carbonization; however, the desired product was not obtained.

Polymerization of Trifluoromethacrylonitrile.—Trifluoromethacrylonitrile was prepared from trifluoroacetone according to Buxton.[7] The polymerizations were carried out in a vacuum system. The catalyst, sodium cyanide, was crystallized from water and dried at room temperature at 7×10^{-3} mm. for 1 week. A weighed quantity, 0.018 g. (3.7×10^{-4} mole) was placed in a reaction vessel and degassed for 0.5 hr. at 0.05 mm. Trifluoromethacrylonitrile, 3.47 g. (0.029 mole), was distilled from the reservoir on the vacuum line to a side arm on the reaction flask which, by rotation, could be inverted to discharge its contents into the flask. The monomer was kept frozen in the side arm with liquid nitrogen until needed. Dimethylformamide was refluxed over phosphorus pentoxide and distilled at reduced pressure prior to storage on the vacuum line over methylenebis(*p,p*-diphenyl diisocyanate). Dimethylformamide, 25 ml., was transferred from its reservoir into the reaction flask and the sodium cyanide dissolved to give a clear solution by stirring for 1 hr. at room temperature under an atmosphere of argon. The solution was cooled to −40°; the monomer was thawed and the side arm emptied into the reaction flask causing an immediate production of orange-brown solution. The polymerization was terminated by addition of 3 ml. of a 2% solution of sulfuric acid in dimethylformamide, and the polymer isolated by precipitation into water containing potassium hydroxide. The polymer was obtained as a pink powder. Polymerizations carried out for 30, 9, and 4 min. gave essentially quantitative yields, m.p. 190° dec. Intrinsic viscosities were determined in dimethylformamide and in cyclohexanone. The curves showed an electrolyte effect; $[\eta]$ was of the order 0.1 $\frac{dl}{g}$.

Anal. Calcd. for $(C_4H_2NF_3)_n$: C, 39.68; H, 1.67; N, 11.57; F, 47.08. Found: C, 40.19; H, 2.03; N, 10.75; F, 45.48.

Hydrolysis of an Ester with a Neighboring Carboxyl and a Quaternary Ammonium Group[1]

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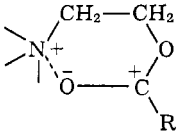
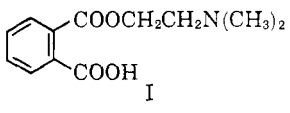
The enhanced reactivity of esters of the choline type[2] has been explained by assuming that the positively charged nitrogen stabilizes a negative charge on the carbonyl oxygen, making the carbonyl carbon more susceptible to attack by a nucleophilic reagent as indicated by:

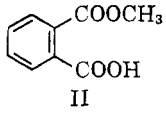


This type of catalysis has been classified by Bender[3] as intramolecular general acid catalysis. The difference in reactivity of esters of cyclohexanol derivatives with a *cis* or a *trans* quaternary nitrogen has been offered as evidence for the above mechanism.[4] By analogy, a neighboring positively charged nitrogen should make the carbonyl carbon more susceptible to neighboring carboxylate attack. It has been shown previously that an ester containing both an ionized and an unionized neighboring carboxyl group is highly reactive, and this effect has been attributed to a stabilization of the transition state by hydrogen bonding between the carbonyl oxygen of the ester and the unionized carboxyl.[5] It was suggested that a similar stabilization might be achieved by ion-pair formation involving the partial negative charge of the carbonyl oxygen and a neighboring cationic group.[5]

To demonstrate this effect, we carried out a study of the *p*H dependence of the rate of hydrolysis of β-*N,N*-dimethylaminoethyl hydrogen phthalate (I). An analogous ester lacking the cationic group, *i.e.*, methyl hydrogen phthalate II has been investigated previously.[6]



I



II

The pseudo-first-order rate constants for the hydrolysis of ester I in various buffers and at different temperatures are given in Table I.

TABLE I

PSEUDO-FIRST-ORDER RATE CONSTANTS FOR THE HYDROLYSIS OF β,*N,N*-DIMETHYLAMINO ETHYL HYDROGEN PHTHALATE

*p*H	10^5k Sec.$^{-1}$ (at 75°)	*p*H	10^5k Sec.$^{-1}$	Temp.
1.11	3.3	7.92	41	75.5
2.82	2.8	6.06	3.0	75.5
3.26	2.7	6.06	0.033	34.5
4.92	3.0	6.06	1.13	65.5
6.39	3.8	6.06	6.65	85.4
6.99	8.1			

In Fig. 1 the logarithms of the rate constants obtained at 75.5° are plotted against pH along with a similar plot for the hydrolysis of methyl hydrogen phthalate taken from ref. 6.

An Arrhenius plot of rates obtained at pH 6.06 gave an activation enthalpy of 23.4 kcal./mole as against 33.7 kcal./mole reported for ester II[6].

The results of this study show that the amphoteric ester I is much more reactive than the acid ester II, but that the hydrolysis rate of I unlike that of II, is pH independent in the region of

(1) Financial support of this research by the Office of Naval Research Contract Nonr-839(31) is gratefully acknowledged.

(2) (a) W. Davis and W. C. J. Ross, *J. Chem. Soc.*, 3056 (1950). (b) E. Schätzle, H. Urheim, M. Rottenberg, and Thürkauf, *Experientia*, **17**, 350 (1961).

(3) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).

(4) G. F. Holland, R. C. Durant, S. L. Friess, and B. Witkop, *J. Am. Chem. Soc.*, **80**, 6031 (1958).

(5) H. Morawetz and I. Oreskes, *ibid.*, **80**, 2591 (1958).

