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Deuterium Isotope Effects and the Influence of Solvent in the Redox and Rearrangement Reactions of 2-Picoline *N*-Oxide and Phenylacetic Anhydride[1]

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The reaction of 2-picoline *N*-oxide with phenylacetic anhydride proceeds by two paths: rearrangement to produce picolyl phenylacetate (**6**), 2-(β-phenylethyl)pyridine (**7**), other minor rearrangement products, and CO_2, and oxidation to give benzaldehyde, 2-picoline, and CO_2. The ratio of the competing processes is sensitive to the incorporation of deuterium at appropriate sites in the reactants, thereby permitting a convenient method for determining hydrogen isotope effects. For rearrangement, a primary kinetic isotope effect value (3.8–4.2) is obtained when reactions of methyl-deuterated and undeuterated 2-picoline *N*-oxide are compared, confirming earlier work on related systems that anhydro base (**5**) formation is rate determining. Oxidation, however, manifests an inverse isotope effect (0.76–0.81, deuterium labeling at the methylene groups of phenylacetic anhydride) which, along with other evidence, suggests reversible enol or enolate formation prior to an SN1′-like rate-determining step to generate the reactive carbocation **3** or its conjugate base. Solvent polarity also significantly, but not dramatically, affects the ratio of the competing pathways. A trend is established which supports the proposed mechanisms if they are modified to include ion pairing phenomena. Furthermore, the influence of solvent polarity is found to be consistent with a dual mode of fragmentation of anhydro base intermediate **5**.

For over two decades there has been considerable interest in both the mechanistic and synthetic aspects of the reactions of carboxylic acid derivatives with the *N*-oxides of pyridine and picoline. The four-electron oxidative decarboxylation of anhydrides (or a mixture of the corresponding acid and acetic anhydride) which possess an acidic α hydrogen by pyridine *N*-oxide produces aldehydes or ketones, carbon dioxide, and pyridine as major products.[2-5] For example, the oxidation of phenylacetic anhydride by pyridine *N*-oxide produces benzaldehyde and proceeds according to the following stoichiometry.

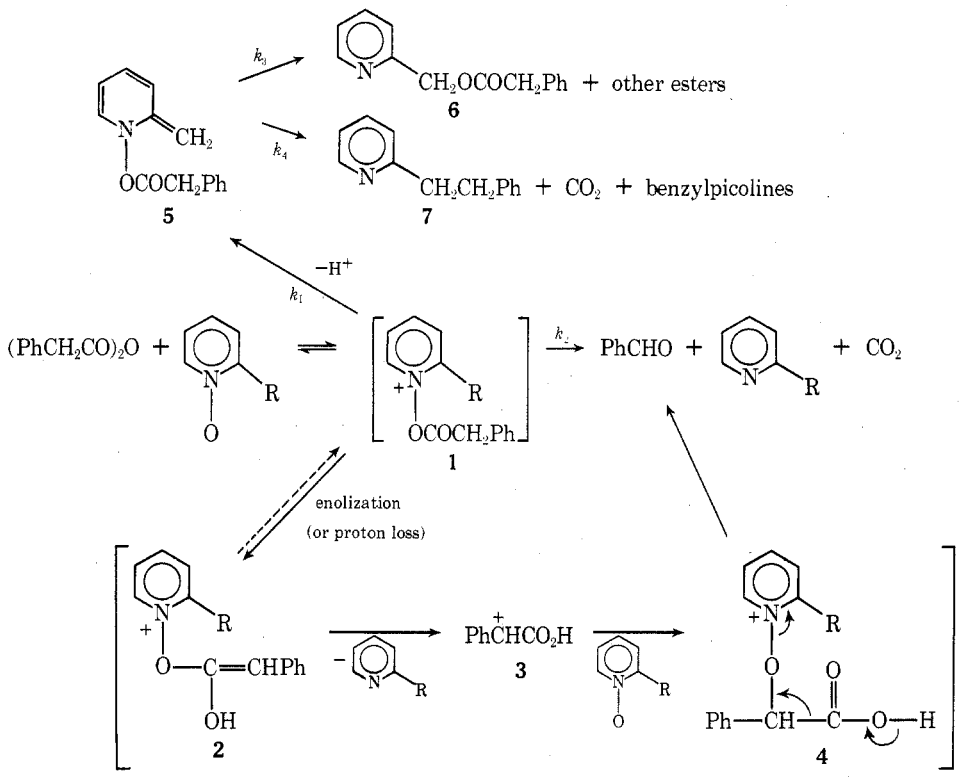
$$(PhCH_2CO)_2O + 2C_5H_5NO \rightarrow PhCHO + 2C_5H_5N + CO_2 + PhCH_2CO_2H$$

