

TABLE I
 ATOM % EXCESS OXYGEN-18

Reactant	Solvent, water	Benzenecarbamoyl benzohydroxamate	Benzenesulfonic acid	Diisopropyl phosphate
Benzenesulfonyl chloride	5.27 ± 0.03	0.00 ± 0.01	0.00 ± 0.01	...
Benzenesulfonyl chloride (control)	3.34 ± 0.03	...	3.21 ± 0.01 ^a	...
Diisopropyl phosphofluoridate (DFP)	5.27 ± 0.03	0.00 ± 0.01	...	0.00 ± 0.01

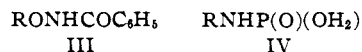
^a Calculated for one oxygen atom.

This reaction has now been investigated using oxygen-18 labeled water as solvent. In straightforward hydrolysis the product acid should contain one labeled oxygen atom per molecule. A control hydrolysis experiment was run without the addition of benzohydroxamic acid and the results are given in Table I. However, in the presence of a hydroxamic acid, if the mechanism proposed is correct, the oxygen atom replacing the halogen is that originally in the hydroxyl group of hydroxamic acid. The oxygen atoms in the carbamoyl hydroxamate are those originally in the hydroxyl and carbonyl groups of hydroxamic acid, since the former is formed by condensation of the isocyanate formed by Lossen rearrangement with unreacted hydroxamic acid. Under the conditions of the reaction there is found to be no isotopic exchange of oxygen between the reactants or the products and water. The cyanate ion is known not to undergo isotopic exchange with water and it is reasonable to assume that the transiently formed aryl isocyanate does not readily undergo exchange either.

The reaction between benzenesulfonyl chloride and benzohydroxamic acid was run in water containing ca. 5% O¹⁸ keeping the pH constant at 7.6. The products, benzenesulfonic acid and O-phenylcarbamoyl benzohydroxamate, were isolated and analyzed for their isotopic oxygen content. Since sulfonic acids often present problems in isotopic analysis, this compound was condensed⁶ with dicyclohexylcarbodiimide in dry dioxane, to form N,N'-dicyclohexylurea. Both disubstituted urea and carbamoyl hydroxamate were analyzed by decomposition on heating with copper bronze, and the carbon dioxide formed was analyzed mass-spectrometrically. As is seen from the table neither product contains any excess oxygen-18. It thus appears that the mechanism involving a Lossen rearrangement is correct.

An analogous reaction was run between diisopropyl phosphofluoridate and benzohydroxamic acid in O¹⁸-enriched water at pH 7.6. The phenylcarbamoyl benzohydroxamate was filtered off and the diisopropyl phosphate isolated by lyophilization and condensed with dicyclohexylcarbodiimide in dry dioxane. Both products were again analyzed for their isotopic oxygen content and found to be unenriched. Thus the breakdown of diisopropyl phosphofluoridate in aqueous solution in the presence of hydroxamic acids follows an analogous mechanism. The results given in Table I show that the reaction with hydroxamic acid in both cases is much faster than the competing hydrolysis, since virtually no oxygen-18 is found in the products. The results also confirm the assumption that no isotopic exchange of oxygen took place between water and any of the reagents.

There has been some discussion³⁻⁵ on the reason for the marked instability of the sulfonated (or phosphorylated) benzohydroxamic acid intermediates which, in the course of all these studies, have never been isolated. It is known^{3,7} that the tendency for substituted hydroxamic acids III to undergo Lossen rearrangement is in-



