Anal Calcd.: C, 18.0; F, 18.9; I, 63.1. Found: C, 17.9; F, 18.9; I, 61.5.

2. **Perfluoropolyphenyl. a. From 1,4-Dibromo-2,3,5,6-tetrafluorobenzene.**—Equal weights of dibromotetrafluorobenzene[5] and activated copper powder (see Kleiderer and Adams[8]) were mixed thoroughly and sealed in a tube under helium. The tube was heated in a furnace for 80 hours at 200°. After cooling, the tube was opened and the contents extracted with benzene. The benzene solution was poured into ethanol and a white solid precipitated. This solid melted at 247–260°. It was identified as a low polymer containing 18.5% bromine corresponding to $Br(C_6F_4)_nBr$, where n = 4–5. The insoluble residue was treated repeatedly with warm nitric acid and concentrated ammonia to remove copper and copper bromide. A light-tan powder remained which contained about 1% of inorganic material. On analysis the compound was found to contain 11.8% bromine, corresponding to $n \cong 8$. No melting point could be obtained upon heating a sample to 360°.

b. From 1,4-Diiodo-2,3,5,6-tetrafluorobenzene.—Activated copper powder was mixed thoroughly with twice its weight of diiodotetrafluorobenzene in an open test-tube. This tube was immersed in an oil-bath and gradually heated to 200° while stirring the contents with a thermometer. At about 200° the reaction became exothermic and the temperature rose rapidly to 290° while the material solidified. It was then heated for an additional half-hour at 250°. The solid was removed, crushed and boiled in benzene. The benzene solution, upon treatment with methanol, yielded only a minute amount of solid. The remaining solid was boiled with pyridine which formed a soluble complex with the copper salt. Subsequently, the solid residue was treated with dilute nitric acid and ammonia, washed with methanol and ether and dried. This sample was analyzed for C, F, and I with the following results: C, 40.6; F, 39.4; I, 14.4. On the basis of the iodine analysis, this indicates $n \cong 10$. The purified sample was a grayish powder which could be heated at 500° in a sealed tube without melting. Some decomposition occurred at this temperature, as evidenced by the appearance of iodine vapor in the tube, but the bulk of the material remained intact.

Acknowledgments.—The authors gratefully acknowledge the aid of Dr. F. L. Mohler and Mr. P. Bradt, who performed the mass spectrometer measurements, and Messrs. R. A. Paulson and L. Machlan, who performed the chemical analyses.

(8) E. C. Kleiderer and R. Adams, THIS JOURNAL, **55**, 4219 (1933).

WASHINGTON, D. C.

Acceleration of the Hydrolysis of Organic Fluorophosphates and Fluorophosphonates with Hydroxamic Acids

BY B. E. HACKLEY, JR., R. PLAPINGER, M. STOLBERG AND T. WAGNER-JAUREGG

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Wilson and Meislich[1] reported that acetylcholinesterase inhibited by diisopropyl fluorophosphate (DFP) can be reactivated in the presence of nicotinhydroxamic acid methiodide. It had been observed previously in this Laboratory that certain hydroxamic acids (RCONHOH) at a *p*H of 7.5 and higher, strongly accelerate the hydrolysis of diisopropyl phosphorofluoridate[2] and of isopropyl methylphosphonofluoridate (sarin). Since the enzyme reactivation reaction and the hydrolysis reaction may be based on a similar principle and their comparison may help to obtain more information about their mechanism, we wish to report briefly some of our experiments.

(1) I. B. Wilson and E. K. Meislich, THIS JOURNAL, **75**, 4628 (1953).

(2) This is the new name for diisopropyl fluorophosphate, as proposed by the American Chemical Society; *Chem. Eng. News*, **38**, 4514 (1952).

The half-time of hydrolysis of sarin in the presence of more than thirty hydroxamic acids of a wide variety of structures ranged from about 1 to 7 minutes (2.3×10^{-3} *M* sarin, 11.5×10^{-3} *M* hydroxamic acid, *p*H 7.6, 30°) as compared with 300 minutes for the spontaneous hydrolysis of sarin. The five most effective hydroxamic acids found, thus far, are sorbhydroxamic acid, *p*-methoxybenzohydroxamic acid, *p*-methylbenzohydroxamic acid, dipicolinhydroxamic acid (pyridine-2,6-dihydroxamic acid) and picolinhydroxamic acid, arranged approximately in order of decreasing activity at *p*H 7.6.