(6) M. L. Bender, F Chloupek, and M. C. Neveu, *ibid.*, **80**, 5384 (1958).

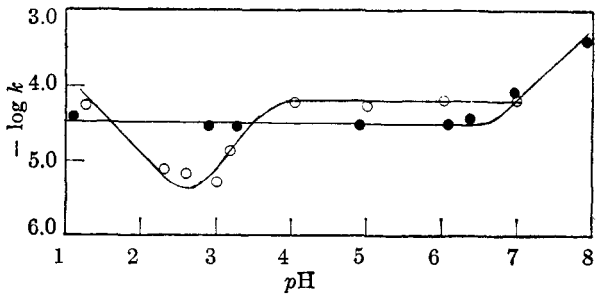


Fig. 1.—The hydrolysis of β-*N*,*N*-dimethylaminoethyl hydrogen phthalate at 75.5°, ●; and of methyl hydrogen phthalate at 109°, ○ (Ref. 6).

carboxyl ionization. It may therefore be concluded that in this *p*H region the bulk of the hydrolysis is due to direct attack of water on the ester group, and that any contribution which intramolecular carboxylate attack may make to the observed hydrolysis rate of I is within the experimental error of the rate constant measurements. If we extrapolate the data from ref. 6 for the fully ionized II at 109° and 84° to a temperature of 75.5°, we find that intramolecular carboxylate attack on the ester group results in a hydrolysis rate constant of 0.079×10^{-5} sec.$^{-1}$. This is less than 3% of the rate constant observed for ester I in the plateau region below *p*H 6.1, so that intramolecular carboxylate attack would not be experimentally detectable in ester I unless it were about four times as efficient as in II. Apparently the cationic group does not produce an effect of this magnitude.

Experimental

β-*N*,*N*-Dimethylaminoethyl Hydrogen Phthalate.—Phthalic anhydride (7.4 g., 0.05 mole) and 17.8 g. (0.2 mole) dimethylaminoethanol were placed in a 250-ml. three-necked round-bottomed flask equipped with a mechanical stirrer. The mixture was stirred at room temperature for 6 hr. The resulting slurry was washed with benzene and recrystallized from ethanol giving small colorless plates, which melt with decomposition 160–170°.

Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.36; N, 5.90. Found: C, 61.02; H, 6.46; N, 5.81.

Kinetics.—The hydrolysis reactions were carried out in buffer solutions less than 0.02 *M* in ionized acid. The ionic strength was adjusted to 0.1 *M* by addition of sodium chloride and the *p*H was determined with a Cambridge Research Model *p*H meter. The rate of reaction was studied by observing the disappearance of the peak due to the the ester at 280 mμ on a Beckman DU spectrophotometer. In order to follow the rate of reaction in this manner the free phthalic acid had to be ionized, since unionized phthalic acid has approximately the same extinction coefficient as the ester. Therefore, for most runs, 2-ml. aliquots of the reaction solution (containing 24 mg. ester/100 ml.) were transferred into 2 ml. of 0.5 *M* phosphate buffer (*p*H 6.06), and the optical density (D) determined at 25.3°. Plots of $-\ln (D-D_\infty)$ were linear in time in all cases, and were used to calculate the first-order rate constant. The formation of phthalic acid in the reaction was proved by the similarity between the spectrum of the ester after hydrolysis and phthalic acid at the same *p*H.

Quaternary Derivatives of Nitrogen-Mustards[1]

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Phosphorylated *N*-mustards, prepared by Friedman and Seligman[3] as well as Arnold and Burseaux,[4] are examples of cytotoxic substances with a so-called "hidden" or "toxagenic" *N*-mustard group. According to the hypothesis, the *N*-phoshorylation or urethane formation of the bis(β-chloroethyl)-amine eliminates the basic character of the amine, preventing the formation of intermediary ethylenimonium salts, which are considered the true alkylating agent. The compounds are therefore nontoxic, inactive *in vitro*, and activated only *in vivo* by phosphamidases restoring the secondary amine.

We report here the properties of *N*-mustard derivatives, which are capable of quaternerizing prior to the eventual hydrolysis of *N*-acyl groups. Although, they are not "toxagenic" derivatives of originally active *N*-mustards, nevertheless, they contain quaternerized chloroethylamino groups. These differ from ethylenimonium salts in being less strained six-membered rings of novel structure. *N* - Bis(β - chloroethyl)phosphoramidic dichloride[3] (I) was first treated with four moles of 1,1-dimethylhydrazine, affording the *N* - bis(β - chloroethyl)phosphoramidate di(2,2 - dimethylhydrazidate) (II) as an oily base. On standing at room temperature for a few hours, or warming it several minutes on the steam bath, the compound bisquaternerized to the unusual heterocyclic system 2,7 - dimethyl - 9 - phospha - 9 - oxo - 10 - azapyridazo[5,6 - *e*]pyridazine - 2,7 - bischloromethylate (III), a water soluble crystalline substance.

On the other hand, phenyl-*N*-bis(β-chloroethyl)-phosphoramidic chloride[3] (IV), prepared from I was also treated with dimethylhydrazine to the tertiary base (V), which in turn, yielded the quaternary 1 - methyl - 3 - oxo - 3 - phenoxy - 4-(β - chloroethyl) - 3 - phospha - 1,2,4 - triazine - 1-chloromethylate (VI).

In connection with our investigations about *N*-mustard urethanes,[5] we also prepared the analogous

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(3) O. M. Friedman and A. M. Seligman, *J. Am. Chem. Soc.*, **76**, 655 (1954).

(4) H. Arnold and F. Burseaux, *Angew. Chemie*, **70**, 539 (1958).