bromine in cyclopentyl bromide must be forced toward an axial position prior to or during overlap of the electrode electrons with the σ^* C–Br bond; and (2) the overlap is the potential-determining step in transition state attainment because of the cycloalkyl halides tested, only in cyclopentyl bromide with bromine forced by the negative electrode into an axial conformation is the backside of the reactive carbon as free as in propyl bromide.[22]

The potential-determining step in polarographic reductions of the SN2 type can be ascribed to the steric requirements of initial overlap rather than steric requirements of a transition state with a planar central carbon atom coördinated with the mercury drop and a departing bromine. The latter state should certainly necessitate as stringent steric conditions as in SN2 displacements. Yet, the $E_{1/2}$ of cyclopentyl bromide is markedly less negative than that of isopropyl bromide and of cycloheptyl bromide, although the SN2 reactivity of the three compounds is of the same order, and cyclohexyl bromide is reduced strikingly more easily than cyclobutyl bromide, even though their SN2 reactivity is quite similar.

The nearly equivalent ease of reduction of cyclopropyl bromide and neopentyl bromide may be an example of anchimeric assistance in polarographic reduction. Overlap of the portion of mercury drop effective in reduction with the delocalized electrons of the cyclopropane ring could force cross-ring overlap with the reactive site. Displacement by an "SNi" process would be thereby aided.

Of course the cautions of Delahay[23] regarding facile correlation of the half-wave potentials of irreversible reduction processes with a polar or steric parameter must be borne in mind. This is especially true of the correlations which have been drawn in the last section of this discussion. However, the high degree of irreversibility of the reduction of RX compounds, and the striking correlation of half-wave potentials with steric factors in the classic series of substituted alkyl halides despite probable slight variation in α, the transfer coefficient, at least indicate that the interpretations given in the latter section may be worthy of consideration, although by no means constituting proof.

Polarographic investigation is continuing in the areas of sterically hindered halogen compounds and of anchimeric effects aided by the field of the dropping mercury electrode.

Acknowledgment.—We are indebted to Dr. Richard E. Robertson for helpful discussions of molecular orbital processes at the dropping mercury electrode.

portion of the mercury drop with the σ^*-orbital of the halogen compound. Then steric interference of neighboring hydrogens with σ^*-overlap would be comparable to that present in the isopropyl bromide. Movement of bromine to an axial conformation can occur relatively readily in cyclopentyl bromide. Forcing the bromine to an axial position by the electrode process would take place only with much greater difficulty in the other cyclic halides of this work.

(22) Flanking methyl groups with closely contiguous hydrogens are present in isopropyl bromide. Hydrogen atoms on β- and γ-methylene groups obscure the backside of the C–Br in cycloheptyl bromide even when the bromine is axial. I-strain and other conformation and polar effects should affect the $E_{1/2}$ of cyclopentyl and cycloheptyl bromides equally.

(23) T. Berzins and P. Delahay, THIS JOURNAL, **75**, 5716 (1953).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN, BROOKLYN 1, N. Y.]

Intramolecular Carboxylate Attack on Ester Groups. The Hydrolysis of Substituted Phenyl Acid Succinates and Phenyl Acid Glutarates[1]

BY ERICK GAETJENS[2] AND HERBERT MORAWETZ

RECEIVED APRIL 6, 1960

The anions of phenyl acid succinate and phenyl acid glutarate are hydrolyzed by a unimolecular mechanism involving an attack of the neighboring carboxylate on the ester function. This reaction is very fast compared to the acetate ion catalyzed hydrolysis of phenyl esters. Reaction rates of these compounds and of 20 substituted phenyl esters were determined. The rate was found to be unusually sensitive to electron-withdrawing *para* substituents. Thus, *p*-nitrophenyl glutarate reacted 540 times as fast as phenyl glutarate, while the analogous intermolecular reactions, the acetate-catalyzed hydrolysis of nitrophenyl acetate and phenyl acetate, had rates differing by a factor of only 15. The high substituent sensitivity of the intramolecular reaction is due almost entirely to variations in the *entropy* of activation. The ionization constants of substituted phenols behave in a strikingly similar manner. The observations are interpreted by assuming that the intermolecular carboxylate attack on phenyl esters leads to a tetrahedrally bonded reaction intermediate, while the intramolecular reaction involves a direct displacement of the phenoxide by the attacking carboxylate. The reaction is 120–200 times as fast with succinates than with the corresponding glutarates. Chloro, bromo, methoxy and acetamido substitution leads to higher rates when the substituent is *ortho* rather than *para*, while methyl and carbomethoxy substituents in the *ortho* position give lower rates. The substituent sensitivies of hydrolytic reactions of substituted phenol derivatives are compared for inter- and intramolecular attack of the nucleophile and for a number of related enzymatic reactions.

Introduction

Phenyl esters carrying carboxyl groups at a suitable spacing to the ester function may be hydrolyzed at an unusually rapid rate because of a nucleophilic attack of the ionized carboxyl on the ester carbon.[3–7] Since under favorable conditions the effect of the carboxylate attack is very much

(1) We are indebted for financial support of this investigation to the Upjohn Co., the Eli Lilly Co. and the National Institutes of Health.

(2) Abstracted from a Ph.D. thesis to be submitted by E. Gaetjens to the Graduate School, Polytechnic Institute of Brooklyn, in June, 1961.

(3) H. Morawetz and P. E. Zimmering, *J. Phys. Chem.*, **58**, 753 (1954).

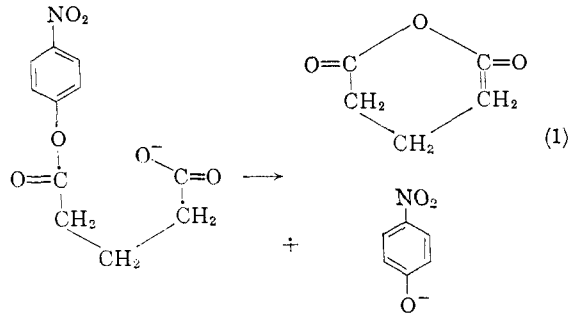
(4) P. E. Zimmering, E. W. Westhead and H. Morawetz, *Biochem. Biophys. Acta*, **25**, 376 (1957).

(5) E. R. Garrett, THIS JOURNAL, **79**, 3401 (1957).