Tables I and II list the half-times of the hydrolysis of DFP in the presence of aliphatic, aromatic and heterocyclic hydroxamic acids.

TABLE I

HYDROLYSIS OF 10^{-6} MOLE OF DFP + 10^{-6} MOLE OF ACETHYDROXAMIC ACIDS IN 2.2 ML. OF BICARBONATE–CO_2 BUFFER, *p*H 7.6 AT 38°[a]

	Half-time of hydrolysis, min.	Moles of acid (as CO_2) produced per mole of DFP at the end of reacn.
DFP alone	2500–3000	2
DFP + acethydroxamic acid	36	1.9
DFP + aminoacethydroxamic acid	29	1.8
DFP + 3-pyridylacethydroxamic acid	23	2.0

[a] The rates of hydrolysis were determined manometrically as described in earlier papers.[3,4,5]

TABLE II

HYDROLYSIS OF 57.5×10^{-6} MOLE OF DFP + 287.5×10^{-6} MOLE OF BENZOHYDROXAMIC ACID AND ITS PYRIDINE ANALOGS IN 34 ML. OF 0.1 *M* KCl AT *p*H 7.6 AND 30°[a]

	Half-time of hydrolysis	Moles of acid produced per mole of DFP at end of reacn.
DFP alone	Several days	2
DFP + benzohydroxamic acid	22 min.	2.2
DFP + nicotinhydroxamic acid	20 min.	2.2
DFP + nicotinhydroxamic acid methiodide	68 min.	0.6
DFP + picolinhydroxamic acid	20 min.	2.0
DFP + picolinhydroxamic acid methiodide	65 min.	0.3
DFP + isonicotinhydroxamic acid	28 min.	2.2
DFP + isoniotinhydroxamic acid methiodide	73 min.	0.4

[a] A Beckman automatic titrator was used in these experiments for the determination of the acid produced during the hydrolysis.

From the figures in Table I it can be seen that introduction of an amino or a pyridino group into the α-position of acethydroxamic acid leads only to slightly increased reactivity with DFP. When a pyridine nucleus is substituted for the phenyl group in benzohydroxamic acid the differences in the observed half-times are even less (Table II).

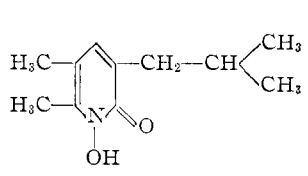
(3) B. J. Jandorf, T. Wagner-Jauregg, J. J. O'Neill and M. Stolberg, THIS JOURNAL, **74**, 1521 (1952).

(4) T. Wagner-Jauregg and B. E. Hackley, Jr., *ibid.*, **75**, 2125 (1953).

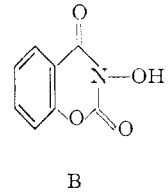
(5) T. Wagner-Jauregg, B. E. Hackley, Jr., *et al.*, *ibid.*, **77**, 922 (1955).

Quaternization of the nitrogen in pyridinehydroxamic acids decreased the reactivity markedly. However, since only 0.3–0.6 mole of acid was titrable with these substances it seems questionable whether the half-times observed in these cases are directly comparable with the other values.[6]

The rate of reaction between DFP or sarin and hydroxamic acids becomes much faster with increasing *p*H of the solution. This demonstrates that probably the hydroxamic acid anion is the reactive form. The common hydroxamic acids are weakly acidic. We determined the pK_a's of fifteen of the hydroxamic acids which reacted rapidly with sarin and found values approximately between 7.8 and 9.3. Two cyclic hydroxamic acids of structure A[7] and B[8] with a pK_a of 5.7 and 6.4, respectively, reacted only at a very slow rate with DFP. The relation between the acidity of the hydroxamic acids and their reactivity with phosphoro- and with phosphonofluoridates will be more extensively discussed in later publications.