The reaction is thought[2-5] to involve acylation of pyridine *N*-oxide, probably reversibly,[6] to yield the *N*-acyloxypyridinium ion **1** (R = H) (Scheme I). The latter cation, by reaction with a second molecule of pyridine *N*-oxide and loss of a pyridine molecule, is then believed to produce the intermediate *N*-(α-carboxybenzyloxy)pyridinium ion **4** (R = H) or the corresponding carboxylate zwitterion.[2,5] Decarboxylative fragmentation of **4** (R = H) (or its conjugate base) as shown would yield benzaldehyde, carbon dioxide, and pyridine.[7]

Although there is substantial evidence for the intermediate **4** (or its conjugate base),[5,8a] the mechanism of the conversion of **1** to **4** is not entirely clear. It has been suggested[2,4,5,8a] that pyridine is displaced from the enol **2** (R = H) of **1** (R = H) by pyridine *N*-oxide in an SN1′ or SN2′ manner. Enolization is consistent with the requirement for an α hydrogen atom.[2b,3c,5] On the basis of the experimental finding that pyridine *N*-oxide is much more nucleophilic than pyridine toward the intermediate, an SN1′ attack involving the α-carboxybenzylcarbenium ion **3**, or its conjugate base, has been favored.[8a] Some such electrophilic intermediate has been trapped by acetic acid and by pyridine, each utilized as solvent.[5] Further evidence for a cationic intermediate of type **3** has been found in the oxidation of 2,3-diphenylpropanoic acid by pyridine *N*-oxide;[8b] in addition to attack by *N*-oxide to ultimately yield the expected oxidation product, the reactive electrophilic species undergoes loss of an adjacent proton to produce an α,β-unsaturated carboxylic acid and it is also attacked by acetate to give the 2-acetoxy derivative of the starting acid.

The reaction of 2-picoline *N*-oxide with phenylacetic anhydride yields, by a similar path, the products of oxidative decarboxylation, benzaldehyde, carbon dioxide, and 2-picoline (Scheme I, R = Me). By an alternative path, the rearrangement products 2-pyridylmethyl phenylacetate (**6**), 3- and 5-phenylacetoxy-2-picoline, 2-(β-phenylethyl)pyridine (**7**), and 3- and 5-benzyl-2-picoline are also obtained[9] (Scheme I). The rearrangement process is thought to pro-

Scheme I[a]



[a] k_1' and k_2' are the corresponding rate constants for the reactions of methyl-labeled N-oxide and benzyl-labeled anhydride, respectively.

ceed through the anhydro base intermediate **5** which arises by proton abstraction from the acylated N-oxide **1** (R = H).[9,10] Dissociation of **5** to a picolyl acylate ion pair,[9,11,12] followed by recombination of the ion fragments, leads to ester products, while homolysis of the N–O bond, with concerted decarboxylation, leads to **7** and benzylpicolines.[9] Traynelis[13a] and Oae[13b] have presented evidence which suggests that anhydro base formation is the rate-limiting step in the rearrangement process when 2-benzylpyridine N-oxide and 2- and 4-picoline N-oxide are treated with acetic anhydride.

The 2-picoline N-oxide–phenylacetic anhydride system readily lends itself to an internal competition method of determining hydrogen isotope effects[14] and identifying rate-determining steps in both the oxidative decarboxylation and rearrangement mechanisms. If 2-picoline N-oxide is treated with phenylacetic anhydride-d_4, and if an α deuterium atom of the anhydride is involved in the rate-determining step of the oxidation process, such as in the formation of an enol or enolate species, or in an equilibrium immediately prior to the rate-determining step, the rate constant for oxidation (k_2', Scheme I) would differ from that (k_2) observed for nonlabeled reactant while the rate constant for rearrangement (k_1) would not be expected to vary.[15] The ratio of rate constants is proportional to the ratio of the yield of oxidation product to that of rearrangement products. A hydrogen isotope effect value, k_H/k_D, may then be calculated for the redox process by comparing the ratio obtained in a control reaction of unlabeled reactants (k_2/k_1) to the one obtained in the labeled reaction (k_2'/k_1). Confirming evidence that anhydro base formation is rate determining in the rearrangement process may be obtained by similarly calculating the hydrogen isotope effect when methyl-deuterated 2-picoline N-oxide is allowed to react with unlabeled phenylacetic anhydride.

The 2-picoline N-oxide–phenylacetic anhydride system is also ideally suited for a study of the effect of solvents on the oxidation and rearrangement mechanisms. Furthermore, if the proposed dual mechanism of fragmentation in the rearrangement process is operative,[9] the degree of homolytic vs. heterolytic cleavage should vary with solvent. In the present paper, we present the results of these kinetic investigations.

It should be noted that in this system the determination of hydrogen isotope effects by the method of competition has an inherent advantage over a direct measurement of k_H and k_D. Variations in product ratios reflect simply the relative rates of decomposition of acylated N-oxide **1** (R = Me), whereas k_H (or k_D) would contain a contribution from a pre-rate-determining equilibrium (acylation) step.[6] The latter could conceivably be subject to a secondary isotope effect when phenylacetic anhydride-d_4 is allowed to react. Determination of hydrogen isotope effects by competition avoids the necessity for knowing the uncertain magnitude of that effect.

