

appears to correlate well with the ground-state delocalization parameter β , which is lowest in the compounds containing corner-shared octahedra. It should be also mentioned that increasing the electronic interaction increases dramatically the intensity of all bands in the visible-near-IR spectra (Table II). This is shown by the large variation of the maximum extinction coefficient, which ranges from 340 mol⁻¹ L cm⁻¹ in [Mo₆O₁₉]³⁻, to ~1300 mol⁻¹ L cm⁻¹ in [XMo₁₂O₄₀] species.

Such a rough analysis does not take into account the nature of the central ion in the tetrahedral cavity. This ion appears to modify noticeably the structure of the polyanion and could thus play a role in the delocalization process. A more careful analysis should take into account not only the interaction between two neighboring molybdenum sites but the whole polyanion.

Acknowledgment. The technical assistance of F. Gatebled and D. Simons is gratefully acknowledged.

Registry No. [MoW₅O₁₉]³⁻, 81193-94-4; [Mo₆O₁₉]³⁻, 71767-69-6; [SiMoW₁₁O₄₀]⁵⁻, 81218-89-5; [PMo₁₂O₄₀]⁴⁻, 53850-86-5; [AsMo₁₂O₄₀]⁴⁻, 76130-01-3; [SiMo₁₂O₄₀]⁵⁻, 57656-95-8; [GeMo₁₂O₄₀]⁵⁻, 76130-24-0; [SiMo₃W₉O₄₀]⁵⁻, 81407-99-0; [PMoW₁₁O₄₀]⁴⁻, 12776-99-7; (NBu₄)₂[Mo₆O₁₉], 12390-22-6; (NBu₄)₄[SiMo₁₂O₄₀], 59138-97-5; (NBu₄)₄[GeMo₁₂O₄₀], 81205-59-6; (NBu₄)₃[PMo₁₂O₄₀], 51542-98-4; (NBu₄)₃[AsMo₁₂O₄₀], 81158-05-6; (NBu₄)₄[SiMoW₁₁O₄₀], 68081-64-1; K₈[SiW₁₁O₃₉], 37300-95-1; K₄[SiMoW₁₁O₄₀], 81205-60-9; (NBu₄)₄[SiMo₃W₉O₄₀], 81158-06-7; Na₉[HSiW₉O₃₄], 81205-57-4; (NBu₄)₃[MoW₅O₁₉], 81193-95-5; H(NBu₄)₄[SiMo₃W₉O₄₀], 81423-62-3; H₄[SiMo₃W₉O₄₀], 81407-98-9; Na₂MoO₄, 7631-95-0; Na₂GeO₃, 12025-19-3; MoO₃, 1313-27-5; As₂O₅, 1303-28-2; Na₂WO₄, 13472-45-2; WO₃, 1314-35-8.

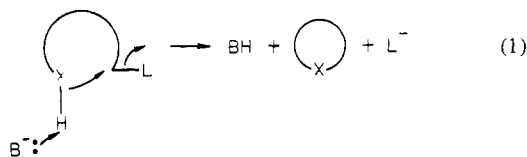
Methylase Models: Studies on General-Base vs. Nucleophilic Catalysis in the Intramolecular Alkylation of Phenols

Jay O. Knipe, Peter J. Vasquez, and James K. Coward*

Contribution from the Department of Pharmacology, Yale University School of Medicine, New Haven, Connecticut 06510, and the Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12181. Received August 31, 1981

Abstract: The ortho substituted phenols, **1** and **3**, have been synthesized as models for the O-methylation of catecholamines, as catalyzed by catechol O-methyltransferase. The decomposition of **1** and **3** was studied at 40 °C over a wide range of pH in both oxyanion and amine buffers. Buffer catalysis of the reaction is observed, and product analyses show that oxyanion buffers catalyze a cyclization reaction to yield chroman (**4**) or 4,4-dimethylchroman (**5**), from **1** or **3**, respectively, in addition to *p*-nitrothioanisole (**6**). In contrast, amine buffers effect the intermolecular demethylation of **1** and **3**, to yield the corresponding *p*-nitrophenyl thioethers, **7** and **8**. The buffer-independent reaction involves cyclization to **4** or **5**, with formation of **6**. Brønsted β values of 1.1 and 0.89 for oxyanion-catalyzed reactions of **1** and **3**, respectively, are in contrast to the β value of 0.27 previously obtained in similar studies with a less acidic cyclopentanol substrate (*J. Am. Chem. Soc.* 1979, 101, 4339). However, other aspects of the oxyanion vs. amine buffer effects are in agreement with our earlier results and lead to the general conclusion that nucleophilic alkylation of alcohols and phenols is subject to general-base catalysis by oxyanion buffer species.

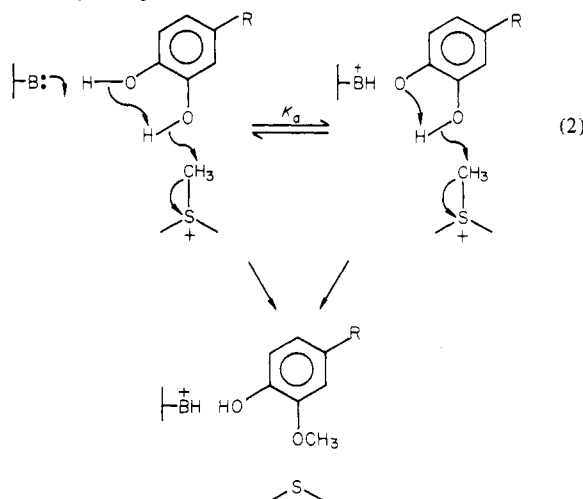
In a previous paper from this laboratory,¹ we demonstrated that several oxyanion buffers could act as general-base catalysts for the intramolecular alkylation of a cyclopentanol. Thus, related reactions of the type shown in eq 1 might be susceptible to similar



catalysis. However, the literature contains only one other reference to buffer catalysis of nucleophilic attack at sp³ carbon; i.e., the borate-catalyzed cyclization of 4-chlorobutanol.² In another study,³ no buffer catalysis was observed in the formation of chromans via intramolecular cyclization of (*o*-hydroxyphenyl)-propyl acetate, mesylate, etc. Thus, the generality of catalysis of nucleophilic reactions at sp³ carbon remains to be explored.

Our own interest in the possibility of general-base-catalyzed nucleophilic displacement at sp³ carbon arose from consideration

of the substrate requirements and kinetic data for the enzyme-catalyzed methylation of catecholamines.⁴ It was suggested that the enzyme, catechol O-methyltransferase (COMT, EC 2.1.1.6), might effect the transfer of a methyl group from the electrophilic donor, *S*-adenosylmethionine (SAM), to the nucleophilic acceptor, (nor)epinephrine, via general-base-catalyzed proton abstraction from one (or both) of the catechol hydroxyl groups. This is shown schematically in eq 2.



* To whom correspondence should be addressed at Rensselaer Polytechnic Institute.