A



B

Approximately two moles of acid is formed during the reactions reported in Table I and II which is indicative of hydrolysis of DFP with formation of HF and $HOPO(OR)_2$. In experiments with benzohydroxamic acid, nicotinhydroxamic acid and picolinhydroxamic acid, using the reaction conditions described in Table II, it was found that 1.5 to 2 moles of hydroxamic acid disappeared during the reaction. This demonstrates that the hydroxamic acids are not true catalysts in the hydrolysis reaction inasmuch as they undergo transformation.

The reaction product between DFP or sarin and benzohydroxamic acid has been isolated and identified as O-phenylcarbamyl benzohydroxamate, $C_6H_5CONHOCONHC_6H_5$ (II). The reaction mechanism probably involves the preliminary phosphorylation of the hydroxamate ion by DFP or by sarin. The unstable phosphorylation product (I), which never could be isolated, undergoes a Lossen rearrangement to give the hydrolyzed DFP or sarin and phenyl isocyanate, which reacts with more hydroxamic acid to give the final isolated product (II)

$$PhCONHOH + FP(O)(OR)_2 = PhCONHOP(O)(OR)_2\,(I) + HF \quad (1)$$

$$I \longrightarrow PhNCO + HOP(O)(OR)_2 \quad (2)$$

$$PhNCO + PhCONHOH = PhCONHOCONHPh(II) \quad (3)$$

$$2PhCONHOH + FP(O)(OR)_2 = PhCONHOCONHPh\,(II) + HF + HOP(O)(OR)_2 \quad (1 + 2 + 3)$$

The same product (II) also can be obtained by the reaction of benzohydroxamic acid with benzenesulfonyl chloride[9,10] instead of DFP or sarin, and the mechanism of the reaction is identical with all three reagents.

With *p*-methylbenzo-, *p*-nitrobenzo-, *p*-cyanobenzo-, picolin- and nicotinhydroxamic acids and sarin, reaction products analogous to O-phenylcarbamyl benzohydroxamate (II) were obtained. Other hydroxamic acids probably follow the same pathway of reaction.

Several hydroxyamidines, RC(=NH)NHOH, which are the imino analogs of hydroxamic acids, have been found to react with DFP or sarin, although much slower than the corresponding hydroxamic acids. In this case stable phosphorylation products could be isolated and will be described in a later publication.

The reactivation of DFP-inactivated cholinesterase by hydroxamic acids might be visualized as a transfer of the phosphoryl group to the hydroxamic acid, with subsequent rearrangement of the hypothetical phosphorylated hydroxamic acid, thus $ChE\text{-}P(O)(OR)_2 + RCONHOH \rightarrow ChE + RCONHOP(O)(OR)_2$ (unstable). There is as yet no experimental proof for this assumption.

Experimental

A. Compounds Investigated.—The hydroxamic acids used in this study were for the most part synthesized in this Laboratory. A few were obtained commercially, and some samples were received as a result of requests from outside agencies (see Acknowledgments).

In general, the hydroxamic acids were prepared by standard procedures from the corresponding carboxylic esters or acid chlorides by reaction with hydroxylamine.[11] Those hydroxamic acids which are water soluble usually were isolated as their relatively insoluble cupric salts. Treatment with hydrogen sulfide removed the copper as copper sulfide and yielded the free hydroxamic acid.

p-Aminobenzohydroxamic acid was obtained from *p*-nitrobenzohydroxamic acid by catalytic reduction in alcohol with platinum oxide at room temperature.

The methiodides were prepared by refluxing the hydroxamic acid in 95% ethanol for 4 hours with a 100% excess of methyl iodide, and were isolated by standard techniques. The reaction of picolinhydroxamic acid with methyl iodide gave poor yields of the desired product together with small amounts of a byproduct.

Table III contains physical and analytical data on *p*-substituted benzohydroxamic acids most of which have not been characterized previously. In Table IV the corresponding data are listed for several heterocyclic hydroxamic acids.

