50 mL). Water (400 mL) was added and the mixture acidified with glacial acetic acid and then extracted with dichloromethane (6 × 100 mL). The combined extracts were dried, evaporated to dryness, and purified by flash chromatography eluting with dichloromethane gradually increasing to 1:4 ether/dichloromethane to give **10** as colorless crystals: yield 65% (14.2 g); mp 210–211 °C (EtOH); IR 3400–2400, 1705, 1595, and 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.18 (s, 4 H, C*H*$_2$O), 6.93 (t, 1 H, *J* = 3 Hz, Ar*H*), 7.27 (d, 2 H, *J* = 3 Hz, Ar*H*), and 7.28–7.51 (m, 10 H, 2 × Ph); ^{13}C NMR ($CDCl_3$) δ 70.46, 107.23, 108.99, 128.16, 128.42, 129.10, 133.17, 137.67, 160.58, and 167.20; mass spectrum (EI) *m/z* 334. Anal. Calcd for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43. Found: C, 75.36; H, 5.70.

Phenyl 3,5-Bis(benzyloxy)benzoate (11). To a solution of the acid **10** (4.60 g, 13.8 mmol) in dry tetrahydrofuran was added phenol (1.55 g, 16.5 mmol) followed by DCC (3.40 g, 16.5 mmol) and 4-(dimethylamino)pyridine (200 mg, 1.65 mmol). The reaction mixture was stirred at room temperature under nitrogen for 6 h and then evaporated to dryness. The crude product was purified by flash chromatography eluting with dichloromethane to give **11** as colorless needles: yield 78% (4.42 g); mp 72–74 °C (MeOH); IR 3020, 1710, and 1220 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.08 (s, 4 H, PhC*H*$_2$O), 6.78 (t, 1 H, *J* = 2 Hz, Ar*H*), 7.10–7.37 (m, 17 H, 3 × Ph*H*, 2 × Ar*H*); ^{13}C NMR ($CDCl_3$) δ 70.36, 107.80, 108.94, 121.64, 125.89, 127.57, 128.15, 128.63, 129.43, 131.43, 136.37, 150.92, 159.89, and 164.81; mass spectrum (EI) *m/z* 410. Anal. Calcd for $C_{27}H_{22}O_4$: C, 79.00; H, 5.40. Found: C, 79.36; H, 5.70.

Phenyl 3,5-Dihydroxybenzoate (12). A mixture of the dibenzyl ester **11** (2.00 g, 4.88 mmol), 10% Pd/C (200 mg), and sodium carbonate (300 mg) in dry tetrahydrofuran (30 mL) was stirred vigorously under an atmosphere of hydrogen until the theoretical amount of hydrogen had been consumed. The reaction mixture was then filtered and evaporated to dryness. The crude product was purified by flash chromatography eluting with 1:9 ether/dichloromethane to give **12** as colorless crystals: yield 90% (1.01 g); mp 174–176 °C (MeOH/H_2O); IR 3600–3100, 1705, 1600, 1340, 1220, and 1190 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 6.77 (t, 1 H, *J* = 3 Hz, Ar*H*), 7.22–7.27 (m, 5 H, Ar*H*), 7.40–7.45 (m, 2 H, Ar*H*), and 8.79 (br s, 2 H, ArO*H*); ^{13}C NMR (acetone-d_6) δ 108.32, 108.83, 122.13, 126.11, 129.75, 131.81, 151.51, 158.52, and 165.07; mass spectrum (EI) *m/z* 230. Anal. Calcd for $C_{13}H_{10}O_4$: C, 67.82; H, 4.40. Found: C, 67.64; H, 4.73.

Phenyl 3,5-Bis(benzoyloxy)benzoate (14). Benzoyl chloride (403 mg, 2.87 mmol, 1.20 equiv) was dissolved in dry tetrahydrofuran (10 mL) and cooled to 0 °C under nitrogen pyridine (0.25 mL) and 4-(dimethylamino)pyridine (40 mg) were added, and stirring was continued for 15 min at 0 °C. The dihydroxy ester **12** (550 mg, 2.39 mmol), dissolved in dry tetrahydrofuran (10 mL), was added dropwise and stirring continued for 1 h at 0 °C and then at room temperature for 16 h. The reaction mixture was evaporated to dryness, redissolved in dichloromethane (50 mL), washed with water (3 × 25 mL), and evaporated to dryness. The crude product was purified by flash chromatography eluting with 1:3 hexane/dichloromethane to give the triester **14** as a white solid: yield 49% (514 mg); mp 137–139 °C; IR 3100–2900, 1720, and 1220 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 7.33–7.37 and 7.46–7.51 (m, 5 H, Ph*H*), 7.59–7.64 and 7.72–7.75 (m, 7 H, 6 × Ar′*H* and Ar*H*), 8.06 (d, 2 H, *J* = 2 Hz, Ar*H*), and 8.22–8.25 (m, 4 H, 4 × Ar′*H*); ^{13}C NMR (acetone-d_6) δ 121.48, 122.07, 122.31, 126.55, 129.36, 129.59, 129.82, 130.31, 132.36, 134.55, 151.58, 152.35, 163.75, and 164.88; mass spectrum (EI) *m/z* 438. Anal. Calcd for $C_{27}H_{18}O_6$: C, 73.96; H, 4.14. Found: C, 73.69; H, 4.28.

