

Aminolysis of Esters. I. Kinetics and Mechanism in Anhydrous Dioxane¹

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Abstract: The kinetics of aminolysis of 11 phenyl esters by various amines have been studied spectrophotometrically under pseudo-first-order conditions in anhydrous *p*-dioxane. The following relationships were found: $k_{\text{obsd}} = k_2(\text{amine}) + k_3(\text{amine})^2$ for the reaction of phenyl dichloroacetate with *n*-butylamine and 3-methoxy-*n*-propylamine, and for the reaction of phenyl difluoroacetate with *n*-butylamine; $k_{\text{obsd}} = k_2(\text{amine})$ for the reaction of phenyl dichloroacetate with *N*-methyl-*n*-butylamine, piperidine, *N,N*-dimethyl-1,3-propanediamine, and *N,N,N'*-trimethyl-1,3-propanediamine, and for the reaction of phenyl difluoroacetate with piperidine and *N*-methyl-*n*-butylamine; $k_{\text{obsd}} = k_2(\text{amine}) + k_3(\text{amine}) + k_3'(\text{amine})(\text{Et}_3\text{N})$ for the reaction of phenyl dichloroacetate and *n*-butylamine where catalytic amounts of triethylamine were added. A series of reactions in cyclohexane was performed, and only third-order kinetics were detected. Rate constants for the reaction of ten different aliphatic esters with *n*-butylamine were correlated by the Taft equation, $\log(k/k_0) = \rho^*\sigma^* + \delta E_s$.

Although much information is available in the literature concerning the aminolysis and ammonolysis of esters, essentially none exists in aprotic solvent systems. Reactions of this type have been extensively investigated in aqueous solution.⁴ Organic solvents have been used by other investigators, but these have been either alcohols,⁵ glycols, dioxane-water, or dioxane-alcohol.⁶

The present study undertakes kinetic studies of this reaction in anhydrous dioxane, in order to establish the order of reaction in this solvent, and to determine whether the same observation of general base catalysis with primary amines, such as has been well established in aqueous solution,^{4a} is obtained. It was also desired to examine the effect of structure of the acyl portion of the ester, in the hope of shedding more light on the mechanism of this reaction in aprotic solvents.

Experimental Section

Materials. *p*-Dioxane was Matheson Coleman and Bell Spectroquality reagent grade solvent. Its purity was checked by infrared, ultraviolet, and vapor phase chromatographic analyses.

Difluoroacetic acid was purchased from K and K Laboratories; distillation at atmospheric pressure gave a distillate of boiling range 125–134°. This corresponds to the boiling point of a 10% water–acid azeotrope.⁷

Sodium phenolate was prepared by reaction of phenol (Fisher Scientific Co., purified by distillation) with sodium in anhydrous benzene.

Amines. *n*-Butylamine, *N*-methyl-*n*-butylamine, 3-methoxy-*n*-propylamine, and *N,N*-dimethyl-1,3-propanediamine were purchased from Matheson Coleman and Bell. Piperidine and triethylamine were obtained from Eastman Organic Chemical Co. The amines were purified by storing overnight over sodium hy-

droxide pellets and then distilling at atmospheric pressure from fresh sodium hydroxide pellets using a 15-in. Vigreux column. The fraction having a constant boiling point was collected and stored in an amber glass bottle over fresh sodium hydroxide pellets.

N,N,N'-Trimethyl-1,3-propanediamine was prepared from 3-chloro-*N,N*-dimethyl-*n*-propylamine hydrochloride (Matheson Coleman and Bell), 20 g (0.11 mole), which was dissolved in 100 ml of distilled water. A solution of 40% aqueous methylamine (Matheson Coleman and Bell), 77.5 g (ca. 1.1 moles), was added, and the mixture was refluxed gently for 6 hr. The cooled reaction mixture was treated with solid potassium hydroxide until some solid remained undissolved. The amine layer which separated was removed, the aqueous layer was extracted several times with ether, and the ether extracts were added to the diamine. The ether solution was washed with saturated sodium hydroxide solution, dried over anhydrous sodium sulfate, and the ether removed on a water bath. The residue was distilled through a 10-in. Vigreux column to give 7.0 g (55% yield) of colorless liquid product.

The degree of purity of each amine was determined by acid–base titration and was checked by vapor phase chromatographic analysis. In the former method, a known weight of the amine dissolved in a known excess of standard hydrochloric acid was titrated against a standard solution of sodium hydroxide using methyl red (pH 4.4–6.2) as an indicator. In the latter method, an F & M Model 720 gas chromatograph with a 3-ft Carbowax column was used. For all amines, a clean single peak was obtained, indicating almost 100% purity.

Refractive indices, boiling points, and infrared spectra were also determined for the amines. A common absorption band between 2900 and 3000 cm^{−1} corresponding to methyl and methylene stretch was observed. The physical constants and degree of purity of the individual amines are listed as follows: *n*-butylamine, bp 77–77.5°, *n*_D²⁰ 1.3976, 99.9% pure (lit.⁷ bp 77°; *n*_D²⁰ 1.4010); *N*-methyl-*n*-butylamine, bp 90–91°, *n*_D²⁵ 1.3997, 100.0% pure (lit.⁷ bp 90–99°, *n*_D¹⁵ 1.4018); 3-methoxy-*n*-propylamine, bp 116–118°, *n*_D²⁵ 1.4315, 100.0% pure (lit.⁸ bp 118°, *n*_D²⁰ 1.4182); *N,N*-dimethyl-1,3-propanediamine, bp 132–133°, *n*_D²⁵ 1.4315, 99.8% (lit.⁹ bp 130–133°); piperidine, bp 104–105.5°, *n*_D²⁵ 1.4500, 99.9% pure (lit.⁷ bp 106°, *n*_D²⁰ 1.4530); triethylamine, bp 88–89°, *n*_D²⁰ 1.4003, 99.9% pure (lit.¹⁰ bp 89–90° *n*_D²⁰ 1.4003); and *N,N,N'*-trimethyl-1,3-propanediamine, bp 140–143°, *n*_D²⁵ 1.4275, 99.8% pure (lit.¹¹ bp 140–142°).