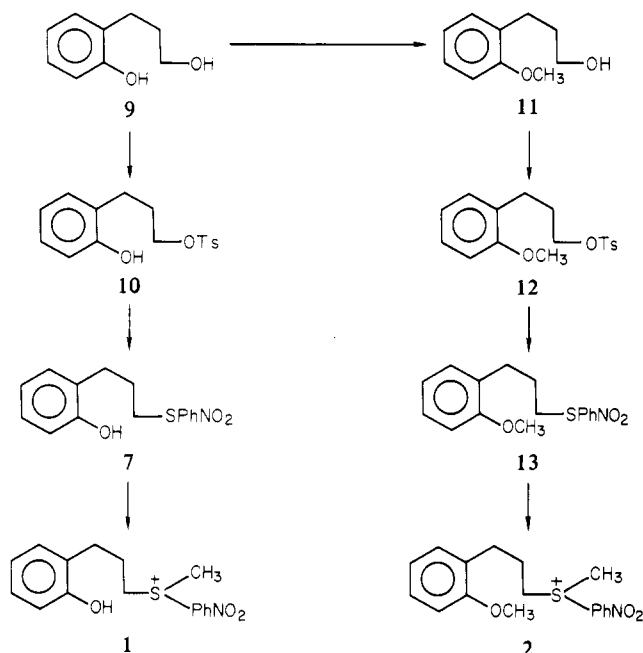
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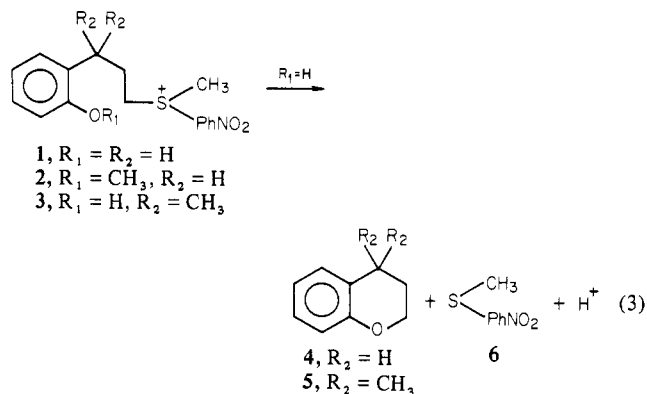
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Scheme I



Since suggesting this mechanism, we have sought to gather experimental evidence for or against it.⁵ The fact that oxanion buffers are effective general-base catalysts of the intramolecular cyclopentanol alkylation mentioned above lends support to this hypothesis. However, the high pK_a of cyclopentanol (ca. 16) is more similar to a ribose hydroxyl (pK_a ca. 13) than to a catechol (pK_a ca. 9–10). Therefore, we have synthesized the phenol sulfoniums **1** and **3** for kinetic studies of the reaction in eq 3. In



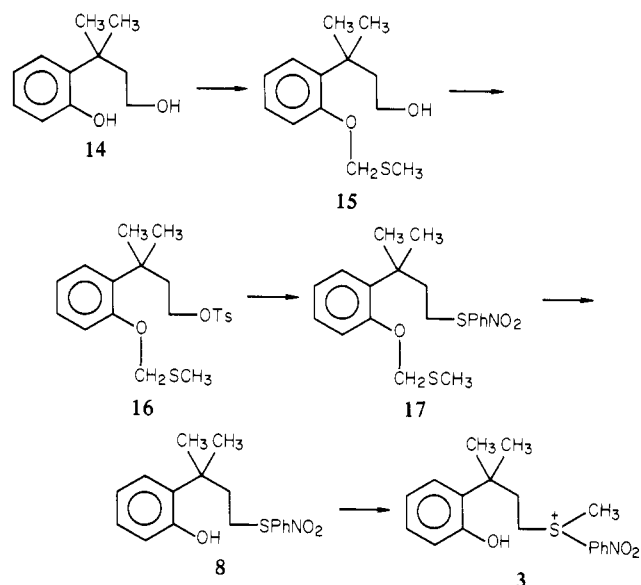
addition, we have synthesized the anisole analogue, **2**, for use in elucidating the role of the phenolic OH group. The phenols, **1** and **3**, with pK_a 's of ca. 10 have been studied over a wide range of pH and temperature. In agreement with the earlier work on the cyclopentanol system,¹ general-base catalysis by oxanion buffers is observed when the phenol is protonated (k_{ROH}), whereas amines effect nucleophilic demethylation to give an (*o*-hydroxyphenyl)propyl thioether; e.g., **7** and **8**. This paper describes detailed studies of the reaction given in eq 3 and provides further evidence for the involvement of general-base catalysis in nucleophilic displacements at sp^3 carbon.

Experimental Section

Schemes I and II outline the syntheses of **1** and **2** and the synthesis of **3**, respectively.

3-(2-Hydroxyphenyl)-1-propanol (9) and 3-(2-Hydroxyphenyl)-1-propyl Tosylate (10). Reduction of the commercially available 3,4-dihydrocoumarin (Aldrich Chemical Co.) with $LiAlH_4$ in ether gave **9**, bp 145 °C (1.1 mm) (lit.³ bp 124–125 °C (0.4 mm)). Tosylation of the primary hydroxyl of **9** to afford **10** was carried out by using *p*-toluene-

Scheme II



sulfonyl chloride in pyridine according to the procedure of Lok and Coward.⁶ The tosylate **10**, obtained as a clear oil after high vacuum drying, had the following 1H NMR ($CDCl_3$) characteristics: δ 7.70, 7.30 (4 H, 2 sets of d, aromatic protons of tosyl group), ca. 6.90 (4 H, m, aromatic protons), 5.22 (1 H, s, phenolic hydroxyl), 4.05 (2 H, t, methylene protons α to the tosyl group; this triplet centered at ca. δ 3.50 in **9**), 2.70, 2.00 (4 H, 2 sets of t, other methylene protons of side chain), 2.45 (3 H, s, *p*-CH₃).

3-(2-Hydroxyphenyl)-1-propyl *p*-Nitrophenyl Sulfide (7). The tosylate **10** was reacted with 4-nitrothiophenol (Aldrich Chemical Co., purified by sublimation) in sodium ethoxide according to the general procedure of Waldron and Reid.⁷ Isolation by preparative TLC (silica gel:hexane; EtOAc, 3:1) gave a yellow oil which solidified upon standing and was recrystallized from ether/petroleum ether to give a compound with the following characteristics: m.p. 69–71 °C; 1H NMR ($CDCl_3$) δ 8.08, 7.15 (4 H, 2 sets of d, aromatic protons of *p*-nitrophenyl ring), ca. 6.90 (4 H, m, aromatic protons), 5.18 (1 H, s, phenolic hydroxyl), ca. 2.80 (4 H, m, methylene protons of side chain, including those α to *p*-nitrophenyl group; note shift of the signal for the α protons relative to that observed with **10**), 2.00 (2 H, t, other methylene protons of side chain). Anal. Calcd for $C_{15}H_{15}NO_3S$: C, 62.26; H, 5.23; N, 4.84; S, 11.08. Found C, 62.54; H, 5.51; N, 4.62; S, 10.81.

3-(2-Methoxyphenyl)-1-propanol (11) and 3-(2-Methoxyphenyl)-1-propyl Tosylate (12). Methylation of the phenolic hydroxyl of **9** was carried out by using CH_3I in 0.1 N NaOH to give **11**, bp 118–120 °C (1.9–2.0 mm) (lit.⁸ 84–87 °C (0.2 mm)). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found C, 72.42; H, 8.69.

The tosylate **12** was prepared as described for **10** and had the following 1H NMR ($CDCl_3$) characteristics: δ 7.68, 7.30 (4 H, 2 sets of d, aromatic protons of tosyl group), ca. 6.92 (4 H, m, aromatic protons), 4.10 (2 H, t, methylene protons α to tosyl group), 3.80 (3 H, s, OCH₃), 2.72, 2.00 (4 H, 2 sets of t, other methylene protons of side chain), 2.45 (3 H, s, *p*-CH₃).

3-(2-Methoxyphenyl)-1-propyl *p*-Nitrophenyl Sulfide (13). Reaction of **12** with 4-nitrothiophenol, as described for **7**, and product isolation after preparative TLC gave **13** as a yellow oil with the following 1H NMR ($CDCl_3$) characteristics: δ 8.05, 7.20 (4 H, 2 sets of aromatic protons of *p*-nitrophenyl ring), ca. 7.00 (4 H, m, aromatic protons), 3.78 (3 H, s, OCH₃), ca. 2.90 (4 H, m, methylene protons of side chain, including those α to the *p*-nitrophenyl group), 2.05 (2 H, t, other methylene protons of side chain). Anal. Calcd for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62; S, 10.57. Found C, 63.61; H, 5.42; N, 4.52; S, 10.84.