Phenyl 3-Hydroxy-5-(benzoyloxy)benzoate (13). Increasing the eluent to dichloromethane and then to 1:19 ether/dichloromethane gave the monophenol **13** as a white solid: yield 39% (310 mg); mp 151–155 °C; IR 3600–3200, 1720, 1700, 1260, and 1190 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 7.17 (t, 1 H, *J* = 2 Hz, Ar*H*), 7.27–7.32 and 7.39–7.46 (m, 5 H, Ph*H*), 7.56–7.63 and 7.69–7.74 (m, 5 H, 3 × Ar′*H* and 2 × Ar*H*), 8.20–8.22 (m, 4 H, 4 × Ar′*H*), and 9.33 (br s, 1 H, ArO*H*); ^{13}C NMR (acetone-d_6) δ 114.73, 115.04, 115.10, 122.27, 126.35, 129.24, 129.79, 129.90, 130.44, 132.14, 134.32, 151.11, 152.72, 159.03, and 164.36; mass spectrum (EI) *m/z* 334. Anal. Calcd for $C_{20}H_{14}O_5$: C, 71.85; H, 4.22. Found: C, 71.62; H, 4.54.

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Registry No. 1, 75750-29-7; **1** (homopolymer), 133551-53-8; **2**, 490-79-9; **3**, 79314-27-5; **10**, 28917-43-3; **11**, 28917-43-3; **12**, 133551-50-5; **13**, 133551-52-7; **14**, 133551-51-6; Me_3SiCl, 75-77-4; PhOH, 108-95-2; PhCOCl, 98-88-4.

Mechanisms for the Uncatalyzed and Hydrogen Ion Catalyzed Reactions of a Simple Quinone Methide with Solvent and Halide Ions

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Abstract: The quinone methide 4-[bis(trifluoromethyl)methylene]cyclohexa-2,5-dienone (**1**) has been prepared in situ from the solvolysis of 4-MeOArC$(CF_3)_2$OTs in 50:50 (v/v) trifluoroethanol/water, and its reactions with solvent and halide ions have been studied. Rate constants for the uncatalyzed and hydrogen ion catalyzed reactions of solvent, Cl^-, Br^-, and I^- with **1** to form the respective phenols 4-HOArC$(CF_3)_2$Y, equilibrium constants for the addition of HI and HBr, and solvent deuterium isotope effects are reported. The equilibrium constant for the addition of HI to **1** is 17-fold larger than for the addition of HBr. The reactions of **1** have been compared with the reactions of the O-methylated analogue 4-MeOArC$(CF_3)_2{}^+$. Methylation of the carbonyl oxygen causes a $\sim 10^{19}$-fold increase in K_{eq} for the addition of Br^- to the electrophile and a large decrease in the selectivity for the addition of solvent and halide ions. Rate constants for the capture of the highly unstable O-methylated carbocation by nucleophilic reagents do not obey the N_+ equation, which requires that carbocation selectivity be independent of electrophile reactivity. The solvent deuterium isotope effects on the uncatalyzed addition of water and bromide ion are $(k_o)_{HOH}/(k_o)_{DOD} = 2.0$ and $(k_{Br})_{HOH}/(k_{Br})_{DOD} = 1.0$, respectively. The difference in the isotope effects on these two reactions may be explained by considering the changes in the interaction of solvent with the water and bromide ion nucleophiles that occur on moving to the reaction transition states. The solvent deuterium isotope effects on the hydrogen ion catalyzed addition of water and bromide ion are $k_H/k_D = 0.68$ and $k_{HBr}/k_{DBr} = 1.0$, respectively. The difference in the isotope effects on these reactions and several other experimental observations are consistent with a stepwise mechanism for the H^+-catalyzed addition of solvent and a concerted mechanism for the H^+-catalyzed reactions of halide ions in which protonation of the carbonyl oxygen and carbon–bromine bond formation occur in a single step.