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

(7) H. Morawetz and E. Gaetjens, *J. Polymer Sci.*, **32**, 526 (1958).

larger than the effect of hydrogen and hydroxyl catalyzed ester hydrolysis, the hydrolytic rate in the pH range 3–6 is found to be proportional to the degree of ionization of the reactive carboxyl group. Bender and his collaborators have shown that neighboring carboxylate may also disrupt alkyl esters[8] and they have demonstrated by tracer experiments that an attack of a carboxylic acid anion on an ester group results in the formation of an anhydride.[9] Thus, the hydrolysis, of *e.g.*, *p*-nitrophenyl glutarate, studied earlier in this Laboratory,[4] could be represented by



(1)

The anhydride formed in this reaction would presumably be rapidly hydrolyzed, but we concerned ourselves in this investigation only with the appearance of the free phenol.

The present paper reports studies of the rates of neighboring carboxylate attack on the ester groups of phenyl acid succinates and phenyl acid glutarates substituted in the benzene ring. The aim of the investigation was to assess the importance of the spacing of the attacking carboxylate from the ester group and to compare substituent effects in intramolecular to similar intermolecular reactions. A representative sample of the compounds was studied over a range of temperatures, so that the substituent effects on reaction rates could be resolved into effects on the entropies and enthalpies of activation.

Results and Discussion

The pH dependence of the hydrolysis rate of the group of esters investigated is illustrated in Table I and Fig. 1 on phenyl succinate. The observed first-order rate constants k may be accounted for in the pH range covered by

$$k = k_{\alpha}\alpha + k_{OH}(OH^-) \qquad (2)$$

where α is the degree of ionization of the free carboxyl group and k_{α} is the first-order rate constant characterizing the intramolecular reaction exemplified by (1). In the case of the succinic acid esters, hydroxyl ion catalysis is negligible at pH 7 where the carboxylic group is fully ionized and α for any lower pH may, therefore, be estimated from the ratio of the observed rate constants at that pH and at pH 7. For glutaric esters, hydroxyl ion catalysis may contribute up to 15% of the rate at pH 7 and it was necessary to determine k_{OH} by kinetic runs at pH 9.7 before (2) could be used to obtain k_{α}. Table I shows that an apparent pK

(8) M. L. Bender, F. Chloupek and M. C. Neveu, THIS JOURNAL, 80, 5384 (1958).

(9) M. L. Bender and M. C. Neveu, *ibid.*, 80, 5388 (1958).

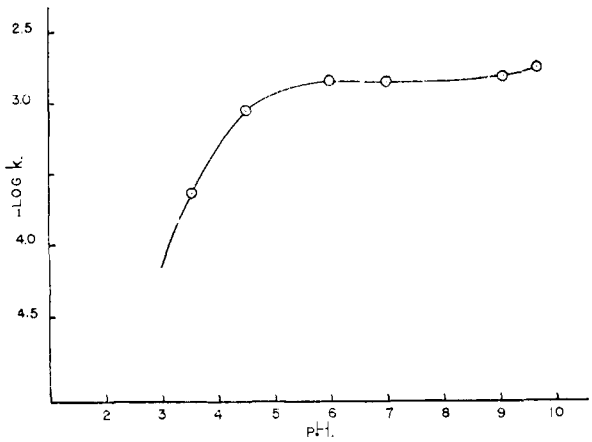


Fig. 1.—Hydrolysis of phenyl acid succinate at 25.3°.

of the reactive carboxyl defined by

$$pK_{app} = pH + \log[(1 - \alpha)/\alpha] \qquad (3)$$

yields consistent values over a wide range of pH.

Table II lists the $k\alpha$ and pK_{app} values for the investigated succinates and glutarates and for some of them $\Delta H^{\ddagger}$ and $T\Delta S^{\ddagger}$, the contributions to the reaction rate due to the enthalpy and entropy of activation. Since we wished to compare substituent effects in intramolecular and intermolecular carboxylate attack on ester groups, we studied also the acetate ion catalyzed hydrolysis of phenyl acetate and *p*-nitrophenyl acetate. These reactions have been studied previously,[9,10] but conditions of solvent media or ionic strength were different from ours, justifying a reinvestigation. The results listed in Table III are quite similar to those of Bender and Neveu.[9]

TABLE I

HYDROLYSIS OF PHENYL SUCCINATE AT 25.3°

Temp., °C.	pH	10^4 (sec.$^{-1}$)	pK_{app}[e]
25.3	9.70	17.6[a]	
25.3	9.10	15.4[a]	
25.3	7.00	14.2[b]	
25.3	6.00	14.2[b]	
25.3	4.50	8.97[c]	4.27
25.3	3.62	2.30[d]	4.33
14.9	7.00	4.87[b]	
14.9	4.50	2.99[c]	4.30
14.9	3.62	0.83[d]	4.31

[a] 0.46 mg. of ester/50 ml. of 0.1 *M* sodium borate buffer, 10-cm. cell. [b] 15.5 mg. of ester/200 ml. of 0.1 *M* potassium phosphate buffer. [c] 15.5 mg. of ester/200 ml. of 0.1 *M* sodium acetate buffer. [d] 15.5 mg. of ester/200 ml. of 0.1 *M* sodium citrate buffer. [e] The pK_{app} value is in reasonable agreement with pK = 4.52 obtained from titration data for monoesters of succinic acid (E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides," Reinhold Publ. Corp., New York, N. Y., 1943, p. 121).

The intramolecular reaction of phenyl acid succinates and glutarates was found to have two striking and unexpected characteristics: (1) The intramolecular reaction is much more sensitive to the effects of strongly electron-withdrawing *para* substituents than the analogous intermolecular reaction. Thus, *p*-nitrophenyl glutarate reacts 540 times as fast as phenyl glutarate, while the acetate

(10) T. C. Bruice and R. Lapinski, *ibid.*, 80, 2265 (1958).

