Kinetic and Thermodynamic Barriers to Carbon and Oxygen Alkylation of Phenol and Phenoxide Ion by the 1-(4-Methoxyphenyl)ethyl Carbocation

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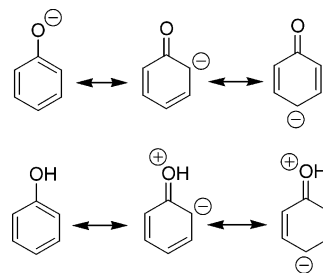
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Abstract: Rate constant ratios for addition of the three nucleophilic sites of phenol to the 1-(4-methoxyphenyl)ethyl carbocation (1^+) in 50/50 (v/v) trifluoroethanol/water were determined from the relative yields of the three phenol adducts, and absolute rate constants were determined from product rate constant ratios for addition of phenol and azide ion to 1^+ using $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-limited reaction of azide ion. A selectivity of 230:20:1 was determined for alkylation of phenol at oxygen, C-4 and C-2 to form **1-OPh** and biphenyls **1-(4-C$_6$H$_4$OH)** and **1-(2-C$_6$H$_4$OH)**, respectively, and of 2:2:1 for alkylation of the corresponding nucleophilic sites of phenoxide ion in diffusion-limited reactions. The Mayr nucleophilicity parameter for C-4 of phenol is $N = 2.0$. Encounter-limited addition of phenoxide ion to 1^+ to form **1-OPh** is faster than encounter-limited addition of oxygen anions that are either more or less basic than phenoxide ion. Only the products of solvolysis are observed from acid-catalyzed cleavage of **1-OPh** in 50/50 (v/v) trifluoroethanol/water, but a 50% yield of biphenyls **1-(4-C$_6$H$_4$OH)** and **1-(2-C$_6$H$_4$OH)** are observed from spontaneous cleavage of **1-OPh**, where the leaving group is phenoxide ion, because of the very low kinetic barriers to collapse of the ion pair intermediate **1$^+$·PhO$^-$**. The 230-fold larger rate constant for O-compared to C-2-alkylation of phenol is due primarily to the larger thermodynamic driving force for oxygen addition. There are similar Marcus intrinsic barriers for these two reactions.

Introduction

The reactivities of phenol and phenoxide ion are strongly affected by the delocalization of an electron pair from oxygen onto the aromatic ring (Scheme 1), which causes a decrease in the basicity of the phenol oxygen and an increase in the basicity of the o- and p-carbons. This change in the relative basicity of carbon and oxygen is not large enough to cause a change in the *preferred* site for addition of the proton, a "hard"[1,2] electrophile, to phenoxide ion. However, alkyl and benzyl halides[3-7] and carbocations,[8-11] which are "softer" carbon electrophiles,
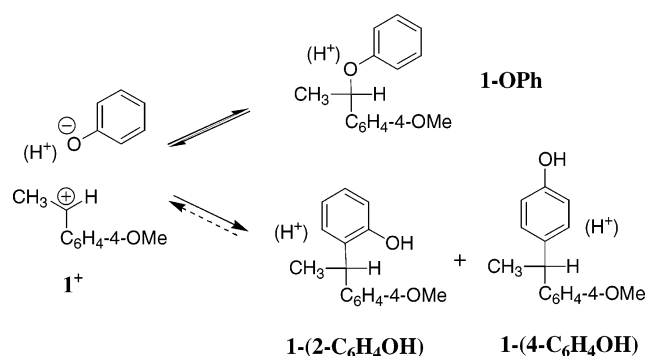

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Scheme 1

react at comparable rates to alkylate both the "hard" oxygen and the "softer" ortho and para ring carbons of phenoxide ion.

Only qualitative conclusions about the underlying cause for the large carbon nucleophilicity of phenol toward carbon electrophiles have been drawn in earlier work. Several studies on ambident carbon and oxygen alkylation of phenoxide ion have focused on characterizing the solvent and salt effects on the relative barriers to bimolecular nucleophilic substitution reactions of these nucleophilic sites with benzyl and allyl halides.[4-7] A thorough modern study has probed the importance of antihydrophobic cosolvent effects in determining the relative barriers to O- versus C-alkylation for bimolecular substitution of phenoxide at the water-soluble electrophile *p*-carboxybenzyl chloride.[3] There have been few studies of ambident nucleophilic addition of phenol and phenoxide ion to carbocations,[8-11] and none to

Scheme 2

dissect the underlying cause for the high basicity of carbon compared with oxygen toward these reactive carbon electrophiles.

The 4-methoxybenzyl and 1-(4-methoxyphenyl)ethyl carbocations have been generated as intermediates of solvolysis[12,13] and photochemical reactions,[14,15] and have been shown to be sufficiently stabilized by electron-donation from the 4-methoxybenzyl ring to diffuse through aqueous solution. Studies to characterize the rate and equilibrium constants for formation and reaction of these carbocations in aqueous solvents have provided a large body of information on the mechanism for solvolysis and carbocation−nucleophile combination reactions.[12,13,16−18]

1-(4-Methoxyphenyl)ethyl phenyl ether (**1-OPh**) undergoes acid-catalyzed cleavage to form phenol and the 1-(4-methoxyphenyl)ethyl carbocation (**1$^+$**); and, **1$^+$** generated by cleavage of 1-(4-methoxyphenyl)ethyl substituted benzoates is trapped by phenol to form **1-OPh** in a reaction that is catalyzed by Brønsted bases.[12,17] We report here the results of a comprehensive study of the spontaneous and acid-catalyzed cleavage of **1-OPh**; and, of carbon and oxygen alklyation of phenol and phenoxide ion by **1$^+$** (Scheme 2). We also report the high-level ab initio calculation of the equilibrium constant for isomerization of **1-OPh** to **1-(2-C$_6$H$_4$OH)** in water. This could not be obtained by experiment, but is needed for a complete description of the rate and equilibrium constants for C- and O-alklyation of phenol by **1$^+$**.

These data provide a thorough description of this important organic reaction, which includes the following: (1) a second relatively rare example of an organic carbon nucleophile, phenoxide ion, with a reactivity toward carbocations that is similar to that of the strong inorganic nucleophile azide ion;[19,20] (2) a description of the relative thermodynamic driving forces and Marcus intrinsic barriers for ambient alkylation of phenol by the carbon electrophile **1$^+$** that is essential to an understanding of the ambident reactivity of this nucleophile; and (3) a unique comparison of the collapse of ion pairs generated by diffusional

encounter between the free ions **1$^+$** and PhO$^-$ and by the spontaneous solvolytic cleavage of **1-OPh**.

Experimental Section

Materials. Unless noted otherwise, inorganic salts and organic chemicals were reagent grade from commercial sources and were used without further purification. The water used for kinetic studies and HPLC analyses was distilled and then passed through a Milli-Q water purification system. Deuterium oxide (99.9+% D) was from Cambridge Isotope Laboratories and deuterium chloride (37wt %, 99.5% D) and CF$_3$CH$_2$OD (99.5% D) were from Aldrich.

Syntheses. The following compounds were prepared by published procedures: 1-(4-methoxyphenyl)ethanol (**1-OH**), 1-(4-methoxyphenyl)ethyl 3,5-dinitrobenzoate (**1-(3,5-dinitrobenzoate)**) and 1-(4-methoxyphenyl)ethyl 4-nitrobenzoate (**1-(4-nitrobenzoate)**).[12] The procedures for the synthesis of the following compounds are given in the Supporting Information: **1-OPh**, **1-(2-C$_6$H$_4$OH)**, and **1-(4-C$_6$H$_4$OH)**.

Preparation of Solutions. Aqueous solutions of 1.0 M sodium azide and sodium acetate were adjusted to pH ≈ 7 with concentrated HClO$_4$ before they were used to prepare mixed trifluoroethanol/water solvents. Solutions of 48/2/50 (v/v/v) trifluoroethanol/phenol/water that contained sodium acetate and/or sodium azide at $I = 0.50$ were prepared by mixing an aqueous solution of the salt (5−20 mM, $I = 1.0$ M, NaClO$_4$ and pH 7) with 96/4 (v/v) trifluoroethanol/phenol. The solutions of 96/4 (v/v) trifluoroethanol/phenol was prepared by mixing TFE at room temperature with liquid phenol at its melting point of 40 °C. Alkaline solutions of azide ion in 48/2/50 (v/v/v) trifluoroethanol/phenol/water were prepared by first mixing 1.0 M NaOH with an equal volume of 96/4 (v/v) trifluoroethanol/phenol and then adding to the resulting solution a measured volume of 48/2/50 (v/v/v) trifluoroethanol/phenol/water that contained 5 mM NaN$_3$ at $I = 0.50$ (NaClO$_4$). Buffered solutions of 50/50 (v/v) trifluoroethanol/water ($I = 0.50$, NaClO$_4$) were prepared by mixing aqueous solutions ($I = 1.0$, NaClO$_4$) which contain 40 mM of the specified buffer with an equal volume of trifluoroethanol.

Stock solutions of 50/50 (v/v) CF$_3$CH$_2$OL/L$_2$O (L = H, D) that contain LCl at $I = 0.50$ (NaClO$_4$) were prepared by mixing CF$_3$CH$_2$OL with an equal volume of L$_2$O that contained LCl ($I = 1.0$ NaClO$_4$). These stock solutions were diluted by mixing with 50/50 (v/v) CF$_3$CH$_2$OL/L$_2$O ($I = 0.5$ NaClO$_4$).

Product Studies. All product studies were at 25 °C. Reactions of **1-(3,5-dinitrobenzoate)** (2 mM) in 48/2/50 (v/v/v) trifluoroethanol/phenol/water were initiated by making a 100-fold dilution of the substrate, dissolved in acetonitrile, into the mixed solvent which contained 5 mM NaN$_3$ and acetate ion (2.5−10 mM). The product yields were determined several times over a 3 h reaction period.