3-[2-((Methylthio)methoxy)phenyl]-3,3-dimethyl-1-propanol (15) and 3-[2-((Methylthio)methoxy)phenyl]-3,3-dimethyl-1-propyl Tosylate (16). The diol **14** was prepared according to the procedure of Borchardt and Cohen,³ mp 112–113 °C (lit. 110–111 °C). Attempts to prepare the *p*-nitrophenyl sulfide **8** from either the 1-mesylate or 1-tosylate of **14** failed, the only detectable product being 4,4-dimethylchroman (**5**), presumably arising from facile intramolecular displacement of the sulfonate

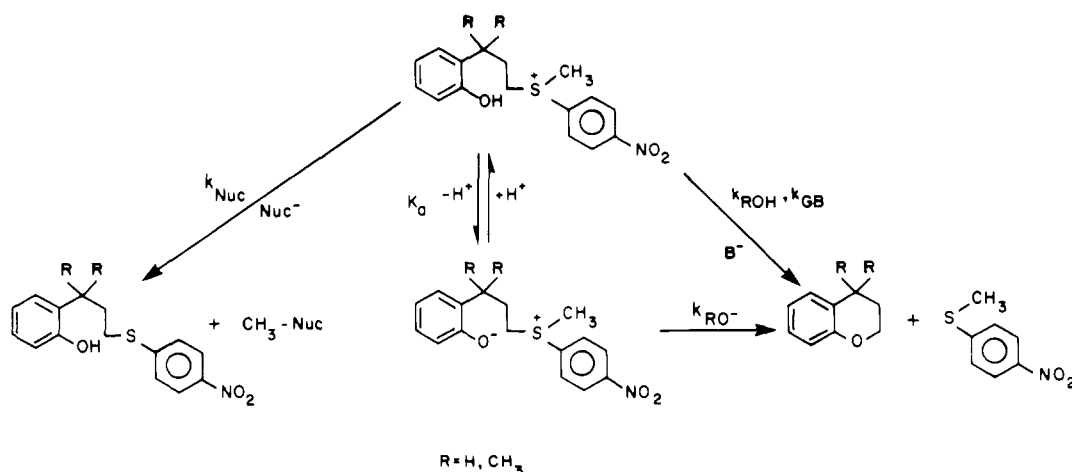
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Scheme III



group by the phenolic hydroxyl. This problem was overcome by blocking the phenolic hydroxyl with the (methylthio)methyl ether functionality, as described by Holton and Davis,⁹ to give 3-[2-((methylthio)methoxy)phenyl]-3,3-dimethyl-1-propanol (**15**). This compound had the following ¹H NMR (CDCl₃) characteristics: δ ca. 7.10 (4 H, m, aromatic protons), 5.20 (2 H, s, O-CH₂-S), ca. 3.40 (2 H, t, methylene protons α to OH), ca. 2.20 (4 H, m, S-CH₃ and methylene protons β to OH), 1.70 (1 H, s, OH), 1.40 (6 H, s, 2 CH₃). Compound **15**, in contrast to **14**, displayed no shift in λ_{max} when dissolved in 0.1 N NaOH, thus further indicating the position of the (methylthio)methyl ether on the phenolic, rather than the aliphatic, hydroxyl group.

Reaction of **15** with tosyl chloride in pyridine proceeded smoothly to give the tosylate **16** as a clear oil with the following ¹H NMR (CDCl₃) characteristics: δ 7.70, 7.25 (4 H, 2 sets of d, aromatic protons of tosyl group), ca. 7.10 (4 H, m, aromatic protons), 5.20 (2 H, s, O-CH₂-S), ca. 3.80 (2 H, t, methylene protons α to tosyl group), ca. 2.30 (8 H, m, methylene protons β to tosyl group, S-CH₃, p-CH₃), 1.40 (6 H, s, 2 CH₃).

3-(2-Hydroxyphenyl)-3,3-dimethyl-1-propyl p-Nitrophenyl Sulfide (8). Reaction of the tosylate **16** with 4-nitrothiophenol in NaOEt gave the 2-hydroxy-protected thioether **17** obtained as a yellow oil with the following ¹H NMR (CDCl₃) characteristics: δ 8.10, 7.20 (4 H, 2 sets of d, aromatic protons of p-nitrophenyl ring), ca. 6.95 (4 H, m, aromatic protons), 5.20 (2 H, s, O-CH₂-S), 2.20 (3 H, s, SCH₃), ca. 2.25 (2 H, m, protons β to p-nitrophenyl sulfide), 1.40 (6 H, s, 2 CH₃).

Removal of the protecting group using HgCl₂ in CH₃CN/H₂O⁹ afforded **8**, a yellow solid with the following characteristics: mp 100–102 °C; ¹H NMR (CDCl₃) δ 8.15, 7.25 (4 H, 2 sets of d, aromatic protons of p-nitrophenyl ring), ca. 6.85 (4 H, m, aromatic protons), 5.15 (1 H, br s, phenolic OH), ca. 2.80 (2 H, t, protons α to p-nitrophenyl sulfide), ca. 2.25 (2 H, t, protons β to p-nitrophenyl sulfide), 1.40 (6 H, s, 2 CH₃). Anal. Calcd for C₁₇H₁₉NO₂S: C, 64.32; H, 6.05; N, 4.41; S, 10.10. Found, C, 64.77; H, 5.90; N, 4.70; S, 9.85.

Preparation of Sulfonium Salts 1, 2, and 3. Methylation of **7**, **13**, and **8** to give **1**, **2**, and **3**, respectively, was carried out by using CH₃I and AgBF₄ in toluene/methylene chloride, as described by Lok and Coward.⁵ Sulfonium salt **1** had the following characteristics: mp 129–131 °C; ϵ = 1.10×10^4 (in H₂O at λ_{max} = 250 nm); ¹H NMR (acetone-d₆) δ 8.50 (4 H, s, aromatic protons of p-nitrophenyl ring), 8.20 (1 H, s, phenolic OH), ca. 6.95 (4 H, m, aromatic protons), 4.00 (2 H, t, methylene protons α to sulfonium), 3.60 (3 H, s, S-CH₃), 2.80 (2 H, t, protons γ to sulfonium), 2.20 (2 H, m, protons β to sulfonium).

The salts **2** and **3** were not isolated but stored in aqueous solution in the cold. For kinetic experiments an aliquot of one of these solutions, sufficient to give a final substrate concentration of ca. 10^{-4} M in the buffer medium, was used. The concentration of the sulfonium salts was estimated by using the extinction coefficient determined for **1**.

Chroman (4) and 4,4-Dimethylchroman (5). The preparation of **4** was accomplished by the phosphoric acid catalyzed dehydration of the diol **9**; **4**, bp 47–49 °C (1 mm) (lit.³ 101–103 °C (20 mm)). The dimethyl derivative **5** was prepared as follows: 1.8 g (10 mmol) of the diol **14** was suspended in 15 mL of dry benzene containing 2 drops of dry pyridine. To this suspension was added, dropwise, a solution of thionyl chloride (distilled), 1.43 g (12 mmol), in 5 mL of benzene. Following 2 h of refluxing the resulting clear yellow solution was diluted with water and the benzene layer washed successively with saturated NaHCO₃ and NaCl. Following drying (MgSO₄), evaporation of the benzene gave 1.25

g (75%) of a yellow oil. Distillation gave 0.80 g (51%) of a clear liquid, bp 44–45 °C (0.3 mm) (lit.³ 44–45 °C (0.3 mm)) having a ¹H NMR spectrum consistent with the desired structure.

Kinetics. Inorganic salts were of reagent grade and used without further purification. Potassium salts were used for buffer preparation in all cases except for formate buffers, where sodium formate was used. Both *N*-methylmorpholine and *n*-butylamine were distilled over barium oxide before use and *N,O*-dimethylhydroxylamine (Aldrich Chemical Co.) was recrystallized from ethanol before use. All buffers used in the course of this work were prepared in double-distilled water, and the ionic strength of all solutions was maintained at 1.0 M with KCl. All kinetic experiments were performed in aqueous media at temperatures ranging from 25 to 40 °C, in a thermostated spectrophotometer. The pH and temperature of each buffer were determined at the beginning and end of each kinetic run, and spectral scans of the products of each kinetic experiment were performed. A kinetic run was defined as complete after it had proceeded ca. 10 half-lives.