TABLE II

HYDROLYSIS OF PHENYL ACID SUCCINATES AND GLUTARATES

Substituents	10^4k, sec.$^{-1}$ [a]	k_{OH}, l. mole^{-1} sec.$^{-1}$ [b]	10^4k_α, sec.$^{-1}$	pK_{app}	$\Delta H^\ddagger$, kcal./mole	$T\Delta S^\ddagger$, kcal./mole
Glutarates						
p-OCH_3	0.044	2.5	0.041	4.63	19.3	−5.5
p-CH_3	.050	2.4	.048		19.5	−5.2
o-CH_3	.0063	0.97	.0053		21.7	−4.4
H	.10	3.1	.098	4.74		
p-Cl	.40	22.5	.37	4.27	20.3	−3.2
o-Cl	1.41				19.7	−3.0
p-Br	0.48	29	0.45	4.37	20.2	−3.1
o-Br	1.31	14.4	1.29			
p-$COOCH_3$	4.8	9.5	4.8	4.70		
o-$COOCH_3$	0.50					
m-NO_2	6.3	48	6.3			
p-NO_2	53	40	53	4.50	19.1	−1.8
Succinates						
p-OCH_3	6.2			4.36	19.0	−2.8
o-OCH_3	12				18.0	−3.4
p-OH	4.9			4.35		
o-OH	12.6			4.22		
H	14.2			4.30		
p-$NHCOCH_3$	32					
o-$NHCOCH_3$	98					
p-Cl	75			4.36		
p-$COOCH_3$ [c]	600					
o-$COOCH_3$ [c]	113					

[a] Concentration of ester varied from 10^{-3} to 10^{-4} *M*, 0.1 *M* potassium phosphate buffer at *p*H 7.0, 25.3°. [b] Concentration of esters varied from 10^{-3} to 10^{-4} *M*, 0.1 *M* sodium borate buffer at *p*H 9.70. [c] Measured by Mr. I. Oreskes.

TABLE III

ACETATE ION CATALYZED HYDROLYSIS OF PHENYL ACETATES AT 60.8° [a]

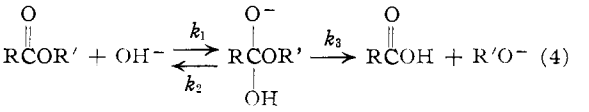
Substituent	[Ac], mole/l.	k_{obs}, sec.$^{-1}$ × 10^5	k_{Ac}, l.-mole^{-1} sec.$^{-1}$ × 10^5
H [b]	0.05	1.25	
	.10	1.75	0.994
	.15	2.19	
	.20	2.55	
m-NO_2 [c]	.05	10.7	
	.10	13.7	6.80
	.15	17.4	
	.20	20.8	
p-NO_2 [d]	.05	21.4	
	.10	29.6	15.0
	.15	35.8	
	.20	43.9	

[a] Acetate buffers at *p*H 5.27, total ionic strength of 0.2 maintained by addition of sodium chloride. [b] 11 mg. of ester/200 ml. of buffer. [c] 40 mg. of ester/200 ml. of buffer. [d] 3.2 mg. of ester/200 ml. of buffer.

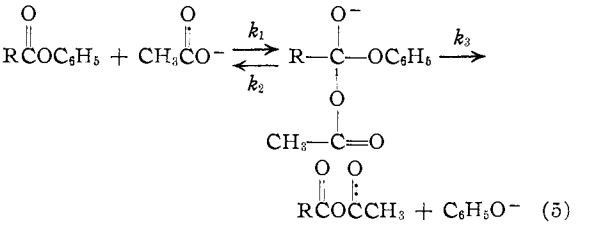
ion catalyzed hydrolysis of *p*-nitrophenyl acetate is only 15 times as fast as that of phenyl acetate.

(2) The activation energies of the intramolecular reaction are essentially unaffected by the electron-donating or electron-withdrawing character of the nuclear substituents, so that the large substituent effect on the reaction rate is due to a change of the entropy of activation. This is a most unusual situation: Hammett has emphasized[11] that the effects of *p*-substitutents would be expected to modify $\Delta H^\ddagger$ while leaving $\Delta S^\ddagger$ unchanged. This means that the effect of substituents should decrease with rising temperature, a conclusion which is borne out by the bulk of experimental data.[12]

We shall now explore the mechanistic consequences of these observations. Bender has demonstrated[13] that the hydroxyl ion catalyzed hydrolysis of carboxylic esters is accompanied by an isotopic oxygen exchange in the unreacted ester and he has interpreted his results by the mechanism



It would be assumed that the attack of acetate on phenyl esters follows an analogous two-step sequence



In the hydroxyl ion catalyzed hydrolysis of ethyl benzoate, a typical alkyl ester, the ratio k_3/k_2 was found to be 4.8.[13] On the other hand, no isotopic exchange was detected in unreacted phenyl benzoate during its hydroxyl ion catalyzed hydrolysis.[14] Bender has reasoned that the reaction still follows scheme 4 but that in this case $k_3/k_2 > 100$, so that isotope exchange would not have been detectable under the experimental conditions.[15] These results indicate that the rate of the hydroxyl ion catalyzed hydrolysis of a phenyl ester is essentially controlled by the rate coefficient k_1. When an acetate ion is the nucleophile, we cannot use the tracer technique to estimate k_3/k_2 and this ratio may well be much smaller than in the hydroxyl ion catalyzed reaction. However, the hydroxyl and acetate catalyzed hydrolyses of phenyl esters are accelerated by the same factor of 14–15 on introduction of a *p*-nitro substituent[9,16] (see Table IV) and this leads us to believe that the analogous reaction step, *i.e.*, the addition of the nucleophile to the ester carbon, must be rate controlling in both cases. It should also be noted that in both these cases the difference in the behavior of phenyl and *p*-nitrophenyl esters is fully accounted for by corresponding differences in the activation energies.

Why should the phenyl ester hydrolyses catalyzed by an intramolecular carboxylate attack behave in such a strikingly different manner? A clue to this problem was provided by recent investigations which showed that variations in the ionization constants of *p*-substituted phenols are brought about mainly by large changes in the entropy of ionization.[17] The sensitivity of the ioni-

(11) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 206.

(12) H. Jaffe, *Chem. Revs.*, **53**, 191 (1953).

(13) M. L. Bender, THIS JOURNAL, **73**, 1626 (1951).

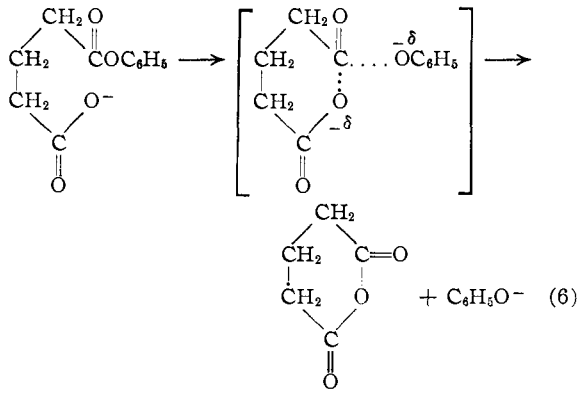
(14) C. A. Bunton and D. N. Spatcher, *J. Chem. Soc.*, 1079 (1956).