Reactions of **1-(3,5-dinitrobenzoate)** (2 mM) in 48/2/50 (v/v/v) trifluoroethanol/phenol/water ($I = 0.5$, NaClO$_4$) which contained azide ion and increasing concentrations of the conjugate bases of solvent were initiated by making a 100-fold dilution of the substrate, dissolved in acetonitrile, into the mixed solvent. After 60 min. [ca. 2 halftimes for reaction of **1-(3,5-dinitrobenzoate)**], sodium phenoxide was neutralized by addition of 1 equiv acetic acid (2 M solution) and the product yields were determined by HPLC analysis. The solution contained 10 μM fluorene, which served as an internal standard to correct for small variations in the volume of the sample analyzed by HPLC.

The perchloric acid-catalyzed reaction of **1-OH** (0.25 mM) in 50/50 (v/v) trifluoroethanol/water that contained 0.5 M HClO$_4$ and 18 mM phenol was initiated by making a 100-fold dilution of the substrate, dissolved in acetonitrile, into the mixed solvent. The acid was neutralized by addition of one equivalent of sodium acetate (2 M solution) at measured reaction times and the product yields were determined by HPLC analysis. The reaction of **1-OPh** in 48/2/50 (v/v/v) trifluoroethanol/phenol/water that contained 0.012 M HClO$_4$ ($I = 0.5$, NaClO$_4$) was initiated by making a 100-fold dilution of the

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substrate in acetonitrile into the mixed solvent to give a final substrate concentration of 2 mM.

HPLC Analyses. The products of reactions of **1-Y** were separated by HPLC as described in previous work,[13,21,22] and detected by their UV absorbance at 274 nm which is λ_{max} for 1-(4-methoxyphenyl)-ethanol. The following compounds were identified by comparison with known standards: **1-OH**, **1-OCH₂CF₃**, **1-OPh**, **1-(4-C₆H₄OH)**, and 4-methoxystyrene. **1-(2-C₆H₄OH)** was identified as the additional peak observed upon HPLC analysis of a synthetic mixture of **1-(2-C₆H₄OH)** and **1-(4-C₆H₄OH)**.

Determination of Rate Constant Ratios and Equilibrium Constants. Ratios of product yields ([P₁]/[P₂]) from reactions at 25 °C were calculated from the ratio of peak areas determined by HPLC analysis (A_1/A_2) and the ratio of extinction coefficients, ($\epsilon_{P2}/\epsilon_{P1}$), at 274 nm using eq 1. The reproducibility of the product ratios from HPLC analysis was ± 10%

$$\frac{[P_1]}{[P_2]} = \left(\frac{A_1}{A_2}\right)\left(\frac{\epsilon_{P2}}{\epsilon_{P1}}\right) \tag{1}$$

$$\frac{k_{Nu1}}{k_{Nu2}} = \frac{[1 - Nu1][Nu2]}{[1 - Nu2][Nu1]} \tag{2}$$

Rate constant ratios for the reactions of nucleophiles Nu1 and Nu2 with **1-Y** were calculated directly from the ratios of product concentrations using eq 2 with the exception of the reactions of **1-(3,5-dinitrobenzoate)** described below. The following extinction coefficients at 274 nm in 70/30 (v/v) methanol/water were determined from the absorbance of known concentrations of synthetic standards [ϵ, (M⁻¹ cm⁻¹)]: **1-OH**, 1400; **1-OPh**, 2550; **1-(4-C₆H₄OH)**, 2850; 4-methoxystyrene, 11 000. The value of $\epsilon_{1-(2-C6H4OH)}/\epsilon_{1-(4-C6H4OH)} = 1.28$ at 274 nm was determined from the ratio of peak areas from HPLC analysis of a mixture of **1-(2-C₆H₄OH)** and **1-(4-C₆H₄OH)** and the ratio of the concentration of these compounds determined from the ratio of the ¹H NMR peak areas of the methine protons. Combining this ratio with $\epsilon = 2850$ M⁻¹ cm⁻¹ for **1-(4-C₆H₄OH)** gives $\epsilon = 3650$ M⁻¹ cm⁻¹ for **1-(2-C₆H₄OH)**. It has been shown that the extinction coefficients for **1-OH**, **1-OCH₂CF₃**, and **1-N₃** are identical at λ_{max} for **1-OH**.[12]

The yields of the products of reactions of **1-(3,5-dinitrobenzoate)** in 48/2/50 (v/v/v) trifluoroethanol/phenol/water ($I = 0.50$, NaClO₄) that contain 4−5 mM NaN₃ and increasing concentrations of lyoxide ion were determined by HPLC analysis. The final concentrations of CF₃CH₂O⁻ and PhO⁻ in this mixed solvent were determined by the following procedure.[23a]

$$(A_{1-OTFE})_{TFEO} = (A_{1-OTFE})_{obsd} - \left[\frac{(A_{1-OH})_{obsd}}{7.6}\right] \tag{3}$$

$$[CF_3CH_2O^-] = \left(\frac{(A_{1-OTFE})_{TFEO}}{(A_{1-N3})}\right)\left(\frac{k_{az}}{k_{TFE}^-}\right)[N_3^-] \tag{4}$$

(1) The concentration of [CF₃CH₂O⁻] was determined from the excess yield of **1-OCH₂CF₃** over that observed when [CF₃CH₂O⁻] = 0 M, using eqs 3 and 4 where, (a) The relative yields of **1-OH**, **1-OCH₂CF₃**, and **1-N₃** can be obtained directly from the relative product peak areas, which have the same extinction coefficient at 274 nm. (b) $(A_{1-OTFE})_{TFEO}$ is the area of the peak for **1-OCH₂CF₃** that forms from the reaction of CF₃CH₂O⁻. (c) $(A_{1-OTFE})_{obsd}$ is the observed area of the peak for **1-OCH₂CF₃** from HPLC analysis. (d) $(A_{1-OH})_{obsd}/7.6$ is the area of the peak for **1-OCH₂CF₃** that forms by reaction of neutral CF₃CH₂OH, calculated from the area of the peak for **1-OH** (A_{1-OH})

and a value of 7.6 for the ratio of the peak areas for **1-OH** and **1-OCH₂CF₃** determined for reaction in 50/50 (v/v) trifluoroethanol/water at neutral pH.[12] (e) (A_{1-N3}) is the area of the peak for **1-N₃**. (f) $k_{az}/k_{TFE}^- = 9$ is the rate constant ratio for addition of azide and trifluorethoxide ion to **1⁺**.[24]

(2) The concentration of phenoxide ion ([PhO⁻]) was then calculated as the difference between the concentration of NaOH used in preparing the mixed solvent, and the value of [CF₃CH₂O⁻] determined from eq 3 and 4.

The reaction of **1-OPh** (2 mM) in 48/2/50 (v/v/v) trifluoroethanol/phenol/water which contained 0.012 M HClO₄ ($I = 0.5$, NaClO₄) was monitored by HPLC analysis until the ratio of the areas for **1-OCH₂CF₃** to **1-OPh** remained constant with time. The equilibrium constant for the conversion of **1-OCH₂CF₃** to **1-OPh** was determined from eq 5, where ([**1-OPh**]/[**1-OCH₂CF₃**])ₑq is the ratio of concentrations of the phenyl and trifluoroethyl ethers observed at chemical equilibrium. The perchloric acid-catalyzed reaction of **1-OH** (0.25 mM) in 50/50 (v/v) trifluoroethanol/water that contained 0.5 M HClO₄ and 18 mM phenol was monitored for several days, until **1-OCH₂CF₃** had undergone quantitative conversion to **1-(4-C₆H₄OH)** and **1-(2-C₆H₄OH)**. Upper limits for the ratio of the concentrations of the C-alkylated phenol adducts and trifluoroethyl ether were calculated using the lowest level of **1-OCH₂CF₃** detectable by HPLC analysis.

Kinetic Studies. The specific acid-catalyzed solvolysis reactions of **1-OPh** at 25 °C in 50:50 (v:v) trifluoroethanol/water were initiated by making a 100-fold dilution of a solution of substrate dissolved in acetonitrile into the mixed solvent containing acetonitrile to give a final concentration of 0.4 mM. The reaction progress was monitored spectrophotometrically at 25 °C by following the increase in absorbance at 269 nm. First-order rate constants, k_{obsd} (s⁻¹), for solvolysis were determined as the slopes of semilogarithmic plots of reaction progress against time, which in all cases were linear for at least three-halftimes.

$$K_{eq} = \left(\frac{[1 - Nu]}{[1 - OCH_2CF_3]}\right)_{eq}\left(\frac{[CF_3CH_2OH]}{[PhOH]}\right) \tag{5}$$

$$\left[\frac{\sum (A_P/\epsilon_P)}{(A_S)_i/\epsilon_S}\right] = \frac{\sum [P]}{[S]_o} = k_{obsd}t \tag{6}$$

The reactions of **1-OPh** (2 mM) in 50/50 (v/v) trifluoroethanol/water that contained 20 mM sodium carbonate or sodium phosphate buffer were monitored by HPLC, using ca. 10 μM of the internal standard fluorene to correct for small variations in the sample volume analyzed by HPLC. First-order rate constants, k_{obsd} (s⁻¹) were determined as the slopes of linear plots of reaction progress against time over the first 2−8% of the reaction using eq 6 where; (a) $\Sigma(A_P/\epsilon_P)$ is the sum of the concentrations of all of the reaction products, calculated from their respective HPLC peak areas (A_P) and extinction coefficients (ϵ_P) at 274 nm, and (b) $(A_S)_i/\epsilon_S$ is the initial concentration of the substrate **1-OPh**.

Ab Initio Calculations. The relative energies of **1-OPh** and **1-(2-C₆H₄OH)** were determined by ab initio calculations using *Gaussian 92.4*.[25] The geometries of the two species were fully optimized at the Hartree−Fock (HF) level using the 6-31G(d) basis set.[26] The two structures were fully characterized as energy minima by vibrational

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(22) Difficulties were experienced in obtaining baseline separation of the large peak for phenol cosolvent from the peaks for the reaction products which were present in much smaller concentrations. Satisfactory separations were observed using the relatively large substrate concentration of 2 mM **1-(3,5-dinitrobenzoate)** and a 10 μL injection volume.

