Intramolecular Catalysis and the Involvement of Tetrahedral Intermediate Partitioning in the Hydrolysis of Benzoylcholine, Benzoylthionocholine, and Their Dimethylamino Analogs[1,2]

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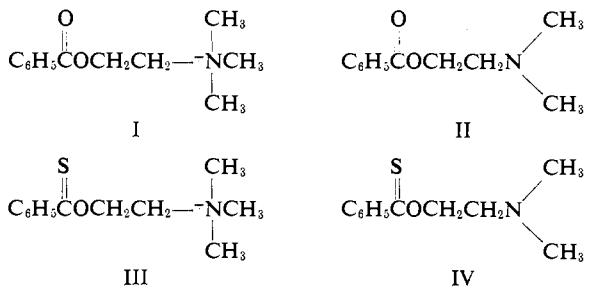
Abstract: The rates of hydrolysis of benzoylcholine, thionobenzoylcholine, and their dimethylamino analogs were measured at 25° in aqueous buffered solutions in the pH range 7–14. The distribution of products obtained in the hydrolysis of the thiono esters is pH dependent; benzoic acid is obtained below pH 9.5 and thiobenzoic acid above pH 11. In moderately basic solutions the tertiary amino esters hydrolyze considerably more rapidly than the corresponding quaternary amino esters. Deuterium isotope effects, product distribution curves, and hydrogen bonding considerations indicate that the rate enhancement is due to intramolecular general base-catalyzed water attack on the carbonyl carbon by the unprotonated ester amino group. In strongly basic solutions (pH >11), the quaternary amino esters hydrolyze more rapidly than their tertiary amino analogs. This is attributed to the differences in pK_a's of the leaving groups and to electrostatic interactions between the positive charge on the nitrogen and the developing negative charge on the carbonyl heteroatom which result in transition state stabilization.

In the hydrolysis of choline or cholinethiol esters and their corresponding dimethylamino analogs, the quaternary amino ester hydrolyzes more rapidly than its dimethylamino analog in strongly basic solutions, while in weakly basic solutions the dimethylamino analog hydrolyzes more rapidly.[5] The enhanced rate of hydrolysis of the dimethylamino esters in weakly basic solutions has been ascribed either to intramolecular general acid–specific base catalysis by the proton of the dimethylammonium group[5c,d,g] or to intramolecular nucleophilic catalysis by the dimethylamino group.[5f,6] To date, however, the exact mechanism by which this intramolecular catalysis occurs has not been explained. An understanding of the nature of this catalysis was obtained through studies of the hydrolysis of benzoylcholine (I), 2-dimethylaminoethyl benzoate (II), thionobenzoylcholine (III), and 2-dimethylaminoethyl thionobenzoate (IV). Inclusion of the thiono esters has allowed a distinction between otherwise indistinguishable mechanisms. The observation that the conformations of analogous 2-dimethylaminoethyl and 2-trimethylammonium ethyl esters and their thiono ester analogs are very similar both in the crystalline state[7] and in D_2O solution[8] minimizes complications introduced by steric differences between the molecules being compared.



I

II

III

IV

Experimental Section

I,[9] II,[5d] III,[10] and IV[10] were prepared according to literature methods. Reaction rates were determined spectrophotometrically with either a Cary Model 15 or a Gilford Model 2400 recording spectrophotometer. Unbuffered rates were measured at constant pH with a Radiometer titrator (TTTlc) and Titrigraph (SBR2c). The spectrophotometer and autotitrator were thermostated at 25.0 ± 0.1.° Measurements of pH were obtained with a Radiometer pH meter 26.

Reaction rates were determined in aqueous solution; ionic strength was maintained at 1.0 (KCl). Buffers employed were potassium bicarbonate 8.9–10.7, *N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid (HEPES) 7.6–8.5, and barbital 7.7–8.4. Buffer dilutions were carried out over the range 0.05–0.20 *M*. Doubly distilled water was used to make up all solutions. The disappearance of thiono ester absorption was followed at 290 nm and the oxo esters at 230. For very slow reactions, reaction mixtures were kept in vials under nitrogen in a thermostated vessel and the absorption was read at intervals. The pH of solutions was determined prior to and at completion of the reaction. First-order kinetics were observed throughout the investigated pH range. The observed rate constants were calculated from slopes of plots of log $(A_t - A_\infty)$ *vs.* time.