Results

The synthesis of 2-trideuteriomethylpyridine N-oxide was attempted by the sodium deuteroxide catalyzed equilibration of the methyl protons of 2-picoline N-oxide with the deuterons of deuterium oxide.[16] However, successive exchanges resulted in the incorporation of deuterium into the α position of the pyridine ring as well as into the methyl group. Since a deuterium atom on the ring should have no significant effect on the reaction mechanism, the compound 2-trideuteriomethyl-6-deuteriopyridine N-oxide was therefore prepared. Analysis by ^{1}H NMR spectroscopy indicated a deuterium content of 98% in the methyl group. Phenylacetic anhydride-d_4 containing 97% deuterium in the benzyl positions was prepared as described in the Experimental Section.

In the first series of reactions the production of benzal-

Table I
Variation in Benzaldehyde and Ester Products with Deuterium Labeling

Reaction[c,d]	% yields[a,b] Benzaldehyde	Picolyl phenylacetates	Ratio of benzaldehyde to picolyl phenylacetates[e]
I	21.5 ± 0.8	25.3 ± 1.3	0.851 ± 0.016
II	36.2 ± 0.8	11.3 ± 0.1	3.21 ± 0.10
III	49.1 ± 0.4	11.6 ± 0.3	4.24 ± 0.10

[a] Yields were determined by VPC (FID). [b] Results are for duplicate experiments, except for I, which was run in triplicate. Reactions were performed simultaneously. [c] I = 2-picoline *N*-oxide, phenylacetic anhydride; II = 2-picoline *N*-oxide-d_4 (98%), phenylacetic anhydride; III = 2-picoline *N*-oxide-d_4 (98%), phenylacetic anhydride-d_4 (97%). [d] 4 equiv of *N*-oxide and 1 equiv of anhydride in 25 ml of benzene heated at reflux under nitrogen for 24 hr. [e] The ratio of each run was determined and the average reported here.

dehyde and esters[17] was taken as a measure of the relative importance of oxidation and rearrangement pathways, respectively, *i.e*, $k_2/k_1 \simeq$ % benzaldehyde/% esters. The yields in control and labeled reactions are presented in Table I. The reaction of labeled *N*-oxide with phenylacetic anhydride (reaction II) gave a ratio of aldehyde to esters (k_2/k_1') of 3.21 ± 0.10. A ratio of 0.851 ± 0.016 was obtained in the nonlabeled control reaction (k_2/k_1) (reaction I). Therefore, a hydrogen isotope effect value of about 3.8 for the rearrangement process may be calculated from eq 1.

$$(k_H/k_D)_{rearr} = k_1/k_1' = (k_2/k_1')/(k_2/k_1) \simeq 3.8 \pm 0.2 \quad (1)$$

Reaction II produced benzaldehyde containing 3% deuterium. The deuterium incorporation probably arose (see below) from the exchange of phenylacetic acid-d_1 (produced in the formation of the anhydro base intermediate) and unreacted phenylacetic anhydride.

When 2-picoline *N*-oxide was allowed to react with the labeled anhydride, the product benzaldehyde was found to contain only 25.5% deuterium. Such a result is suggestive of considerable loss of deuterium in the anhydride by exchange with water, phenylacetic acid, or ester products. It was then shown that under the reaction conditions phenylacetic anhydride readily exchanges α deuterons in the presence of acetic acid, 2-picoline, and water. Because of this exchange *the reaction of 2-picoline N-oxide and labeled anhydride does not permit a direct determination of the hydrogen isotope effect for the oxidative process.*

However, if deuterated anhydride is treated with deuterated *N*-oxide, the ratio of benzaldehyde to ester products is now a measure of k_2'/k_1'. The quotient of this value and the nonlabeled reaction value is

$$k_2'/k_1' \div k_2/k_1 = k_1/k_1' \times k_2'/k_2 \quad (2)$$

where $k_1/k_1' = 3.8 \pm 0.2$ (vide supra).

When the reaction of 2-picoline *N*-oxide-d_4 and phenylacetic anhydride-d_4 (reaction III) was conducted under strictly anhydrous conditions, a ratio of aldehyde to esters of 4.24 ± 0.10 was obtained. Equation 2 may then be solved for k_2/k_2', the hydrogen isotope effect for the oxidation pathway, to give 0.76 ± 0.07, or $(k_D/k_H)_{oxidn} = 1.3 \pm 0.1$.

The k_H/k_D values determined above for both rearrangement and oxidation were checked at an earlier stage of the reaction. When 2-picoline *N*-oxide-d_4 and unlabeled phenylacetic anhydride were heated in refluxing benzene for 30 min, an aldehyde to ester ratio of 3.46 was observed. This corresponds to an isotope effect of 4.1 for the rearrangement process. Comparison of the ester yield with that at the end of 24 hr indicated 70% reaction. Similarly, a mixture of labeled *N*-oxide and labeled anhydride heated in refluxing benzene for only 5 min gave an aldehyde to ester ratio of 4.95, corresponding to a k_H/k_D value of 0.65 for oxidation. The reaction was 38% complete.