(23) (a) These solutions were prepared by adding sodium hydroxide to a large excess concentration of phenol (0.23 M, pK_a = 10.0) and trifluoroethanol (6.6 M, pK_a = 12.4). The conversion of hydroxide ion to trifluoroethoxide and phenoxide ion was essentially quantitative, because phenol and trifluoroethanol are much stronger acids than water (pK_a = 15.7). (b) The apparent rate constant ratios for addition of water and azide ion to **1-OPh** to form **1-OH** and **1-N₃** respectively, calculated from data in Table 1, remain constant within the experimental error (± 10%) as [NaOH]ₜ is increased from 0 to 0.083 M. This shows that there is no significant formation of **1-OH** by (i) Addition of hydroxide ion to the carbocation reaction intermediate **1⁺**,[12] because there is essentially quantitative protonation of hydroxide ion by phenol and trifluoroethanol and (ii) Addition of solvent anion (hydroxide, trifluoroethoxide or phenoxide ion) to the carbonyl group of **1-(3,5-dinitrobenzoate)**.
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Table 1. Yield of Products Determined by HPLC Analyses of the Reaction of **1-(3,5-Dinitrobenzoate)** in 48/2/50 (v/v/v) TFE/PhOH/H$_2$O in Basic Solutions that Contain Azide Ion[a]

[N$_3^-$] M	[NaOH]$_t$ M[b]	[PhO$^-$] M[c]	1-OH %	1-OCH$_2$CF$_3$ %	Styrene[d] %	1-N$_3$ %	1-OPh %	1-(2-C$_6$H$_4$OH) %	1-(4-C$_6$H$_4$OH) %
0.005	0	0	55.9	7.5	0.021	32.1	4.2	0.018	0.21
0.0049	0.0083	0.0079	42.4	5.8	0.11	21.9	13.6	5.8	10.5
0.0048	0.017	0.0132	31.5	5.5	0.17	16.7	19.8	9.3	17.0
0.0047	0.033	0.027	25.0	4.9	0.21	10.6	24.6	12.3	22.4
0.0042	0.083	0.058	12.6	5.2	0.29	5.3	31.1	16.4	29.0

[a] For reactions at 25 °C in 50/50 (v/v) trifluoroethanol/water (I = 0.50, NaClO$_4$). [b] [NaOH]$_t$ is the concentration, after dilution, of sodium hydroxide used to prepare this solution. [c] The concentration of phenoxide ion that is formed by deprotonation of hydroxide ion, calculated as described in the text. [d] 4-Methoxystyrene.

frequency calculations. In both cases, the computed harmonic vibrational frequencies are all positive. Electron correlation effects were included through single-point energy calculations at the hybrid DFT B3LYP/6-31G(d) level[27,28] using the HF/6-31G(d) geometries. Solvation effects were examined using the isodensity surface polarizable continuum model (IPCM) by single-point energy calculations at the B3LYP/6-31G(d)//HF/6-31G(d) level.[29] A dielectric constant of 78.4 was used to represent the solvent water.

Results

The product yields from the reaction of 2 mM **1-(3,5-dinitrobenzoate)** in 48/2/50 (v/v/v) trifluoroethanol/phenol/water (I = 0.50, NaClO$_4$) that contained 5.0 mM NaN$_3$ and either 5 mM or 10 mM NaOAc were determined by HPLC analyses and are reported in Table 1. These product yields were determined after one to two reaction halftimes, at which point no more than 10% of the azide ion was consumed in forming the azide ion adduct **1-N$_3$**.[22] The slow cleavage of **1-OPh** catalyzed by the 3,5-dinitrobenzoic acid product was noted in early experiments. Therefore, these reactions were run in the presence of a small concentration of acetate ion in order to neutralize this carboxylic acid. **1-OPh** was stable under these reaction conditions. Identical product yields were observed for reactions in the presence 5.0 and 10 mM acetate ion.[30]

The yield of products from the reaction of **1-(3,5-dinitrobenzoate)** in solutions of 48/2/50 (v/v/v) trifluoroethanol/phenol/water (I = 0.50, NaClO$_4$) that contain 4−5 mM NaN$_3$ and increasing concentrations of phenoxide ion are also reported in Table 1. The basic solvents were prepared by mixing aqueous sodium hydroxide with 96/4 (v/v) trifluoroethanol/phenol. Table 1 reports values for [NaOH]$_t$, the concentration of NaOH (after dilution) used to prepare the mixed solvent. The concentrations of phenoxide ion in these solutions were then calculated as the difference between [NaOH]$_t$ and the value of [CF$_3$CH$_2$O$^-$] as described in the Experimental section.[23a,b]

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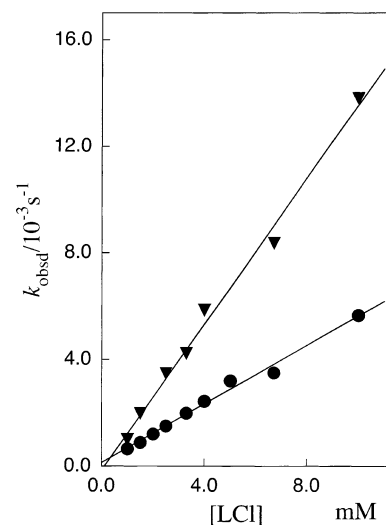(30) The yield in these reactions of **1-OAc** from the reaction of acetate ion was < 1%.

Figure 1. Effect of increasing concentrations of LCl on k_{obsd} (s^{-1}) for solvolysis of **1-OPh** in 50/50 (v/v) CF$_3$CH$_2$OH/H$_2$O (HCl, ●) and in 50/50 (v/v) (v/v) CF$_3$CH$_2$OD/D$_2$O (DCl, ▼) at 25°C and I = 0.50 maintained with NaClO$_4$.

The solvolysis of **1-OPh** was monitored by following the decrease in absorbance at 269 nm. Figure 1 shows the increase in k_{obsd} (s^{-1}) for solvolysis of **1-OPh** that was determined at increasing [HCl] or [DCl] for reactions in 50/50 (v/v) CF$_3$CH$_2$OH/H$_2$O (HCl) and in 50/50 (v/v) CF$_3$CH$_2$OD/D$_2$O (DCl) at 25°C (I = 0.50, NaClO$_4$). Values of k_H = 0.55 and k_D = 1.37 M^{-1} s^{-1} for specific-acid catalysis of solvolysis of **1-OPh** in H$_2$O and D$_2$O, respectively, were determined from the slopes of these plots.

The products of the reaction of **1-OPh** in 50/50 (v/v) trifluoroethanol/water at 25 °C (I = 0.50, NaClO$_4$) and in solutions of increasing pH were determined by HPLC analysis. Values of k_{obsd} (s^{-1}) for the reaction of **1-OPh** and the yields of the reaction products are reported in Table 2. The values of pH$_w$ reported in Table 2 are the observed pH of the buffers in water, before mixing with the trifluoroethanol cosolvent. The reaction of **1-OPh** in 48/2/50 (v/v/v) trifluoroethanol/phenol/water that contained 0.012 M HClO$_4$ (I = 0.50, NaClO$_4$) was monitored by HPLC. Solvolysis of **1-OPh** to form **1-OCH$_2$CF$_3$** and **1-OH** is much faster than formation of **1-(4-C$_6$H$_4$OH)** and **1-(2-C$_6$H$_4$OH)**. The ratio of the concentrations of the former compounds decreases to a limiting value of ([**1-OPh**]/[**1-OCH$_2$CF$_3$**])$_{eq}$ = 0.10 after a reaction time of 1 day. This ratio then remains constant as **1-OPh**, **1-OCH$_2$CF$_3$**, and **1-OH** undergo slower conversion to **1-(4-C$_6$H$_4$OH)** and **1-(2-C$_6$H$_4$OH)**. Combining ([**1-OPh**]/[**1-OCH$_2$CF$_3$**])$_{eq}$ = 0.10 with the ratio of the concentration of the reactants (eq 5) gives K_O = 0.29 for conversion of **1-OCH$_2$CF$_3$** to **1-OPh** (Scheme 3).

Table 2. First-Order Rate Constants and Product Yields for Solvolysis of **1-OPh** in 50/50 (v/v) Trifluoroethanol/Water[a]

			products[d]			
			1-OH	1-OCH$_2$CF$_3$	1-(2-C$_6$H$_4$OH)	1-(4-C$_6$H$_4$OH)
buffer	pH$_w$[b]	k_{obsd}/s^{-1} [c]	%	%	%	%
phosphate	7.8	13.5 × 10^{-9}	80.5	8.6	6.3	4.6
	8.3	6.3 × 10^{-9}	68.4	7.9	13.7	10.0
	8.5	4.9 × 10^{-9}	61.8	7.4	17.8	13.0
carbonate	9.0	2.9 × 10^{-9}	45.1	6.6	28.7	19.5
	10.0	2.9 × 10^{-9}	43.1	8.0	29.2	19.8

[a] For reactions at 25 °C in 50/50 (v/v) trifluoroethanol/water ($I = 0.50$, NaClO$_4$). [b] The initial pH of the buffered aqueous solution, prior to mixing with an equal volume of trifluoroethanol. [c] The first-order rate constant for solvolysis of **1-OPh**, determined by the method of initial rates. [d] The product yields were determined by HPLC analyses.