Each experiment was carried out by using a fixed ratio of basic to acidic buffer species but at three different total buffer concentrations (μ = 1.0 M with KCl). Typically, the concentration of the substrate in the buffer solution was ca. 10^{-4} M. Reactions were followed by monitoring the increase in optical density at 350 nm, indicative of formation of a p-nitrophenyl thioether from the corresponding sulfonium compound (λ_{max} ca. 250 nm). Under the pseudo-first-order conditions of these experiments, a plot of $\ln(A_\infty - A_t)$ vs. time was linear over at least 3 half-lives. Further analysis of the data is discussed in the Results.

In order to verify the identity of the products of a kinetic experiment, we carried out preparative experiments as follows: **1** (ca. 1 mmol) was stirred with 1 L of either 0.1 N KOH or *N*-methylmorpholine buffer (1.0 M total buffer concentration, with a 1:1 ratio of basic to acidic species) at 30 °C until the reaction was judged complete by spectrophotometry (ca. 20 min for KOH and 120 min for *N*-methylmorpholine). Following this period, the mixture was extracted with three volumes of ether, the ether washed with saturated NaCl and dried with MgSO₄ (prior to washing and drying the ether from the *N*-methylmorpholine experiment, dry HCl was passed into the ethereal solution to precipitate *N*-methylmorpholine-hydrogen chloride, which was removed by filtration). Following concentration of the ether extract to a small volume, the residue was chromatographed on preparative TLC plates, developed in hexane:EtOAc (3:1). The bands were visualized under UV light, scraped from the plates, and eluted with CHCl₃. The identity of each compound was established by NMR.

Product Analysis. The analysis of the products formed in a kinetic experiment was performed by using both high-performance liquid chromatography (HPLC) and a fluorometric assay. All HPLC analyses were carried out by using a system comprised of the following components: two Altex 110-A pumps coupled to an Altex Model 420 microprocessor capable of carrying out isocratic or gradient elution, an Altex analytical UV detector, an Altex analytical optical unit equipped with either a 280- or a 340-nm filter, and a Linear recorder. A Whatman Partisil PXS 10/25 ODS reverse-phase column and a mobile phase comprised of either 50 or 60% methanol/water (isocratic elution) was found to give the best separation of the required compounds. The products formed in a kinetic experiment were identified by comparing their retention times with those of known compounds under identical conditions. Aliquots (ca. 25–100 μ L) from a kinetic run were injected directly onto the HPLC column. The thioethers **6**, **7**, **8**, and **13** were detected by using the 340-nm filter, while the chromans **4** and **5** were detected by using the 280-nm filter.

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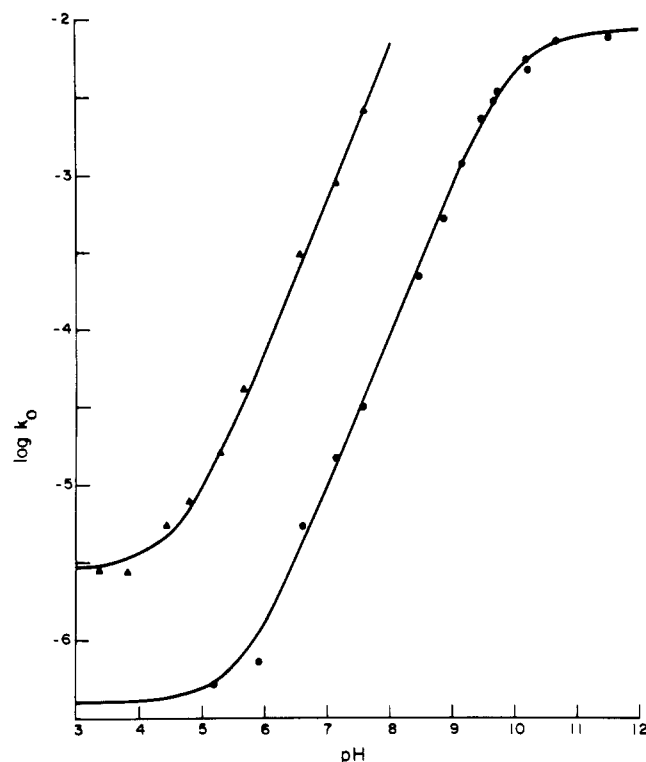


Figure 1. pH-rate profile for the reaction of 1 (●) and 3 (▲) in oxyanion buffers at 40 °C.

Table I. pK_{app} and k_{RO^-} Values for the Reaction of 1 in Aqueous Oxyanion Buffers at Various Temperatures

temp, °C	pK_{app}^a	$10^3 k_{RO^-}, s^{-1}$
40	9.97	8.58
37	10.01	5.52
34	10.07	3.44
31.5	10.16	2.50
28	10.31	1.58

^a Values calculated as described in the Results.

Fluorescence was measured on a Farrand Model 801 spectrofluorometer, with corrected excitation module and beam differential control, and recorded on an LKB Model 6530 flat-bed recorder. The presence of the chromans 4 and 5 in a kinetic experiment was demonstrated by analyzing for fluorescence intensity at an excitation wavelength of 275 nm and an emission wavelength of 303 nm. The concentration of both chromans was determined by using a standard curve of fluorescence intensity vs. chroman concentration.¹⁰ Such a curve was constructed by using stock solutions of either chroman or *p*-nitrothioanisole, 6, in 10% THF/H₂O. Varying amounts of the chroman stock solution were placed in 3 mL of 0.1 N KOH which contained 1×10^{-4} M *p*-nitrothioanisole, approximately the concentration formed in a typical kinetic experiment, and the fluorescence intensity was measured.

Results

The reaction of 1 in aqueous oxyanion buffers (hydroxide, carbonate, borate, hexafluoro-2-propanol, phosphate, and acetate) was studied over a wide pH range at 40 °C and over a more limited pH range (ca. 10–13, using carbonate and hydroxide) at several lower temperatures. The reaction observed proceeds according to Scheme III (k_{ROH} , k_{GB} , or k_{RO^-} depending on buffer used and pH, see below). The dimethyl analogue 3 of 1 reacts in a similar fashion but at a much faster rate. In contrast to the behavior of these phenols, the methyl ether 2 is inert under the same conditions.

Shown in Figure 1 are the pH-rate profiles for the decomposition of 1 and 3 at 40 °C in aqueous oxyanion buffers (borate data omitted, see Discussion). Such profiles fit a general rate law (eq 4), where k_0 is the observed rate constant extrapolated to zero

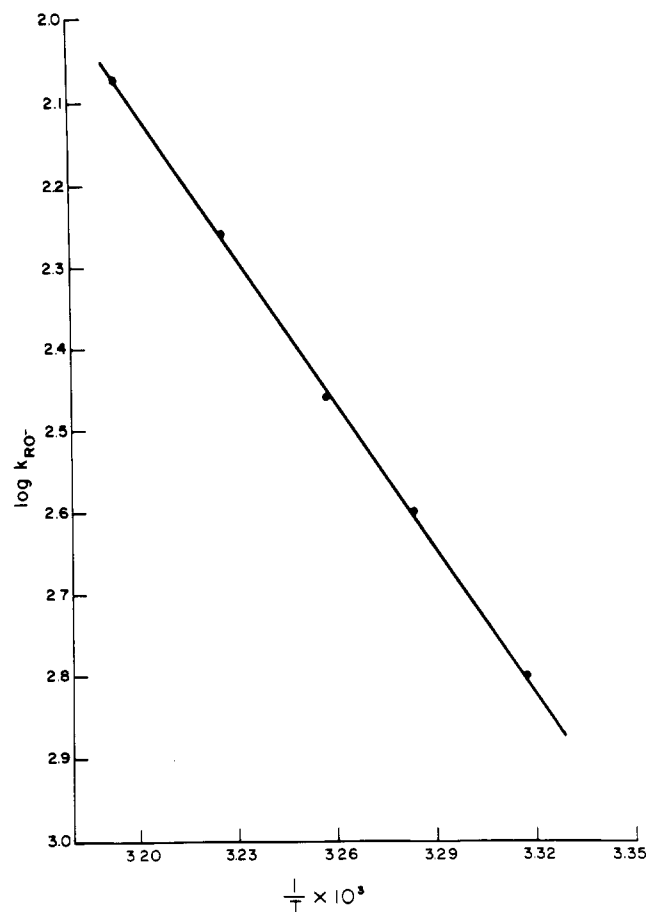


Figure 2. Arrhenius plot constructed from the data given in Table I.

$$k_0 = k_{H_2O} + k_{OH^-}[OH^-] \quad (4)$$

total buffer (B_T) concentration. The data presented in Figure 1 indicate that the reaction of 1 is pH independent at low pH (lower plateau of pH profile) and becomes pH dependent at pH > ca. 6. This pH dependent (slope = 1.0) region gives way to an upper plateau on the profile which is associated with the k_{OH^-} term of eq 4. As in the case of the cyclopentanol sulfonium, discussed in a prior publication,¹ the apparent k_{H_2O} and k_{OH^-} terms in eq 4 are associated with the phenolic hydroxyl of 1 and 3.

