Aminolysis of Phenyl Salicylate in Acetonitrile. A Study of Intramolecular Catalysis in an Aprotic Solvent

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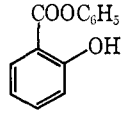
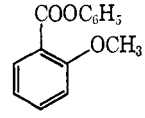
Abstract: Phenyl salicylate reacts considerably faster than phenyl *o*-methoxybenzoate in acetonitrile solutions of *n*-butylamine. The nature of this anchimeric assistance by the *o*-hydroxyl group was investigated because of the relevance of intramolecular catalysis in aprotic media to the mechanism of enzyme action. The reactions have the following properties: (1) the aminolyses of the two esters are both second order in amine; (2) triethylenediamine, an unhindered tertiary amine, catalyzes both reactions; (3) *n*-butylamine hydrochloride inhibits slightly the rate of aminolysis of phenyl salicylate, whereas the hydrochloride salt catalyzes the aminolysis of phenyl *o*-methoxybenzoate; (4) there is no spectrophotometric evidence for ion or ion-pair formation between amine and phenyl salicylate. These results are consistent with an intermolecular general base–intramolecular general acid mechanism for the reaction of phenyl salicylate with *n*-butylamine in acetonitrile.

Phenyl salicylate (A) reacts considerably faster with *n*-butylamine in acetonitrile than does phenyl *o*-methoxybenzoate (B). This anchimeric assistance by the *o*-hydroxyl group was of great interest to us because of the relevance of catalysis in aprotic media to the mechanism of enzyme action.[1-4] For example, the catalytic site of crystalline chymotrypsin contains a carboxyl group buried among hydrophobic side chains.[5] Unfortunately, nothing is really known about the mechanism and efficiency of intramolecular catalytic processes in aprotic solvents. Snell and coworkers[2] are the only ones who have determined the kinetics of an intramolecular catalyzed ester reaction in a nonhydroxylic medium. They found that the rate of aminolysis of methyl salicylate in dioxane is greater than that of phenyl *p*-hydroxybenzoate, but they did not specify the mechanism of the catalysis. The results of our experiments with phenyl salicylate lead to more detailed conclusions about the role of the hydroxyl group.



A



B

Experimental Section

Materials. Phenyl salicylate (Eastman) was crystallized twice from hexane and dried under reduced pressure. *n*-Butylamine (Fisher) was distilled over calcium hydride using a 10-in. vacuum-jacketed Vigreux column. Acetonitrile (Eastman Spectro) was boiled under reflux over anhydrous sodium carbonate for 2 hr and distilled then and stored under nitrogen. *n*-Butylamine hydrochloride was crystallized from methanol–ethyl acetate. Triethylenediamine (Houdry) was purified by crystallization in heptane followed by sublimation. N-*n*-Butylsalicylamide was prepared by boiling under reflux for 18 hr a mixture of 15 ml of methyl salicylate and 25 ml of *n*-butylamine. The product, after work-up from aqueous acid, was distilled twice, bp 135–150° (0.15–0.20 mm).

Phenyl *o*-Methoxybenzoate. *o*-Methoxybenzoyl chloride (1.7 g, 0.010 mole) and phenol (1.0 g, 0.011 mole) were added to about 60 ml of dry pyridine that had been cooled in an ice bath. After 30 min the reaction mixture was allowed to warm up to room temperature and remain there overnight. The pyridine solution was then added to 200 ml of water, forming an oil which was separated from the water. The oil solidified when volatile impurities were removed with the aid of a rotary evaporator. The product was crystallized three times from methanol, mp 57–58°. The carbonyl stretching band appears at 5.78 μ.

Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.85; H, 5.47.

Kinetics. The procedure is given here for one particular run, and it is typical of that used throughout. A solution of 0.178 *M* *n*-butylamine in acetonitrile was equilibrated at 25.0 ± 0.1° in a stoppered cuvette placed within the thermostated chamber of a Cary 14 spectrophotometer. The wavelength was set at 350.0 mμ. A small amount (25 μl) of an acetonitrile solution of phenyl salicylate was added rapidly to the cuvette (with the aid of a stirring rod flattened at one end) such that the initial ester concentration was 1.29×10^{-4} *M*. The increase in absorbance (0.1 slidewire) was then traced as a function of time. The reaction was followed to completion, and the first-order plot was linear to greater than 2 half-lives.