Quinone methides are of considerable interest as the reactive intermediates formed upon reductive activation of mitomycin C[1] and anthracyclines,[2] in the biosynthesis of neolignan,[3] and as a product of tyrosinase-catalyzed oxidation of α-methyl dopa methyl

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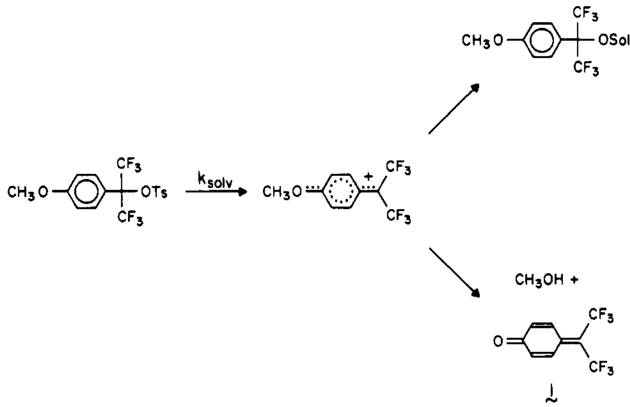
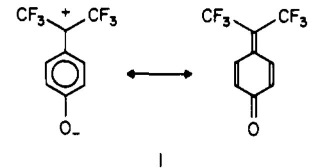
Scheme I



ester.[4] However, there have been few studies of the reactions of simple quinone methides with nucleophilic reagents, because these highly unstable compounds are difficult to prepare.[5-7] We recently reported that the quinone methide **1** is a product of the aromatic substitution reaction of water at 4-MeOArC$(CF_3)_2{}^+$ (Scheme I).[8] **1** is relatively stable in 50:50 (v/v) trifluoroethanol/water ($t_{1/2}$ = 11 h), and in methanol **1** is 100-fold less reactive than an analogue with hydrogens at the methide carbon.[8] The surprisingly low reactivity of **1** (a 4-$^-$O-substituted carbocation) was attributed to (a) steric hindrance by the α-CF_3 substituents to the addition of solvent and (b) enhanced resonance delocalization of positive charge into the aromatic ring, which minimizes interactions between this charge and the CF_3 dipole but also increases the "intrinsic" kinetic barrier to carbocation capture by nucleophilic reagents.[8-10]



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This paper reports the results of a study of the uncatalyzed and hydrogen ion catalyzed reactions of **1** with solvent and halide ions, and it includes a thorough analysis of the kinetics and thermodynamics of the halide ion reactions. The principal objective of this work is to draw comparisons between nucleophile addition to **1** and addition reactions at the more electrophilic O-methylated (4-MeOArC$(CF_3)_2{}^+$) or O-protonated (4-HOArC$(CF_3)_2{}^+$) carbocations. Methylation of **1** at oxygen decreases the halftime for reaction of the electrophile with 50:50 (v/v) trifluoroethanol/water from 11 h to under 1 μs.[8] The 10^{11}-fold range of reactivities spanned by **1** and 4-MeOArC$(CF_3)_2{}^+$ is extremely broad, wider even than the range of reactivity of the carbocations that were studied in the development of the N_+ scale for nucleophile reactivity.[11] The nucleophile selectivities for the reaction of the latter carbocations, and other relatively stable electrophiles, are independent of electrophile reactivity and are fit by a single-parameter equation (log $k_N/k_{HOH} = N_+$).[11a,b] What is not known is whether or not nucleophile selectivities remain constant for the reaction of very highly destabilized carbocations, or if there is a decrease in selectivity due to a Hammond effect.[12] I report here that the destabilization of **1** by methylation of the oxygen substituent leads to a substantial decrease in the selectivity of the electrophile toward reaction with halide ions and solvent.

Protonation of **1** at oxygen will increase the reactivity of **1** toward nucleophilic reagents, and this will appear as class e catalysis of the reaction by the hydrogen ion.[13] The H^+-catalyzed reaction may follow either a stepwise mechanism through the protonated quinone methide intermediate 4-HOAr$(CF_3)_2{}^+$ or a concerted mechanism where proton transfer and carbon–nucleophile bond formation occur in a single step, which avoids the unstable intermediate. Experiments are reported here that distinguish between these mechanisms for the hydrogen ion catalyzed reactions of solvent and halide ions.