Deuterium isotope effects were determined at 25.0° in 99.7% deuterium oxide. In order to maintain a constant pD, all rates in D_2O were determined autotitrimetrically. The pD values were taken as the pH meter readings plus 0.40.[11] Pseudo-first-order rate constants were calculated from plots of ln (base added$_\infty$ − base added$_t$) *vs.* time.

Results

The pH–rate profiles for the hydrolysis of I and II are given in Figure 1. Figure 2 shows the pH–rate profiles for the hydrolysis of III and IV. Rate and dissociation constants are provided in Table I. Examination of

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(10) S.-H. Chu and H. G. Mautner, *J. Med. Chem.*, **11**, 446 (1968).

(11) T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65**, 1079 (1961).

Table I. Kinetically Apparent and Titrimetric Dissociation Constants of Investigated Esters and Rate Constants for Their Hydrolysis

Compd	pK_{app}	pK_a	k_{OH^-}, M^{-1} sec^{-1}	k_{H_2O}, M^{-1} sec^{-1}	k', M^{-1} sec^{-1}	k'', M^{-1} sec^{-1}
I			5.6×10^{-1}			
II	8.47	8.47	5.8×10^{-2}		4.8×10^{-5}	16
III			3.0×10^{-1}	4.0×10^{-6}		
IV	8.15	8.10	8.6×10^{-2}		1.1×10^{-4}	78

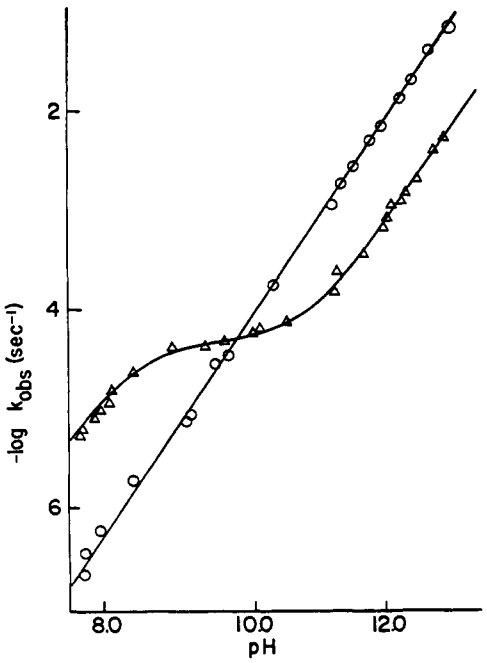


Figure 1. pH-rate profile for the hydrolysis of I (○) and II (△) at 25°.

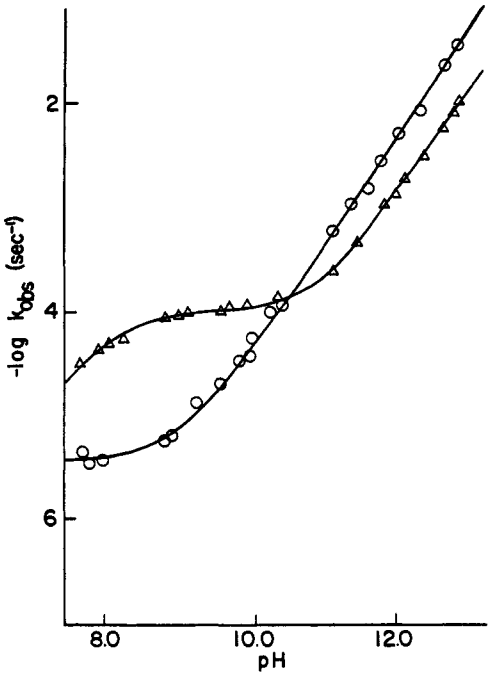


Figure 2. pH-rate profile for the hydrolysis of III (○) and IV (△) at 25°.