Esters. Phenyl Dichloroacetate. Dichloroacetyl chloride (prepared from Matheson Coleman and Bell dichloroacetic acid by the method of Brown¹²), 14.4 g (0.098 mole), and 7.8 g (0.083 mole) of phenol were placed in a 150-ml, ground-joint, round-

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(4) See, for example, (a) W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **88**, 104 (1966); (b) L. R. Fedor, T. C. Bruice, K. L. Kirk, and J. Meinwald, *ibid.*, **88**, 108 (1966), and references listed therein.

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bottomed flask with a water condenser, and the mixture was refluxed until evolution of HCl gas ceased (about 5 hr). The mixture was dissolved in excess hot petroleum ether and filtered. The white solid ester which crystallized on cooling the filtrate was recrystallized from petroleum ether to give 13.4 g (80% yield) of the crystalline solid, melting at 48–49° (lit.¹³ mp 38.5–49.5°). The infrared spectrum of an emulsion of this solid in Nujol showed absorption bands at 1775 (C=O stretch), 1600 (C=C stretch), 1497 (aromatic H—C=C stretch), and 1200⁻¹ cm⁻¹ (C—C=C stretch).

Phenyl Difluoroacetate. Into a 200-ml, three-necked, round-bottomed flask fitted with condenser, dropping funnel, and thermometer, was introduced 8 g (0.07 mole) of sodium phenolate. To this, 7.3 g of the water–acid azeotrope (0.067 mole of difluoroacetic acid) was added. The mixture was stirred with a magnetic stirrer while cooling to 10° in a crushed ice–salt bath. From the dropping funnel, 5.5 g (0.036 mole) of phosphorus oxychloride was added portionwise to maintain the temperature at 10° (the excess POCl₃ was used to consume the water present in the azeotrope). After the addition was complete, the reaction mixture was allowed to warm to room temperature and heat was gently applied while stirring until evolution of HCl gas ceased. After 2 hr, the flask was cooled, and the reaction mixture was extracted with ether. After removal of ether with a water aspirator, the liquid residue was distilled (23 mm), and the fraction having bp 88–92° was collected and refractionated twice to give 7.0 g of a colorless liquid, bp 90–91° (23 mm), *n*_D²⁰ 1.4617, *d*₄^{21.7} 1.262 g/cc. *Anal.* Calcd for C₈H₆F₂O₂: C, 55.81. Found: C, 55.6. The infrared spectrum of a liquid sample showed absorption bands at 1790 (C=O stretch), 1600 (C=C stretch), 1500 (aromatic H—C=C stretch), 1215 (O—C=C stretch), and 1115 cm⁻¹ (F₂C—) (not reported in the literature).

Phenyl Trichloroacetate. Into a 1-l. three-necked flask fitted with a stirrer, condenser, and dropping funnel, was placed 23 g (0.2 mole) of sodium phenolate and 300 ml of dry benzene. From the separatory funnel, 37 g (0.2 mole) of freshly prepared trichloroacetyl chloride (prepared by the method of Brown¹²) was added with stirring. After the addition was complete, the reaction mixture was stirred for 45 min. The sodium chloride which separated was removed by filtration and the solvent removed on a rotary evaporator. The residue was distilled (1.0 mm) and the fraction boiling at 98–101° was collected and redistilled. The final product was obtained at 100–101° (1.0 mm) [lit.¹³ 122° (14 mm), *n*_D²⁰ 1.5232]. The yield was 13.5 g (28.7%).

Phenyl Chloroacetate. This was prepared in the same manner as phenyl trichloroacetate. The solid obtained had mp 40–41° [lit.¹³ bp 140–141° (31 mm)].

Phenyl Methoxyacetate. This was prepared by the same method as phenyl trichloroacetate, except that phenol was used instead of sodium phenolate. The ester, 11.6 g (71%), had bp 127–128° (13 mm), *n*_D²⁵ 1.5000, *d*₄^{21.7} 1.11 g/cc. *Anal.* Calcd for C₈H₁₀O₃: C, 65.0. Found: C, 65.3. This compound was not reported in the literature.

Phenyl Formate. This was prepared by the method of Buzas, Engell, and Freon.¹⁴ The final product was obtained in 6.9-g (57%) yield and had bp 62–64° (8 mm), *n*_D²⁵ 1.5055 [lit.¹⁵ bp 178–178.5° (8 mm), *n*_D¹⁵ 1.5094].

Phenyl Cyanoacetate. This was prepared by the method of Ziegler and co-workers¹⁶ except that sodium phenolate was used instead of phenol. The white crystalline product was obtained in 5-g (31%) yield and had mp 39–40° (lit.¹⁶ mp 41°).

Phenyl Phenylacetate. This was prepared according to the Schotten–Baumann reaction.¹⁷ The ester, 4.5 g (60% yield), was obtained as white needle-like crystals, mp 39.5–40.5° (lit.¹⁸ 39–40°).

Phenyl Acetate. This was prepared by the method of Chattaway¹⁹ from acetic anhydride and phenol. The product was a colorless liquid, bp 72–74° (11 mm), *n*_D²⁵ 1.5020 [lit.¹⁹ bp 78° (10 mm), *n*_D²⁰ 1.5030].