Scheme 3
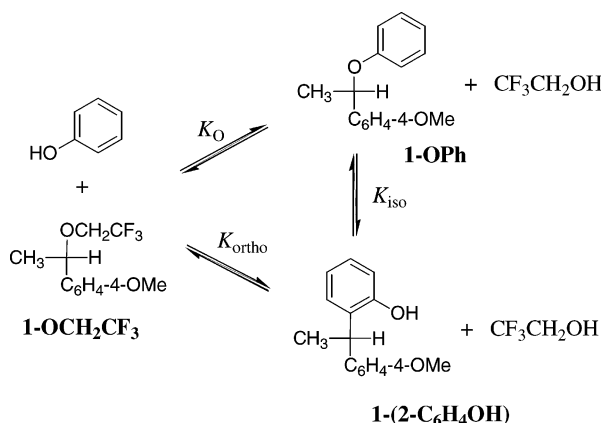
Table 3. Calculated Relative Energies of **1-OPh** and **1-(2-C$_6$H$_4$OH)**

	calculation		
compd	HF/6-31G(d)	B3LYP/6-31G(d)	IPCM/B3LYP/6-31G(d)
1-OPh [a]	0.0	0.0	0.0
1-(2-C$_6$H$_4$OH) [b]	−1.9 (−1.7)[c]	−1.5 (−1.3)[c]	−4.9 (−4.7)[c]

[a] Total energies for the O-adduct are −727.04713, −731.65820, and −731.66146 hartrees at the HF/6-31G(d), B3LYP/6-31G(d), and IPCM/B3LYP/6-31G(d) level, respectively. The difference in energy between the continuum IPCM and B3LYP calculations gives the difference in the free energy of solvation of **1-OPh** and **1-(2-C$_6$H$_4$OH)**. [b] The difference in kcal/mol between the energies for formation of **1-(2-C$_6$H$_4$OH)** and **1-OPh**. [c] The computed change in Gibbs free energy that includes the changes in entropy and enthalpy for reaction at 298 K.

The reaction of **1-OH** at 25 °C in 50/50 (v/v) trifluoroethanol/ water that contained 0.50 M perchloric acid ($I = 0.50$, NaClO$_4$) and 18 mM phenol was monitored by HPLC over a period of 7 days. At the end of this time the conversion of **1-OH** to **1-(2-C$_6$H$_4$OH)** and **1-(4-C$_6$H$_4$OH)** was essentially quantitative, and there was no sign that equilibrium had been achieved. The ratio of the concentrations of **1-OCH$_2$CF$_3$**, **1-(2-C$_6$H$_4$OH)**, and **1-(4-C$_6$H$_4$OH)** at the time when **1-OCH$_2$CF$_3$** could just be detected by HPLC analysis is 1:25:114. Combining [**1-OCH$_2$CF$_3$**]/ [**1-(2-C$_6$H$_4$OH)**] = 25 and [TFE]/[Phenol] = 380 gives a lower limit of $K_{ortho} > 9500$ (Scheme 3). The values of K_{ortho} and K_O were combined to give $K_{iso} = K_{ortho}/K_O > 9500/0.29 > 33\,000$ for isomerization of **1-OPh** to **1-(2-C$_6$H$_4$OH)**.

1-(2-C$_6$H$_4$OH) was calculated to be 1.7 kcal/mol more stable than **1-OPh** in the gas phase at the HF/6-31G(d) level (Table 3). The inclusion of electron correlation effects at the higher B3LYP/6-31G(d) level of theory leads to a small 0.4 kcal/mol

correction of the relative energy difference to 1.3 kcal/mol. The free energies of solvation of **1-(2-C$_6$H$_4$OH)** and **1-OPh** by water were calculated using a continuum solvation model to be −5.4 kcal/mol and −2.0 kcal/mol respectively, which corresponds to 3.4 kcal/mol more favorable solvation of the former compound. Combining the 1.3 kcal/mol difference in the stability of **1-(2-C$_6$H$_4$OH)** and **1-OPh** in the gas phase with the 3.4 kcal/mol difference in the free energy for solvation by water gives $\Delta G_{iso}^o = -4.7$ kcal/mol for the isomerization of **1-OPh** to **1-(2-C$_6$H$_4$OH)** in water (Scheme 3).

Discussion

1-(4-Methoxyphenyl)ethyl derivatives undergo solvolysis in mixed aqueous/organic solvents by a D$_N$ + A$_N$ (S$_N$1)[31] reaction mechanism through a "liberated" carbocation intermediate **1$^+$** which partitions between the diffusion-limited addition of azide ion and the slower addition of solvent.[12,32] Rate constants for addition of the different nucleophilic sites of phenol to **1$^+$** (Scheme 4) may be determined from the product rate constant ratios k_{az}/k_{Nu} (eq 2) and $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-limited reaction of azide ion.[12,15,32]

Addition of Phenol to 1$^+$. The reaction of **1-(3,5-dinitrobenzoate)** in 48/2/50 (v/v/v) trifluoroethanol/phenol/water ($I = 0.50$, NaClO$_4$) in the presence of azide ion at neutral pH gives seven products, whose yields are reported in Table 1. Three of these products are from addition of phenol to **1$^+$**; **1-OPh**, **1-(2-C$_6$H$_4$OH)** and **1-(4-C$_6$H$_4$OH)** (Scheme 4); three are from addition of other nucleophiles: **1-OH**, **1-OCH$_2$CF$_3$**, and **1-N$_3$**; and, a small yield of 4-methoxystyrene forms by deprotonation of **1$^+$** in a reaction that is not shown in Scheme 4 (≤ 0.3%).

The left-hand side of Table 4 reports rate constant ratios for partitioning of **1$^+$** between addition of trifluoroethanol (k_{TFE}) and phenol ($k°_O$, $k°_{para}$ and $k°_{otho}$, Scheme 4) determined from the ratio of product yields (eq 2) and absolute rate constants calculated from these rate constant ratios using $k_{TFE} = 8 \times 10^5$ M^{-1}s^{-1}.[12,15] The ca. 20-fold larger yield of the oxygen compared to carbon adducts for addition of phenol shows that the hydroxyl group of phenol is more nucleophilic than the ring carbons toward **1$^+$** in a mostly aqueous solvent. The nucleophilic reactivity of the *para* carbon of phenol is 11-fold greater than the *ortho*-carbon, possibly because of greater steric hindrance to reaction of the *ortho*-carbon.

Mechanism for Oxygen Alkylation of Phenol. The second-order rate constants for addition of alkyl alcohols to **1$^+$** increase with increasing alcohol pK_a and these data are correlated by the Brønsted coefficient of $\beta_{nuc} = 0.32$ (Figure 2A).[24] The rate constant k_{ROH} for addition to **1$^+$** of a hypothetical alkyl alcohol with the same pK_a = 10 as for phenol, obtained by extrapolation of the linear Brønsted correlation (Figure 2A), is 6-fold smaller than k_{TFE} for addition of trifluoroethanol. By comparison, the rate constant k_{PhOH} for addition of phenol is 16-fold greater than k_{TFE} (Table 4), which corresponds to a 2.0 unit positive deviation of log k_{PhOH} from this Brønsted correlation.

The larger reactivity of the aryl alcohol (phenol) compared with alkyl alcohols toward **1$^+$** is due to either: (1) a stabilizing interaction that is expressed at the ether product **1-OPh** and to an equal or smaller extent at the transition state for formation

(31) Guthrie, R. D.; Jencks, W. P. *Acc. Chem. Res.* **1989**, *22*, 343−349.
(32) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 4689−4691.

Scheme 4
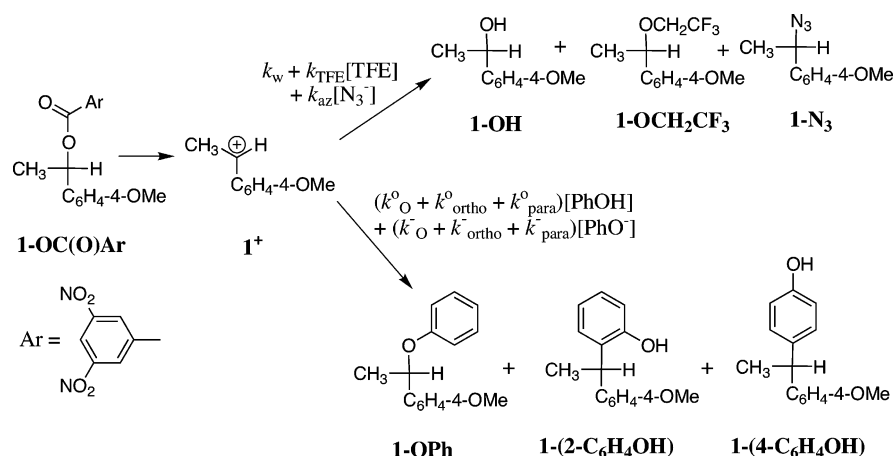
Table 4. Product Rate Constant Ratios and Absolute Rate Constants for Addition of Phenol and Phenoxide Ion to 1^{+a}

nucleophile	reacting atom $(k_{Nu})^b$	$k_{Nu}/k_{TFE}{}^c$	$k_{Nu}{}^d$ M^{-1}s^{-1}	$k_O/k_C{}^f$	nucleophile	reacting atom $(k_{Nu})^b$	$k_{Nu}/k_{az}{}^c$	$k_{Nu}{}^e$ M^{-1}s^{-1}	$k_O/k_C{}^f$
OH (phenol)	oxygen $(k^o{}_O)$	16	1.3×10^7		O$^-$ (phenoxide)	oxygen $(k^-{}_O)$	0.39 ± 0.007	2×10^9	
	p-carbon $(k^o{}_{ortho})$	0.8	6×10^5	20		p-carbon $(k^-{}_{ortho})$	0.41 ± 0.008	2×10^9	1.0
	o-carbon $(k^o{}_{para})$	0.07	6×10^4	230		o-carbon $(k^-{}_{para})$	0.22 ± 0.005	1×10^9	0.5