Duplicate runs, which were often carried out independently by the two authors using different solutions, agreed to better than 3%. The rate constants do not vary if unpurified reagent grade acetonitrile is used rather than purified spectro material. Nor does the mode of purification of the spectro acetonitrile have any effect; solvent purified over phosphorus pentoxide gives the same rate constants as solvent purified over anhydrous sodium carbonate. No impurities could be detected in the acetonitrile by vapor phase chromatographic analysis. Addition of large amounts of water (0.45 *M*) caused less than a 35% change in the rate constants for aminolysis of the esters. A 9% increase in k_{obsd} occurred when the initial phenyl salicylate concentration was increased from 1.29×10^{-4} to 1.17×10^{-3} *M*; all the reported runs use the smaller substrate concentration. Solutions of *n*-butylamine in acetonitrile were used the day they were prepared, although their standing for several days had no effect.

Product Analysis. A kinetic run was performed as described above using 0.46 *M* amine. The spectrum at completion of the reaction was then secured. This spectrum agreed well with the sum of the spectra of N-*n*-butylsalicylamide and phenol in 0.46 *M* amine. For example, the extinction coefficient of the products of the kinetic run at 270 mμ is 2460; the extinction coefficient for amide and phenol at 270 mμ are 820 and 1600, respectively, for a total of 2420.

Spectrophotometric Search for Ion Pairing. There is no evidence for ion or ion-pair formation between phenyl salicylate and *n*-butylamine in acetonitrile in the concentration range studied. The spectrum of phenyl salicylate in 0.33 *M* *n*-butylamine–acetonitrile is within experimental error of the spectrum in pure acetonitrile. The spectrum in the amine solution was obtained by setting the Cary 14 at a fixed wavelength, adding the ester to a cuvette containing 0.33 *M* amine, recording immediately the absorbance *vs.* time, and extrapolating the absorbance to zero time assuming it took 15 sec for mixing. The procedure was repeated for other

(1) P. R. Rony, *J. Am. Chem. Soc.*, **90**, 2824 (1968).
(2) R. L. Snell, W. Kwok, and Y. Kim, *ibid.*, **89**, 6728 (1967).
(3) F. M. Menger, *ibid.*, **88**, 3081 (1966).
(4) D. E. Koshland and K. E. Neet, *Ann. Rev. Biochem.*, **37**, 359 (1968).
(5) D. M. Blow, J. J. Birktoft, and B. S. Hartley, *Nature*, **221**, 337 (1969).

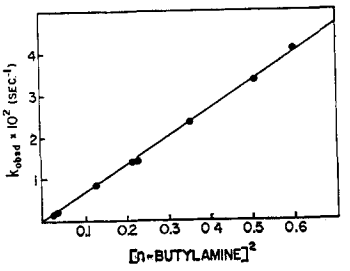


Figure 1. Plot of observed rate constants for *n*-butylaminolysis of phenyl salicylate in acetonitrile at 25.0° *vs.* [*n*-butylamine]^2. Initial ester concentration = 1.29×10^{-4} *M*. The value of k_1 (eq 1) is obtained from the slope of this plot.

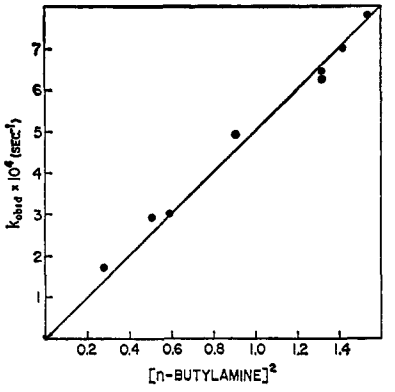


Figure 2. Plot of observed rate constants for *n*-butylaminolysis of phenyl *o*-methoxybenzoate in acetonitrile at 25.0°. *vs.* [*n*-butylamine]^2. Initial ester concentration = 1.67×10^{-4} *M*.

wavelengths. This experiment, of course, does not preclude the presence of ionic species in concentrations too small to be detected by the spectrophotometric analysis. It is interesting, however, that the absorbance of N-*n*-butylsalicylamide at 350 mμ does increase with amine concentration, indicating the presence of a complex whose formation constant is roughly 5.7×10^{-2} M^{-1}. Intramolecular hydrogen bonding between the amide hydrogen and the phenolate anion may contribute to the stability of this complex.