Phenyl Propionate. Into a 100-ml, round-bottomed flask was placed 0.1 mole of phenol in 35 ml of dry benzene. To this, 0.12

mole of propionyl chloride (prepared by the method of Brown¹²) and 1.2 g of magnesium metal were added. A condenser was added and the mixture refluxed on a water bath until evolution of hydrogen chloride ceased. The flask was cooled; 25 ml of ether was added, and the mixture filtered. The filtrate was extracted once with 5% aqueous sodium hydroxide and three times with 50-ml portions of cold water. After drying over sodium sulfate, and removal of solvent with a rotary evaporator, the residue was distilled under reduced pressure. The fraction boiling at 82–85° (2 mm) was collected and redistilled. The final product was obtained in 9-g (60%) yield and had bp 82–83°, *n*_D²⁵ 1.4952 [lit.²⁰ bp 98–99° (8 mm), *n*_D²⁵ 1.5003].

Phenyl Pivalate. This was prepared by the same method as phenyl propionate. The clear liquid product was obtained in 20-g (70%) yield and had bp 109–111° (21 mm), *n*_D²⁵ 1.4761 [lit.²⁰ bp 118–119° (35 mm)].

Kinetics. A Bausch and Lomb Spectronic 505 ultraviolet spectrophotometer with jacketed cell compartment was used for the kinetic measurements. Water at 25.5 ± 0.1° was circulated through the cell compartment by means of a constant-temperature bath unit, Haake Circulator Series F. The reactions were carried out in 1-cm, ground-glass-stoppered, fused silica absorption cells.

The reactions were followed by rate of appearance of the phenol peak at 274 mμ. The corresponding amides and esters showed no absorption in the 230–290-mμ region. Complete spectra taken for several mixtures of amide and phenol in *p*-dioxane corresponded to the spectra of pure phenol solutions having the same concentration of phenol. Also, complete spectra taken at the end of each kinetic run corresponded to the spectra of phenol solutions of the same concentration. Beer's law was found to be obeyed within the concentration and wavelength range employed.

Stock solutions of esters, usually about 10⁻² *M*, were prepared and the concentrations checked by comparing the optical density with that calculated from the Beer's law relationship at 274 mμ. Stock amine solutions were prepared and the concentration determined by acid–base titration. Appropriate concentrations of amine and ester were prepared by dilution of the stock solutions with *p*-dioxane. All ester concentrations were 5.00 × 10⁻⁴ *M*.

Reactions were followed to 90–99% completion, with at least 15 readings taken. For kinetic runs which could be completed in a day or less, the reactions were carried out in the absorption cells. For slower runs, the reactions were begun in 25-ml volumetric flasks. A sample was removed and placed in the cell in the instrument, and the cell was returned to the constant-temperature bath. The cell was allowed to remain in the instrument for the first day, frequent readings being taken. The solution in the cell was discarded and aliquots were removed from the flask for all subsequent readings.

The reference solution was that of dioxane containing an equal amine concentration to that being used in the particular run.

Comparison of the spectra of a completed reaction and a mock solution consisting of the phenol, amine, and amide in *p*-dioxane in the expected concentrations showed a consistency within 1–2% transmittance units. In all runs, at least a tenfold excess of amine over ester was used in order to obtain pseudo-first-order kinetics. Duplicate or triplicate runs were performed for each concentration, and readings taken in any single kinetic run covered a rate of 85% transmittance units.

Stoichiometry and Isolation of Products. Authentic samples of *N*-*n*-butyldichloroacetamide and of 1-difluoroacetyl piperidine were prepared by independent methods. Laboratory quantities of two reactions were carried out: (1) phenyl dichloroacetate with *n*-butylamine, (2) phenyl difluoroacetate with piperidine. The expected amides were obtained in about 70% yield and were identical in physical properties with the authentic samples.

Results. Pseudo-first-order kinetics were obtained for all runs. Reactions were followed to 90–99% completion with at least 15 points being taken, and good first-order plots of log (*D* – *D*_∞) against time were obtained as shown in Figure 1. In all kinetic runs the ester concentration was 5.0 × 10⁻⁴ *M*. The average deviation from the mean value of the rate constant in duplicate or triplicate experiments was ± 5% or less.

For the reactions of primary amines with all esters except phenyl methoxyacetate, the following rate equation was obtained

$$k_1/(\text{amine}) = k_2 + k_3(\text{amine})$$

This is illustrated in Figure 2, where a plot of *k*₁/(amine) against amine concentration gives a straight line.

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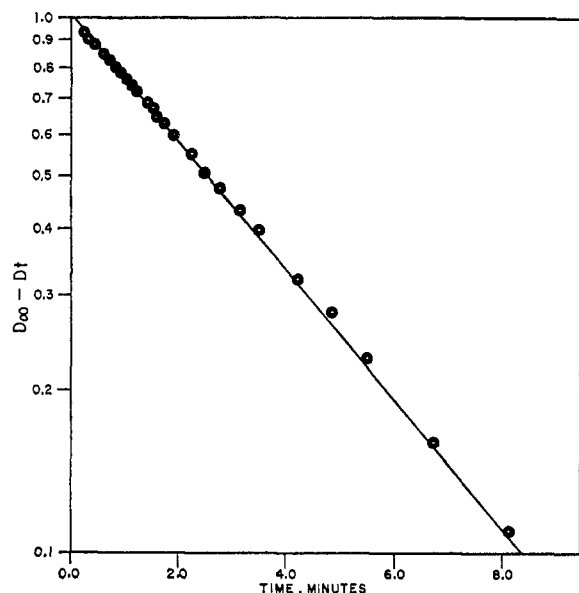


Figure 1. Typical first-order plot for aminolysis of phenyl esters. Reaction of 0.180 *M* *N*-methyl-*n*-butylamine with phenyl dichloroacetate.