The data obtained are consistent with a rate law of the type given in eq 5, where K_a refers to the dissociation constant of the

$$k_0 = k_{ROH} \left[\frac{a_H}{K_a + a_H} \right] + k_{RO^-} \left[\frac{K_a}{K_a + a_H} \right] \quad (5)$$

phenolic groups of 1 or 3. Estimates of the pK_{app} of 1 at various temperatures have been made by determining the rates of reaction of 1 at high pH (k_{RO^-}) in hydroxide or carbonate/bicarbonate buffer. A determination of the pH at the "break point", and hence pK_{app} ,¹¹ was achieved after obtaining the best fit of the data to a curve having a particular theoretical pK_a . From the data obtained for 1, pK_a values from such kinetic measurements and the values of k_{RO^-} at each temperature are given in Table I. An Arrhenius plot of these data are given in Figure 2. Such a plot allows estimation of the following activation parameters for the k_{RO^-} reaction: $E_a = 26.7$ kcal/mol, $\Delta G^\ddagger = 21.5$ kcal/mol, $\Delta H^\ddagger = 25.6$ kcal/mol, and $\Delta S^\ddagger = +13.6$ eu. At 40 °C, values of $k_{ROH} = 4.0 \times 10^{-7} s^{-1}$ and $k_{RO^-} = 2.9 \times 10^{-6} s^{-1}$ for 1 and 3, respectively, were obtained from the low pH data of Figure 1 to give an initial

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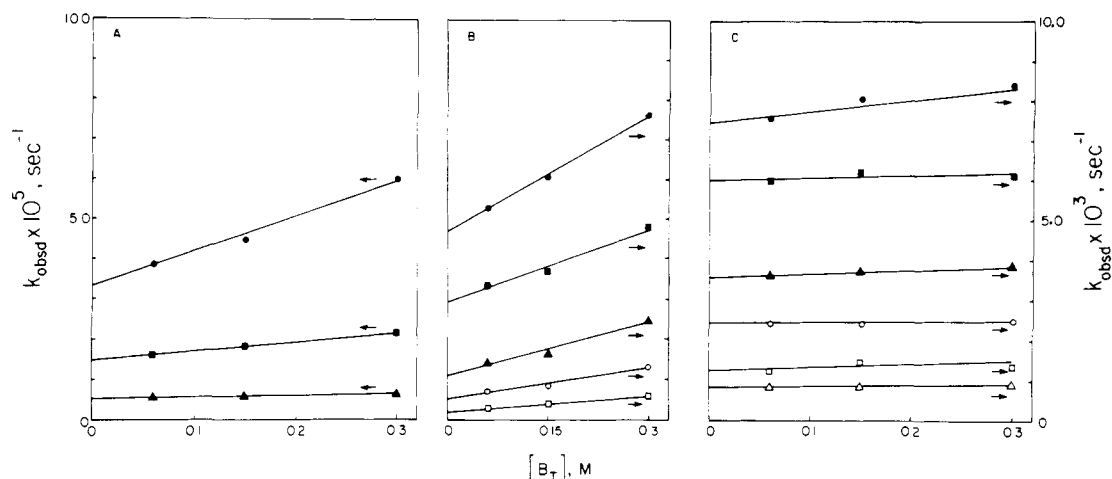


Figure 3. The effect of total buffer (B_T) on the observed rate of cyclization of **1**. Panel A, phosphate buffer: ●, [B]:[BH] = 9:1, pH 7.65; ■, [B]:[BH] = 3:1, pH 7.15; ▲, [B]:[BH] = 1:1, pH 6.65. Panel B, hexafluoro-2-propanol: ●, [B]:[BH] = 9:1, pH 10.20; ■, [B]:[BH] = 3:1, pH 9.84; ▲, [B]:[BH] = 1:1, pH 9.20; ○, [B]:[BH] = 1:2, pH 8.90; □, [B]:[BH] = 1:5, pH 8.50. Panel C, carbonate: ●, [B]:[BH] = 9:1, pH 10.70; □, [B]:[BH] = 3:1, pH 10.20; ▲, [B]:[BH] = 1:1, pH 9.80; ○, [B]:[BH] = 1:2, pH 9.50; □, [B]:[BH] = 1:5, pH 9.15; △, [B]:[BH] = 1:9, pH 8.95.

Table II. Second-Order Rate Constants for the Reactions of **1** and **3** in Oxyanion Buffers, at 40 °C^a

buffer	pK_a	$k_B, s^{-1} M^{-1}$	
		1	3
formate	3.35	^b	2.74×10^{-6}
acetate	4.76	3.14×10^{-7}	3.20×10^{-5}
phosphate	6.54	9.66×10^{-5}	3.56×10^{-3}
borate ^c	8.90	1.65×10^{-2}	
hexafluoro-2-propanol	9.22	2.95×10^{-2}	

^a Rate constants determined by using eq 6–8. ^b Not determined.

^c Borate buffer data not used in Brønsted plot (Figure 4). See text.

value, which was refined by an iterative fit to eq 5. Because of the rapid rate of reaction **3** at pH > 8, values of k_{RO^-} and pK_{app} could not be obtained directly from the experimental data. These values were obtained by assuming a value of pK_{app} for **3** equal to that obtained experimentally for **1** and then fitting the data of Figure 1 to eq 5 to obtain $k_{RO^-} = 6.3 \times 10^{-1} s^{-1}$ for **3**. A similar method was used in our earlier work with the cyclopentanol system,¹ in which a pK_a estimated at ca. 16 made it impossible to obtain a direct measure of k_{RO^-} .

The data presented herein indicate that both **1** and **3** are subject to general-base catalysis by oxyanion buffers in aqueous solution (k_{GB} , Scheme III). Such buffer catalysis is most easily demonstrated when the pK_a of the buffer is significantly lower than that of the substrate (**1**, pK_a 9.97 at 40 °C). This is seen in the plots of raw data (k_{obsd} vs. total buffer concentration) given in Figure 3 for the reaction of **1** in either phosphate, hexafluoro-2-propanol, or carbonate, at 40 °C. With both phosphate and hexafluoro-2-propanol, increasing the ratio of basic to acidic buffer species results in a steeper slope, indicating catalysis by the basic species. Similar behavior is seen with acetate and borate buffers (data not shown). However, the effects seen with borate buffer may not involve simply general-base catalysis (see Discussion). General-base catalysis is also seen in the reactions of **3** with formate, acetate, and phosphate buffers (data not shown). The inability to observe general-base catalysis with carbonate buffer is due to the fact that the pK_a of carbonate (9.78 at 40 °C) is quite similar to that estimated for **1** (9.97 at 40 °C). All oxyanion buffers having a pK_a less than that of **1** acted as general-base catalysts for the reaction of **1**.