^{a} For reactions at 25 °C in 50/50 (v/v) trifluoroethanol/water ($I = 0.50$, NaClO$_4$). ^{b} The rate constants k_{Nu} defined in Scheme 4. ^{c} Product rate constant ratio for partitioning of 1^+ between addition of trifluoroethanol and the different nucleophilic sites of phenol or phenoxide ion. The reported errors are the standard deviations from these linear correlations. ^{d} Absolute rate constants determined from the product rate constant ratio and $k_{TFE} = 8 \times 10^5$ M^{-1}s^{-1} (ref 12). ^{e} Absolute rate constants determined from the product rate constant ratio and $k_{az} = 5 \times 10^9$ M^{-1}s^{-1} (ref 12). ^{f} Rate constant ratio for addition of the nucleophilic oxygen and carbon of phenol or phenoxide ion.
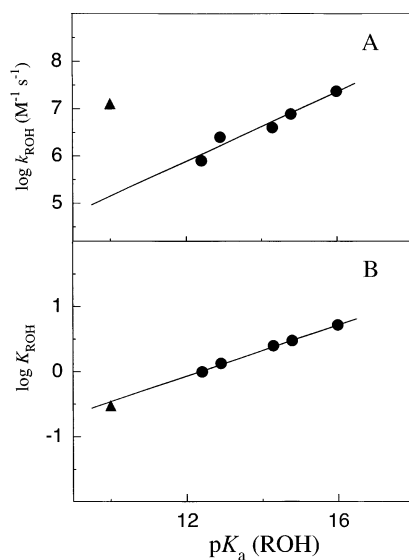

Figure 2. Brønsted correlations of rate and equilibrium constants for addition of alkyl alcohols (●) and phenol (▲) to 1^+ in 50/50 (v/v) trifluoroethanol/water at 25 °C and $I = 0.50$ maintained with NaClO$_4$. **A**. Correlation of second-order rate constants for nucleophilic addition of alkyl alcohols. [24] **B**. Correlation of dimensionless equilibrium constants for the reaction of alkyl alcohols shown in Scheme 5. [34a]

of **1-OPh**; or (2) a stabilizing interaction that is unique to the transition state and that results in a lower Marcus intrinsic barrier for addition of aryl compared with alkyl alcohols. [33] The observation that the equilibrium constant $K_{ROH} = 0.29$ (ROH

Scheme 5
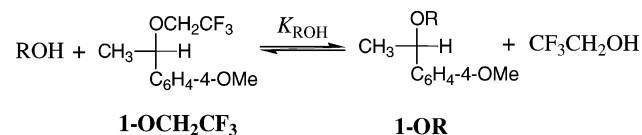
= PhOH, Scheme 5) for conversion of **1-OCH$_2$CF$_3$** to **1-OPh** lies on a linear logarithmic correlation of log K_{ROH} against the pK_a of other alkyl alcohols[34a] (Figure 2B) shows that there is no special stabilization of **1-OPh** in comparison with alkyl ethers **1-OR**. We conclude that the enhanced reactivity of phenol compared with alkyl alcohols reflects the smaller Marcus intrinsic barrier for addition of phenol. The smaller intrinsic barrier for formation of aryl compared to alkyl ethers is manifested in the cleavage direction by the larger second-order rate constant for acid-catalyzed cleavage of **1-OPh** ($k_H = 0.55$ M^{-1}s^{-1}, this work) than for cleavage of **1-OMe** ($k_H = 0.038$ M^{-1}s^{-1}). [34b]

The lower intrinsic barrier for addition of phenol than for addition of alkyl alcohols to 1^+ might be due to a more shallow curvature along the reaction coordinate for stepwise addition of the former nucleophile to form the protonated ether product. [33,35] However, we are unable to provide a rationalization for such a difference in the shape of reaction coordinates for addition of alkyl and aryl alcohols by a common reaction mechanism. Alternatively, the high nucleophilic reactivity of phenol may reflect a change from a stepwise mechanism to a

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(34) (a)Rothenberg, M. E.; Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1985**, *107*, 1340−1346. (b) Footnote 59 of ref 18.

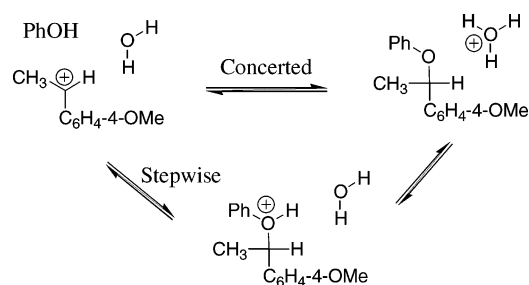(35) Jencks, W. P. *Bull. Soc. Chim. Fr.* **1988**, 218−224.

Scheme 6

PhOH

Ph

CH_3 + H

C_6H_4-4-OMe

Concerted

CH_3

C_6H_4-4-OMe

Stepwise

CH_3

C_6H_4-4-OMe

Chart 1

2-OMe   **2-OPh**   **1-OPh**

OCH_3

CH_3O——H

C_6H_4-4-OMe

CH_3O——H

C_6H_4-4-OMe

CH_3——H

C_6H_4-4-OMe

k_H/k_D 0.33   0.65   0.40

Scheme 7

stepwise-preassociation or concerted (Scheme 6) mechanism for addition of phenol to 1^+. This proposal is consistent with the following observations:[17,36−40] (1) There is good evidence that the addition of alkyl alcohols to carbocations[17,41] and to oxocarbenium ions[42,43] proceeds by a stepwise mechanism through an oxonium ion intermediate. The decrease in the pK_a of the alkyl alcohol nucleophile from 12.4 for trifluoroethanol to 10 for the aryl alcohol phenol will favor a change to a concerted mechanism for the uncatalyzed reaction (Scheme 6). This is because the change to a more weakly basic alcohol oxygen will cause a destabilization of the protonated ether reaction intermediate that will favor the concerted reaction mechanism that avoids its formation.[17,40] (2) There is a change from no detectable catalysis by carboxylic acids, to a substantial rate acceleration from concerted general acid catalysis, as the alkyl alcohol leaving group is changed from strongly to weakly basic for solvolytic cleavage of substituted benzaldehyde acetals to form an oxocarbenium ion.[36] Likewise, in the reverse carbocation−nucleophile addition direction there is a change from no detectable catalysis by carboxylate ions of alkyl alcohol addition to 1^+, to an easily observed Brønsted general base catalyzed reaction as the alcohol is changed from ethanol to trifluoroethanol. These observations show that the change to a more weakly basic leaving group/nucleophile should favor a concerted mechanism for reversible water "catalyzed" formation of 1^+ from **1-OR**. (3) The solvent deuterium isotope effect of $k_H/k_D = 0.33$ on specific acid-catalyzed solvolysis of 4-methoxybenzaldehyde dimethyl acetal[39] (Chart 1) is consistent with equilibrium protonation of **2-OMe**, which shows a large inverse equilibrium solvent deuterium isotope effect, followed by the rate determining C−O bond cleavage to form 2^+ for which there can be no more than a small primary solvent isotope effect. The increase to $k_H/k_D = 0.65$ for cleavage of the mixed acetal
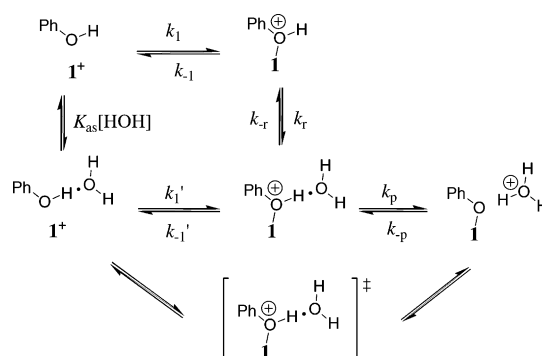
2-OPh,[39] where the leaving group is weakly basic phenol, is consistent with a change to a concerted reaction mechanism, and the attenuation of the inverse solvent isotope effect by a primary deuterium isotope effect for a reaction in which proton transfer and C−O bond cleavage are coupled. There must be the same difference in the mechanism for addition of the aryl alcohol phenol and the alkyl acohol methanol to the oxocarbenium ion 2^+ for reaction in the reverse direction.

In summary, these results show that there is a specific stabilization of the transition state for addition of weakly basic phenol compared to alkyl alcohols to 1^+, and, they are consistent with a change from a stepwise to concerted mechanism (Scheme 6) that has been observed to occur for related reactions as the leaving group/nucleophile is made more weakly basic. However, the solvent deuterium isotope effect of $k_H/k_D = 0.40$ for specific-acid-catalyzed cleavage of **1-OPh** in 50/50 (v/v) trifluoroethanol/water (Figure 1) is only marginally larger than $k_H/k_D = 0.33$ for stepwise cleavage of **2-OMe** in water. This shows that the transition state for acid-catalyzed cleavage of **1-OPh** is similar to that for the fully stepwise mechanism, where the protonated phenyl ether is "trapped" by deprotonation by solvent (k_1, k_r, k_p, Scheme 7). It suggests that the cleavage of **1-OPh** might proceed by a stepwise preassociation mechanism (K_{as}, k_1', k_p, Scheme 7):[44−46] the advantage of the preassociation pathway compared to the fully stepwise "trapping" is due to stabilization of the rate-determining transition state for k_1' by the hydrogen bond to solvent.[37,45]

There must be the same favored, low free-energy pathway for formation and breakdown of **1-O(H)Ph$^+$** that is hydrogen bonded to water (Scheme 7).[44−46] Therefore, the relative barriers for the stepwise "trapping" and for the stepwise preassociation reaction mechanism in the direction of cleavage of **1-OPh** are determined by the relative values of k_{-r} for cleavage of this hydrogen bond and k_{-1}' for heterolytic ionization to form 1^+.[44−46] The value of k_{-r} is smaller than the maximum value of 10^{11} s^{-1} for the reorganization of solvent,[47−49] because the substantial barrier to cleavage of the strong hydrogen bond between water and **1-O(H)Ph$^+$** should lower this rate constant by 100-fold or more.[50] An estimate $k_{-1}' \approx k_{-1} \approx 7 \times 10^7$ s^{-1} can be obtained using the relationship $k_{-1} = k_H K_a$, where $k_H = 0.55$ M^{-1} s^{-1} is the second-order rate constant for specific acid-

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(38) Bunton, C. A.; Davoudazedeh, F.; Watts, W. E. *J. Am. Chem. Soc.* **1981**, *103*, 3855−3858.
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(41) Gandler, J. R. *J. Am. Chem. Soc.* **1985**, *107*, 7.
(42) Fife, T. H. *Adv. Phys. Org. Chem.* **1975**, *11*, 8218−8223.
(43) Cordes, E. H.; Bull, H. G. *Chem. Rev.* **1974**, *74*, 581−603.