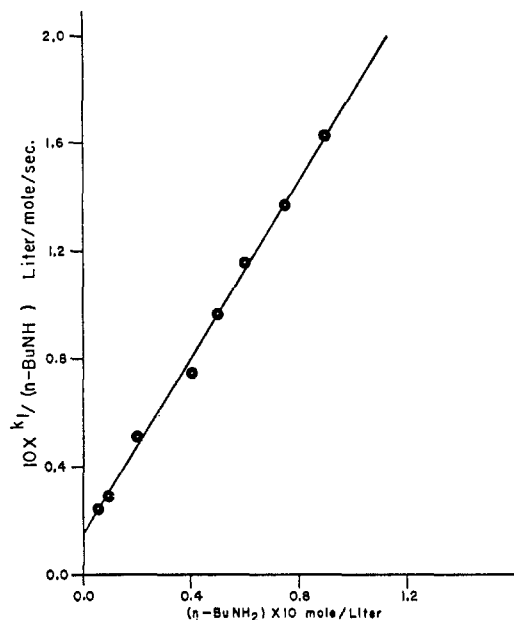


Figure 2. Plot of $k_1/(\text{amine})$ against amine concentration for the reaction of phenyl dichloroacetate with *n*-butylamine in *p*-dioxane at 25.5°.

Simple second-order kinetics were found for the reactions of secondary amines and diamines with all esters, and for the reaction of phenyl methoxyacetate with *n*-butylamine, as shown in Figure 3, where a plot of k_1 against amine concentration gives a linear relationship. That is

$$k_1 = k_2(\text{amine})$$

For the reaction between *n*-butylamine and phenyl dichloroacetate, with triethylamine added as a catalyst, the following relationship was found

$$k_1 = k_2(\text{amine}) + k_3(\text{amine})^2 + k_3(\text{Et}_3\text{N})(\text{amine})$$

Since in this series both the ester and *n*-butylamine concentrations were held constant and the triethylamine concentration varied, plots of k_1 against triethylamine concentration were linear as shown in Figure 4. The calculated intercept of this plot, equal to k_2 .

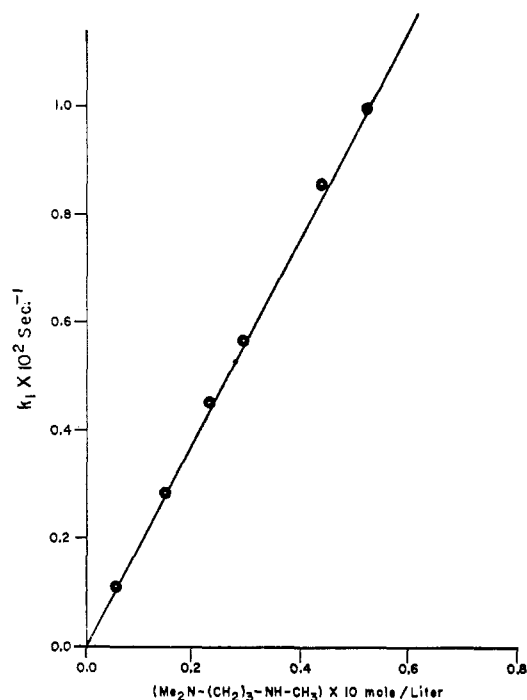


Figure 3. Simple second-order plot for the reaction of phenyl dichloroacetate with *N,N,N'*-trimethyl-1,3-propanediamine in *p*-dioxane at 25.5°.

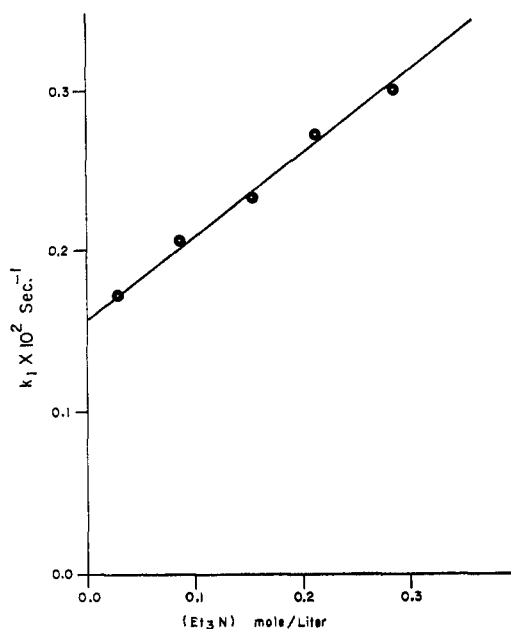


Figure 4. Plot of k_1 against triethylamine concentration for *n*-butylaminolysis of phenyl dichloroacetate in *p*-dioxane at 28.0°; *n*-BuNH₂ concentration is held constant (0.021 *M*).

(amine) + $k_3(\text{amine})^2$ agrees within experimental precision with the experimentally determined pseudo-first-order rate constant for aminolysis of phenyl dichloroacetate by *n*-butylamine in the absence of triethylamine under the same conditions of temperature and *n*-butylamine concentration.

Values of k_2 , k_3 , and k_3' were calculated by the method of least squares and are summarized in Tables I, II, and III.

In a series of experiments carried out in cyclohexane on the reaction of *n*-butylamine with phenyl dichloroacetate, only third-order kinetics were obtained, as shown in Figure 5, where no intercept was obtained from a plot of $k_1/(\text{amine})$ against (amine).

Table I. Kinetic Expressions and Associated Rate Constants Determined with a Series of Nitrogen Bases in *p*-Dioxane, at 25.5°