Due to the increasing proportion of k_{RO^-} (scheme III) relative to k_{GB} at pH > ca. 7, eq 6–8 were used to derive a second-order

$$k_{obsd} - k_0 = \frac{k_B[B]a_H}{a_H + K_{a1}} + \frac{k_{BH}[BH]a_H}{a_H + K_{a1}} \quad (6)$$

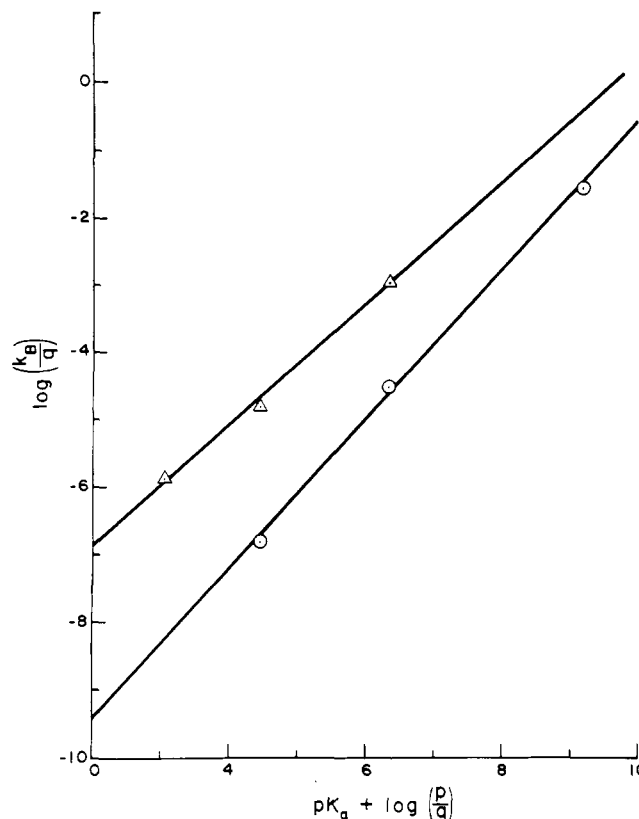


Figure 4. Brønsted plots constructed from the data given in Table II for **1** (○) and **3** (△). Statistical corrections, according to the procedure of Bell,¹⁸ have been applied to the values given in Table II.

$$k_{obsd} - k_0 = \left(\frac{k_B[BH]K_{a2}}{a_H} + k_{BH}[BH] \right) \frac{a_H}{a_H + K_{a1}} \quad (7)$$

$$\left(\frac{k_{obsd} - k_0}{[BH]} \right) \left(\frac{a_H + K_{a1}}{a_H} \right) = \frac{k_B K_{a2}}{a_H} + k_{BH} \quad (8)$$

rate constant (k_B) for all buffers. In these equations [B] and [BH] are the concentration of the basic and acidic buffer species, respectively. K_{a1} and K_{a2} are the dissociation constants of the substrate **1** or **3** and the buffer, respectively. For the buffer, K_{a2} was determined from pK_{a2} , the pH of a solution containing a 1:1 ratio of basic to acidic species, [B]:[BH], at 40 °C. The rate

Table III. Summary of the Reaction of 1 in Amine Buffers, at 40 °C

amine ^a	B _T , M	B/BH ^b	pH	<i>k</i> _{obsd} , s ⁻¹	<i>k</i> ₀ , s ⁻¹	% formed ^c	
						7	6
NBA	0.50	9/1	11.34	1.13 × 10 ⁻²	8.99 × 10 ⁻³	0	100
	0.25	9/1	11.31	1.04 × 10 ⁻²		0	100
	0.10	9/1	11.30	9.34 × 10 ⁻³		0	100
NBA	0.50	3/1	10.88	1.04 × 10 ⁻²	8.34 × 10 ⁻³	0	100
	0.25	3/1	10.86	9.46 × 10 ⁻³		0	100
	0.10	3/1	10.89	8.70 × 10 ⁻³		0	100
NBA	0.50	1/1	10.36	8.68 × 10 ⁻³	7.79 × 10 ⁻³	0	100
	0.25	1/1	10.35	8.29 × 10 ⁻³		0	100
	0.10	1/1	10.37	7.95 × 10 ⁻³		0	100
NMM	1.00	9/1	8.71	4.08 × 10 ⁻⁴	3.99 × 10 ⁻⁴	6.1	93.9
	0.50	9/1	8.73	4.03 × 10 ⁻⁴		3.5	96.5
	0.20	9/1	8.73	4.02 × 10 ⁻⁴		1.0	99.0
NMM	1.00	3/1	8.23	1.80 × 10 ⁻⁴	1.43 × 10 ⁻⁴	18.4	83.6
	0.50	3/1	8.27	1.60 × 10 ⁻⁴		8.6	91.4
	0.20	3/1	8.26	1.51 × 10 ⁻⁴		2.2	97.8
NMM	1.00	1/1	7.72	8.31 × 10 ⁻⁵	5.63 × 10 ⁻⁵	46.9	53.1
	0.50	1/1	7.75	6.93 × 10 ⁻⁵		32.6	67.4
	0.20	1/1	7.78	6.18 × 10 ⁻⁵		24.0	76.0
DMHA	0.50	3/1	5.23	1.05 × 10 ⁻⁵	2.33 × 10 ⁻⁷	37.9	62.1
	0.25	3/1	5.22	4.96 × 10 ⁻⁶		38.5	61.5
	0.10	3/1	5.21	2.48 × 10 ⁻⁶		36.0	64.0
DMHA	0.50	1/1	4.77	5.93 × 10 ⁻⁶	5.97 × 10 ⁻⁷ ^d	42.8	57.2
	0.25	1/1	4.75	3.27 × 10 ⁻⁶		30.9	69.1

^a Abbreviations: NBA, *n*-butylamine; NMM, *N*-methylmorpholine, DMHA, *N,O*-dimethylhydroxylamine. ^b Ratio of basic to acidic buffer species. ^c Detected by LC analysis, see Experimental Section. ^d Some uncertainty is attached to this value because only two data points were available for its estimation.

constants *k_B* and *k_{BH}* refer to the portion of the total reaction catalyzed by, respectively, the basic and acidic species. The hydrogen ion activity (*a_H*) was calculated from the pH of the particular kinetic run. For each ratio of [B]:[BH] the pH value was taken to be that of the highest buffer concentration, B_T. The observed rate constants, *k_{obsd}*, were corrected for any change in initial buffer pH due to dilution at constant [B]:[BH]. This is especially critical in the transition region of the profile, between the low pH and high pH plateaus, where the mole fraction of the more reactive phenolate is extremely sensitive to any change in pH. The desired rate constant, *k_B*, was obtained directly as the slope by a plot of the data according to eq 8. The rate constant for catalysis by the acidic species, *k_{BH}*, was obtained from the *y* intercept of the plot. In these plots, the *y* intercepts were zero or had a slight negative value; i.e., *k_{BH}* ≤ 0. The values of *k_B* obtained by this procedure are given in Table II, and a Brønsted plot of these data is given in Figure 4 (*β* = 1.1 (1), *β* = 0.89 (3)).

The reactions of 1 in the presence of amine buffers (*N,O*-dimethylhydroxylamine, *N*-methylmorpholine, and *n*-butylamine) were also studied. The data obtained with these three buffers are given in Table III. It is apparent from these data that no buffer catalysis occurs with *n*-butylamine and very little with *N*-methylmorpholine (9:1 and 3:1 buffer ratios), presumably because at the pH of these solutions, the amount of 1 in the phenol form is low relative to that in the ionized (phenoxide) form. Therefore, from Scheme III, *k_{RO}*⁻ is larger than *k_{Nuc}*. On the basis of our earlier studies,¹ such behavior is expected.

In order to substantiate the mechanisms proposed in Scheme III, product analyses were carried out on both oxyanion and amine runs. As described in the Experimental Section, a fluorometric procedure was used to identify both chroman (4) and 4,4-dimethylchroman (5). HPLC was used for the identification of the thioethers 6–8. Chroman (4) was detected by both the fluorometric and LC assay in the kinetic runs following the reaction of 1, and the dimethylchroman, 5, was detected by the fluorometric assay in the kinetic runs following reaction of 3, with all the oxyanions studied. LC analysis also indicated that, in oxyanion buffers, *p*-nitrothioanisole, 6, was the only sulfide present following reaction of 1 and 3. The absence of 7 or 8 indicates that neither 1 nor 3 are S-demethylated in oxyanion buffers. A spectrophotometric determination, utilizing *ε* for both 4 and 6, indicated that these compounds are formed in essentially stoichiometric amounts in a kinetic experiment. Such data establish the mechanism of

decomposition of 1 and 3 depicted in Scheme III for oxyanion buffers.