Table II
Variation in 2-Picoline and Ester Products with Deuterium Labeling

Reaction[c,d]	% yields[a,b] 2-Picoline	Picolyl phenylacetates	Ratio of 2-picoline to picolyl phenylacetates[e]
I	23.9 ± 0.1	25.6 ± 0.5	0.936 ± 0.020
II	37.0 ± 0.4	9.39 ± 0.16	3.94 ± 0.03
III	53.5 ± 0.7	11.0 ± 0.2	4.87 ± 0.16

[a] Yields were determined by isothermal VPC (TC). [b] Results are for duplicate experiments. [c] Reactions correspond to those in Table I. [d] 4 equiv of 1.0 *M* *N*-oxide (benzene) and 1 equiv of anhydride heated at reflux under nitrogen for 24 hr. [e] The ratio of each run was determined and the average reported here.

Under experimental conditions in which *N*-oxide is the limiting reagent it had been shown that some product benzaldehyde was consumed in a Perkin-type condensation with excess phenylacetic anhydride.[9] Conceivably, then, the variation in benzaldehyde yields in the above series of reactions (particularly reaction III) could reflect an unknown contribution from changes in the amount of product destruction due to a condensation isotope effect. In order to eliminate that uncertainty, a second series of reactions was performed in which 2-picoline was analyzed as a measure of the oxidation pathway. The results are presented in Table II. By the method discussed above, hydrogen isotope effects of 4.2 ± 0.1 and 0.81 ± 0.06 can be calculated for the rearrangement and oxidation processes, respectively. The values are in good agreement with those determined in the first series of reactions.[19]

The effects of several solvents on the ratio of oxidation to rearrangement and of homolytic to heterolytic fragmentation are summarized in Table III.

Discussion

The magnitude of the k_H/k_D value for the rearrangement process (3.8–4.2) is clearly indicative of a primary isotope effect and is further confirmation of the suggestion[13] that removal of a methyl proton from 1 (R = Me) to form the anhydro base intermediate **5** is the rate-determining step in that pathway. Oae et al.,[13b] utilizing a kinetic method which results in an overall isotope effect for the rearrangement rather than an isotope effect proceeding from the *N*-acyloxypicolinium ion as in the present report, found a value of 6.3 for the reaction of acetic anhydride with 2-picoline *N*-oxide in dioxane.

A more striking observation to be noted from the deuterium labeling study is that the replacement of hydrogen by deuterium atoms at the benzylic position of phenylacetic anhydride *enhances* the production of benzaldehyde, i.e., k_D/k_H is 1.2–1.3 for the oxidative decarboxylation process. Such an inverse isotope effect may be readily rationalized if one assumes that the hydrogen transfer step is reversible.[20] Consistent with this assumption is an equilibrium involving formation of an enol or enolate prior to the rate-determining step (Scheme I, with dotted arrow as a real arrow). Since a chemical equilibrium depends upon the rates of the forward and reverse reactions, the position of enol or enolate equilibrium would be slightly affected by the substitution of deuterium for benzylic hydrogen atoms. The direction of shift would be expected to be toward enolization since the zero-point energy for the stretching vibration of the OH bond is greater than for the CH bond.[14a] The equi-

Table III
Variation in Yields of Oxidation and Rearrangement Products with Solvent

Solvent (ϵ)	% yields[a]		Ratio of benzaldehyde to picolyl phenylacetates	2-(β-Phenylethyl)-pyridine, %[a,b]	Ratio of 2-(β-phenylethyl)-pyridine to picolyl phenylacetates
	Benzaldehyde	Picolyl phenylacetates			
Benzene (2.3)	21.5 ± 0.8	25.3 ± 1.3	0.851 ± 0.016	7.01 ± 0.31	0.268 ± 0.004
	(23.1 ± 0.5)[c]	(28.6 ± 1.1)	(0.808 ± 0.013)		
o-Dichlorobenzene (9.9)	22.5	26.7	0.845	*d*	*d*
Benzonitrile (25)	32.5	29.4	1.11	6.40	0.217
Sulfolane (44)	31.0 ± 1.3	20.7 ± 0.5	1.50 ± 0.09	2.75 ± 0.20	0.133 ± 0.006
	(31.7)[c]	(20.1)	(1.58)		

[a] Yields were determined by VPC (FID). Results are for duplicate experiments where ranges are given. [b] Yields are relative, not absolute (see Experimental Section). [c] 2,6-Lutidine added. [d] Not determined.

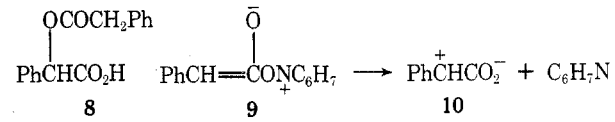
librium constant is increased, and the oxidation reaction rate therefore is accelerated.