creased by electron-withdrawing properties of the group R. Both sulfonyl and phosphoryl groups have marked electron-withdrawing properties due to the polarity of the S=O and P=O bonds (structures I and II). The effect of these groups is reflected^{8a,b} in the sensitivity of N-substituted phosphoramidic acids (IV) to acid catalysis. The hydrolysis of N-benzoylphosphoramidic acid (IV, R = C₆H₅CO) is acid catalyzed in concentrated acid solution, due to protonation of the amido nitrogen. On the other hand, the rates of hydrolysis of diphenyl-N-dihydroxyphosphinylphosphoramidic acid^{8a} (IV, R = (C₆H₅O)₂PO) and of N-benzene-sulfonylphosphoramidic acid^{8b} (IV, R = C₆H₅SO₂) are unaffected by quite high acidities (up to 8 N HClO₄ in the latter case). Presumably the strong electron withdrawal by the polar groups makes the nitrogen of the phosphoramidic acid less susceptible to protonation. In the substituted hydroxamic acids (III, R = C₆H₅SO₂- and R = (*i*-PrO)₂PO-) this electron withdrawal increases the tendency to positive charge on nitrogen, thereby facilitating migration of the phenyl group. This accounts for the lability of the intermediates I and II, which rearrange before they can be isolated.

Experimental

Materials.—O¹⁸-Enriched water was obtained from the Separation Plant of the Weizmann Institute. Benzohydroxamic acid was synthesized by the method of Hauser and Renfrow⁹ (m.p. 129–130°, lit. 125–128°). Diisopropyl phosphofluoridate was prepared as described by Saunders and Stacey,¹⁰ and benzenesulfonyl chloride was a commercial sample.

Reaction of Benzenesulfonyl Chloride with Benzohydroxamic Acid.—Benzenesulfonyl chloride (0.5 ml.) was added to a solution of benzohydroxamic acid (0.5 g.) in O¹⁸-enriched water (50 ml., 5.27% O¹⁸) in a beaker with a magnetic stirrer. The pH was kept at 7.6 by means of a TTI Radiometer pH-meter using a 0.1 N solution of NaOH in O¹⁸-enriched water. After a time equal to about five times the half-life,¹ the benzenecarbamoyl benzohydroxamate was filtered off and dried *in vacuo*. The filtrate was treated with Dowex 50, filtered and lyophilized. The solid residue was dissolved in dry dioxane (30 ml.) to which a solution of dicyclohexylcarbodiimide (0.5 g.) in dry dioxane (10 ml.) was added. After a few minutes a dense white precipitate of the urea was formed which was filtered off, washed with dry dioxane, and dried *in vacuo* (m.p. 220–223°, lit.¹¹ 220–225°). The control was run under identical conditions of reaction and isolation, without hydroxamic acid.

Reaction of Diisopropyl Phosphofluoridate with Benzohydroxamic Acid.—This reaction was performed in analogous manner to that described above using 0.65 g. of diisopropyl phosphofluoridate and 0.5 g. of benzohydroxamic acid in 40 ml. of O¹⁸-enriched water taking suitable safety precautions. Benzenecarbamoyl benzohydroxamate was isolated and dried. Diisopropyl hydrogen phosphate was isolated from the filtrate by lyophilization and condensed with dicyclohexylcarbodiimide in dry dioxane. The precipitated urea was filtered off, washed with dry dioxane and dried *in vacuo* (m.p. 220–223°).

Isotopic Analysis.—All four products were analyzed by heating small samples (25 mg.) with a trace of copper bronze in a sealed tube to 325° for 0.5 hr. The results are presented in the above table. The O¹⁸-enriched water was analyzed by the hypobromite method of Anbar.¹²

(8) M. Halmann, A. Lapidot and D. Samuel: (a) *J. Chem. Soc.*, 4672 (1960); (b) *ibid.*, 3158 (1961).

(9) C. R. Hauser and W. B. Renfrow, Jr., in "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 67.

(10) B. C. Saunders and G. J. Stacey, *J. Chem. Soc.*, 695 (1948).

(11) M. Smith, J. G. Moffatt and H. G. Khorana, *J. Am. Chem. Soc.*, **80**, 6204 (1958).

(12) M. Anbar, *Intern. J. Appl. Radiation Isotopes*, **3**, 134 (1958).

(6) H. G. Khorana, *Chem. Rev.*, **53**, 1945 (1953); A. Lapidot, S. Pinchas and D. Samuel, *Proc. Chem. Soc.*, 109 (1962); M. Halmann, *J. Chem. Soc.*, 305 (1959).

(7) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 499.