Experimental Section

Materials. 2,2,2-Trifluoroethanol, D_2O (99.8 and 99.96% D), and $DClO_4$ (99% D) were purchased from Aldrich. Deuterated trifluoroethanol (CF_3CD_2OD, 99% D) was purchased from Cambridge Isotope Laboratories. Water was distilled and passed through a Milli-Q purification system. Inorganic acids and salts were of reagent grade and were used without further purification. 4-MeOArC$(CF_3)_2$OTs was prepared by a published procedure.[10a]

Kinetic Methods. The reaction of **1** was studied at 25 °C in 50:50 (v/v) trifluoroethanol/water at a constant ionic strength of 0.50 maintained with $NaClO_4$. Solvents of 50:50 (v/v) CF_3CH_2OH/D_2O were prepared by mixing equal volumes of acidic ($DClO_4$) or neutral solutions of halide ion in D_2O (99.8% D, I = 0.50, $NaClO_4$) with CF_3CH_2OH, to give a solvent of 89% D at the hydroxylic sites.

1 was generated in situ from 4-MeOArC$(CF_3)_2$OTs.[8] A 30-μL portion of a solution (ca. 0.015 M) of 4-MeOArC$(CF_3)_2$OTs in acetonitrile was added to 2 mL of 50:50 (v/v) trifluoroethanol/water. After >10 halftimes for the solvolysis of 4-MeOArC$(CF_3)_2$OTs (3–5 min), 1.0 mL of a solution of NaY (Y = Cl, Br, or I) and $HClO_4$ in the same solvent was added, and the disappearance of **1** was monitored at 283 nm.[8]

Pseudo-first-order rate constants for the reaction of **1** were calculated from the slopes of semilogarithmic plots of reaction progress against time over ≥3 halftimes for the reaction. The rate constants were reproducible to ±5%. Second-order rate constants were calculated from the least-squares slope of a linear plot of five or more values of k_{obsd} against the concentration of the reagent that was varied.

Product Analyses. UV Spectroscopy. Solutions of 50:50 (v/v) trifluoroethanol/water (I = 0.50, $NaClO_4$) containing **1** and 4-HOArC$(CF_3)_2$I or 4-HOArC$(CF_3)_2$Br at chemical equilibrium were prepared by generating **1** as described above (the final concentration of 4-MeOArC$(CF_3)_2$OTs was 5×10^{-5} M) and then adding measured amounts of $HClO_4$ and NaBr or NaI. The disappearance of **1** at 283 nm was monitored until equilibrium was established. The ratio [4-HOArC$(CF_3)_2$Y]/[**1**] at equilibrium was calculated from eq 1, where A_0 is the

$$[HOArC(CF_3)_2Y]/[\mathbf{1}] = (A_0 - A_{eq})/(A_{eq} - A_{min}) \qquad (1)$$

absorbance at 283 nm of a solution that contains only **1** ($[Y^-]$ = 0 M), A_{eq} is the absorbance observed at chemical equilibrium, and A_{min} is the absorbance of a solution that contains (essentially) only 4-HOArC-

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Table I. Rate and Equilibrium Constants for the Reaction of Halide Ions with 1[a]

Y^-[b]	$[H^+]$,[c] M	range of $[Y^-]$, M	$(k_Y)_{obsd} = k_Y + k_{HY}[H^+]$, $M^{-1}\ s^{-1}$[d]	k_{HY}, $M^{-2}\ s^{-1}$[e]	k_Y, $M^{-1}\ s^{-1}$[f]	K_T, M^{-2}[g]
Cl^-	0.0055	0.05–0.16	0.022	0.44	0.020	
	0.011	0.04–0.16	0.024			
	0.017	0.04–0.15	0.028			
	0.028	0.03–0.14	0.032			
	0.042	0.04–0.21	0.038			
Br^-	0.021	0.017–0.083	0.29	3.7	0.21	6.4×10^4
	0.042	0.017–0.083	0.36			
	0.062	0.017–0.083	0.44			
	0.083	0.017–0.083	0.52			
Br^- (in D_2O)[h]	0.012	0.017–0.083	0.27	3.7	0.22	
	0.023	0.017–0.083	0.30			
	0.035	0.017–0.083	0.34			
	0.058	0.017–0.083	0.44			
I^-	0.025	0.0008–0.004	14.1	81	11.7	1.1×10^6
	0.042	0.0008–0.004	14.9			
	0.125	0.0012–0.0062	21.4			
	0.25	0.0012–0.0062	32.1			

[a] In 50:50 (v/v) trifluoroethanol/water ($I = 0.50$, $NaClO_4$). [b] As the sodium salt. [c] $HClO_4$. [d] The slope of a plot of five values of k_{obsd} against $[Y^-]$ for the reaction of **1** in the presence of a fixed concentration of hydrogen ion. [e] The slope of a plot of $(k_Y)_{obsd}$ against $[H^+]$ (Figure 2B). [f] The intercept of a plot of $(k_Y)_{obsd}$ against $[H^+]$ (Figure 2B). [g] The slope of a plot of $[4\text{-HOArC}(CF_3)_2Y]/[\mathbf{1}]$ against $[H^+][Y^-]$ (Figure 1). [h] For reaction in a solvent of 50:50 (v/v) CF_3CH_2OH/D_2O (89% D at hydroxylic sites).