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(47) Giese, K.; Kaatze, U.; Pottel, R. *J. Phys. Chem.* **1970**, *74*, 3718−3725.
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(49) Kaatze, U.; Pottel, R.; Schumacher, A. *J. Phys. Chem.* **1992**, *96*, 6017−6020.

catalyzed cleavage of **1-OPh** and $K_a \approx 10^{8.1}$ M^{-1} [51] is the acidity constant for **1-O(H)Ph$^+$**. We conclude that the values of k_{-1}' and k_{-r} from Scheme 7 are similar. However, it is not possible to rigorously demonstrate that the preassociation reaction mechanism is viable, because of the uncertainty in the acidity constant K_a for **1-O(H)Ph$^+$** and in the rate constant k_{-r} for hydrogen bond cleavage.

If the reaction proceeds by a concerted mechanism that avoids formation of the protonated intermediate, then the inverse solvent deuterium isotope effect of $k_H/k_D = 0.40$ would require that proton transfer from hydronium ion be essentially complete at a transition state which shows a strong similarity to the protonated intermediate **1-O(H)Ph$^+$**. Therefore, for either the stepwise preassociation or concerted mechanism, the 3 kcal/mol advantage for addition of phenol compared with the fully stepwise addition of alkyl alcohols, that can be calculated from the 2 unit positive deviation of log k_{PhOH} from the Brønsted correlation shown in Figure 2A must be due mainly to stabilization of this transition state by hydrogen bonding to the hydronium ion catalyst.

Addition of Phenoxide Ion to 1$^+$. The rate constant ratios k^-_O/k_{az}, k^-_{para}/k_{az}, and k^-_{ortho}/k_{az} for addition of phenoxide ion to **1$^+$** to form **1-OPh**, **1-(4-C$_6$H$_4$OH)**, and **1-(2-C$_6$H$_4$OH)**, respectively, (Scheme 4) were determined as the slopes of linear correlations (Figure 3) of the ratio of product yields $[\mathbf{1 - Nu}]/[\mathbf{1 - N_3}]$ against the ratio of the nucleophile concentrations according to eq 7, where R_o is the limiting ratio observed for the reaction in a neutral solution. Combining these ratios with $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-limited reaction of azide ion gives the values for $k_{Nu} = k^-_{-O}$, k^-_{para}, or k^-_{ortho} reported in Table 4.

$$\frac{[\mathbf{1 - Nu}]}{[\mathbf{1 - N_3}]} = \left(\frac{k_{Nu}[PhO^-]}{k_{az}[N_3^-]}\right) + R_o \qquad (7)$$

The sum of the ratios for partitioning of **1$^+$** between carbon and oxygen alkylation of phenoxide ion $(k^-_O + k^-_{para} + k^-_{ortho})/k_{az}$ is equal to 1.0, and the total rate constant for addition of phenoxide ion $[k_{PhO} = k^-_O + k^-_{para} + k^-_{ortho}]$ is equal to $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-limited reaction of azide ion.[12,15,32] We conclude that the addition of phenoxide to **1$^+$** proceeds by fast and effectively *irreversible* formation of a carbocation–anion pair that partitions between reaction with the three nucleophilic sites of phenoxide ion with a net rate constant that is greater than the rate constant for separation of the ion pair to free ions ($k_{-d} \approx 1.6 \times 10^{10}$ s^{-1}).[24] The selectivity

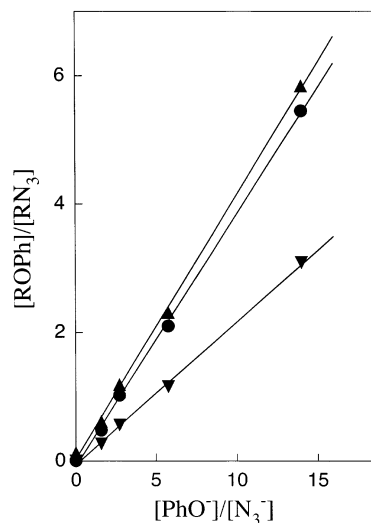**Figure 3.** The effect of increasing the ratio of the concentrations of reactants phenoxide and azide ion ($[PhO^-]/[N_3^-]$) on the ratio of the yields of the products of solvolysis of **1-(3,5-dinitrobenzoate)** in 50/50 (v/v) trifluoroethanol/water at 25°C and $I = 0.50$ maintained with NaClO$_4$: (▲), ROPh = **1-OPh**; (●), ROPh = **1-(4-C$_6$H$_4$OH)**; (▼), ROPh = **1-(2-C$_6$H$_4$OH)**.

for addition of the different nucleophilic sites of phenoxide ion to **1$^+$** (2:2:1, Table 4) is much smaller than that for addition of the same nucleophilic sites of phenol (230:20:1). This is consistent with a large Hammond-type shift toward a very "early" transition state for addition of strongly nucleophilic phenoxide ion to **1$^+$**.[52]

Nucleophilicity of Phenol Carbon. Equation 8 has been shown by Mayr and co-workers to correlate data for a large set of carbon nucleophiles.[53–55] Values of $N = 1.9$ and 0.9, respectively, for the reaction of the *para-* and *ortho*-carbons of phenol can be calculated from eq 8 using $E = 3.9$ for the electrophilicity parameter and $s \approx 1$ for addition of carbon nucleophiles to carbocations,[53] where $E = 3.9$ was also calculated from eq 8, using $k_{Nu} = 1 \times 10^8$ s^{-1} [12] for addition of water to **1$^+$**, and $N = 5.1$ and $s = 0.89$ for addition of water to carbon electrophiles.[55]

$$\log k_{Nu} = s(N + E) \qquad (8)$$

The value of $N = 1.9$ for alkylation of the *para* carbon of phenol falls between the values of $N = -1.6$ [53] and 3.7 [54] reported for alkylation of methoxybenzene and aniline, respectively. This shows that activation of the phenol ring for reaction as a nucleophile by an $-OH$ group is between the activation by $-OCH_3$ and $-NH_2$ groups, and is consistent with the relative values of Hammett substituent constant $\sigma^R = (\sigma^+ - \sigma^n)$ determined for these groups; $\sigma^R_{NH2} = -1.2$, $\sigma^R_{OH} = -0.75$, $\sigma^R_{OMe} = -0.66$.[56]

Encounter-Limited Reactions of Alkoxide and Aryloxide Anions. Phenoxide ion is a rare example of a carbon nucleophile that undergoes diffusion-controlled addition to **1$^+$** with a rate constant similar to that for the very good inorganic nucleophile azide ion. The ratio of $k_{Nu}/k_{az} = 1.0$ determined by analysis of the products of partitioning of the α−(N,N-dimethylthiocar-

(50) The rate constant ratio k_r/k_{-r} defines the strength of the hydrogen bond between the very strong acid **1-O(H)Ph$^+$** (p$K_a \approx -8.1$, ref 51) and water. A value of $k_r/k_{-r} = 100$ would correspond to $\Delta G° \approx -2.7$ kcal/mol for stabilization of **1-O(H)Ph$^+$** by a hydrogen bond to solvent. By comparison, the hydrogen bond between water and the $-OH$ group of the 4-hydroxybenzyl carbocation (p$K_a = -2$) provides a 4 kcal/mol stabilization of this carbocation toward addition of water to form 4-hydroxybenzyl alcohol, compared with addition of water to the 4-methoxybenzyl carbocation to form 4 methoxybenzyl alcohol [M. M. Toteva; M. Moran; T. L. Amyes; J. P. Richard *J. Am. Chem. Soc.* **2003**, *125*, 8814−8819.

(51) The pK_a for **1-O(H)Ph$^+$** is estimated from p$K_a = -3.4$ for **1-O(H)Me$^+$**, with the assumption that the phenyl for methyl substitution will have the same 4.69 unit effect on this pK_a as for phenyl substitution at trimethylammonium ion (p$K_a = 9.76$) to give dimethylanilinium ion (p$K_a = 5.07$). The pK_a for **1-O(H)Me$^+$** was estimated from p$K_a = -2.52$ for protonated dimethyl ether (Bonvicini, P.; Levi, A.; Lucchini, V.; Modena, G.; Scorrano, G. *J. Am. Chem. Soc.* **1973**, *95*, 5960−5964), $\sigma_I = 0.11$ and $\sigma_I = -0.01$ for the 4-MeOC$_6$H$_4$- and Me- substituents respectively [Charton, M. *Prog. Phys. Org. Chem.* **1981**, *13*, 119−251], and, $\rho_I = 8.75$ [footnote 9 of ref 68] for ionization of alcohols of structure R^1R^2CHOH.