(15) M. L. Bender, *Chem. Revs.*, **60**, 53 (1960).

(16) E. Tommila and C. N. Hinshelwood, *J. Chem. Soc.*, 1801 (1938).

(17) (a) P. Fernandez and L. G. Hepler, THIS JOURNAL, **81**, 1783 (1959). (b) H. M. Papee, W. J. Canady, T. W. Zawidzki and K. J.

zation constants of phenols to *p*-substituents is also very similar to that of the intramolecular reaction of phenyl acid succinates or glutarates as shown in Fig. 2.[18] For instance, the factor by which the introduction of a *p*-nitro group increases the ionization constant of phenol has variously been reported as 680[17a] or 640[18a] while we found *p*-nitro substitution to accelerate the reaction of phenyl acid glutarate by a factor of 540. Thus, the intramolecular carboxylate attack on phenyl ester groups parallels the ionization of phenols in two important respects, the sensitivity to electron-withdrawing *p*-substituents and the entropic nature of such substituent effects. This similarity suggests that in the transition state of the rate-determining step of the intramolecular reaction the phenoxide group is largely ionized. This seems to exclude the possibility of the formation of an intermediate such as shown in 5, pointing to a mechanism in which the expulsion of the phenoxide is synchronized with the bond formation between the carboxylate nucleophile and the ester carbon[19]



(6)

In this mechanism the intermediate would be present in negligible concentration and the kinetically determined pK_{app} should be equal to the pK of the carboxyl group of the reagent and should depend little on the phenol substituents. The data in Table II show that such variations as are observed in pK_{app} cannot be correlated with the

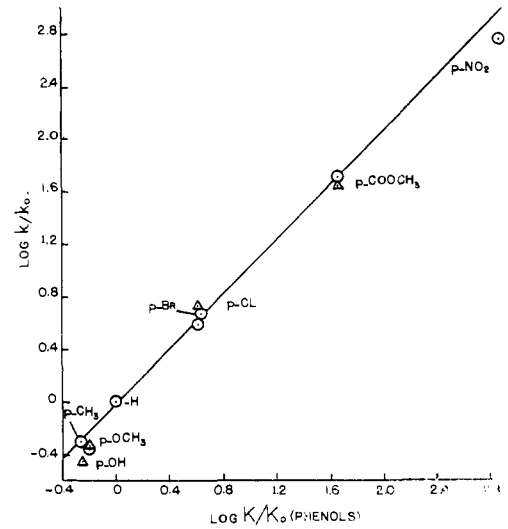


Fig. 2.—Correlation of the rates of the intramolecular carboxylate attack on the ester groups of phenyl acid succinates and glutarates with the ionization constants of the phenols: Δ, succinates; O, glutarates.

electron-withdrawing power of the substituents. In this respect our systems differ markedly from the substituted phenyl esters of γ-4-(imidazolyl)-butyric acid, where the pK_{app} was found to drop by 0.67 with the introduction of a *p*-nitro substituent.[20] This phenomenon was interpreted as meaning that an appreciable fraction of the reagent was present in the form of the reaction intermediate.

The distinction between a reaction such as represented by (6) in which the resonance stabilization of the transition state is substantially above that of the reagent, and a mechanism such as represented by (5) in which this is not the case, may be strikingly illuminated by a comparison of effects produced by *m*-nitro and *p*-nitro substituents. Taft has suggested[21] that whenever resonance stabilization effects contribute to the effect of a substituent on a reaction rate or equilibrium, the Hammett equation should be modified to

$$\log (k/k^\circ) = \sigma\rho + \psi \qquad (7)$$

where k° and k are the rates or equilibrium constants of the unsubstituted and the substituted reagent. respectively, σ is the substituent constant characteristic of reactions in which changes in resonance stabilization are not important, ρ is the reaction constant and ψ is a parameter characterizing the contribution of resonance between the substituent and the reaction center. Since σ values for reactions which do not involve changes in resonance stabilization are given as 0.78 and 0.71 for *p*-nitro and *m*-nitro substituents, respectively,[12,22] and since ψ appears to be negligible for *m*-nitro substituents, we may estimate ψ from

$$\psi = \log (k_{p\text{-nitro}}/k^\circ) - (0.78/0.71) \log (k_{m\text{-nitro}}/k^\circ) \qquad (8)$$

The results given in Table IV show that ψ has

Laidler, *Trans. Faraday Soc.*, **55**, 1734 (1959). The large increase in the entropy of ionization on *p*-substitution with an electron-withdrawing substituent is undoubtedly due to the delocalization of the ionic charge and the consequent release of bound water from the phenoxide. As would be expected, an electron-donating *p*-substituent produces the reverse effect. The situation with respect to the ΔH of ionization is more complex. ΔH is made slightly more negative both by the electron-withdrawing *p*-NO_2 and the electron-donating *p*-CH_3. We have to consider here the aggregate of several effects. Electron-withdrawing substituents should weaken the O–H bond, delocalize the charge and "melt" water oriented around the charges. The first two effects will make a negative contribution, the last a positive contribution to ΔH. In comparing *p*-nitrophenol and *p*-cresol, $\Delta\Delta F^\circ = -4.35$ kcal./mole, while $\Delta\Delta H$ is only 0.4 kcal./mole.

(18) In addition to ref. 17, the following sources were used for ionization constants of phenols: (a) C. M. Judson and M. Kilpatrick, THIS JOURNAL, **71**, 3110 (1949); (b) R. A. Robinson and A. I. Biggs, *Trans. Faraday Soc.*, **51**, 901 (1955); (c) E. F. G. Herington and W. Kynaston, *ibid.*, **53**, 138 (1957); (d) A. I. Briggs, *ibid.*, **52**, 35 (1956); (e) E. E. Sager, M. R. Schooley, A. S. Carr and S. F. Acree, *J. Res. Natl. Bureau Standards*, **35**, 521 (1945).

(19) An alternative interpretation would retain the tetrahedral intermediate but assume that $k_2 >> k_3$, so that k_3 which involves the formation of a phenoxide ion, would become rate determining. In adopting this interpretation it would have to be explained why k_2/k_3 should be small in the intermolecular, but high in the intramolecular reaction and this interpretation seems, therefore, rather unconvincing.