$(CF_3)_2Y$, recorded at high values of $[H^+][Y^-]$. The concentration of acid in these solutions was calculated by adding 5×10^{-5} M to the concentration of $HClO_4$ in order to include *p*-toluenesulfonic acid, which is a product of the reaction of $4\text{-MeOArC}(CF_3)_2OTs$.

NMR Spectroscopy. **1** was prepared from the solvolysis of $4\text{-MeOArC}(CF_3)_2OTs$ (0.02 M) in 80:20 (v/v) CF_3CD_2OD/D_2O (99.96% D).[8] This solution was monitored by NMR (400 MHz) for 3 h, during which time the intensity of the signals for the ring protons of **1** (doublets at $\delta = 7.82$ and 6.61 ppm, $J = 10$ Hz)[8] decreased by 66% and a new pair of doublets appeared at $\delta = 7.66$ and 6.98 ppm ($J = 8$ Hz). These new signals are attributed to the ring protons of $4\text{-HOArC}(CF_3)_2OH$. Only a low yield of the trifluoroethanol adduct to **1** is expected, because of the high reactivity of water relative to trifluoroethanol toward α-CF_3-substituted 4-methoxybenzyl carbocations.[8,9a]

HPLC Analyses. The products of the reaction of $4\text{-MeOArC}(CF_3)_2OTs$ were resolved by HPLC as described in previous work.[8,9a,14] The products were detected at 268 nm, which is λ_{max} for $4\text{-MeOArC}(CF_3)_2OH$.[8]

The reaction of **1** with 50:50 (v/v) trifluoroethanol/water was followed by HPLC, and the product of the reaction was identified as the new peak, which grew at the expense of the peak for **1**. The new peak was unusually broad and showed a long tail. These chromatographic properties are consistent with the presence of the ionizable phenol oxygen of $4\text{-HOArC}(CF_3)_2OH$. The adduct of Br^- to **1** is too unstable to be characterized by HPLC.[8]

Calculation of Nucleophile Selectivities. Nucleophile selectivities (k_{Nu}/k_s, M^{-1}) for the reaction of $4\text{-MeOArC}(CF_3)_2OTs$ with halide ions were calculated from the slope and the intercept of a plot of $1/[\text{area}]_{RNu}$ against $1/[Nu]$ (eq 2), where $[\text{area}]_{RNu}$ is the peak area for the nucleophile adduct, determined by HPLC analyses, and $[\text{area}]_{max}$ is the maximum peak area observed for quantitative conversion of the substrate to the nucleophile adduct.[9a]

$$1/[\text{area}]_{RNu} = 1/[\text{area}]_{max}(1 + k_s/k_{Nu}[Nu]) \qquad (2)$$

Results

NMR and UV spectral data for **1** and NMR data for the adduct of azide ion to **1** ($4\text{-HOArC}(CF_3)_2N_3$) have been reported in previous work.[8] NMR and HPLC analyses of the product of the reaction between **1** and water (Experimental Section) are as expected for $4\text{-HOArC}(CF_3)_2OH$.

In 50:50 (v/v) trifluoroethanol/water ($I = 0.50$, $NaClO_4$) at low $[H^+]$, the equilibrium between **1** and its iodide or bromide ion adducts (Scheme II) is established before there is significant addition of solvent to **1**. The ratio of the concentrations of **1** and the bromide ion or iodide ion adducts at chemical equilibrium were calculated from eq 1. Data at changing $[H^+][Y^-]$ were fit to eq 3, as shown in Figure 1. The slope of this plot is equal to K_T, the equilibrium constant for the formation of $4\text{-HOArC}(CF_3)_2Br$ from **1**, H^+, and Br^-. Values of K_T for the addition of HBr and HI to **1** are given in Table I.