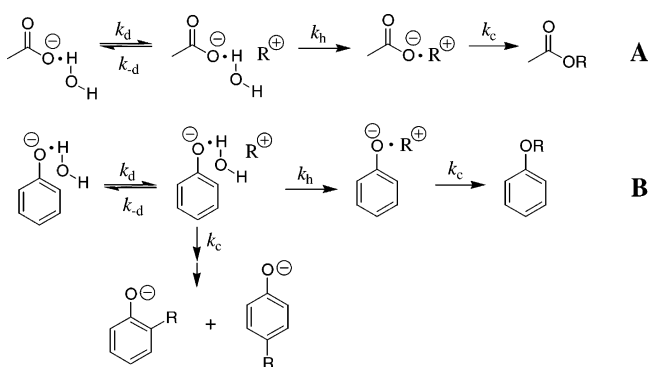(52) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334−338.
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Scheme 8

bamoyl)-4-methoxybenzyl carbocation between addition of 2-(dimethylamino)-6-methoxybenzothiophene and azide ion provides a second example of a carbon nucleophile with a reactivity comparable to that for azide ion.[19,20]

The rate constants for addition of azide and thiolate anions to ring-substituted 1-phenylethyl carbocations increase up to the diffusion-controlled limit ($k_{Nu} = k_d = 5 \times 10^9$ M^{-1} s^{-1}) as the carbocation is destabilized by electron-withdrawing ring substituents,[12,14,24,57] but the "limiting" rate constant for encounter-controlled addition of acetate and trifluoroethoxide anion to ring-substituted 1-phenylethyl carbocations is ~10-fold smaller than for a simple diffusion-limited reaction.[24] These small rate constants for encounter-controlled reactions provide evidence that formation of encounter complexes between carbocations and oxygen-anions in water is limited in some way by rate of desolvation of the nucleophilic anion.

The rate constant $k_{-O} = 2 \times 10^9$ M^{-1} s^{-1} for addition of phenoxide ion to $\mathbf{1}^+$ is 4-fold larger than the limiting rate constants for encounter-limited addition of acetate and trifluoroethoxide ion to ring-substituted 1-phenylethyl carbocations. We have suggested that the rate constant for formation of contact ion pairs to oxyanions, which limits the rate of these carbocation-nucleophile addition reactions, is roughly equal to k_h for cleavage of a hydrogen bond between the nucleophile and solvent that frees an electron pair at oxygen to react with $\mathbf{R}^+$ (Scheme 8A).[24,58,59] However, this model cannot account for the relative reactivity of acetate, phenoxide and trifluoroethoxide ions (Table 5). The strength of hydrogen bonds to anions is proportional to anion basicity,[60,61] and if hydrogen bond strength alone controlled the rate constants for these encounter-limited reactions the largest rate constant would be observed for addition of acetate ion, which forms the weakest hydrogen bond to solvent, instead of for the more basic phenoxide ion.

The larger rate constant for encounter-limited addition of phenoxide compared to acetate ion (Table 5) provides evidence that loss of a hydrogen-bonded water from oxygen at phenoxide ion [desolvation] is faster than the corresponding process at the less basic acetate ion. Since no significant desolvation of oxygen is required for formation of the carbocation-phenoxide ion pair that collapses to the carbon-adducts $\mathbf{1}$-(4-C$_6$H$_4$OH) and $\mathbf{1}$-(2-C$_6$H$_4$OH), we suggest that this complex forms at essentially

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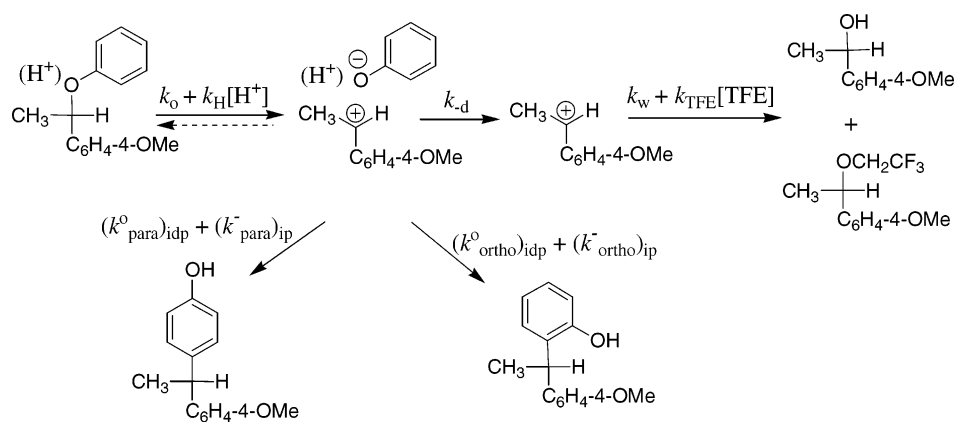(58) Richard, J. P. *J. Chem. Soc., Chem. Commun.* **1987**, 1768−1769.
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Table 5. Limiting Rate Constants for Encounter-Limited Addition of Nucleophilic Anions to Ring-Substituted 1-Phenylethyl Carbocations[a]

nucleophile	pK_a	$(k_{Nu}/k_{az})_{lim}$[b]	$(k_{Nu})_{lim}$/M^{-1} s^{-1} [c]
CH$_3$CO$_2^-$ [d]	4.8	0.10	5×10^8
PhO$^-$ [e]	10.0	1.0[f](0.4)[g]	5×10^9 [f](2×10^9)[g]
CF$_3$CH$_2$O$^-$ [d]	12.4	0.10	5×10^8

[a] For reactions at 25 °C in 50/50 (v/v) trifluoroethanol/water ($I = 0.50$, NaClO$_4$). [b] The limiting partition rate constant ratio for encounter-limited addition of azide ion and the nucleophilic oxyanion. [c] The limiting rate constant for encounter-limited addition of the oxyanion, calculated from the partition rate constant ratio and $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-limited reaction of azide anion. [d] Data from ref 24. [e] This work. [f] The value of k_{Nu}/k_{az} or k_{Nu} calculated as the sum of the rate constants for reaction of the three nucleophilic sites of phenoxide ion. [g] The value of k_{Nu}/k_{az} or k_{Nu} for oxygen addition of phenoxide ion.

the diffusion-controlled limit and then partitions between addition of the ring carbon atoms to $\mathbf{1}^+$ and desolvation at oxygen followed by oxygen addition (Scheme 8B). The relatively low barrier to desolvation of phenoxide ion within the initial ion-pair might reflect the disruption of the solvation shell about phenoxide ion that occurs with the development of stabilizing hydrophobic interactions between the aromatic ring of phenoxide ion and $\mathbf{1}^+$.

Reactions of Intimate Ion Pairs and Ion−Dipole Pairs. The perchloric-acid-catalyzed cleavage of $\mathbf{1}$-OPh in 50/50 (v/v) trifluoroethanol/water gives only $\mathbf{1}$-OH and $\mathbf{1}$-OCH$_2$CF$_3$ and no detectable $\mathbf{1}$-(4-C$_6$H$_4$OH) and $\mathbf{1}$-(2-C$_6$H$_4$OH) from reaction of an ion−dipole pair (idp).[12] This is because the phenol leaving group is weakly nucleophilic and undergoes diffusional separation to free ions faster than addition to $\mathbf{1}^+$ to form $\mathbf{1}$-(4-C$_6$H$_4$OH) and $\mathbf{1}$-(2-C$_6$H$_4$OH) [$(k^o_{para})_{idp} + (k^o_{ortho})_{idp} < < k_{-d} \approx 1.6 \times 10^{10}$ M^{-1} s^{-1},[24] Scheme 9].

The observed rate constants for solvolysis of $\mathbf{1}$-OPh level off at a constant value at high pH (Table 2), because of a change in the preferred pathway for the cleavage of $\mathbf{1}$-OPh from an acid-catalyzed to an uncatalyzed reaction. There is a corresponding change in the yields of the solvolysis reaction products (Table 2), because the phenoxide ion leaving group for the uncatalyzed (spontaneous) reaction is strongly nucleophilic. The ca. 50% yield of $\mathbf{1}$-(4-C$_6$H$_4$OH) and $\mathbf{1}$-(2-C$_6$H$_4$OH) from spontaneous solvolysis of $\mathbf{1}$-OPh shows that the net rate constant for collapse of the carbocation−anion pair (ip) to carbon adducts is comparable to that for irreversible separation to free ions [$(k^-_{para})_{ip} + (k^-_{ortho})_{ip} \approx k_{-d}$, Scheme 9]. This is the same requirement as for observation of a diffusion-limited reaction between free phenoxide ion and $\mathbf{1}^+$, and provides independent evidence that the formation of this complex by encounter of free ions is nearly irreversible.

Spontaneous solvolysis of $\mathbf{1}$-OPh yields an excess of the ortho compared to para phenol adduct ([$\mathbf{1}$-(2-C$_6$H$_4$OH)]/[$\mathbf{1}$-(4-C$_6$H$_4$OH)] = 1.5, Table 2), despite the larger steric barrier to ortho, compared to para, addition that was proposed to account for the difference in the yields of the respective adducts from diffusion-controlled addition of phenoxide ion to $\mathbf{1}^+$ ([$\mathbf{1}$-(2-C$_6$H$_4$OH)]/[$\mathbf{1}$-(4-C$_6$H$_4$OH)] = 0.55, Table 1). The 3-fold difference in the relative yields of $\mathbf{1}$-(2-C$_6$H$_4$OH) and $\mathbf{1}$-(4-C$_6$H$_4$OH) from these two reactions shows that these carbon adducts cannot form by partitioning of *the same* ion pair intermediate.