(20) T. C. Bruice and J. M. Sturtevant, THIS JOURNAL, **81**, 2860 (1959).

(21) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," ed. M. J. Newman, John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 13.

(22) H. Van Bekkum, P. E. Verkade and B. M. Webster, *Rec. trav. chim.*, **78**, 815 (1959).

TABLE IV

SUBSTITUENT SENSITIVITY OF ENZYMATIC AND NON-ENZYMATIC HYDROLYSES OF PHENOL DERIVATIVES

Reagent	Catalyst	$k_{p\text{-}NO_2}/k^\circ$	ψ	Reaction type	Ref.
PhOH	...	650	1.05	Ionization equil.	17[a]
PhOAc	OH^-	14	0.07	Intermol. non-enz.	15
PhOAc	AcO^-	15	.26	Intermol. non-enz.	[a]
$\bar{O}CO(CH_2)_3COOPh$	OH^-	13	− .20	Intermol. non-enz.	[a]
$(EtO)_2POOPh$	OH^-	226	.23	Intermol. non-enz.	34
PhOAc	Imidazole	197	.51	Intermol. non-enz.	21
$\bar{O}CO(CH_2)_3COOPh$	...	540	.74	Intramolecular	[a]
IBAPE[b]	...	78	− .03	Intramolecular	19
PhOAc	Lipase (k_s)	1.5		Enzymatic	31
Phenyl D-glucoside	Emulsin (k_s)	17.1	−0.21	Enzymatic	33
Phenyl D-glucoside	Emulsin ($1/K_m$)	13.6	.27	Enzymatic	33
$PhOSO_3^-$	Sulfatase (k_s)	16.6	.22	Enzymatic	32
$PhOSO_3^-$	Sulfatase ($1/K_m$)	12.5	.24	Enzymatic	32
$(EtO)_2POOPh$	Cholinesterase (k_s)	180,000	1.86	Enzymatic	34

[a] This investigation. [b] γ-(4-Imidazolyl)-butyric acid phenyl ester.

small values wherever substituent effects are small, while ψ assumes relatively large values in the ionization equilibrium of phenols and in the intramolecular carboxylate catalysis of ester hydrolysis. This seems to confirm our assumption of the mechanism of this reaction. In one case, the hydroxyl catalyzed hydrolysis of phenyl acid glutarates, *m*-nitro substitution was found to be somewhat more effective than the introduction of a *p*-nitro group and the apparent ψ becomes negative. The effect is hard to explain, particularly since the hydroxyl ion catalyzed reaction of nitrophenyl acetates gives, as expected, the higher value for the *p*-substituted ester.[16]

The question arises, why the carboxylate attack on an ester function should follow a different path in the intermolecular and the intramolecular reaction. The intramolecular reaction has a significantly higher activation energy (*e.g.*, 19.1 kcal./mole found by us for the intramolecular reaction of *p*-nitrophenyl acid glutarate as against 15.7 kcal./mole reported by Bender and Neveu[9] for the acetate ion catalyzed hydrolysis of *p*-nitrophenyl acetate) and it would seem, therefore, that steric restrictions inherent in ring formation divert the reaction path to a direction which would otherwise be avoided as energetically unfavorable. The only other comparison of substituent effects in analogous intermolecular and intramolecular reactions is, to our knowledge, the imidazole-catalyzed hydrolysis of substituted phenyl acetates[23] and the hydrolysis of substituted phenyl esters of γ-4-(imidazolyl)-butyric acid.[20] In these cases, *p*-nitro substitution had actually a smaller effect on the intramolecular reaction, causing an 80-fold acceleration as against a 200-fold acceleration observed in the intermolecular case. The comparison is probably significant although the solvent medium contained 50 volume % of ethanol in the first, but only 28.5 volume % ethanol in the second case.

As would be expected, an alteration in the spacing of the carboxylate from the ester group changes the intramolecular reaction rate by a factor which depends little on the phenyl ester substituent. Table V lists k_S/k_G, the ratio of the rate constants for the succinate and glutarate monoesters, respectively, and this ratio is found to lie in the range of 124 to 203. This indicates an unusually large difference in the ease of formation of a five-and six-membered ring. Formation constants of metal chelates are usually only 10–20 times higher for five- than for six-membered rings[24] and in the intramolecular carboxylate displacement of bromine, γ-bromovalerate reacts only 25 times as fast as γ-bromocaproate.[25]

TABLE V

STERIC EFFECTS IN THE INTRAMOLECULAR CATALYSIS OF THE HYDROLYSIS OF PHENYL ACID SUCCINATES AND GLUTARATES

Substituent	$(k_S/k_G)_{para}$	k_o/k_p Succinates	k_o/k_p Glutarates
$-OCH_3$	150	1.96	
$-CH_3$			0.11
−OH		2.55	
−H	145		
−Cl	203		3.58
−Br			2.85
$-COOCH_3$	124	0.19	0.10
$-NHCOCH_3$		3.08	

Table V also lists k_o/k_p, the ratio of the rate constants of phenyl acid succinates and glutarates substituted in the *o*- and *p*-positions, respectively. Since both inductive and resonance effects are very similar in these two positions, k_o/k_p has been suggested[26] as a rough measure of the steric effect of *o*-substitution. Such effects might be expected to be somewhat smaller in intramolecular than in analogous intermolecular reactions. On the other hand, Bunnett has demonstrated that "*o*-substituents of high polarizability would in general tend, after allowance had been made for their electronic and steric effects, to accelerate reactions with nucleophiles of high polarizability."[27,28] Bunnett's suggestion seems to be applicable in our case

(23) T. C. Bruice and G. L. Schmir, THIS JOURNAL, **79**, 1663 (1957).

(24) H. Morawetz, *Fortschr. Hochpolym. Forsch.*, **1**, 1 (1958).

(25) The γ-bromovalerate rate constant at 25° is given by H. W. Heine, E. Becker and J. T. Lane (THIS JOURNAL, **75**, 4514 (1953)). The corresponding constant for γ-bromocaproate was extrapolated from data at 30 and 40° given to us by Prof. Heine.

(26) R. W. Taft, Jr., M. S. Newman and F. H. Verhoek, THIS JOURNAL, **72**, 4511 (1950).

(27) J. F. Bunnett, *ibid.*, **79**, 5969 (1957).