Amine (<i>M</i>)	Reaction kinetics	No. of <i>k</i> detns	<i>k</i> ₂	<i>k</i> ₃	<i>k</i> ₃ '
Phenyl Dichloroacetate					
<i>n</i> -Butylamine (0.006–9.00)	<i>k</i> ₂ (E)(A) + <i>k</i> ₃ (E)(A) ²	17	0.0143	1.65	
Piperidine (0.121–1.21)	<i>k</i> ₂ (E)(A)	10	0.0478		
<i>N</i> -Methyl- <i>n</i> -butylamine (0.0240–33.3)	<i>k</i> ₂ (E)(A)	13	0.0245		
3-Methoxy- <i>n</i> -propylamine (1.70–8.51)	<i>k</i> ₂ (E)(A) + <i>k</i> ₃ (E)(A) ²	12	0.0347	1.15	
<i>N,N</i> -Dimethyl-1,3-propanediamine (0.281–0.702)	<i>k</i> ₂ (E)(A)	15	2.70		
<i>N,N,N'</i> -Trimethyl-1,3-propanediamine (0.576–5.18)	<i>k</i> ₂ (E)(A)	12	0.199		
<i>n</i> -Butylamine (0.01); triethylamine (2.78–28.5)	<i>k</i> ₂ (E)(A) + <i>k</i> ₃ (E)(A) ² + <i>k</i> ₃ (E)(A)(Et ₃ N)	12			0.264
Phenyl Difluoroacetate					
<i>n</i> -Butylamine (0.70–2.16)	<i>k</i> ₂ (E)(A) + <i>k</i> ₃ (E)(A) ²	22	0.01	22.8	
Piperidine (0.288–7.71)	<i>k</i> ₂ (E)(A)	14	0.246		
<i>N</i> -Methyl- <i>n</i> -butylamine (0.954–8.59)	<i>k</i> ₂ (E)(A)	21	0.124		

Table II. Kinetic Expressions and Associated Rate Constants for the Reactions of a Series of Phenyl Esters, RCOOPh, with *n*-Butylamine in *p*-Dioxane, at 25.5°

R	<i>k</i> ₂ , M ⁻¹ sec ⁻¹	<i>k</i> ₃ , M ⁻² sec ⁻¹	No. of <i>k</i> detns	<i>k</i> ₃ / <i>k</i> ₂	Amine concn range, <i>M</i>
Cl ₃ C	0.107	41.2	20	286	0.007–0.025
F ₃ CH	0.100	22.8	22	228	0.70–2.16
Cl ₂ CH	0.0143	1.65	17	115	0.006–9.00
NCCH ₃	6.59 × 10 ⁻³	4.16 × 10 ⁻²	13	6.42	0.044–0.486
ClCH ₂	1.73 × 10 ⁻³	2.12 × 10 ⁻³	13	12.2	0.121–0.883
CH ₃ OCH ₂	8.31 × 10 ⁻⁴	...	18	...	0.101–0.901
H	7.86 × 10 ⁻³	5.44 × 10 ⁻²	14	6.90	0.070–0.490
PhCH ₂	9.83 × 10 ⁻⁶	4.01 × 10 ⁻⁵	12	4.08	0.221–2.40
CH ₃	8.09 × 10 ⁻⁴	5.95 × 10 ⁻⁴	17	0.74	0.080–2.63
CH ₃ CH ₂	4.85 × 10 ⁻⁶	1.82 × 10 ⁻⁵	12	3.76	1.64–4.38
(CH ₃) ₃ C	1.17 × 10 ⁻⁷	1.06 × 10 ⁻⁷	8	0.91	1.02–4.76

Table III. Phenyl Methoxyacetate

Amine (<i>M</i>)	Reaction kinetics	No. <i>k</i> detns	<i>k</i> ₂
<i>n</i> -Butylamine (0.10–0.901)	<i>k</i> ₂ (E)(A)	18	8.31 × 10 ⁻⁴
<i>N</i> -Methyl- <i>n</i> -butylamine	<i>k</i> ₂ (E)(A)	8	6.30 × 10 ⁻⁵

The polar and steric susceptibility parameters for this series were as follows

	ρ*	δ
<i>k</i> ₃	+3.03	+1.08
<i>k</i> ₂	+2.14	+1.03

Discussion

Mechanism of Base Catalysis. The disappearance of the second-order rate constant when cyclohexane is used as solvent seems to indicate that the second-order term obtained in the reaction of phenyl esters with *n*-butylamine represents a solvent-catalyzed term, rather than an uncatalyzed term. This suggests that the reaction of phenyl esters with secondary amines may proceed *via* a different mechanism than that with primary amines. In this paper, only the mechanism involving general base catalysis will be discussed.

Consistent with the observations are eq 1 and 2. In the first step, the intermediate II is pictured as forming by nucleophilic attack of nitrogen with simultaneous protonation of the carbonyl, in order to avoid the use of ionic intermediates, which are considered here

The kinetic data for the series of esters excluding phenyl methoxyacetate was found to be correlated by the Taft equation of the type

$$\log (k/k_0) = \sigma^* \rho^* + \delta E_s^{21}$$

Both second- and third-order constants were correlated by this equation, as shown in Figures 6 and 7. Figure 8 shows the scatter obtained when a correlation of the type $\log (k/k_0) = \sigma^* \rho^*$ was attempted; similar scatter was obtained from plots of $\log (k/k_0)$ against *E*_s, log relative rate constants for alkaline specification of esters, and acid dissociation constants (Hammett-type plot).