These data require that, if $\mathbf{1}^+ \cdot$PhO$^-$ were to form as an intermediate of both spontaneous solvolysis of $\mathbf{1}$-OPh and
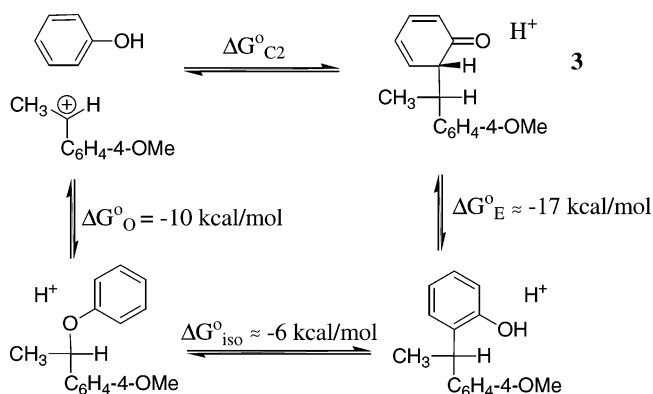
Scheme 9

Scheme 9

diffusional encounter between 1^+ and phenoxide ion, then the ion pair must collapse to product faster than reorganization of phenoxide ion within the solvent cage $[(k^-_{para})_{ip} + (k^-_{ortho})_{ip} \geq k_{reorg} \approx 10^{11}$ s$^{-1}]$.[62] In this case, the relatively high yield of **1-(2-C$_6$H$_4$OH)** from spontaneous solvolysis of **1-OPh** would be due to the placement initially of a C-2 ring carbon of phenoxide in a position to add to 1^+. Alternatively, formation of **1-(2-C$_6$H$_4$OH)** from an appropriately oriented cation and anion may occur at the limiting rate for a bond vibration and without passage over a significant energy barrier, in which case the mechanism for rearrangement of **1-OPh** to **1-(2-C$_6$H$_4$OH)** is best described as concerted.[31,45] The advantage of any concerted reaction must be small, because **1-(2-C$_6$H$_4$OH)** and **1-(4-C$_6$H$_4$OH)** form at similar rates from solvolysis of **1-OPh** and the latter compound should form by a stepwise pathway. This is because the transition state for a competing concerted reaction, with partial bonds between the benzylic and *both* the phenoxide oxygen and the C-4 carbon, should be strongly disfavored on steric grounds.

Intrinsic Reactivity of Phenol Carbon and Oxygen. The greater reactivity of the phenol oxygen compared with carbon toward 1^+ may reflect the larger thermodynamic driving force $\Delta G°$ and/or the smaller intrinsic barriers Λ for oxygen compared with carbon addition to this electrophile,[33,63,64] where Λ is defined as the barrier for a thermoneutral reaction that can be calculated from the experimental rate and equilibrium constants using eq 9.[65] Such intrinsic barriers are not often reported for organic reactions, even though they play an important role in determining the rate constants for these reactions.[33,64,66−68]

$$\log k = \frac{1}{1.36}\left\{17.44 - \Lambda\left(1 - \frac{1.36\log K_{eq}}{4\Lambda}\right)^2\right\} \quad (9)$$

There is little selectivity between carbon and oxygen alkylation of phenoxide ion by 1^+, where any difference in the Marcus intrinsic barriers for these reactions has been strongly attenuated by the large reaction driving force. Oxygen addition of neutral phenol to form **1-OPh** is strongly favorable with $K_O = k_{PhOH}/k_H = 2.4 \times 10^7$ (Scheme 10) and $\Delta G°_O = -10$ kcal/mol, calculated using $k_H = 0.55$ M^{-1} s^{-1} and $k_{PhOH} = 1.3 \times 10^7$ M^{-1} s^{-1} (Table 4). Substitution of values of k_{PhOH} and K_O

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Scheme 10

into eq 9 [65] gives $\Lambda = 12.3$ kcal/mol for the Marcus intrinsic barrier for addition of phenol to 1^+.[63,64] This is similar to an earlier estimate of $\Lambda = 12.2$ kcal/mol of the intrinsic barrier for addition of water to $1+$ in a solvent of 50/50 trifluoroethanol/water.[69]

It is more difficult to estimate the intrinsic barrier to carbon alkylation of phenol, because little is known about the unstable initial product of this reaction, the cyclohexa-3,5-dienone **3** (Scheme 10). The thermodynamic driving force for addition of the C-2 carbon of phenol to 1^+ to form **1-(2-C$_6$H$_4$OH)** has been estimated using the thermodynamic cycle shown in Scheme 10 where: (1) $\Delta G°_O = -10$ kcal/mol (above). (2) $\Delta G°_E = -17$ kcal/mol is the free energy for tautomerization of the parent cyclohexa-3,5-dienone.[70a] A similar value has been assumed for tautomerization of **3**. (3) $\Delta G°_{iso} < -6$ kcal/mol is a lower limit estimated from $K_{iso} > 33\,000$ (Scheme 3, Results section). This is a lower limit for K_{iso} because **1-OH** is converted essentially quantitatively to **1-(2-C$_6$H$_4$OH)** and **1-(4-C$_6$H$_4$OH)** in acidic solutions of trifluoroethanol/water. (4) $\Delta G°_{C2} = \Delta G°_O + \Delta G°_{iso} - \Delta G°_E < 1$ kcal/mol.

The value of $\Delta G°_{C2}$ is an upper limit calculated using a limit of $\Delta G°_{iso} < -6$ kcal/mol for the favorable isomerization of **1-OPh** to **1-(2-C$_6$H$_4$OH)**. However, the true value of $\Delta G°_{iso}$ is

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unlikely to be much more negative than -6 kcal/mol, because a similar value of $\Delta G^\circ_{iso} = -5$ kcal (Table 3) was *calculated* using high level ab initio theory and a continuum model to estimate the differential solvation of **1-OPh** and **1-(2-C₆H₄OH)**. We conclude that addition of phenol to **1**⁺ to form **1-(2-C₆H₄OH)** is close to a thermal neutral reaction with $\Delta G^\circ_{C2} \approx 0$ kcal/mol.

Substitution of $K_C \approx 1$ and $k_{C2} = 6 \times 10^4$ M⁻¹ s⁻¹ (Table 4) into eq 9 gives $\Lambda \approx 11$ kcal/mol for the Marcus intrinsic barrier for nucleophilic addition of the C-2 carbon of phenol of **1**⁺, which is slightly smaller than $\Lambda = 12.2$ kcal/mol estimated for nucleophilic addition of the phenol oxygen to **1**⁺. We have proposed that oxygen addition of phenol to **1**⁺ proceeds by a mechanism in which proton transfer and C−O bond formation are concerted, so that this reaction gives **1-OPh** and H⁺ directly (Scheme 6). If carbon addition of phenol to **1**⁺ is by a similar concerted reaction mechanism, then the intrinsic barriers reported here for carbon and oxygen alkylation of phenol may be compared directly.

The situation is more complicated if carbon addition is by a stepwise mechanism to form the protonated cyclohexa-3,5-dienone, because the driving force for phenol addition to **1**⁺ will need to be adjusted for ΔG° for proton transfer from the intermediate to water. The pK_a for this acid is not known. However, the pK_a must be perturbed downward, substantially, from the pK_a of 10 for the parent phenol and upward, substantially, from the pK_a of -3.1 for the simple ketone acetone,[70b] so that proton transfer to solvent should be neither strongly endogonic or exogonic. If this is the case, then only a small correction of the above intrinsic reaction barrier $\Lambda \approx 11$ kcal/mol will be required. This should not affect the qualitative conclusions that the intrinsic barrier for C-alkylation of phenol is similar to that for O-alkylation; and, that the larger rate constant for oxygen compared with carbon addition of phenol to **1**⁺ (Table 4) is therefore due primarily to the $\sim$10 kcal/mol larger driving force for oxygen addition.

There are many reactions of organic cations and anions which show dramatic increases in Marcus intrinsic barriers with increasing stabilization of the ion by delocalization of charge to distant atoms. This strong correlation between intrinsic reaction barrier and ground-state stabilization by resonance delocalization of charge provides strong evidence that there is a large fractional loss of stabilizing resonance interaction at the transition states for reactions of organic ions.[33,67,71,72] The observation of similar intrinsic barriers for addition of the *ortho*-carbon and oxygen of phenol to **1**⁺ flies in the face of this trend. A larger intrinsic barrier is predicted for carbon addition on the basis of resonance considerations alone, because a large loss in resonance stabilization of the aromatic ring is expected to occur on proceeding to transition state for alkylation at C-2.

We propose that, as for many other reactions, the requirement for localization of electron density at the *o*-phenol carbon at

Scheme 11
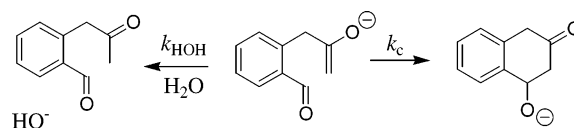
the transition state for carbon-addition to **1**⁺ does have the effect of increasing the intrinsic reaction barrier, but that this increase is masked by transition state stabilization through the more favorable, stabilizing, overlap of the relevant molecular orbitals at the soft−soft C−C nucleophile−electrophile pair compared with the corresponding orbitals at the hard−soft O−C pair.[2,73] We find that there is a > 6 kcal/mol driving force for isomerization of **1-OPh** to **1-(2-C₆H₄OH)** [ΔG°_{iso}, Scheme 10], which is consistent with the notion that C−C bond formation is favored thermodynamically compared with C−O bond formation. The formation of C−C compared with C−O bonds will be favored *kinetically* by a tendency of the so-called soft−soft interaction to reduce the intrinsic reaction barrier, provided there is a large development of this product stabilizing interaction between soft nucleophiles and soft electrophiles at the transition state for covalent bond formation.[67,71,74]

The Marcus intrinsic barriers for protonation of an acetone-like enolate by water ($\Lambda = 14.7$ kcal/mol for k_{HOH}, Scheme 11), and for intramolecular addition of this enolate to a benzaldehyde-like carbonyl group ($\Lambda = 14.1$ kcal/mol for k_C) are also similar, despite the large difference in electronic reorganization at the hard electrophile (water) and the soft electrophile (the carbonyl group) that occurs on proceeding to the respective reaction transition states for nucleophile addition.[75] Computational studies to model the relative intrinsic barriers for the reactions of hard (phenol oxygen) and soft (*o, p*-phenol carbon and simple enolates) nucleophiles, with hard (HOH) and soft (**1**⁺ and the carbonyl group) electrophiles could provide a more rigorous rationalization for the qualitative correlations between organic structure and intrinsic reaction barriers.

Supporting Information Available: Details of procedures for the synthesis of **1-OPh**, **1-(2-C₆H₄OH)**, and **1-(4-C₆H₄OH)**. This material is available free of charge via the Internet at http://pubs.acs.org.

JA037328N

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