(28) J. D. Reinheimer and J. F. Bunnett, *ibid.*, **81**, 315 (1959).

since the data in Table V show that the polar methoxy, hydroxy, chloro and bromo substituents give more reactive esters with the substituent in the *o*-position, while with the non-polar methyl substituent, the *p*-compound is eight times more reactive. With carbomethoxy, the large bulk of the substituent probably accounts for the relatively low reactivity of the *o*-substituted compound. In the case of the acetamido substituent, the high reactivity of the *o*-substituted ester may be due to a participation of the substituent in hydrogen bonding of the transition state, an effect which was previously suggested to account for the extremely rapid hydrolysis of the singly ionized form of *o*-carboxyphenyl acid succinate.[29]

Comparison with Enzymatic Reactions.—Some years ago it was suggested[30] that reactions involving an intramolecular attack on a reactive group may serve as models for reactions of enzyme–substrate association complexes. Since the present investigation tends to show that the mechanism of seemingly analogous intermolecular and intramolecular reactions may be quite different, it will be useful to compare the character of substituent effects in enzymatically catalyzed reactions of phenol derivatives with that of various non-enzymatic reactions.

Conventionally, the kinetics of enzymatic reactions are represented by the sequence

$$E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES$$

$$ES \xrightarrow{k_3} E + \text{products} \qquad (9)$$

where E, S and ES stand for concentration of enzyme, substrate and their association complex, respectively. We obtain then, under the usual experimental steady state conditions

$$-dS/dt = k_3E_tS/(K_m + S) \qquad (10)$$

where E_t is the total enzyme concentration and $K_m = (k_3 + k_2)/k_1$. However, this representation may not be adequate for the action of esteratic enzymes, since Hartley and Kilby[31] have shown that the chymotrypsin-catalyzed hydrolysis of *p*-nitrophenyl acetate proceeds in two steps, involving the transfer of the acyl group to the enzyme, followed by an enzyme deacylation reaction. Similar mechanisms seem to characterize other esteractic enzymes.[32] We have then

$$E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES$$

$$ES \xrightarrow{k_3} E' + \text{phenol}$$

$$E' \xrightarrow{k_4} E + \text{acid} \qquad (11)$$

For the steady state this leads to

$$-dS/dt = k_3'E_tS/(K_m' + S) \qquad (12)$$

$k_3' = k_3k_4/(k_3 + k_4)$; $K_m' = [(k_2 + k_3)/k_1] \times [k_4/(k_3 + k_4)]$

Let us now compare the sensitivity of various enzymatically catalyzed hydrolyses of phenol derivatives to substituent effects. Table IV shows that this sensitivity varies within extremely broad limits and three patterns of behavior may be distinguished: (a) The lipase-catalyzed hydrolysis of phenyl acetates was found[33] to be almost free of substituent effects, with a *p*-NO_2 group producing less than a doubling of k_3' and even less of a change in K_m'. It is hard to account for this observation on the basis of our present knowledge, since any nucleophile involved in the enzymatic reaction would be expected to be more sensitive to substituent effects. (b) The enzymatically catalyzed hydrolysis of phenyl sulfates[34] and phenyl β-D-glucosides[35] has both k_3' and K_m' modified on *p*-NO_2 substitution by factors of 13–17, strikingly similar to the values of k_{p-NO_2}/k^0 observed for the acetate and hydroxyl catalyzed hydrolyses of phenyl esters. However, it is surprising that K_m' varies inversely as k_3'. This would seem to indicate that $k_2 >> k_3$, that k_2 depends little on substituents and k_1 has a similar substituent sensitivity as the hydroxyl or acetate ion catalyzed hydrolysis of phenyl acetates. This result suggests that the reversible step is probably not a mere molecular association of enzyme and substrate, but is analogous to the reversible step of 4 and 5. It may also be noted that the enzymatic hydrolysis of phenyl β-D-glucosides was anomalous in that the *m*-nitro derivative was more reactive than the *p*-nitro compound, just as we found with the hydroxyl ion catalyzed hydrolysis of phenyl acid glutarates. The enzymatic reaction was further accelerated when the nitro substituent was placed in the *o*-position, the rate then being almost ten times as high as with the *p*-nitro compound. The effect seems to be similar to the Bunnett effect[26,27] discussed earlier, being in this case noticeable even with substituents in the *m*-position.

(*c*) The hydrolysis of diethyl phenyl phosphates catalyzed by erythrocyte cholinesterase[36] has the highest substituent sensitivity of any known reaction of a phenol derivative, the *p*-NO_2 compound reacting 180,000 times as fast as the unsubstituted ester. It may be noted that the hydroxyl ion catalyzed reaction of this reagent has also a rather high substituent sensitivity, although ψ has a low value—in contrast, the value of $\psi = 1.86$ observed in the enzymatic reaction is much higher than that for the ionization equilibria of phenols. It would appear that this enzymatic reaction must involve a mechanism for which we do not know as yet any non-enzymatic analogs.

Acknowledgment.—We are indebted to Professors F. M. Beringer, M. L. Bender, T. C. Bruice and M. Goodman for their critical reviews of the manuscript.

Experimental

Starting Materials.—All the phenols utilized in this investigation were readily available commercially with the

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(30) H. Morawetz and E. W. Westhead, Jr., *J. Polymer Sci.*, **16**, 273 (1955).
(31) Hartley and Kilby, *Biochem. J.*, **50**, 672 (1952); **56**, 288 (1954).
(32) H. Gutfreund, *Disc. Faraday Soc.*, **20**, 167 (1955).
(33) O. Gawron, C. J. Grelecki and M. Duggan, *Arch. Biochem. Biophys.*, **44**, 455 (1953).
(34) K. S. Dodgson, B. Spencer and K. Williams, *Biochem. J.*, **64**, 216 (1956).
(35) R. L. Nath and H. N. Rydon, *ibid.*, **57**, 1 (1954).
(36) W. N. Aldridge and A. N. Davidson, *ibid.*, **51**, 62 (1952).