The possibility of enolization or enolate anion formation being rate determining is eliminated since a value of $(k_H/k_D)_{oxidn}$ less than unity was obtained (0.76–0.81). In view of the kinetic work by Koenig,[4] in the case of reaction of 4-picoline N-oxide with phenylacetic anhydride, in which the disappearance of anhydride was found to be first order in N-oxide concentration, and consistent with our earlier study of pyridine and pyridine N-oxide nucleophilicities,[8a] the present finding of an inverse isotope effect strongly suggests that the slow step for the oxidation process is the SN1′ attack of pyridine N-oxide on the enol **2** (R = Me) or its enolate anion. That is, fragmentation of **2** or its conjugate base to picoline and **3** or its conjugate base is rate determining.

The variation in yields of oxidation and rearrangement products with solvent (Table III) establishes a trend that is in agreement with the postulated mechanisms. One would expect the rate constant for oxidation, k_2, to remain relatively unaffected as solvent polarity is varied, since charge is neither created nor destroyed in the equilibrium step (enolization or enolate formation) or in the rate-determining step (the loss of picoline from the enol or enolate). However, k_1, the rate constant for rearrangement, should decrease significantly as the solvent polarity increases, since the process proceeds through a transition state in which charged species are neutralized (anhydro base formation). The effect of increasing solvent polarity on these rate constants, as reflected in the yield ratio of benzaldehyde to picolyl phenylacetates, is a 31% increase in the rate of oxidation relative to that of rearrangement upon proceeding from benzene to benzonitrile and a corresponding increase of 76% from benzene to sulfolane. The result is thus consistent with a decrease in the rate constant for rearrangement (k_1) with an increase in solvent polarity.

Although the trend is in the expected direction, the magnitude of rate change is somewhat surprising since one might expect k_1 to decrease by several powers of ten when the dielectric constant of the solvent is increased 20-fold (benzene to sulfolane).[21] The observed change in k_2/k_1 of less than twofold might be rationalized by assuming that the cationic intermediate **1** (R = Me) and the phenylacetate anion exist as an ion pair.[22] If this is so, the reaction paths of **1** would only be marginally susceptible to the effect of dielectric change.

If the phenylacetate were indeed a counterion to the α-carboxybenzylcarbenium ion **3**, it would seem that a significant amount of phenylacetylmandelic acid (**8**), resulting from attack of the phenylacetate counterion on the cation **3**, should form. Since this is not the case,[5] we prefer formation of the enolate **9** around which no counteranion is likely to be present. The phenylacetate ion is neutralized by proton abstraction from **1** (R = Me) to give the acid and enolate species (**9**) which then loses 2-picoline to give the zwitterion **10**.[25,26]



In view of the suggestion that intermediate **1** (R = Me) proceeds to react in an ion pair, then the addition of base to the reaction solution, for the purpose of attempting to determine whether an enol or enolate species is involved in the equilibrium prior to the rate-determining step, would not be expected to change k_2/k_1 appreciably. In agreement with this expectation no significant change in the yield ratio of benzaldehyde and esters was observed when 2,6-lutidine was added (in a mole ratio of 1:1 with the anhydride) to the reaction in solvents benzene or sulfolane (Table III).

A final aspect of this study concerns the effect of solvents on the modes of cleavage which the anhydro base **5** may undergo (Table III). Heterolytic fragmentation of the NO bond, k_3 (Scheme I), produces the 2-picolyl cation and phenylacetate anion which recombine to produce picolyl phenylacetates. On the other hand, homolytic fragmentation, k_4 (Scheme I), with concerted decarboxylation, produces 2-picolyl and benzyl radicals, which upon recombination yield 2-(β-phenylethyl)pyridine and benzylpicolines.[9] The rate constant ratio of homolytic to heterolytic fragmentation (k_4/k_3) is proportional to the ratio of the yields of 2-(β-phenylethyl)pyridine[27] and esters. Table III records the yield ratios observed in several solvents.

The rate constant for heterolytic fragmentation (k_3), a process in which ionic species are formed, would be expected to increase as solvent polarity increases, whereas the rate constant for homolytic fragmentation (k_4) should be rather insensitive to solvent changes. As shown in Table III, the yield ratio of 2-(β-phenylethyl)pyridine to picolyl phenylacetates does indeed decrease as solvent polarity is increased. This result reflects the expected increase in k_3 and lends additional support to the proposed dual mechanism of fragmentation of anhydro base intermediate **5**. Furthermore, the 20-fold change in solvent dielectric (benzene to sulfolane) once again has a rather small effect on the ratio of rate constants, which decreases only twofold. The small solvent effect on the competition between heterolysis and homolysis can once again be explained by ion pairing; the anhydro base **5** probably rearranges to the ester **6** by way of a tight ion pair, a suggestion which is consistent with Oae's labeling studies[24] and is in complete accord with current theory.[10-12]

Experimental Section[28]