B. Reaction of Hydroxamic Acids with DFP or with Sarin.—This reaction was carried out in a similar manner as described for benzenesulfonyl chloride in an earlier paper.[9] The products obtained are listed in Table V.

Decomposition (in some cases with shrinking and browning, in others with melting and evolution of gas bubbles) probably occurs at the temperature at which carbon dioxide is liberated, with formation of the corresponding N,N'-diarylurea: $RCONHOCONHR = (RNH)_2CO + CO_2$.

The second decomposition (melting) points (in Table V given in parentheses) are rather close to the melting points of the corresponding diaryl ureas, except in the case of the *p*-nitrophenyl derivative (the decomposition point of N',N'-

(6) The ratio of the half-times for the reaction of 10^{-6} mole of DFP with 5×10^{-6} mole of nicotinhydroxamic acid and its methiodide, respectively, in bicarbonate buffer under the conditions of Table I was found to be approximately 1:4. *Ca.* 1.2 moles of acid was produced in the reaction of DFP with nicotinhydroxamic acid methiodide.

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(8) A. Einhorn and K. Mettler, *Ber.*, **35**, 3650 (1902).

(9) M. Stolberg, R. Tweit, G. M. Steinberg and T. Wagner-Jauregg, THIS JOURNAL, **77**, 765 (1955).

(10) C. D. Hurd and L. Bauer, *ibid.*, **76**, 2791 (1954).

(11) Review articles: H. L. Yale, *Chem. Revs.*, **33**, 209 (1943); F. Mathis, *Bull. soc. chim. France*, **5**, D9 (1953); H. Henecka and P. Kurtz in Houben-Weyl-Müller, **8 III**, 684 (1952); specific examples: formhydroxamic acid, L. W. Jones, THIS JOURNAL, **20**, 28 (1898); glycinehydroxamic acid, *cf.* ref. 7; mandelhydroxamic acid, L. W. Jones and L. Neuffer, THIS JOURNAL, **39**, 667 (1917).

TABLE III

p-SUBSTITUTED BENZHYDROXAMIC ACIDS

Acid	Recrystallized from	M.p., °C.[a]	Analyses, % Calculated C	H	N	Found C	H	N	pK_b[b]
p-Chlorobenzohydroxamic	EtOH; EtOH + H_2O	185	49.1	3.5	8.2	49.1	3.4	8.40	[c]
p-Nitrobenzohydroxamic	H_2O; acetone; acetone + petr. eth.; dioxane	186	46.2	3.3	15.4	46.2	3.4	15.6	8.01
p-Methylbenzohydroxamic	Acetone + petr. ether	154	63.6	6.0	9.3	63.7	6.1	9.6	8.93
p-Methoxybenzohydroxamic	Acetone + petr. eth.	163	57.4	5.4	8.4	57.7	5.2	8.1	9.03
p-Aminobenzohydroxamic	EtOH + petr. eth.	185	52.2	5.3	18.4	55.1	5.5	17.9	9.32
p-Cyanobenzohydroxamic	Water	176	59.2	3.7	17.3	58.9	3.7	17.0	8.16
p-Fluorobenzohydroxamic	Acetone + petr. eth.	165	54.2	3.9	9.1	54.7	4.0	8.8	8.70

[a] Uncorrected; determined with the Berl–Kullman copper melting point block. [b] Obtained by determination of the pH of a half-neutralized 0.01 *M* solution of the acid in 0.1 *M* KNO_3 (Dr. R. Swidler). [c] Too insol. in H_2O to determine pK_a.