Results

The *n*-butylaminolyses of phenyl salicylate (A) and phenyl *o*-methoxybenzoate (B) in acetonitrile at 25.0° have the following characteristics.

(1) The reaction of phenyl salicylate is second order in amine in the concentration range studied (Figure 1). A plot of k_{obsd} *vs.* [*n*-butylamine]^2 is linear and has a zero intercept. The reaction of phenyl *o*-methoxybenzoate with *n*-butylamine is also second order in amine (Figure 2), but the over-all third-order rate constant is 132 times smaller than that for phenyl salicylate.[6]

(2) The reaction of phenyl salicylate with *n*-butylamine (pK_a = 18.26 in acetonitrile)[7] in the presence of triethylenediamine[8] (pK_a = 18.29 in acetonitrile)[7] obeys the rate expression given in eq 1. A plot of k_{obsd}/[*n*-butylamine] *vs.* [*n*-butylamine] at a constant [triethylenediamine], shown in Figure 3, is consistent with eq 1.

(6) By way of comparison, intramolecular general base catalysis in the hydrolysis of *p*-nitrophenyl 5-nitrosalicylate (34.4% dioxane–water) results in a 30-fold rate increase: M. L. Bender, F. J. Kézdy, and B. Zerner, *J. Am. Chem. Soc.*, **85**, 3017 (1963).

(7) J. F. Coetzee and G. R. Padmanabhan, *ibid.*, **87**, 5005 (1965).

(8) H. Anderson, C. Su, and J. W. Watson [*ibid.*, **91**, 482 (1969)] suggested the use of this unhindered tertiary amine in the study of aminolyses in aprotic solvents.

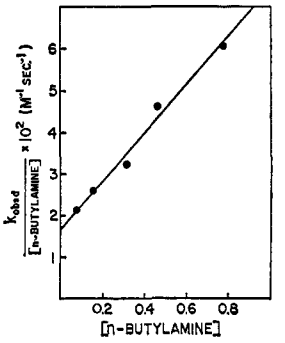


Figure 3. Plot of k_{obsd}/[*n*-butylamine] *vs.* [*n*-butylamine] for the reaction of phenyl salicylate with *n*-butylamine in the presence of 0.205 *M* triethylenediamine. The value of k_2 (eq 1) is obtained from the intercept of this plot.

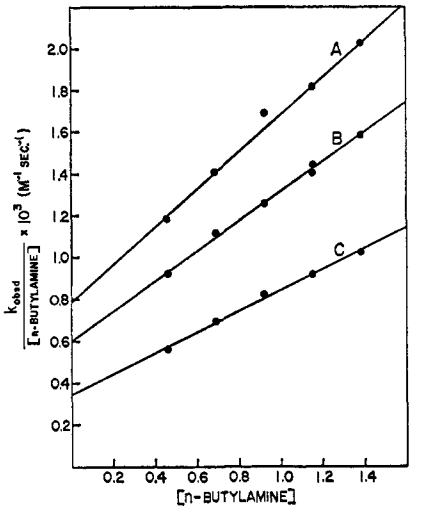


Figure 4. Plot of k_{obsd}/[*n*-butylamine] *vs.* [*n*-butylamine] for the reaction of phenyl *o*-methoxybenzoate with *n*-butylamine in the presence of (A) 0.104 *M*, (B) 0.0625 *M*, and (C) 0.0208 *M* *n*-butylamine hydrochloride.

$$k_{obsd} = k_1[BuNH_2]^2 + k_2[BuNH_2][\text{triethylenediamine}] \quad (1)$$

A plot of k_{obsd} *vs.* [triethylenediamine] at a constant [*n*-butylamine] (not shown) is also linear as predicted by eq 1. The values of k_1 and k_2 of eq 1 are 6.6×10^{-2} M^{-2} sec^{-1} and 3.6×10^{-2} M^{-2} sec^{-1}, respectively.