2-Picoline N-Oxide-d_4. To a solution of 50.0 g (2.50 mol) of deuterium oxide (99.8% D, Stohler Isotope Chemicals) and 100 ml of dry dioxane in a flask equipped with a reflux condenser and

magnetic stirrer was added piece by piece 1.4 g of freshly cleaned metallic sodium. The resulting sodium deuterioxide concentration was approximately 5%. Then 54.5 g (0.500 mol) of 2-picoline *N*-oxide was introduced into the two-phase system and the reaction mixture was stirred and heated at reflux (100°) for 3 hr. After being cooled, the aqueous sodium deuteroxide layer was removed by pipet. The remaining solution was filtered, and the filtrate neutralized with a concentrated solution of deuterium chloride in deuterium oxide. (A deuterium chloride solution of approximately 35% concentration was prepared by slowly adding 11 g of freshly distilled thionyl chloride to 20 g of deuterium oxide.) Removal of the cosolvent on a rotatory evaporator left the pale yellow crude liquid *N*-oxide and solid sodium chloride. The crude *N*-oxide was subjected to three additional exchanges. Each exchange utilized 50.0 g (5 equiv) of deuterium oxide, 1.4 g of sodium, and 100 ml of dioxane under the procedure outlined above. Before the final exchange was accomplished, the dioxane was heated at reflux over calcium hydride overnight and distilled at 101°, and all glassware used was flame dried.

Carbon tetrachloride was added to the crude liquid *N*-oxide and sodium chloride suspension, and the salt was removed by filtration through a medium porosity sintered-glass filter. Thorough evaporation of the solvent left the crude *N*-oxide. Vacuum distillation (93–95°, 0.25 mm) of the material afforded 55.0 g (97%) of the pure, white, crystalline product, which was stored in a vacuum desiccator ($CaSO_4$). Decreases in the integrated ^1H NMR signals at τ 1.7 (α-H) and 7.6 ($-CH_3$) indicated 98% deuterium incorporated at each site.

Phenylacetic Anhydride. Phenylacetic anhydride was prepared in 72% yield by the method of Cohen and Fager.[9] The anhydride was further purified by dissolving in ether, washing the solution successively with 10% sodium carbonate solution and water, drying it over calcium sulfate, and cooling in powdered dry ice to give a white, crystalline solid: mp 72.0–72.5° (lit.[9] mp 72.5–73.0°); ^1H NMR (CCl_4) τ 6.4 (s, 4 H), 2.85 (s, 10 H).

Phenylacetic Anhydride-d_4. Phenylacetonitrile-d_2 was prepared as follows. A vigorously stirred solution of 58.5 g (0.500 mol) of phenylacetonitrile, 50.0 g (2.50 mol) of deuterium oxide (99.8% D, Columbia Organic Chemicals), and 150 g of pyridine which had been dried over 4 Å molecular sieve (Linde) was heated at reflux (100°) for 23 hr. Then 10% aqueous hydrogen chloride was added to the reaction mixture until it became acidic to litmus. The solution was extracted with ether, and the combined extracts were dried over Drierite. Evaporation of the solvent left colorless, partially deuterated phenylacetonitrile. The nitrile was subjected to three additional exchanges by the same procedure. Each exchange utilized 5 equiv of deuterium oxide in a 75% pyridine solution. An ir spectrum of the deuterated phenylacetonitrile indicated a decrease in the signal at 3.38–3.44 μ, the appearance of the signal at 4.73 μ, and the disappearance of the signal at 7.08 μ (C–H stretch, C–D stretch, and C–H bend, respectively). An integrated ^1H NMR spectrum was consistent with essentially complete deuteration. No α protons were detectable in the τ 6.25–6.35 region.

To a solution of 30 g (1.5 mol) of deuterium oxide and 120 ml of dry dioxane was added piece by piece 11.5 g (0.50 mol) of freshly cleaned metallic sodium. The phenylacetonitrile-d_2 from above was added, and the solution was vigorously stirred and heated at reflux (100°) for 84 hr. Throughout this period the reaction solution was swept with dry nitrogen to remove ammonia. Evaporation of the solvent left a pink solid. The crude solid was washed with anhydrous[29] ether to whiteness to yield, after drying in an oven at 110°, 78.9 g (98%) of pure white material. An integrated ^1H NMR spectrum of the sodium phenylacetate-d_2 (D_2O) indicated no α hydrogens in the τ 6.3–6.8 region.

Phenylacetic anhydride-d_4 was then prepared as follows.[31] To a suspension of 10.0 g (0.063 mol) of sodium phenylacetate-d_2, 40 ml of acetonitrile (refluxed over calcium hydride overnight and distilled at 80.5°), and 5 g of activated 3 Å molecular sieves was added dropwise and with stirring a solution of 5.96 g (0.031 mol) of pure[32] *p*-toluenesulfonyl chloride in 20 ml of acetonitrile. The reaction mixture was heated at reflux (81°) for 2 hr. Evaporation of the solvent left a white solid which was added to 150 ml of anhydrous ether. The suspension was filtered and the filtrate cooled in powdered dry ice to give a white, crystalline solid which was collected in a Büchner funnel and dried in a vacuum desiccator ($CaSO_4$) to yield 6.7 g (84%) of pure product, mp 72.5–73.0°. An integrated ^1H NMR spectrum of the phenylacetic anhydride-d_4 indicated 97% deuteration in the α position at τ 6.4.