Included in Table III are data on product analyses (identification of 6 and 7 only) of the reaction mixtures following reaction of 1 in amine buffers. No demethylation is observed with 1 in *n*-butylamine buffer, consistent with the observation of no buffer catalysis, and very little demethylation is seen when either the 9:1 or 3:1 ratios of *N*-methylmorpholine are studied. A significant amount of demethylation occurs only with *N*-methylmorpholine (1:1 ratio) and *N,O*-dimethylhydroxylamine. Apparently at the pH of the latter kinetic runs, the contribution of *k_{RO}*⁻ is lowered to a point where only *k_{ROH}* is operating (to give cyclization to 4) and at this point *k_{Nuc}* will effectively compete with *k_{ROH}*, leading to a mixture of products.

To further characterize the products of the reactions of 1 in either oxyanions or amine buffers, the preparative experiments described in the Experimental Section were carried out. The results from these experiments are summarized in Table IV. These data, together with the fluorescence and LC results described above, further substantiate the mechanisms presented in Scheme III, i.e., general-base catalysis by added oxyanion buffers vs. nucleophilic demethylation by amines.

Discussion

We have previously shown that nucleophilic displacement reactions at sp³ carbon can be catalyzed by general bases such as oxyanion buffers.¹ Our initial work was limited to the intramolecular alkylation of a cyclopentanol by an alkyl sulfonium. In the work described above, we have extended this observation to a phenolic system; viz., 1 and 3, in which we are able to study possible buffer effects on both the neutral (*k_{ROH}*) and ionized (*k_{RO}*⁻) form of the substrate. As expected for general-base-catalyzed proton abstraction, no buffer catalysis of the reaction of the phenolate substrate (*RO*⁻) is observed. In contrast, reaction of the neutral substrate (*ROH*) is catalyzed by oxyanions, in a manner reminiscent of the general-base catalysis observed with the cyclopentanol system.¹ A significant difference between these two rare examples of general-base-catalyzed S_N2 reactions, is the value of *β* = ca. 1.0 for the phenols (Figure 4) vs. *β* = 0.3 for the cyclopentanol previously studied by us. Based on the wealth of data available for reactions at sp² carbon,¹² one could conclude

Table IV. Summary of the Results of Preparative Kinetic Experiments

reaction soln	amount of substrate (1)	amounts recovered ^b		
		4	6	7
0.1 N KOH	1.0 mmol (391 mg)	0.85 mmol (114 mg)	0.87 mmol (147 mg)	
1:1 NMM ^a	0.50 mmol (196 mg)	0.25 mmol (33 mg)	0.23 mmol (38 mg)	0.28 mmol (82 mg)

^a Indicates that the solution is *N*-methylmorpholine with the basic and acidic species present in a 1:1 ratio ($B_T = 1.0$ M). ^b After elution from preparative TLC plates, see Experimental Section.

that a value of $\beta = 1.0$ suggests a mechanism in which proton transfer from the substrate to the base catalyst is virtually complete in the transition state. However, examples of general-base catalysis of reaction at sp^3 carbon are so rare that more data with different systems must be obtained before drawing definitive conclusions about the nature of the transition state from β values only. Nonetheless, the fact that the anisole derivative **2** is completely inert in oxyanion buffers under conditions where **1** and **3** are rapidly converted to the chromans (**4** and **5**) and *p*-nitrothioanisole (**6**) indicates that proton removal is of critical importance both in the reactions of phenols **1** and **3** reported here and in the reaction of the cyclopentanol derivative reported previously. The difference in the acidity of the proton being removed in the phenol ($pK_a = \text{ca. } 10$) vs. the cyclopentanol ($pK_a = \text{ca. } 16$) is reflected in the different sensitivity toward catalysis by general bases ($\beta = 1.0$ vs. 0.3). Thus, in the absence of data supporting unusually high β values for general-base catalysis of reactions at sp^3 carbon such as observed with reactions involving carbon acids,¹³ we conclude that a value of $\beta = 1.0$ indicates a transition state in which proton abstraction is nearly complete in the case of the phenols **1** and **3** vs. a transition state in which proton transfer is only partially complete in the case of the less acidic cyclopentanol.

The Brønsted β values discussed above were derived from data obtained by using acetate, phosphate, and hexafluoro-2-propanol as buffers for **1** and with formate, acetate, and phosphate as buffers for **3**. Although carbonate ($pK_a = 9.78$) buffer was also employed in studies with **1**, data such as shown in Figure 3 revealed little, if any, general-base catalysis by carbonate, as expected when the buffer $pK_a \approx$ substrate pK_a . When borate ($pK_a = 8.9$) was used as a buffer with **1**, apparent general-base catalysis was observed with $k_B = 1.65 \times 10^{-2}$. This value of k_B is exactly as predicted from the Brønsted equation for this reaction (Figure 4). However, the k_0 values obtained by extrapolation to zero borate buffer concentration at higher pH are not in accord with values of k_0 obtained over a wide range of pH using other buffers (Figure 1). Although k_0 derived from data obtained at pH 8.9, (1:1 base:acid form of buffer) fits the general rate equation of eq 5, data obtained at higher pH 9.5–10.0 (3:1 and 9:1 base:acid) deviate negatively by up to twofold from the predicted value. Therefore, the apparent rate of the non-buffer-catalyzed (lyate) reaction is decreased in the presence of increasing amounts of borate anion. HPLC analysis of the borate reaction solutions showed formation of only the chroman, **4**, and *p*-nitrothioanisole, **6**, as was observed with all other oxyanion buffers. A satisfactory explanation for this anomalous behavior is not readily apparent. Therefore k_0 and k_B values obtained by using borate buffer have not been included in data reduction to obtain values for k_{ROH} , k_{RO^-} , and β (Figures 1 and 3).

The use of amine buffers with phenol **1** was studied. Amines do not effect general-base-catalyzed cyclization to the chroman, **4**, and *p*-nitrothioanisole (**6**) but rather participate in the intermolecular dealkylation of **1** to give **7** (Table III). This is also in agreement with our previous results with the cyclopentanol system, although we have not studied the dealkylation reaction as extensively in the work reported here. The data of Table III show, however, that intermolecular dealkylation by a good nucleophile such as *n*-butylamine ($pK_a = 10.3$) cannot compete with the facile intramolecular reaction of the phenolate substrate ($k_{RO^-} = 8.58 \times 10^{-3} \text{ s}^{-1}$). As the pH is decreased and the ratio of phenolate to phenol decreases, apparent catalysis of the reaction by amine

buffers is observed. Product analysis data (Table III) show that this amine-mediated increase in k_{obsd} is accompanied by an increase in the amount of **7** formed. As pH is decreased, k_{ROH} becomes the major contributor to the lyate reaction, and this slower intramolecular rate ($k_{RO^-}:k_{ROH} = \text{ca. } 10^4$) can be challenged effectively by the intermolecular dealkylation by less basic amine buffers (e.g., *N*-methylmorpholine, $pK_a = 7.6$; *N,O*-dimethylhydroxylamine, $pK_a = 4.7$). As expected, the anisole derivative **2** is dealkylated by amine buffers to give **13**. In addition, however, as the concentration of amine (e.g., *N*-methylmorpholine) is decreased, the formation of *p*-nitrothioanisole (**6**) is observed to the exclusion of the dealkylated material **13**. Regardless of amine concentration, the reaction does not appear to go to completion, and large (50–75%) amounts of a *p*-nitrophenylsulfonium salt (λ_{max} 252 nm) are observed on UV scans of the kinetic runs. Although the detailed chemistry behind these observations has not been completely elucidated, it is clear that the methoxy group of **2** is participating in the reaction to produce **6**, presumably via a methyl oxonium derivative of **4**. The complexity of the reactions of **2** in amine buffers further emphasizes the importance of charge (i.e., proton) removal in the reactions of **1** and **3** in aqueous buffers.