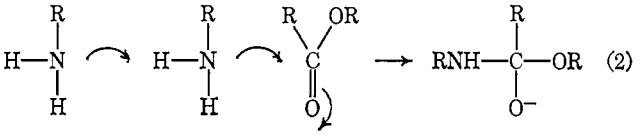
(3) The aminolysis of phenyl *o*-methoxybenzoate is likewise catalyzed by triethylenediamine according to eq 1. The values of k_1 and k_2 are 5.0×10^{-4} and 2.2×10^{-4} M^{-2} sec^{-1}, respectively.

(4) *n*-Butylamine hydrochloride (0.063 *M*) decreases the observed rate of aminolysis of phenyl salicylate in 0.59 *M* *n*-butylamine by 20% relative to the rate in pure 0.59 *M* *n*-butylamine. A small inhibition such as this could be the result of hydrogen bonding of *n*-butylamine molecules to the protonated amine. The aminolysis of phenyl *o*-methoxybenzoate, on the other hand, is *catalyzed* by the hydrochloride salt (Figure 4). This catalysis is not a "salt effect" since tetraethylammonium perchlorate (0.10 *M*) does not change the rate of aminolysis of phenyl *o*-methoxybenzoate in 1.2 *M* *n*-butylamine. Nor is the hydrochloride salt catalysis due solely to the presence of chloride ion since tetraethylammonium chloride causes a much smaller rate enhancement than that shown in Figure 4.

(5) Amine solutions of phenyl salicylate display no absorption in the region of 350–375 mμ which could be attributed to ionized substrate. The spectra of phenyl salicylate in 0.33 *M* *n*-butylamine and in pure acetonitrile are identical.

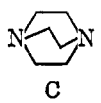
Discussion

The third-order nature of the aminolysis of phenyl *o*-methoxybenzoate (B) is best explained by the general base mechanism shown in eq 2. The rate-determining



step in this mechanism is assumed to be formation of the tetrahedral intermediate which can collapse either to starting materials or to products. It is likely that the reactive entity in eq 2 is an amine dimer, but it is impossible to prove this from kinetic data.

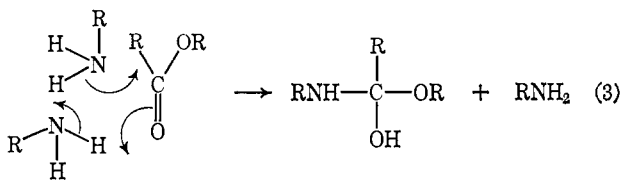
The general base mechanism (eq 2) is supported by the observed catalysis of the aminolysis of phenyl *o*-methoxybenzoate by the unhindered tertiary amine, triethylenediamine (C). *n*-Butylamine and triethylenediamine have the same pK_a in acetonitrile.[7] The two amines should therefore be similar in their ability to catalyze the reactions by means of a general base mechanism, and this is found to be the case. The values of k_1 and k_2 of eq 1 differ by a factor of only 2.



C

The observation that the rate of aminolysis of phenyl *o*-methoxybenzoate is enhanced by *n*-butylamine hydrochloride (Figure 4) is also consistent with the proposed general base mechanism (eq 2). This catalysis is not the result of a "salt effect" because tetraethylammonium perchlorate does not perturb the aminolysis. Nor is the catalysis due solely to the chloride ion because the catalytic effect of tetraethylammonium chloride is much less than that shown in Figure 4. We conclude that *n*-butylamine hydrochloride (the strongest possible acid in the amine solutions) enhances the rate of formation of the tetrahedral intermediate by stabilizing the developing negative charge on the carbonyl oxygen *via* hydrogen bonding.

In a previous paper,[3] we proposed that *n*-butylaminolysis of *p*-nitrophenyl acetate in chlorobenzene proceeds by means of a cyclic concerted mechanism (eq 3).