General Procedure for the Reaction of Phenylacetic Anhydride with 2-Picoline *N*-Oxide in Benzene. In the first series of reactions approximately 3.5 g of 2-picoline *N*-oxide (bp 104–108, 0.3 mm) or its labeled derivative was transferred within a drybox to the reaction flask. Anhydrous benzene (25 ml) and sufficient labeled or unlabeled phenylacetic anhydride (about 2.0 g) to give a 4:1 mole ratio of *N*-oxide to anhydride were added. The solution was heated at reflux (80°) for 24 hr under an atmosphere of dry nitrogen. Quantitative analysis of the yields of benzaldehyde (15% Carbowax 20M column at 130°, 14 min) and picolyl phenylacetates (3% OV-17 column at 200°, 20–28 min) in an aliquot were determined directly by VPC (FID). Durene (9.3 min) and triphenylmethane (42 min), respectively, were employed as internal standards.

In the second series of reactions approximately 34 ml of 1.0 *M* 2-picoline *N*-oxide in anhydrous benzene was added to phenylacetic anhydride (mole ratio 4:1). After heating the solution at reflux for 24 hr under nitrogen, an aliquot was analyzed by VPC (TC, 3% OV-17) for yields of 2-picoline (7.2 min at 90°) and picolyl phenylacetates (23–26 min at 240°). Triphenylmethane (30 min at 240°) was used as an internal standard. Benzaldehyde, 2-picoline, and esters were identified by comparison of retention times with those of authentic samples. A summary of the yield data in both series of labeled and unlabeled runs is presented in Tables I and II.

The benzaldehyde product in reactions II and III (Table I) was analyzed for deuterium content. Respectively, 3 and 74% deuterium enrichments were found.

Product Yields at an Earlier Stage of the Reaction. A mixture of 3.37 g (29.8 mmol) of 2-picoline *N*-oxide-d_4 and 1.88 g (7.4 mmol) of phenylacetic anhydride in 25 ml of dry benzene was heated at reflux under nitrogen for 30 min to yield 27.3% benzaldehyde and 7.90% picolyl phenylacetates, i.e., $k_2/k_1' \simeq 3.46$.

Similarly, a mixture of 3.80 g (33.6 mmol) of 2-picoline *N*-oxide-d_4, 2.16 g (8.4 mmol) of phenylacetic anhydride-d_4, and ca. 6 g of activated 3 Å molecular sieves in 25 ml of dry benzene heated at reflux for 5 min gave 16.8% benzaldehyde and 3.40% esters, i.e., $k_2'/k_1' = 4.95$.

Reaction of Anhydride with N-Oxide in Solvents Other than Benzene. By the general procedure outlined above 2-picoline *N*-oxide and phenylacetic anhydride (mole ratio 4:1) were heated at 80° in *o*-dichlorobenzene, benzonitrile (aniline free), and sulfolane. The yields of benzaldehyde and esters are recorded in Table III.

Comparison of retention times with those of an authentic sample[33] enabled the identification of 2-(β-phenylethyl)pyridine (3% OV-17 at 150°, 42.5 min). A relative yield was obtained by assuming an arbitrary response factor (area ratio of sample to standard vs. weight ratio of sample to standard) of 2.00. Aliquots from the reactions run in benzene, benzonitrile, and sulfolane were analyzed, using triphenylmethane (60 min) as an internal standard. The yields are given in Table III.

Reaction of Anhydride with *N*-Oxide and Added Base. A mixture of 2.85 g (26.2 mmol) of 2-picoline *N*-oxide, 1.66 g (6.52 mmol) of phenylacetic anhydride, and 0.712 g (6.65 mmol) of freshly distilled 2,6-lutidine in 25 ml of dry benzene heated at reflux for 24 hr under nitrogen gave 22.7% benzaldehyde and 27.6% picolyl phenylacetates. In a duplicate run in benzene the corresponding yields were 23.6 and 29.7%. A mixture of 2.80 g (25.7 mmol) of 2-picoline *N*-oxide, 1.64 g (6.46 mmol) of phenylacetic anhydride, and 0.691 g (6.46 mmol) of 2,6-lutidine in 25 ml of dry sulfolane yielded 31.7% benzaldehyde and 20.1% picolyl phenylacetates after heating at 80° for 24 hr.

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Registry No.—2-Picoline *N*-oxide-d_4, 56783-17-6; deuterium oxide, 7789-20-2; 2-picoline *N*-oxide, 931-19-1; phenylacetic anhydride, 1555-80-2; phenylacetic anhydride-d_4, 56783-18-7; phenylacetonitrile, 140-29-4.

