarin molecule in a manner similar to catechol, the most probable reactive form is tautomer A.

Thus the interpretations presented above offer support to the mechanism originally postulated.[12c]



Experimental

Ionization Constants.—The pK_a's reported in Table I were obtained from conventional potentiometric titrations in the presence of 0.1 *M* potassium nitrate. All compounds reported except for *o*-hydroxybenzohydroxamic acid were either sufficiently soluble in water to titrate directly with standard base or stable in alkali so that excess standard base could be added and back titrated with standard acid. Due to the slight decomposition of *o*-hydroxybenzohydroxamic acid in alkali, the value reported is uncertain.

Kinetic Method.—The half-times of hydrolysis of Sarin in the presence of various hydroxamic acids are reported in Table I. The values were obtained by measuring the rate of addition of standard alkali taken up by the reaction mixture when maintained at a fixed *p*H by a Beckman autotitrator. The reaction was carried out as follows: a quantity of the hydroxamic acid was dissolved in 0.1 *M* potassium nitrate solution contained in a jacketed beaker through which water of 30.5 ± 0.2° was circulated from a thermostatically controlled bath. The final concentration of the hydroxamic acid in these experiments was 10^{-3} *M*. The solution was adjusted to *p*H 7.6 and the volume to 245 ml.

A stock solution of 0.65 ml. of Sarin (99% pure) in 100 ml. of water was prepared fresh daily. *Caution* should be exercised since Sarin is *extremely toxic* in both the liquid and vapor phase and must be handled in a hood of large capacity. In the *p*H range of 4 to 6, which the solution assumed, Sarin is resistant to hydrolysis. A 5-ml. aliquot was then added to the hydroxamic acid solution. The final concentration of the solution with respect to Sarin was 10^{-4} *M*. The quantity of standard 0.01 *N* sodium hydroxide delivered by the autotitrator *vs.* time was recorded.

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(13) J. D. Roberts and R. A. Carboni, THIS JOURNAL, **77**, 5554 (1955).

(14) M. S. Newman and S. H. Merrill, *ibid.*, **77**, 5552 (1955).

[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Rearrangement and Decarboxylation Reactions of N,N-Dimethylglycine Oxide

BY C. C. SWEELEY AND E. C. HORNING

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Ferric ion-catalyzed reactions of dimethylglycine oxide were studied in aqueous solution over the *p*H range 2–9. It was found that two modes of N-oxide rearrangement occurred; the products were formaldehyde and sarcosine, and dimethylamine and glyoxylic acid. In addition to these rearrangement reactions, a decarboxylation reaction also occurred, with a maximum rate near *p*H 8. The products of this reaction were carbon dioxide, formaldehyde and dimethylamine; these correspond to the products of oxidative decarboxylation of an α-amino acid.

A preliminary report from this Laboratory described a ferric ion-catalyzed rearrangement reaction of *t*-amine oxides.[1] This rearrangement (reaction A) was presumed to give a carbinolamine (II); the observed reaction products were a secondary amine (through reaction B) and formaldehyde or formic acid and the *t*-amine (reaction C). These products are equivalent to those ex-

(1) M. S. Fish, C. C. Sweeley and E. C. Horning, *Chemistry and Industry*, R. 24 (1956).