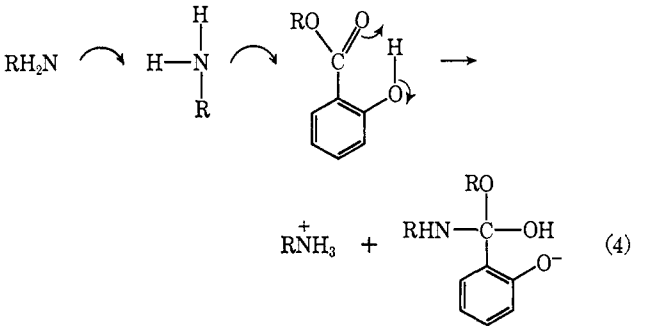


Anderson, *et al.*,[8] disagreed with this interpretation. They concluded that the aminolysis in chlorobenzene is a general base process (similar to the mechanism we now propose for ester aminolysis in acetonitrile) because triethylenediamine catalyzes the reaction. The problem with the chlorobenzene studies[3,8] is that the basicities of the amines are unknown. Anderson, *et al.*, state that triethylenediamine is 150 times less basic than *n*-butylamine, but this is a value obtained in *water* (dielectric constant = 78.5). The two amines have, in fact, the same pK_a in acetonitrile (dielectric constant = 37.5).[7] Extrapolation to chlorobenzene, a solvent with a dielectric constant of 5.6, suggests that the basicity of triethylenediamine exceeds that of *n*-butylamine. Preliminary work of ours on amine–nitrophenol complexation in chlorobenzene confirms this conclusion. Thus, there is a strong possibility that the triethylenediamine-catalyzed reaction in chlorobenzene is a general base-like process involving a powerful tertiary amine base, while the third-order *n*-butylaminolysis of *p*-nitrophenyl acetate proceeds by the cyclic mechanism of the type proposed by ourselves[3] and many other workers.[9-13] One reason for selecting acetonitrile for the present salicylate study was that pK_a values are known in this solvent, and therefore the amines can be meaningfully compared.

It must be realized that the distinction between a general base catalysis (eq 2) and a cyclic concerted process (eq 3) is a subtle one. Charge formation in the cyclic mechanism occurs to the extent that the process is not completely concerted, and the degree of concertedness in eq 3 depends on the particular time scale one wishes to deal with. Thus, general base catalysis and the fully concerted mechanism are merely two extremes. In acetonitrile (dielectric constant = 37.5) the aminolysis of phenyl *o*-methoxybenzoate resembles the general base mechanism which entails separation of charge in the formation of the tetrahedral intermediate.

We now turn our attention to the main question of why aminolysis of phenyl salicylate (A) in acetonitrile is 132 times faster than aminolysis of phenyl *o*-methoxybenzoate (B). Aminolysis of phenyl salicylate is second order in amine (Figure 1); the reaction is catalyzed by triethylenediamine according to the rate expression given in eq 1. Since triethylenediamine and *n*-butylamine catalysis are of similar magnitude (k_1 and k_2 of eq 1 are 6.6×10^{-2} and 3.6×10^{-2} M^{-2} sec^{-1}, respectively), and since the two amines have the same pK_a in acetonitrile, the over-all third-order nature of the aminolysis of phenyl salicylate must reflect a general base mechanism. The simplest explanation of the anchimeric assistance by the *o*-hydroxyl group, therefore, is an intramolecular general acid catalysis coupled with an intermolecular general base catalysis (eq 4). If this mechanism is correct, then the intramolecular general

(9) A. S. Shawali and S. S. Biechler, *J. Am. Chem. Soc.*, 89, 3020 (1967).
(10) P. J. Lillford and D. P. N. Satchell, *J. Chem. Soc., B*, 897 (1968).
(11) L. M. Litvinenko and N. M. Oleinik, *Zh. Obshch. Khim.*, 33, 2287 (1963).
(12) T. C. Bruice and M. F. Mayahi, *J. Am. Chem. Soc.*, 82, 3067 (1960).
(13) It has been claimed[8] that the reactivity of 1,4,5,6-tetrahydropyrimidine toward *p*-NPA in chlorobenzene disproves the bifunctional cyclic mechanism we had proposed for benzamidine,[3] but this does not appear to us to be the case. The carbonyl group of the ester may be situated above the plane of both of these amidines for maximum orbital overlap, thereby permitting simultaneous attack of an amidine nitrogen and delivery of a proton to the carbonyl oxygen. Such a geometry allows the N–H bond to be parallel to the p orbitals of the amidine N–C double bond as is required for a fully concerted process. Some of the best evidence for a cyclic concerted amine acylation in an aprotic solvent appears in P. J. Lillford and D. P. N. Satchell, *J. Chem. Soc., B.*, 54 (1968). It was found that acylation of *m*-chloroaniline by dimethylketene in ether is catalyzed by triethylamine relatively less effectively than by a second *m*-chloroaniline molecule. Since triethylamine is a stronger base than *m*-chloroaniline by seven orders of magnitude (water), it is unlikely that a general-base type of mechanism is operative.