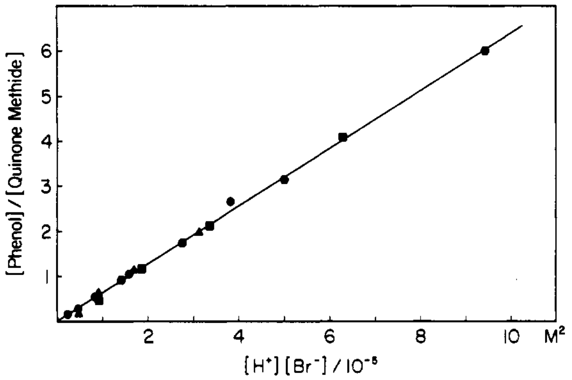
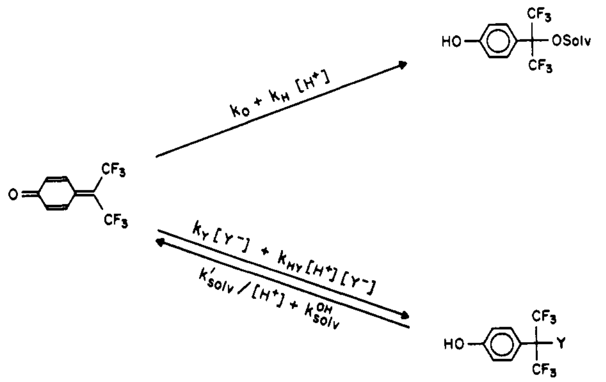


Figure 1. Product ratios against $[H^+][Br^-]$ for equilibria established at 25 °C in 50:50 (v/v) trifluoroethanol/water ($I = 0.50$, $NaClO_4$): (●), $[Br^-] = 0.022$ M and $[H^+] = 1 \times 10^{-4}$ to 1.7×10^{-3} M; (■), $[Br^-] = 0.044$ M and $[H^+] = 1 \times 10^{-4}$ to 7×10^{-4} M; (▲), $[Br^-] = 0.089$ M and $[H^+] = 1 \times 10^{-4}$ to 7×10^{-4} M; (●), $[Br^-] = 0.1334$ M and $[H^+] = 1 \times 10^{-4}$ to 7×10^{-4} M.

Scheme II



$$[\text{HOArC}(CF_3)_2Y]/[\mathbf{1}] = K_T[H^+][Y^-] \qquad (3)$$

Pseudo-first-order rate constants for the reaction of **1** at 25 °C in 50:50 (v/v) trifluoroethanol/water ($I = 0.50$, $NaClO_4$) were determined under conditions where the equilibrium strongly favors the formation of the nucleophile adducts ($[\text{HOArC}(CF_3)_2Y]/[\mathbf{1}]$

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(14) Richard, J. P.; Rothenberg, M. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1361–1372.

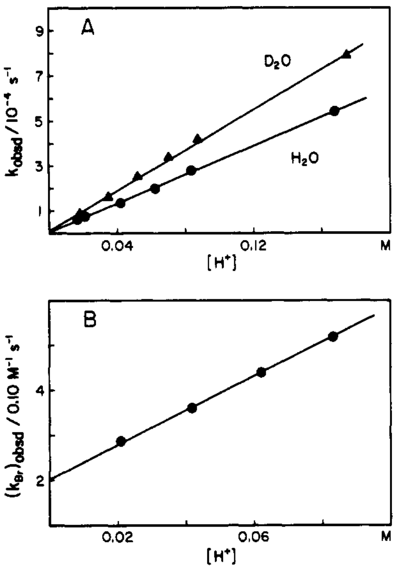


Figure 2. Dependence of k_{obsd}, the observed pseudo-first-order rate constants for the reaction of solvent with **1**, and $(k_{Br})_{obsd}$, the observed pseudo-second-order rate constants for the addition of bromide ion to **1**, on the concentration of hydrogen ion. The reactions were at 25 °C in 50:50 (v/v) trifluoroethanol/water ($I = 0.50$, $NaClO_4$): (A) data for the solvent reactions (H_2O and D_2O) and (B) data for the reaction of bromide ion.

Table II. Solvent Deuterium Isotope Effects on the Reaction of **1**[a]

rate constant[b]	rate constant in 50:50 (v/v) CF_3CH_2OH/D_2O (89% D)[c]	calcd for 100% D[d]	k_{HOH}/k_{DOD}[e]
$(k_o)_{DOD}$ (s^{-1})	9.4×10^{-6}	8.4×10^{-6}	2.0
$(k_{Br})_{DOD}$ (M^{-1} s^{-1})	0.22	0.22	1.0
k_D (M^{-1} s^{-1})	4.5×10^{-3}	4.7×10^{-3}	0.68
k_{DBr} (M^{-2} s^{-1})	3.7	3.7	1.0

[a] At 25 °C ($I = 0.50$, $NaClO_4$). [b] The rate constants are defined in eq 4. [c] Experimental rate constants. [d] Rate constants calculated from the experimental values in 89% D, as described in the text. [e] The solvent deuterium isotope effect.

> 20). The data were fit to eq 4, which was derived for Scheme II.

$$k_{obsd} = k_o + k_H[H^+] + k_Y[Y^-] + k_{HY}[H^+][Y^-] \qquad (4)$$

$$(k_Y)_{obsd} = k_Y + k_{HY}[H^+] \qquad (4a)$$

The terms in eq 4 were evaluated as follows.