Figures 1 and 2 reveals that for the quaternary esters (I and III), I is subject to OH^- and III to OH^- and H_2O catalysis (eq 1). The observed rate constants for the

$$k_{obsd} = k_{H_2O}[H_2O] + k_{OH^-}[OH^-] \quad (1)$$

hydrolysis of the tertiary amino esters (II and IV) were fitted to the log k_{obsd} *vs.* pH profiles *via* eq 2 where K_a

$$k_{obsd} = k'\frac{K_a}{K_a + a_H} + k_{OH^-}[OH^-] \quad (2)$$

refers to the dissociation constant of the dimethylammonium group. Certain buffers have been reported to act as general catalysts in the hydrolysis of similar oxo and thiono esters,[5f,5g,12] but no buffer catalysis was observed in this study.

The distribution of products obtained from the hydrolysis of the thiono esters is pH dependent. In Figures 3 and 4, the molar absorptivity of the product at 290 nm is plotted *vs.* pH for the quaternary and tertiary amino thiono esters, respectively. Above pH 11 thiobenzoic acid is the main product of the hydrolysis reaction while below pH 9.5 benzoic acid is the only carbonyl reaction product. From the molar absorptivity of thiobenzoic acid in strong base at 290 nm, it appears that above pH 11, III hydrolyzes to form 100% thiobenzoic acid while IV yields about 75% thiobenzoic acid.

The autotitrimetrically determined spontaneous (k_{H_2O}) rate of hydrolysis of II was determined in water and deuterium oxide at three pH (pD) values. The value $(k_{H_2O}/k_{D_2O}) = (5.2 \pm 0.3 \times 10^{-5}$ sec$^{-1}/2.1 \pm 0.1 \times 10^{-5}$ sec$^{-1}) = 2.5$ indicates transfer of a proton in the transition state. Because of the complex series of equilibria involving several intermediates as evidenced by the pH-dependent product distribution (see Discussion), the rate of hydrolysis of IV could not be obtained autotitrimetrically.

Repetitive scans taken during the hydrolysis of III at pH 12.4 showed tight isosbestic points at 331 and 248 nm indicating the absence of a buildup of any intermediate species. Repetitive scans taken during the hydrolysis of the compound at pH 9.5 and those taken during the hydrolysis of IV at pH 12.4 and at pH 9.5 maintained the isosbestic point at 331 nm but not at 248. A buildup and eventual decay of an intermediate absorbing at 230 nm could be detected.

Discussion

The pH–rate profiles of Figures 1 and 2 show that in strong base the quaternary amino ester is hydrolyzed more rapidly than is the corresponding tertiary amino ester. The data in Table I indicate that the second-order rate constant for hydroxide ion attack on I is 9.7 times greater than that for attack on II. In the case of the thiono esters the quaternary/tertiary ratio is 3.5.

The increased rate of hydroxide ion attack upon quaternization of the amino group can be attributed partially to a change in pK_a of the leaving group (choline

(12) S. G. Smith and R. J. Feldt, *J. Org. Chem.*, 33, 1022 (1968).

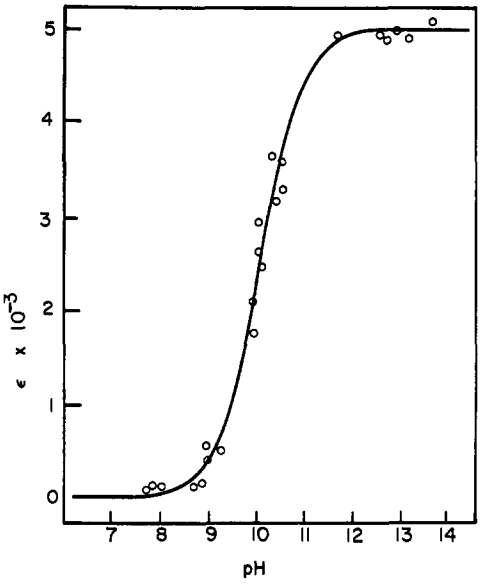


Figure 3. Molar absorptivity of the hydrolysis products of III at 290 nm as a function of pH.