TABLE IV

HETEROCYCLIC HYDROXAMIC ACIDS

Acid	Crystallized from	M.p., °C.[a]	Analyses, % Calculated C	H	N	I	Found C	H	N	I	pKa[b]
Picolinhydroxamic[12]	H_2O; acetone + petr. eth.	120	52.17	4.35	20.35	45.3	52.5	4.60	20.30	..	8.7
Methiodide	Ethanol + ether	165	30.02	3.23	10.0	45.3	30.0	3.3	9.6	45.6	5.5
Nicotinhydroxamic[12]	Ethanol; acetone + petr. eth.	165	52.17	4.35	20.35		51.8	4.40	20.0		8.3
Methiodide	Dimethylformamide + ether	187	30.02	3.23	10.0	45.3	30.4	3.20	10.0	45.6	6.5
Isonicotinhydroxamic[12]	Water	161	52.17	4.35	20.35		52.2	4.5	20.3		7.8
Methiodide	Dimethylformamide + ether	205	30.02	3.23	10.0	45.3	29.8	3.2	10.2	45.5	6.3
Isocinchomeronhydroxamic	Water	215	42.64	3.57	21.31		42.9	3.4	21.9		
Pyridine-2,6-dihydroxamic	Water	217	42.64	3.57	21.31		42.4	3.6	21.2		
Pyrazinehydroxamic	Water	168	43.16	3.62	30.2		43.3	3.6	29.8		8.1
Pyrazine-2,3-dihydroxamic	H_2O; H_2O + EtOH	163	36.4	3.05	28.3		35.8	3.3	27.7		

[a] See footnotes for Table III. [b] Determined from the potentiometric titration curve of a 0.04 *M* solution of the acid in 0.1 *M* KCl, using 0.1 *N* NaOH for neutralization. The pK_a values of the methiodides were determined (in the absence of KCl) by Dr. G. Gilbert, who will discuss their possible significance for the reaction with DFP in a later paper.

TABLE V

O-ARYLCARBAMYL ARYLHYDROXAMATES, RCONHOCONHR

R	Decomposition (melting) pt., °C.	Formula (mol. wt.)	Analyses, % Calculated C	H	N	Found C	H	N
C_6H_5–	177 (234)	$C_{14}H_{12}N_2O_3$(256.1)	65.5	4.7	10.9	65.7	4.8	11.4
p-CN–C_6H_4–	272 (277)	$C_{16}H_{10}N_4O_3$(306.1)	62.7	3.3	18.3	62.2	3.4	18.6
p-NO_2–C_6H_4–	264 (274)	$C_{14}H_{10}N_4O_7$(346.1)	48.5	2.9	16.2	48.3	3.0	15.8
p-CH_3O–C_6H_4–	168 (218–224)	$C_{16}H_{16}N_2O_5$(316.1)	60.7	5.1	8.9	61.7	5.3	9.3
2-Pyridyl	159 (170)	$C_{12}H_{10}N_4O_3$(258.1)	55.8	3.9	21.7	55.6	4.1	
3-Pyridyl	118 (204)	$C_{12}H_{10}N_4O_3$(258.1)	55.8	3.9	21.7	55.5	4.3	21.3

di-(*p*-nitrophenyl)-urea is 312°, with sublimation starting at 300°).

Pure N,N′-diphenylurea (m.p. 235°) was obtained from phenylcarbamyl benzohydroxamate by refluxing its dioxane solution. 3-Pyridylcarbamyl nicotinhydroxamate on heating to 120–130° yielded N,N′-di-(3-pyridyl)-urea, m.p. 217–219° (from aqueous alcohol).

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(12) T. S. Gardner, E. Wenis and F. A. Smith, THIS JOURNAL, **73**, 5455 (1951), described the hydrochloride of this hydroxamic acid.

Orientation in Aromatic Substitution: A Theoretical Study of the Competition between Groups

BY S. L. MATLOW[1] AND G. W. WHELAND

RECEIVED NOVEMBER 5, 1954

In 1942, there was described[2] an approximate quantum-mechanical method for calculating the orientation in aromatic substitutions by electrophilic, nucleophilic and radical reagents. More recently, Dewar[3] has developed a much simpler, but less general, procedure that is based upon the same fundamental assumptions regarding the structures of the activated complexes, and that leads to the same kinds of information. Each of these earlier papers was restricted to the study of monosubstituted benzenes; the present one, on the other hand, considers the reactions of more complex molecules in which there is competition be-

(1) Atomic Energy Commission Predoctoral Fellow, 1952–1953.
(2) G. W. Wheland, THIS JOURNAL, **64**, 900 (1942).
(3) M. J. S. Dewar, *ibid.*, **74**, 3357 (1952).