(1) $k_o = 1.7 \times 10^{-5}$ s^{-1} for the uncatalyzed addition of solvent to **1** was determined for the reaction in solvent that contained only 0.50 M $NaClO_4$.

(2) $k_H = 3.2 \times 10^{-3}$ M^{-1} s^{-1} for the hydrogen ion catalyzed addition of solvent to **1** is the slope of a plot of k_{obsd} against [H$^+$] (Figure 2A).

(3) Observed second-order rate constants $(k_Y)_{obsd}$ for the reaction of halide ions were determined from the slopes of plots of pseudo-first-order rate constants k_{obsd} against [Y$^-$] for reactions at fixed [H$^+$]. $(k_Y)_{obsd}$ increases with increasing concentrations of hydrogen ion, showing that the addition of Y$^-$ to **1** is catalyzed by the proton. These data were fit to eq 4a: The second-order rate constant k_Y for the direct addition of Y$^-$ to **1** and the third-order rate constant k_{HY} for the reaction catalyzed by hydrogen ion were determined from the intercept and the slope, respectively, of a plot of $(k_Y)_{obsd}$ against [H$^+$] (Figure 2B). Rate constants for the reaction of **1** with halide ions are reported in Table I.

Rate constants for the reaction of **1** with solvent and bromide ion in 50:50 (v/v) CF_3CH_2OH/D_2O (89% D at hydroxylic sites) are given in Table II. The rate constants in Table II for the reaction in CF_3CH_2OD/D_2O (100% deuterium at hydroxylic sites) were calculated by extrapolation, assuming a linear relationship between the observed rate constants at 0 and 89% deuterium and the mole fraction of deuterium at hydroxylic sites.[15]

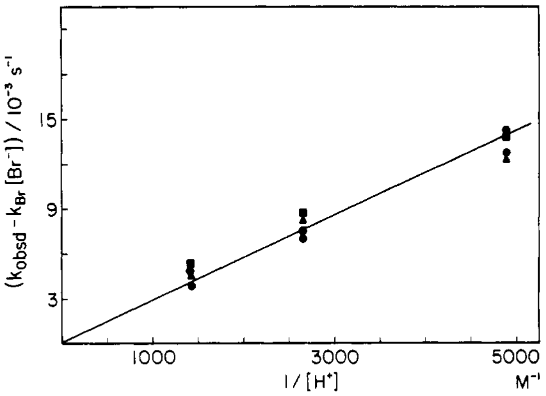
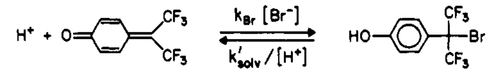


Figure 3. Fit to eq 5 of the data for the reaction of **1** with Br$^-$ at 25 °C in 50:50 (v/v) trifluoroethanol/water ($I = 0.50$, $NaClO_4$): (●), [Br$^-$] = 0.022 M and [H$^+$] = 2×10^{-4} to 1.7×10^{-3} M; (■), [Br$^-$] = 0.044 M and [H$^+$] = 2×10^{-4} to 7×10^{-4} M; (▲), [Br$^-$] = 0.089 M and [H$^+$] = 2×10^{-4} to 7×10^{-4} M; (●), [Br$^-$] = 0.1334 M and [H$^+$] = 2×10^{-4} to 7×10^{-4} M.

Scheme III



Pseudo-first-order rate constants for the *approach to chemical equilibrium* were determined for the addition of Br$^-$ to **1** under conditions where both (a) 4-HOAr$C(CF_3)_2Br$ and **1** are present at significant concentrations at chemical equilibrium and (b) the rate of uncatalyzed addition of halide ion to **1** is much faster than the rate of acid-catalyzed addition of bromide ion ($k_{Br} \gg k_{HBr}[H^+]$) and much faster than the rate of solvent addition to **1** ($k_{Br}[Br^-] \gg k_o + k_H[H^+]$). The observed first-order rate constants were fit to eq 5 (Figure 3), derived for Scheme III, where

$$k_{obsd} = k_{Br}[Br^-] + k'_{solv}/[H^+] \qquad (5)$$

$k_{Br}[Br^-]$ (Table I) and $k'_{solv}/[H^+]$ are the rate constants for the uncatalyzed formation and the specific-base-catalyzed breakdown of 4-HOAr$C(CF_3)_2Br$, respectively. The slope of the plot of ($k_{obsd} - k_{Br}[Br^-]$) against 1/[H$^+$] is $k'_{solv} = 2.6 \times 10^{-6}$ M s^{-1}.