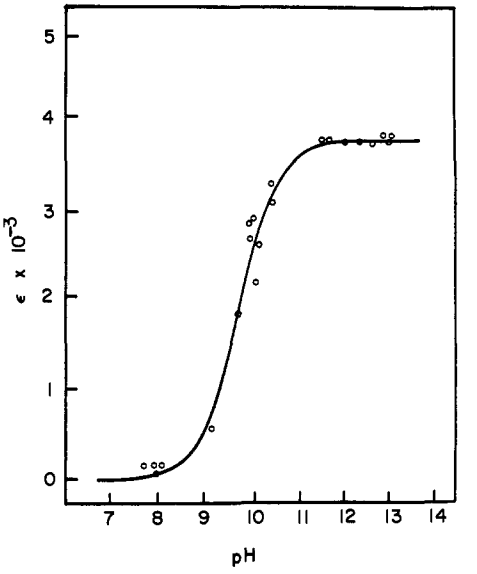
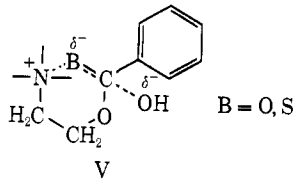


Figure 4. Molar absorptivity of the hydrolysis products of IV at 290 nm as a function of pH.

has a pK_a of 13.9[13] while the pK_a of dimethylaminoethanol is *ca.* 15[14]) and partially to the positively charged nitrogen atom being situated in such a way that electrostatic interactions with the developing negative charge on the carbonyl heteroatom may occur and cause stabilization of the transition state V. The fact that quaterni-



V

zation of the dialkylamino group accelerates the hydrolysis of the oxygen ester more than it does the thiono ester may be attributed to (a) the greater polarizability of a C=S bond as compared with a C=O bond which would allow the transition state to be reached sooner with a thiono ester, thereby decreasing the effect of a change in pK_a of the leaving group, and (b) the large size and diffuse charge of the sulfur atom which would make electrostatic interactions less favorable.

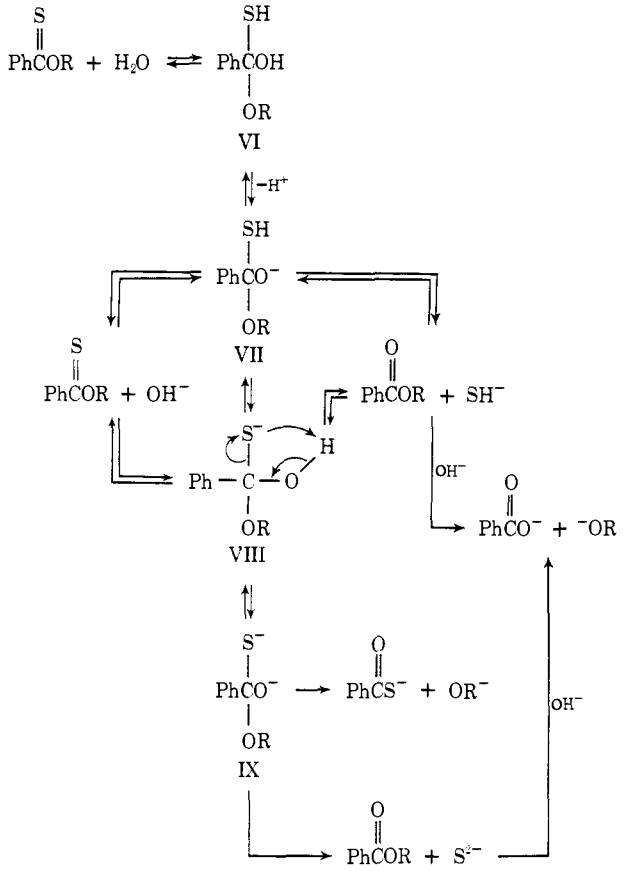
It is unlikely that the rate enhancement induced by quaternization is due to polarization, in the ground state, of the carbonyl group by the positively charged trimethylammonium grouping as has been previously proposed.[5a] Conformational studies of analogous esters indicate that, in the ground state, conformation is maintained by interaction between the trimethylammonium group and the acyloxy oxygen adjacent to the carbon or thiocarbonyl carbon.[15]