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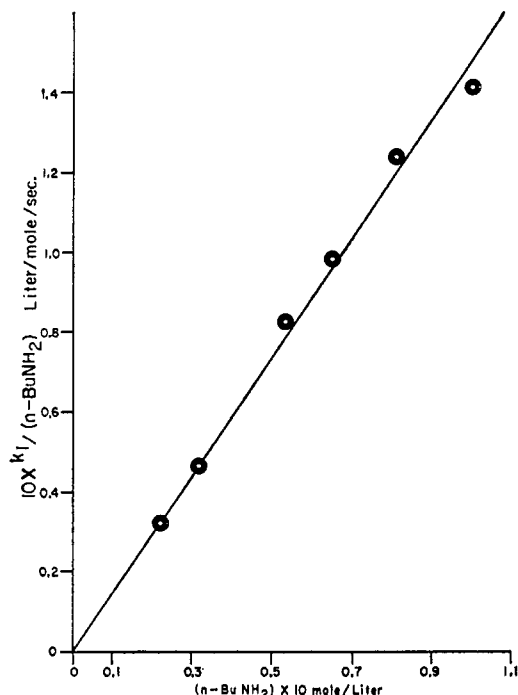
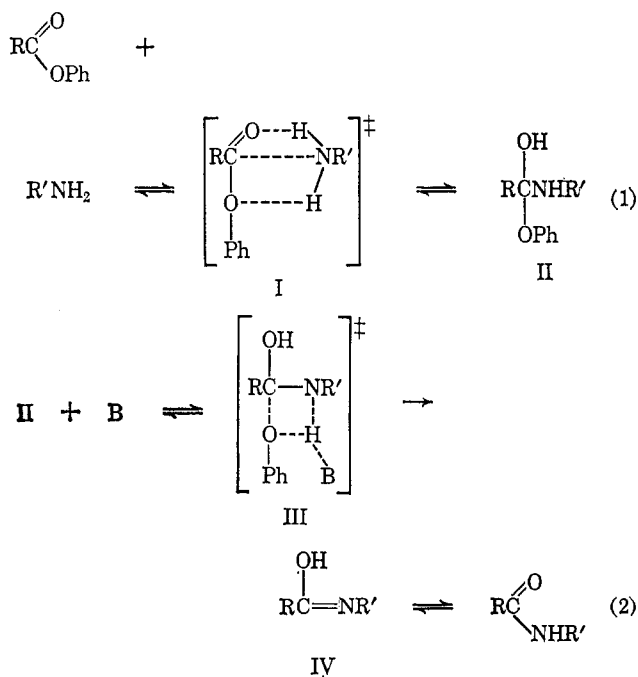


Figure 5. Plot of $k_1/(\text{amine})$ against amine concentration for the reaction of phenyl dichloroacetate with *n*-butylamine in cyclohexane at 25.5°.

as having little importance since the reaction takes place in a solvent of low dielectric constant. Construction of Godfrey models has shown that this simultaneous bond formation is sterically and geometrically feasible.



In the second step, the intermediate is shown as losing phenol by protonation of phenoxy group by amine nitrogen, assisted by the base catalyst B. In this study, B could be another molecule of attacking amine, triethylamine, or the solvent, dioxane.

This stepwise scheme is, of course, kinetically indistinguishable from a concerted mechanism, as follows

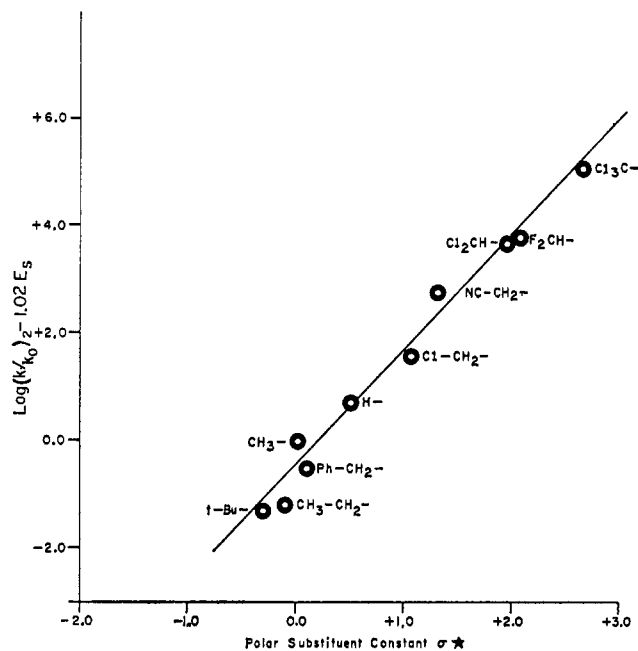


Figure 6.

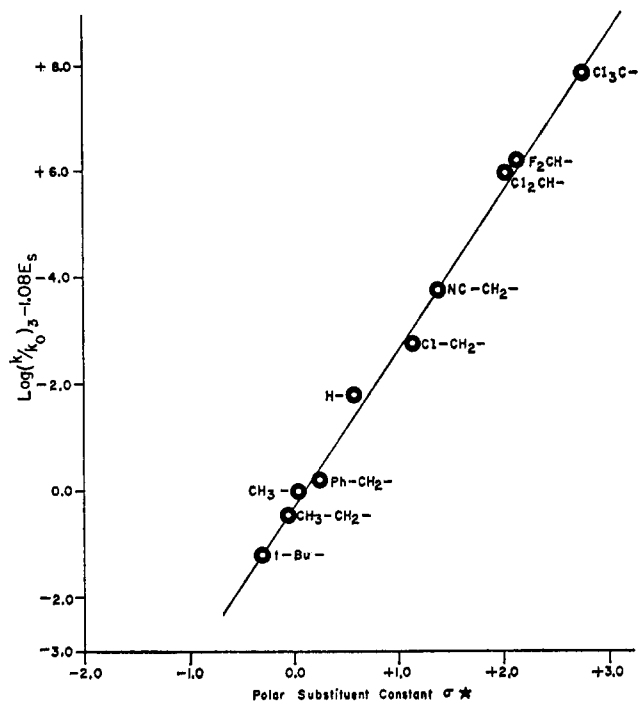
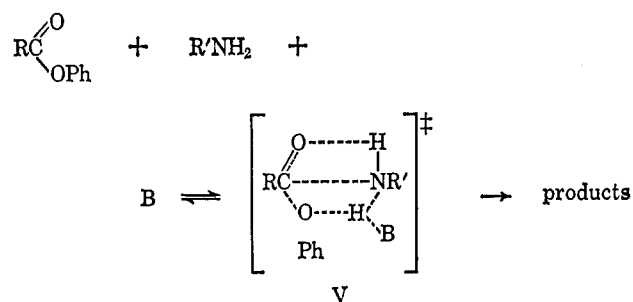


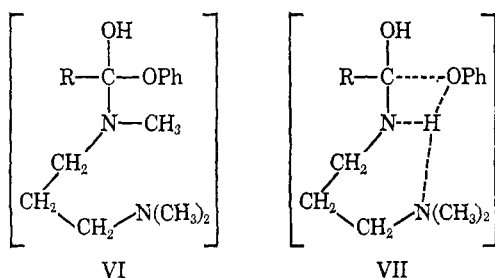
Figure 7.