The buffer-independent reaction of **1** and **3** have been studied over a wide range of pH at 40 °C (Figure 1) and over a more limited range of pH at lower temperatures (28–37 °C) in order to obtain the activation parameters described in the Results. (Table II, Figure 2). The values of k_{ROH} for **1** and **3** vs. the corresponding values of k_{RO^-} are consistent with the ΔpK_a of the conjugate acids, ROH_2^+ vs. ROH . A Brønsted plot of these data together with data obtained previously for the cyclopentanol system¹ leads to a value of $\beta_{Nuc} = 0.3$ (Figure 5). This β value for a series of intramolecular nucleophilic reactions is in good agreement with our previous results with intermolecular nucleophilic reactions,¹⁴ where a β value of 0.36 was obtained. β values of 0.14–0.41 have been reported for the general reactions, $Nuc: + CH_3X \rightarrow CH_3Nuc + X^-$, with the value depending on the nature of X and the solvent.¹⁵ The activation parameters obtained from the temperature dependence of k_{RO^-} show a very large $\Delta S^\ddagger = 13.6 \text{ cal/(deg mol)}$, in contrast to corresponding data in the cyclopentanol system, where $\Delta S^\ddagger = -3.7 \text{ cal/(deg mol)}$ for k_{RO^-} .¹ One interpretation of these data is that the phenolate ion is more heavily solvated than the cyclopentoxide ion, and extensive desolvation is required in going from the ground state to the transition state. Such desolvation would be associated with a large positive ΔS , apparently overcoming an otherwise negative ΔS^\ddagger . Data of this type do not shed much light on the large rate enhancements seen in both the present work with phenols **1** and **3** and in previous work with a cyclopentanol. Since the corresponding intermolecular reactions are extremely slow, it is difficult to calculate effective molarities¹⁶ with great accuracy. However, rough estimates on the cyclopentanol system,¹ and the phenols indicate that the effective molarities are both ca. 10^5 M, despite large differences in ΔS^\ddagger . More accurate rate data on the intermolecular reactions will be required to fully explore the basis for these enhancements.

General catalysis of S_N2 reactions, although rare, is not unprecedented. As mentioned in the introduction, the initial observation of this type of catalysis was by Swain, Kuhn, and Schowen² in the cyclization of 4-chlorobutanol to tetrahydrofuran.

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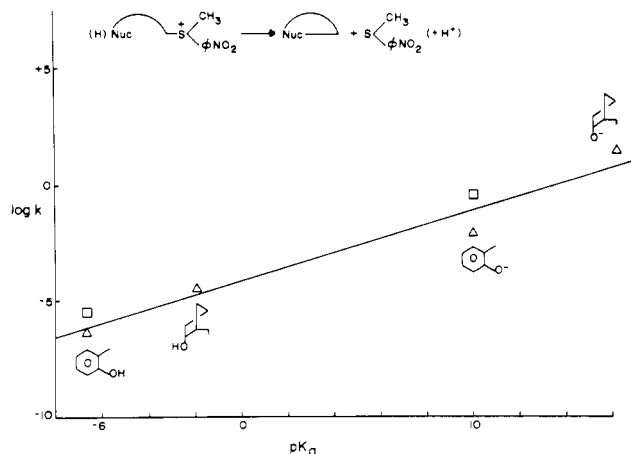
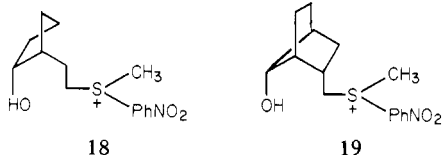


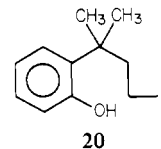
Figure 5. Brønsted plot of $\log k_{\text{ROH}}$ or $\log k_{\text{RO}^-}$ vs. $\text{p}K_{\text{a}}$ of the conjugate acid. $\text{p}K_{\text{a}}$ data: phenol, Arnett, E. M. *Prog. Phys. Org. Chem.* **1963**, *1*, 223; alcohol, Perdoncin, G.; Scorrano, G. *J. Am. Chem. Soc.* **1977**, *99*, 6983; phenoxide, this research; alkoxide, ref 1. In the phenol-phenoxide pairs, the dimethyl system (3) is indicated by open squares.

They observed catalysis by borate, but not by acetate, and presented a three-point Brønsted plot (H_2O , borate, OH^-) with $\beta = 0.25$. More recently, our studies with the cyclopentanol derivative **18** established general base catalysis by a variety of



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oxyanion buffers with $\beta = 0.27$. Subsequent studies by Irie and Tanida¹⁷ with **19** extended the observations of general base catalysis. An unusual finding in the latter study was the apparent catalysis by general acids (e.g., acetic acid); similar general-acid catalysis has not been observed in our studies of **18**. The present work has extended the observation of general-base catalysis of $\text{S}_{\text{N}}2$ reactions further by demonstrating the susceptibility of phenols such as **1** and **3** to this type of catalysis. Previous studies by Borchardt and Cohen³ failed to provide evidence for buffer catalysis in cyclization reactions of molecules of type **20**. The



$\text{X} = -\text{OSO}_2\text{CH}_3, -\text{OPO}(\text{OEt})_2, -\text{COOCl}_3$

main difference between **20** and the phenols (**1** and **3**) studied in the present work is the nature of the leaving group. The leaving groups in **20** are all negatively charged (from a neutral starting material), whereas the leaving group in **1** and **3** is neutral (from a previously charged starting material). Although slightly different reaction conditions prevailed in the studies with **20** (40% dioxane-60% H_2O) vs. the present work (100% H_2O), it is not clear why no general-base catalysis was observed in the reactions of **20**. Additional research will be required to delineate structural features which lead to general catalysis in $\text{S}_{\text{N}}2$ reactions. As part of this research effort, we have recently completed the synthesis of compounds which are similar to **3** but contain a poorer alkyl thioether leaving group (e.g., 5'-(methylthio)adenosine).

Acknowledgment. This research was supported by a grant from the United States Public Health Service, NIH.

Registry No. **1**, 81246-41-5; **2**, 81246-42-6; **3**, 81246-43-7; **4**, 254-04-6; **5**, 40614-27-5; **6**, 1849-36-1; **7**, 81246-44-8; **8**, 81246-45-9; **9**, 1481-92-1; **10**, 81246-46-0; **11**, 10493-37-5; **12**, 81246-47-1; **13**, 81246-48-2; **14**, 40614-20-8; **14** 1-mesylate, 40614-15-1; **14** 1-tosylate, 81255-45-0; **15**, 81246-49-3; **16**, 81246-50-6; **17**, 81246-51-7; 3,4-dihydrocoumarin, 119-84-6.

Molecular Structures of Nucleosides and Nucleotides. 2. Orthogonal Coordinates for Standard Nucleic Acid Base Residues

Robin Taylor* and Olga Kennard*¹

Contribution from the Crystallographic Data Centre, University Chemical Laboratory, Cambridge CB2 1EW, England. Received July 27, 1981

Abstract: A least-squares minimization procedure was used to derive orthogonal coordinates for "standard" nucleic acid base residues. The dimensions of the standard residues are as close as possible to the average dimensions observed in crystal structures, subject to the necessity for ring closure. The residues were assumed to be precisely planar, and an examination of 67 nucleoside and nucleotide crystal structures suggests that this assumption is justified.

The use of "standard" nucleic acid base residues has many applications in model-building calculations and in the determination, refinement, and interpretation of nucleoside and nucleotide crystal structures.² In the present context, a standard residue is defined as one whose molecular dimensions are as close as possible to the average dimensions observed in crystal structures, subject to the necessity for ring closure. The standard residues

in current use are generally derived from mean bond lengths and valence angles reported by Voet and Rich in 1970.³ The large number of structure determinations that have appeared in the literature since then has prompted a recent redetermination of these values,⁴ using 90 crystal structures⁵ retrieved from the

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