While studying the hydrolysis of the thiono esters, it was observed that the ratio of products (benzoic/thiobenzoic acid) depended on pH (Figures 3 and 4). A similar product distribution pattern has been reported for the hydrolysis of ethyl thionobenzoate in 40% aqueous acetone and in 50% aqueous dioxane.[12,16] In moderately basic solutions the thiono esters hydrolyze to give benzoic acid; in strongly basic solutions the carbonyl hydrolysis product is entirely, from the hydrolysis of III, and predominantly, from the hydrolysis of of IV, thiobenzoic acid. In Figures 3 and 4, theoretical titration curves have been drawn through the experimental points suggesting that loss of a proton from an intermediate species is responsible for the change in reaction product. The reactions of Scheme I account for the observed pH dependence of products. A similar scheme has been postulated by Smith and Feldt.[12]

In moderately basic solutions, water or hydroxide ion attack on a thiono ester leads to intermediates VI and VII, respectively. The lowest pH at which these hydrolysis studies were carried out was 7.5; thus intermediate VI can be ignored since its pK_a can be estimated to be less than 5.9, using Kreevoy's correlation of acid dissociation constants of mercaptans with Taft σ^* parameters.[12,17] The greater acidity of thiols as compared with alcohols indicates that the mercaptide anion VIII should predominate over the alkoxide anion VII. The hydrosulfide ion (pK_a = 6.94)[18] is a much better leaving group than is the alkoxide ion (pK_a of choline = 13.9, pK_a of 2-dimethylaminoethanol = ~15). The lack of formation of any thiobenzoic acid in moderately basic solutions suggests that the superiority of the hydrosulfide ion as a leaving group either allows all decomposition to take place through intermediate VII or encourages intermediate VIII to undergo a prototropic shift. This shift can occur in a four-center process as indicated in Scheme I or through a water molecule or through acid–base equilibria. Thus, in weakly basic solutions the benzoate ester is formed as an intermediate

(13) R. M. C. Dawson, *et al.*, "Data for Biochemical Research," Clarendon Press, Oxford, 1959.
(14) P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, 82, 795 (1960).
(15) (a) F. P. Canepa, P. Pauling, and H. Sörum, *Nature (London)*, 210, 907 (1966); (b) E. Shefter and H. G. Mautner, *Proc. Nat. Acad. Sci. U. S.*, 63, 1253 (1969); (c) C. C. J. Culvenor and N. S. Ham, *Chem. Commun.*, 537 (1966); (d) R. J. Cushley and H. G. Mautner, *Tetrahedron*, 26, 2151 (1970); (e) C. C. J. Culvenor and N. S. Ham, *Chem. Commun.*, 1242 (1970).
(16) S. G. Smith and M. O'Leary, *J. Org. Chem.*, 28, 2825 (1963).
(17) (a) M. M. Kreevoy, E. T. Harper, R. E. Duvall, H. S. Wilgres. III, and L. T. Ditsch, *J. Amer. Chem. Soc.*, 82, 4899 (1960); (b) R. W, Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 13.
(18) R. C. Brasted, "Comprehensive Inorganic Chemistry," Vol. 8, Van Nostrand, Princeton, N. J., 1961, p 37.

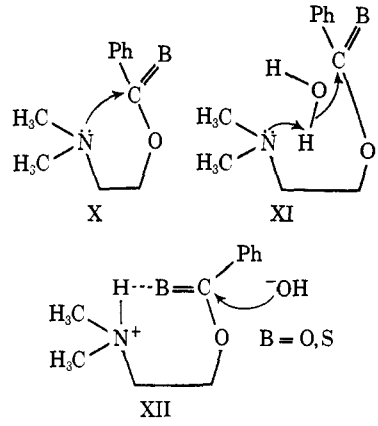
Scheme I



which hydrolyzes to the observed product, benzoic acid. When the basicity of the reaction medium is sufficient to cause formation of the dianion IX, the alkoxide anion is a better leaving group than the sulfur dianion and thiobenzoic acid is the carbonyl product. The choline anion is a somewhat better leaving group than the 2-dimethylaminoethylate anion. Thus, under strongly alkaline conditions the hydrolysis of III results in exclusive formation of thiobenzoic acid, while under similar conditions only 75% of the reaction product of IV is thiobenzoic acid, the remaining 25% being benzoic acid.