Our data do not permit a distinction between these two alternatives at the present time; however, our ob-

servations are consistent with the protonation of the phenoxy group by the amine hydrogen, rather than by the base catalyst. Catalysis by triethylamine, a tertiary amine, and the observation that base catalysis does not occur with secondary attacking amines, seem to substantiate this. Although the mechanism in aqueous solution may not be the same as that in dioxane, it is interesting that much of the literature data for aqueous solutions is consistent with this explanation. For example, in aminolysis of phenyl acetate, Jencks and co-workers found general base catalysis for the primary amines *n*-butylamine, hydroxylamine, glycine, and glycyglycine,²² methylamine, ethylamine, and *n*-propylamine,^{4a} but not for the secondary amines piperidine and morpholine.²² Bruice and co-workers²³ obtained no general base catalysis for three cyclic secondary amines. One notable exception is the observation of Jencks and Carriuolo²² that general base catalysis does occur for the reaction of dimethylamine with phenyl acetate. This amine will be investigated in dioxane solution in this laboratory.

Intramolecular Catalysis. The observation of second-order kinetics without general base catalysis in the reactions of two diamines with phenyl esters in dioxane is in agreement with the results of Bruice and Willis²⁴ who found no general base catalysis for a series of diamines in aqueous solution. One may suggest an explanation in terms of intramolecular catalysis, as shown below



A reaction involving the intermediate VI might be expected to proceed more slowly than that involving VII since the pictured catalytic effect cannot operate in VI. In fact, the observation was made that the reaction of *N,N*-dimethyl-1,3-propanediamine with phenyl dichloroacetate had a rate constant 13 times as large as that for the reaction of *N,N,N'*-trimethyl-1,3-propanediamine with the same ester, as can be seen from the data in Table I.

An analogous explanation may be given to explain the lack of external base catalysis for phenyl methoxyacetate, where the methoxy group might act as the base, B, in the proposed mechanism. If one accepts the idea that dioxane may act as a base catalyst in this reaction, extrapolation to include the methoxy group is not too difficult. Again, a difference in rate constants by a factor of 13 (Table III) between the two amines, *n*-butylamine (the faster) and *N*-methyl-*n*-butylamine, is consistent with this, since in the latter the catalytic effect is not expected to operate.

The Effect of Structure. The probability of a coincidental fit to the Taft equation $\log k/k_0 = \rho^*\sigma^* + \delta E_s$

(22) W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **82**, 675 (1960).

(23) L. R. Fedor, T. C. Bruice, K. L. Kirk, and J. Meinwald, *ibid.*, **88**, 108 (1966).

(24) T. C. Bruice and R. G. Willis, *ibid.*, **87**, 531 (1965).

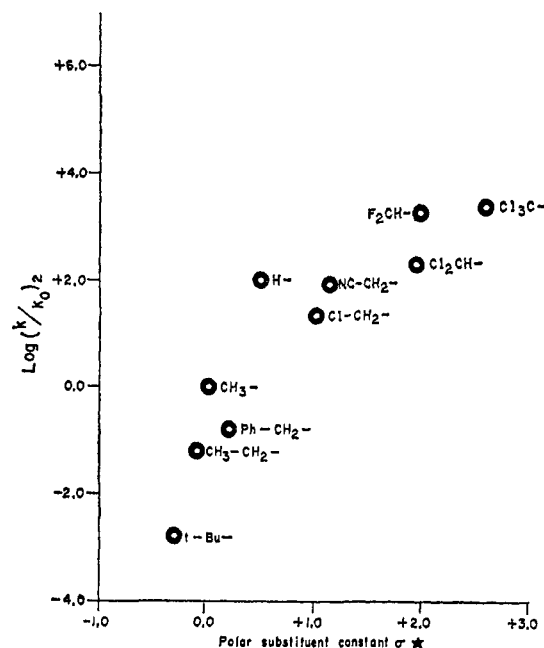


Figure 8.

is very small, since the lack of generality of this equation is well established; indeed, only two other reaction series have been found to be correlated by this equation, *viz.*, the methanolysis of 1-menthyl esters²⁵ and the alkylation of amino acids by acetonitrile.²⁶ In the present study, a range of eight powers of 10 in the rate constants was covered, increasing the unlikelihood of a coincidental fit to the equation.

Comparison of the reaction parameters of the solvent-catalyzed reaction and the amine-catalyzed reaction shows that the reaction with the stronger base is much more susceptible to polar requirements than is the solvent-catalyzed reaction. On the other hand, the steric requirements appear to be independent of the nature of the catalyzing base. This can also be seen by examination of the rate constant ratios, k_3/k_2 , shown in Table I. The ratios are large for those substituents having large electron-withdrawing properties, and decrease to around one for the alkyl substituents.

These observations may be reconciled with the proposed mechanism as follows. If the decomposition of the intermediate is considered to be rate determining, then this will be made more difficult with increased polar requirements of the acyl substituent. The base-catalyzed decomposition of the intermediate, then, could be considered to require a much stronger base to remove the phenol than would be needed for compounds having substituents of lesser polarity. The first step, on the other hand, would be facilitated by electron-withdrawing substituents, and the larger over-all rate for these compounds may be considered to be due to a greater "piling up" of the intermediate than occurs with compounds having substituents of lesser polarity.

Work is now in progress to investigate the effect of different donor groups in the acyl portion of the ester, both to seek a Brønsted relationship if this be base catalysis, and to determine the effect of proximity to the reaction center by addition of methylene groups between

(25) W. A. Pavelich and R. W. Taft, Jr., *ibid.*, **79**, 4935 (1957).