TABLE VI

PHENYL ACID SUCCINATES AND GLUTARATES

Ester	No.	Substituent	M.p., °C.[a]	Recrystn. solvent	Analyses, %[b] Calcd. C	Calcd. H	Calcd. N, Cl, Br	Found C	Found H	Found N, Cl, Br
Glutarate	I	*m*-NO_2	99–99.5	Benzene	52.17	4.38	5.53	52.32	4.55	5.69
Glutarate	II	*p*-Cl	86.5–87	Benzene–pentane	54.45	4.57	14.61	54.42	4.63	14.46
Glutarate	III	*o*-Cl	34.5–35.5	Heptane	54.45	4.57	14.61	54.52	4.65	14.64
Glutarate	IV	*p*-$COOCH_3$	105–105.5	Benzene	58.64	5.30		58.49	5.40	
Glutarate	V	*p*-Br	102.5–103	Benzene–pentane	46.01	3.86	27.83	46.09	3.83	27.91
Glutarate	VI	*o*-Br	34–34.5	Ether–pentane	46.01	3.86	27.83	46.06	3.91	27.78
Glutarate	VII	*p*-OCH_3	89.5–90	Benzene	60.49	5.92		60.53	6.00	
Glutarate	VIII	*p*-CH_3	83–83.5	Ether–pentane	64.85	6.35		64.82	6.44	
Glutarate	IX	*o*-CH_3	44.5–45	Ether–pentane	64.85	6.35		64.92	6.39	
Glutarate	X	H	45–46	Benzene–heptane	63.45	5.81		63.15	5.81	
Succinate	XI	*p*-Cl	115–115.5	Benzene	52.53	3.97	15.51	52.54	4.03	15.53
Succinate	XII	*p*-$NHCOCH_3$	136–137	MEK–pentane	57.37	5.22	5.58	57.21	5.27	5.75
Succinate	XIII	*o*-$NHCOCH_3$	119–120	Ether–pentane	57.37	5.22	5.58	58.00	5.52	5.69
Succinate	XIV	*p*-OCH_3	117.5–118	Benzene	58.92	5.40		58.84	5.30	
Succinate	XV	*o*-OCH_3	70–70.5	Benzene–pentane	58.92	5.40		59.27	5.40	
Succinate	XVI	*p*-OH[c]	174–175							
Succinate	XVII	*o*-OH[c]	122–123							

[a] Uncorrected. [b] Microanalyses by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y., and by Dr. K. Ritter. Basel, Switzerland. [c] With this compound the elemental analysis differed from theory by more than the allowed range. However, the kinetics of the hydrolysis were strictly first order, so that the rate constants obtained are believed to be reliable,

exception of *o*-hydroxyacetanilide, which was prepared by the acetylation of *o*-aminophenol[37] and *p*-carbomethoxyphenol, m.p. 126–127° (reported[38] m.p. 127°), which was prepared by the esterification of *p*-hydroxybenzoic acid.

Phenyl acetate and *p*-nitrophenyl acetate were from Eastman Kodak Co. (white label).

Glutaric anhydride was prepared from glutaric acid[39] and succinic anhydride was a commercial product (Eastman white label).

Phenyl Acid Glutarates and Succinates.—Of the compounds investigated, only *p*-nitrophenyl acid glutarate (m.p. 96–97°) and phenyl acid succinate (m.p. 98°) have been reported previously.[40,41] The analyses, melting points and solvents used for recrystallization for the other compounds are listed in Table VI. The method reported by Bischoff, *et al.*,[41] for the preparation of phenyl acid succinate was found to be also applicable to the preparation of the succinates and glutarates listed in Table VI. Although the yields are low (20–40%), the method is simple and expedient. In a typical procedure, 0.05 mole of the appropriate phenol was dissolved in a beaker containing an ice-cold solution of 0.05 mole of sodium hydroxide in 100 ml. of water. This was followed by the addition of 0.05 mole of succinic anhydride or glutaric anhydride and the mixture was stirred for 5 minutes and acidified with concd. hydrochloric acid. The resulting precipitate was filtered, dried and recrystallized to a constant melting point. This procedure was slightly modified in the case of the following compounds:

(a) **Compounds III, VI, IX, XV.**—Proceeding as above, acidification of the reaction mixture resulted in the formation of an oily phase which was separated from the aqueous phase, and diluted with 50 ml. of ether. The ether solution was washed with water, dried over anhydrous magnesium sulfate, and the ether removed under reduced pressure. The residue was taken up in the appropriate solvent, and recrystallized to a constant melting point.

(b) ***o*-Hydroxyphenyl Acid Succinate.**—Following the general procedure, acidification of the reaction mixture did not give a precipitate. The reaction mixture was extracted with ether, the extract was dried over anhydrous magnesium sulfate, the ether removed under reduced pressure, and the solid residue recrystallized to a constant melting point.

Rate Measurements.—In all rate measurements, the rates of release of the various phenols was followed spectrophotometrically on a Beckman DU spectrophotometer. The following wave lengths (mμ) were used: phenol 270, catechol 280, hydroquinone 289, guaiacol 293, *o*-methoxyphenol 285, *p*-cresol 277, *o*-cresol 270, *p*-chlorophenol 280, *o*-chlorophenol 274, *p*-bromophenol 280, *o*-bromophenol 274, *p*-carbomethoxyphenol 255, *p*-acetaminophenol 280, *o*-acetaminophenol 279, *m*-nitrophenol 350, *p*-nitrophenol 351. The temperature was controlled to ±0.05°; runs in the neighborhood of 0° were carried out in a Dewar flask containing a mixture of crushed ice and water and the temperature variation was less than ±0.1°. Two techniques were employed: technique I for reactions with a half-life longer than 6 minutes and technique II for faster reactions.

Technique I.—Dioxane stock solutions containing a weighed quantity of ester were prepared, the esters being stable in dioxane. In a typical run, the reaction vessel, consisting of a 250-ml. volumetric flask containing 200 ml. of the appropriate buffer solution, and the dioxane stock solution were brought to constant temperature in a thermostated bath. The reaction was initiated by adding 1 ml. of dioxane solution to the reaction vessel. At appropriate time intervals, 10-ml. aliquots were withdrawn from the reaction vessel and quenched in bottles containing 10 ml. of 0.2 *N* hydrochloric acid. The optical density (D) of these solutions was measured in 1-cm. quartz cuvettes against a blank of 0.2 *N* hydrochloric acid. The reactions were followed to 50–80% completion and an "infinity reading" D_∞ was taken after 10 half-lives. The observed first-order rate constants were obtained as the slopes of plots of ln $(D_\infty - D)$ *vs.* time. Good linear first-order plots were obtained (7–10 readings).

Technique II.—For fast runs, the Beckman DU spectrophotometer was used with a special cylindrical cell 10 cm. long with 50-ml. capacity, fitted with a stirrer designed to prevent the formation of bubbles and a glass jacket through which water from a thermostated bath was circulated. In a typical run, 50 ml. of buffered solution were pipetted into the cell and allowed to reach constant temperature. The spectrophotometer was zeroed against the buffer with the optical density scale set on zero. Then, 1 ml. of a stock solution of the ester in dioxane previously equilibrated in the thermostated bath was injected into the cell from a syringe.