Repetitive scans of the hydrolysis of the thiono esters show a buildup of the benzoate ester at 230 nm at pH's where the benzoate ester has a slower rate of hydrolysis than the corresponding thiono ester. Since the rate of hydrolysis of the thiono esters is monitored by the decrease in absorption at 290 nm, and neither the intermediate benzoate ester nor benzoic acid, which is formed in a slow step from the intermediate, has any significant absorption at this wavelength, the observed rate constant obtained refers to the rate of decomposition of the thiono ester.

The pH–rate profiles of Figures 1 and 2 show that in weakly basic solutions the tertiary amino esters hydrolyze considerably faster than the quaternary amino esters. This accelerated rate of hydrolysis may be attributed to intramolecular nucleophilic attack by the unprotonated dimethylamino group X, intramolecular general base-catalyzed water attack XI, or intramolecular general acid-catalyzed hydroxide ion attack XII. The mechanisms of X, XI, or XII are kinetically equivalent. If mechanism X or XI is operating, the k' term of eq 2 is the nucleophilic rate constant or the second-order rate constant for water attack, respectively. The



$K_a/(K_a + a_H)$ term is the fraction of total ester in the free base form. (Only the free base form is considered since the N-protonated species is unable to participate in nucleophilic or general base catalysis.) If mechanism XII is operating, eq 2 may be written as

$$k_{obsd} = k''[OH^-]\frac{a_H}{K_a + a_H} + k_{OH}[OH^-] = \frac{k''K_w}{K_a + a_H} + k_{OH}[OH^-] \quad (3)$$

where k'' is the second-order rate constant for general acid-catalyzed hydroxide ion attack, $a_H/(K_a + a_H)$ is the fraction of total ester that exists as the N-protonated species, and K_w is the ion product constant of water.

Intramolecular nucleophilic catalysis X differs from XI and XII in that it does not involve the transfer of a proton in the transition state. The hydrolysis of the oxo ester II is associated with a deuterium kinetic solvent isotope effect of 2.5. This value is indicative of the transfer of a proton in the transition state. Mechanism X, when B is oxygen, must be eliminated unless a preequilibrium O to N acyl shift followed by rate-determining attack of water is occurring. This appears extremely unlikely in view of the large differences (>6) in pK_a's of the amino and alcoholic groups.[19] For the thiono ester IV, mechanism X can be eliminated since it cannot account for the observed buildup of benzoate ester in weakly basic solutions. In addition, the hydrolyses of III and IV occur through similar intermediates as indicated by the similar pH-dependent product distributions of Figures 3 and 4. Since there is no possibility of nucleophilic catalysis for III, it is unlikely that this mechanism is operating for IV.

Thus, the increased rate of hydrolysis of the tertiary amino esters in moderately basic solutions must be attributed to either mechanism XI or XII. If hydrolysis is occurring *via* mechanism XI, the second-order rate constants for water attack are 1.1×10^{-4} and 4.8×10^{-5} M^{-1} sec^{-1} for the thiono and oxo esters, respectively (Table I). If hydrolysis is occurring *via* mechanism XII, the second-order rate constants for hydroxide ion attack on the N-protonated thiono and oxo esters are 78 and 16 M^{-1} sec^{-1}, respectively. Both mechanisms result in plausible values for the second-order rate constants. If, however, mechanism XII is operating, the rate of hydroxide ion attack on the N-protonated tertiary amino ester is 280 times (k''II/k_{OH}-II) greater than on the unprotonated compound in the case of the

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oxo ester and 910 times (k''IV/k_{OH}-IV) greater in the case of the thiono ester. Since it is known that carbonyl oxygen has greater ability to accept hydrogen bonds than does thiocarbonyl sulfur,[20] general acid catalysis by the N-protonated amino group should not be markedly more effective in enhancing the rate of hydroxide ion attack on the thiono ester as compared with its effect on the oxo ester. From the above, one is led to conclude that the most plausible explanation for the enhanced rate of hydrolysis of the tertiary amino esters in moderately basic solutions is intramolecular general base-catalyzed attack of water, mechanism XI.