(26) M. Friedman and J. S. Wall, *ibid.*, **86**, 3735 (1964).

the carbonyl and the donor group. Entropies of activation will also be obtained, and the mechanism of the uncatalyzed reaction will be investigated more fully.

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A New Approach to the Synthesis of α -Hydroxy- β -diketones and γ -Bromo- α -hydroxy- β -diketones and Their Phosphate Esters

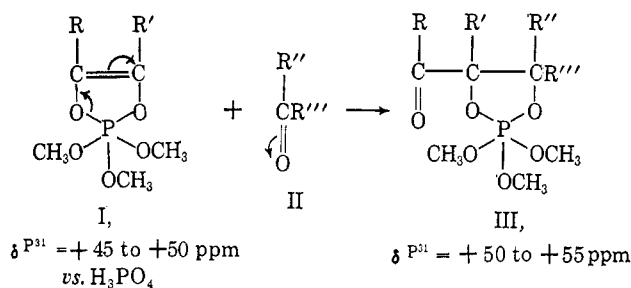
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Abstract: 2,2,2-Trimethoxy-4,5-dimethyl-1,3,2-dioxaphospholene, made from trimethyl phosphite and biacetyl, reacted with ketene, $\text{CH}_2=\text{C}=\text{O}$, and gave 2,2,2-trimethoxy-4-methylene-5-acetyl-5-methyl-1,3,2-dioxaphospholane in over 90% yield. This phospholane was quantitatively converted by hydrogen chloride into the dimethyl phosphate ester of 3-methylpentan-3-ol-2,4-dione (diacetylmethylcarbinol). The phosphorus-free hydroxydiketone was made from the phospholane or the phosphate in boiling aqueous benzene. Bromination of the phospholane gave the dimethyl phosphate ester of 1-bromo-3-methylpentan-3-ol-2,4-dione.

The formation of a carbon-carbon single bond by the nucleophilic addition of a 2,2,2-trialkoxy-1,3,2-dioxaphospholene² (I) to a carbonyl function II was first reported in 1961.³ This condensation reaction made available the new 2,2,2-trialkoxy-1,3,2-dioxaphospholanes⁴ (III).



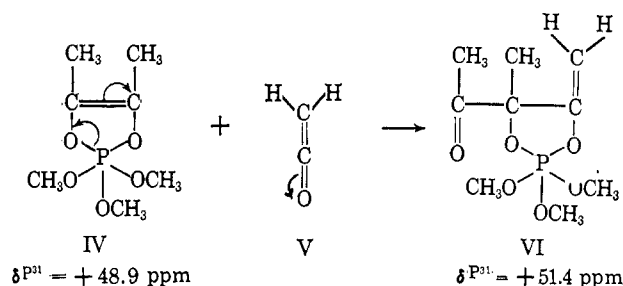
The phospholanes III could be transformed into cyclic and open-chain phosphate esters, and into phosphorus-free polyoxygenated functions.⁵ Some of the phospholanes were also capable of undergoing molecular rearrangements when heated in methanol solution.^{4,6}

This paper describes the condensation of a phospholene I with ketene,⁷ and discloses a new approach to the

synthesis of α -hydroxy- β -diketones and γ -bromo- α -hydroxy- β -diketones and their phosphate esters.

Results

Reaction of Ketene with the Trimethyl Biacetylphosphite 1:1 Adduct IV. The reaction of ketene V with 2,2,2-trimethoxy-4,5-dimethyl-1,3,2-dioxaphospholene (IV) took place at 0° in methylene chloride solution. The product was 2,2,2-trimethoxy-4-methylene-5-acetyl-5-methyl-1,3,2-dioxaphospholane (VI) isolated in 90% yield.



The phospholane VI probably arose in a concerted nucleophilic addition of the phospholene IV to the ketene V without the formation of an intermediate dipolar ion like VII.⁸ However, the transient formation of undetectably small amounts of VII cannot be excluded.

The pentaoxyphosphorane VI was distinguished from the isomeric tetraoxyalkylphosphorane VIII on the basis of the following spectral data.

(7) While this work was in progress, A. J. Kirby [*Tetrahedron*, **22**, 3001 (1966)] published experiments involving the phospholene IV and carbon disulfide. Our studies of the reactions of IV, and of related phospholenes, with a number of systems having cumulated double bonds will be published in a separate communication.

(8) (a) F. Ramirez, A. V. Patwardhan, and C. P. Smith, *J. Org. Chem.*, **30**, 2575 (1965); (b) *ibid.*, **31**, 474 (1966).

(1) This investigation was supported by Public Health Service Grant No. CA-04769-08 from the National Cancer Institute, and by the National Science Foundation, Grant GP-6690-Y.

(2) For a review, see F. Ramirez, *Pure Appl. Chem.*, **9**, 337 (1964).

(3) (a) F. Ramirez and N. Ramanathan, *J. Org. Chem.*, **26**, 3041 (1961); (b) F. Ramirez, N. Ramanathan, and N. B. Desai, *J. Am. Chem. Soc.*, **84**, 1317 (1962); (c) F. Ramirez, N. B. Desai, and N. Ramanathan, *Tetrahedron Letters*, 323 (1963).

(4) For a review, see F. Ramirez, *Bull. Soc. Chim. France*, 2443 (1966).

(5) (a) F. Ramirez, A. V. Patwardhan, N. B. Desai, and S. R. Heller, *J. Am. Chem. Soc.*, **87**, 549 (1965); (b) F. Ramirez, N. Ramanathan, and N. B. Desai, *ibid.*, **85**, 3465 (1963); (c) F. Ramirez, S. B. Bhatia, and C. P. Smith, *Tetrahedron*, in press.

(6) F. Ramirez, H. J. Kugler, and C. P. Smith, *Tetrahedron Letters*, 261 (1965).