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(17) The absolute yields of benzylpicolines were not determined in these experiments since they would be expected to vary in direct proportion to the yields of esters. Unlike reaction II, the relative rates of heterolytic and homolytic fragmentation in reaction III (see below) may be somewhat affected by a secondary isotope effect at the benzylic position. However, assuming a maximum effect of 1.1^{18} and a ratio of esters to benzylpicolines of ca. 2.0,[9] the magnitude of error in the resulting calculation is only 4%. Hence, the yields of benzylpicolines were ignored and the rate of rearrangement was assumed to be directly proportional to the yields of esters.
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(22) Although the possibility of ion pairing may at first seem remote in sulfolane, it must be remembered that in dipolar aprotic solvents the anion is poorly solvated because it cannot form a hydrogen bond with the solvent. In fact, SN1-like ionization is not common in such solvents.[23]
(23) A. Parker, *Q. Rev., Chem. Soc.*, **16**, 163 (1962).
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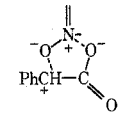
(25) It is also possible that the α-carboxybenzylcarbenium ion **3**, being very acidic, could lose a proton to the phenylacetate anion rather than form a CO bond to it.
(26) The high selectivity of the electrophilic intermediate for pyridine *N*-oxide[8a] might be explained by a 1,3-dipolar interaction of **10** with the *N*-oxide.



(27) Because of an impurity which eluted with either 2-methyl-3-benzylpyridine or 2-methyl-5-benzylpyridine, the yields of those isomers, which represent ca. 20% of the total yield of the three benzylpicoline isomers, were not determined on the VPC. However, it could be estimated from the chromatogram that the yields of the two isomers varied in direct proportion to the yield of the third isomer, 2-(β-phenylethyl)pyridine (**7**). Therefore, the yield of the latter is proportional to the rate of homolysis.
(28) Melting points were determined on a Thomas-Kofler micro hot stage utilizing a stage-calibrated thermometer and are thus corrected. Boiling points are uncorrected. Infrared spectra were determined on Beckman IR-8 or Perkin-Elmer 467 spectrophotometers. Proton magnetic resonance spectra were determined on Varian A-60 or 360 instruments; chemical shifts are relative to internal tetramethylsilane for samples prepared in organic solvents and to the sodium salt of 3-(trimethylsilyl)-1-propanesulfonic acid for samples in aqueous solution. Analytical gas chromatography was performed on Varian 1860-3 (FID) or 920 (TC) instruments equipped with Disc 204 integrators. For determining yields, the responses of authentic samples were calibrated against those of various standards. Isomers were assumed to have identical responses. Isotopic analyses were performed at 20 eV on an LKB 9000 combined gas chromatograph–mass spectrometer equipped with an accelerating voltage alternator.
(29) Sodium phenylacetate slowly exchanges α protons in the presence of 0.05 *M* deuteroxide ion and deuterium oxide.[30] Therefore, to the extent that any sodium deuteroxide remains in the reaction mixture under discussion, redissolving the sodium phenylacetate-d_2 salt in water and washing with ether would dilute the deuterium atom content of the salt.
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(31) It was found that phenylacetic anhydride-d_4 readily exchanges α deuterons in the presence of acidic protons. Therefore, in order to prepare a highly enriched anhydride, all glassware used was oven dried, and the weighings and reagent transfers were performed in a drybox containing phosphorus pentoxide as desiccant. The anhydrous conditions prevent hydrolysis of tosyl chloride to tosyl acid.
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Cleavage of Cyclic Ethers by Magnesium Bromide–Acetic Anhydride. SN2 Substitution at a Secondary Site

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Cyclic ethers are cleaved by magnesium bromide and acetic anhydride in acetonitrile to yield bromoacetates. The reaction occurs readily at room temperature with tetrahydrofuran and substituted tetrahydrofurans. Tetrahydropyrans require higher temperature for cleavage. When *cis*- and *trans*-2,5-dimethyltetrahydrofuran are individually subjected to cleavage conditions a single diastereoisomeric bromoacetate is produced from each. The bromoacetates in turn when exposed to sodium hydroxide in warm ethylene glycol are converted to the specific isomers from which they were formed. Since the reclosure reaction must occur with inversion, the cleavage reaction must also be an inversion process. The mechanism of cyclic ether cleavage with magnesium bromide–acetic anhydride is thus shown to be exclusively an SN2 process.

The ability of Lewis acids and acid anhydrides to cleave ethers has been known since the early part of this century. The reactions have been extensively studied from the standpoints of product composition, mechanism, and stereochemistry, and the subject has been reviewed in detail.[1,2] Despite the "textbook" nature of the process, the search for methods for the formation and cleavage of ethers remains of interest. Ethers serve as effective stable blocking groups for hydroxyl functions and their use in this regard is ubiquitous in organic synthesis. Recently reports of the development of two ether cleavage reagent systems using acid anhydrides have appeared.[3,4]