(4)

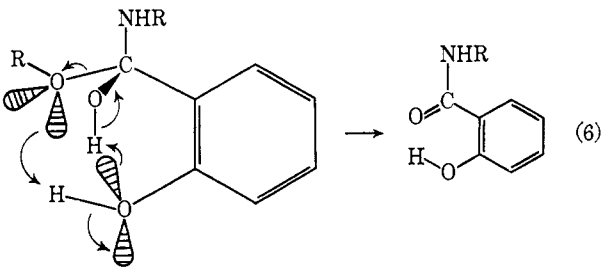
acid catalysis could preclude catalysis by an external general acid, and this is found to be the case. Unlike the aminolysis of phenyl *o*-methoxybenzoate, the aminolysis of phenyl salicylate is *not* enhanced by *n*-butylamine hydrochloride. General acid catalysis by the *o*-hydroxyl group is, of course, chemically reasonable since it is known that in aprotic solvents the carbonyl oxygen of salicylate esters is chelated to the neighboring phenolic hydrogen.[14]

The over-all third-order aminolysis of phenyl salicylate can be also explained by a mechanism involving ion or ion-pair formation (eq 5). Equation 5 seems unlikely for the following reasons. First of all, it was not possible to detect the presence of ionic species by spectrophotometric analysis; the spectra of phenyl salicylate in *n*-butylamine solutions and in pure acetonitrile are identical. This does not preclude the presence of spectrophotometrically undetectable traces of catalytically active ionic material. But if there were, for example, 0.1% ionic phenyl salicylate, then the rate enhancement associated with this species would seem abnormally large[6] (132,000). A better argument against kinetically important anionic phenyl salicylate (ArO^- in eq 5) is based on the observation that *n*-butylamine hydrochloride does not substantially reduce the rate of reaction. If eq 5 were correct, then addition of hydrochloride salt would drive the equilibrium to the left and inhibit the reaction. The lack of inhibition by *n*-butylamine hydrochloride cannot be used as evidence against a reactive ion pair ($ArO^- {}^+NH_3R$ in eq 5), and at the present time such a species cannot be discounted. It must be pointed out, however, that if one of the two amine molecules is tied up in an ion pair (and acts as a general acid in the transition state), then the second nucleophilic amine molecule must react *without* the aid of a general base. Yet general base catalysis is a favorable reaction mode, as was shown in the aminolysis of phenyl *o*-methoxybenzoate. For these reasons, aminolysis of phenyl salicylate in acetonitrile is believed to occur by an intermolecular general base–intramolecular general acid process (eq 4).

$$[ArOH + NH_2R \rightleftharpoons ArO^- {}^+NH_3R \rightleftharpoons ArO^- + {}^+NH_3R] \xrightarrow{RNH_2} \text{products} \quad (5)$$

(14) T. Yasunaga, N. Tatsumoto, H. Inoue, and M. Miura, *J. Phys. Chem.*, 73, 477 (1969).

There are two general ways in which the *o*-hydroxyl group can catalyze the aminolysis of phenyl salicylate. The neighboring group may accelerate the formation of the tetrahedral intermediate,[15] as we have just described, or else it may effect a more favorable partitioning of the intermediate toward product. Equation 6 shows a



(6)

mechanism in which the hydroxyl group assists the breakdown of a neutral intermediate to product. Molecular models demonstrate that the nonbonded oxygen electrons are perfectly situated for this process. The hydroxyl group is, in effect, acting as an intramolecular bifunctional catalyst. Although there is no evidence that such a mechanism occurs in the aminolysis of phenyl salicylate, we present it as an interesting type of hydroxyl group involvement which may be kinetically important in systems where a poor leaving group must depart into a nonpolar medium.

Acknowledgment. Support for J. H. Smith by a National Defense Education Act Fellowship is gratefully acknowledged.

(15) The aminolyses mechanisms have been discussed in terms of a tetrahedral intermediate, but as D. P. N. Satchell and I. I. Secemski, [*J. Chem. Soc., B*, 130 (1969)] point out, there is no evidence demanding the presence of such an intermediate in aprotic solvents. Equation 4 could be written equally well as a direct displacement in which the *o*-hydroxyl group facilitates departure of the phenoxide anion.