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Solvolyses of Aryldineopentylcarbinyl, Aryl-*tert*-butylneopentylcarbinyl, and Aryldi-*tert*-butylcarbinyl *p*-Nitrobenzoates. Effects of the Bulky Alkyl Groups at the Reaction Center and Substituents in the Aryl Ring

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Abstract: Three series of aryldialkylcarbinyl *p*-nitrobenzoates, in which the aryl rings are variously substituted for the evaluation of substituent effects, were prepared and their solvolysis rates were determined in 70% aqueous acetone at several temperatures. They were aryldineopentylcarbinyl (**6**-Z), aryl-*tert*-butylneopentylcarbinyl (**7**-Z), and aryldi-*tert*-butylcarbinyl (**8**-Z) *p*-nitrobenzoates. For comparison, the corresponding aryldimethylcarbinyl *p*-nitrobenzoates (**5**-Z) and methyldineopentylcarbinyl (**9**), -*tert*-butylneopentylcarbinyl (**10**), and -di-*tert*-butylcarbinyl (**11**) *p*-nitrobenzoates were prepared and similarly solvolyzed. Relative rates for the unsubstituted α-phenyl compounds at 100° are 1 for **5**-H, 0.19 for **6**-H, 0.81 for **7**-H, and 0.093 for **8**-H. Those for the *p*-trifluoromethylphenyl compounds are 6.3×10^{-6} for **5**-CF_3, 2.9×10^{-6} for **6**-CF_3, 25×10^{-6} for **7**-CF_3, and 8.8×10^{-6} for **8**-CF_3. The $\rho\sigma^+$ treatment gives straight lines in all the α-aryl systems and the ρ values are -3.74 for **5**-Z, -2.91 for **6**-Z, -2.64 for **7**-Z, and -1.30 for **8**-Z. The reactivity variations with substituents are discussed in terms of steric hindrance to resonance stabilization of the aryl group and relief of strain due to the bulky *tert*-butyl and/or neopentyl groups. Products from **6**-H and **7**-H were comprised of olefins arising simply from β elimination along with some unrearranged alcohols. Those from **8**-H comprised an olefin produced by elimination with methyl rearrangement and a cyclopropane derivative resulting from γ elimination. The solvolysis rates of the phenyldialkylcarbinyl *p*-nitrobenzoates relative to those of the methyldialkylcarbinyl *p*-nitrobenzoates, k_{Ph}/k_{Me}, were found to be 220 for the dimethyl, 0.24 for the dineopentyl, 0.63 for the *tert*-butylneopentyl, and 0.19 for the di-*tert*-butyl system.

Solvolyses of primary, secondary, and tertiary α-arylcarbinyl halides or ionizable esters have been intensively investigated yielding significant results of practical and theoretical interest.[1-3] A *p*-methoxy substituent in the aryldimethylcarbinyl chloride system raises the hydrolysis rate by a factor of 3360, while a *p*-nitro substituent decreases it by a factor of 2.57×10^{-4}. These substituent effects were correlated by Brown and coworkers with electrophilic aromatic substitution reactions by a $\rho\sigma^+$ free energy relationship.[3,4] In a previous paper,[5] we investigated the solvolyses of tertiary α-arylcycloalkyl and -polycycloalkyl chlorides, and the solvolysis reactivities were discussed in terms of the effects of substituents in the aryl rings and relief of torsional and/or steric strain accompanying the change in coordination number of the reaction center from four in the ground state to three in the cationic transition state. The effect of aryl substituents in each cycloalkyl system gave an individual linear $\rho\sigma^+$ relationship, and it was suggested that the smaller ρ value of α-arylcyclopentyl chlorides compared with those of α-arylcyclobutyl and α-arylcyclohexyl chlorides results from strain relief in the transition state.

When methyl groups in *tert*-butyl chloride or ionizable esters are replaced by such bulky groups as *tert*-butyl and/or neopentyl, the reaction center of the molecules becomes more crowded and the rate of solvolysis becomes larger. The first proposed explanation of these effects was rate-enhancing "B strain."[6,7] For example, the *p*-nitrobenzoates of tri-*tert*-butylcarbinol, di-*tert*-butylneopentylcarbinol, *tert*-butyldineopentyl-

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