(37) H. E. Fierz-David and W. Kuster, *Helv. Chim. Acta*, **22**, 94 (1939).

(38) P. Pfeiffer and R. Seydel, *Z. physik. Chem.*, **137**, 115 (1928).

(39) W. J. Hickinbottom, "Reactions of Organic Compounds," Longmans, Green and Co., New York, N. Y., p. 227.

(40) P. E. Zimmering, Ph.D. Thesis, Polytechnic Institute of Brooklyn, 1955.

(41) C. A. Bischoff and A. Von Hedenström, *Ber.*, **35**, 4076 (1902).

The optical density was then preset at selected values and the times increments for the attainment of these successive optical densities were measured using two stopwatches.

Activation parameters were calculated from plots of $\log (k/T)$ *vs.* $(1/T)$ by the method of least squares. Kinetic runs were carried out at four temperatures over an interval of 30°. The standard deviations[42] of $\Delta H^{\ddagger}$ and $T\Delta S^{\ddagger}$ were, in three typical cases, ± 0.3 kcal./mole.

(42) W. J. Youden, "Statistical Methods for Chemists," John Wiley and Sons, Inc., New York, N. Y., 1951, p. 42.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE SPRAGUE ELECTRIC CO., NORTH ADAMS, MASS.]

Rates, Products and Salt Effects in the Reactions of Benzyldimethylanilinium Ion with Ethoxide Ion in Ethanol

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RECEIVED APRIL 15, 1960

The rates of reaction of benzyldimethylanilinium bromide with sodium ethoxide and lithium ethoxide in ethanol at 50.8 ± 0.1° have been measured. The effects due to added neutral salts and variations in the anion associated with the quaternary ammonium ion have been studied. Measurements were also made of the rates of solvolysis of the quaternary ammonium salts and of benzyl bromide in the same solvent and at the same temperature.

The S$_N$2 displacement on a quaternary ammonium ion by a negatively charged nucleophile, *e.g.*, hydroxide ion or ethoxide ion, cited as an example of this charge type,[1] has received only scant quantitative study. Two such reactions, the rates of which have been measured, are those of benzyl- and *p*-alkyl substituted benzylpyridinium ions with ethoxide ion in ethanol[2] and of *p*-nitrophenyltrimethylammonium ion with thiocyanate ion in methanol.[3] Neither of the above studies presented detailed evidence to show that the reactions were, in fact, second-order nor investigated salt effects, in spite of the fact that salt effects in reactions of this type are sufficiently large to make the determination of reaction order difficult and to make the significance of a rate constant determined at a single set of initial concentrations questionable.[4]

This paper presents data on the rate of reaction of benzyldimethylanilinium ion with ethoxide ion in ethanol at 50.8 ± 0.1°. In most of the measurements the quaternary ammonium ion was added as the bromide, but some experiments were also carried out with the nitrate and the picrate. The nucleophile was introduced as either sodium ethoxide or lithium ethoxide, and lithium nitrate and lithium chloride were used as neutral salts in some experiments. In connection with the above determinations it also became necessary to study the solvolysis of benzyl bromide and the solvolyses of benzyldimethylanilinium bromide, nitrate and picrate, all in ethanol at 50.8 ± 0.1°. Our purpose in presenting these results is to direct attention to the formidable problems that stand in the way of a quantitative understanding of this reaction.

Results

Table I presents data on the rate of the reaction of benzyldimethylanilinium bromide with sodium ethoxide, and Table II records similar results using lithium ethoxide as the nucleophile. The measurements were generally carried to 60% reaction or beyond. The rate constants, given in column 4 of these tables, were calculated from the slopes of the best straight lines through the experimental points of second-order plots, which were in all cases satisfactory, with none of the experimental points deviating appreciably from the line. The fifth column of these tables gives the square root of the average ionic strength over that portion of the run which was actually followed experimentally.

TABLE I

RATES OF REACTION OF BENZYLDIMETHYLANILINIUM BROMIDE AND SODIUM ETHOXIDE IN ABSOLUTE ETHANOL AT 50.8 ± 0.1°

$R_4N^+Br^-$, mole l.$^{-1}$	NaOEt, mole l.$^{-1}$	Added $LiNO_3$, mole l.$^{-1}$	$k_2 \times 10^4$, l. mole^{-1} sec.$^{-1}$	$\mu^{1/2}$
0.01962	0.01054	0	38.9	0.162
.02119	.01608	0	27.3	.180
.02142	.01563	0	29.4	.180
.04912	.01065	0	27.2	.236
.04863	.01565	0	21.6	.242
.05024	.01598	0	19.8	.245
.01953	.04947	0	19.9	.248
.04884	.03072	0	16.5	.262
.05024	.08798	0	10.9	.347
.04889	.09831	0	11.3	.360
.05011	.2193	0	7.16	.500
.02037	.01653	0.02104	14.1	.233
.02095	.01653	.04052	8.80	.270
.02041	.01662	.05815	6.61	.300
.02055	.01672	.07825	5.01	.333

The data of Table III are presented to show how the rate of reaction of benzyldimethylanilinium ion with ethoxide ion is affected by varying the nature of the anion associated with the quaternary ammonium ion.

To assure that the results tabulated in Tables I–III really represent rates of reaction with ethoxide ion, unaffected by an accompanying first-order solvolysis of the quaternary ammonium ion, the solvolyses of benzyl bromide and of benzyldimethylanilinium bromide, nitrate and picrate in absolute ethanol at 50.8 ± 0.1° were determined. The reaction of benzyl bromide, the

(1) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 346.

(2) C. W. L. Bevan, E. D. Hughes and C. K. Ingold, *Nature*, **171**, 301 (1953).

(3) B. A. Bolto and J. Miller, *J. Org. Chem.*, **20**, 558 (1955).

(4) The sulfonium salts, in contrast, have received more detailed attention. For some recent studies see, (a) C. G. Swain and L. E. Kaiser, THIS JOURNAL, **80**, 4089 (1958); (b) C. G. Swain, L. E. Kaiser and T. E. C. Knee, *ibid.*, **80**, 4092 (1958); (c) E. D. Hughes, C. K. Ingold and Y. Pocker, *Chemistry & Industry*, 1282 (1959).