The yields of 4-MeOAr$C(CF_3)_2Y$ from the reaction of 4-MeOAr$C(CF_3)_2OTs$ with I$^-$ or Cl$^-$ in 50:50 (v/v) trifluoroethanol/water ($I = 0.50$, $NaClO_4$) were determined by HPLC analysis. Rate constant ratios $k_I/k_s = 230$ M^{-1} and $k_{Cl}/k_s = 15$ M^{-1} for these reactions were obtained from the fit of the product data to eq 2 (Experimental Section).

Discussion

Reaction Pathways. The solvolysis of 4-MeOAr$C(CF_3)_2OTs$ in 50:50 (v/v) trifluoroethanol/water proceeds by an S_N1 ($D_N + A_N$)[40a] mechanism through an intermediate (4-MeOAr$C(CF_3)_2^+$) that partitions between addition of water to the benzylic carbon, to give a 67% yield of aliphatic substitution products, and addition to the C-4 ring carbon, to give a 33% yield of **1** (Scheme I).[8] The intermediate is also trapped by the attack of nucleophiles at the benzylic carbon;[8] the capture of 4-MeOAr$C(CF_3)_2^+$ by azide ion is diffusion-limited and serves as a "clock" for the reaction of other nucleophiles.[8] Rate constant ratios k_{az}/k_{Nu} were calculated from k_{Nu}/k_s, determined from product analysis, and k_{az}/k_s

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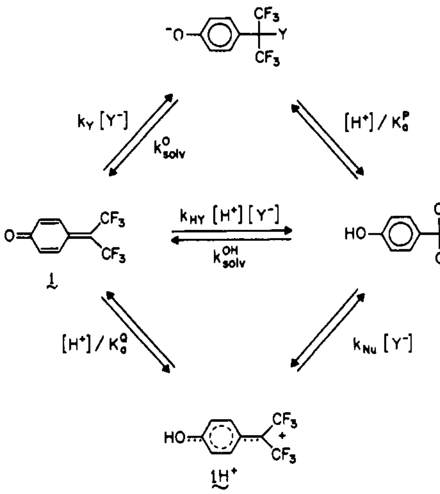
[15] The linear extrapolation assumes that there is one proton "in flight" at the transition state. If the reaction involves concerted motion of more than one proton, then the plots of k_{obsd} against f_D will be curved: Gold, V. *Adv. Phys. Org. Chem.* **1969**, *7*, 259–331. However, the possibility that these plots might show curvature does not introduce significant error into the extrapolated values given in Table II, because the curvature is small over the range of the present extrapolation from 89 to 100% D: Venkatasubban, K. S.; Davis, K. R.; Hogg, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 6125–6128. Hogg, J. L.; Phillips, M. K.; Jergens, D. E. *J. Org. Chem.* **1977**, *42*, 2459–2461. Matta, M. S.; Andracki, M. E. *J. Am. Chem. Soc.* **1985**, *107*, 6036–6039.

Scheme IV



$= 1100\ M^{-1}$.[8] The following rate constants for the capture of 4-MeOArC(CF$_3$)$_2^+$ were calculated from these ratios and an estimated[16] rate constant of $k_{az} = 5 \times 10^9\ M^{-1}\ s^{-1}$ for the diffusion-limited reaction of azide ion: $k_{Cl} = 7 \times 10^7\ M^{-1}\ s^{-1}$, $k_{Br} = 2.3 \times 10^8\ M^{-1}\ s^{-1}$,[8] $k_I = 1 \times 10^9\ M^{-1}\ s^{-1}$, and $k_s = 4.5 \times 10^6\ s^{-1}$.[8]

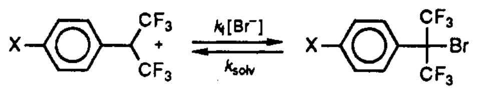
The addition of HY to **1** may proceed by several pathways (Scheme IV): uncatalyzed addition of Y$^-$ to **1** (k_Y, Table I) to form 4-$^-$OArC(CF$_3$)$_2$Y, which is then rapidly protonated ($A_N{}^{\ddagger} + A_HD_{xh}$),[40a,b] and hydrogen ion catalyzed addition of Y$^-$ to **1** (k_{HY}, Table I) by either a stepwise ($A_HD_{xh} + A_N{}^{\ddagger}$) or concerted ($A_NA_HD_{xh}$) mechanism. The corresponding pathways for the reverse, cleavage, reaction of 4-HOArC(CF$_3$)$_2$Y are, respectively, deprotonation of 4-HOArC(CF$_3$)$_2$Y followed by expulsion of Y$^-$ ($A_{xh}D_H + D_N{}^{\ddagger}$) and cleavage of 4-HOArC(CF$_3$)$_2$Y by a stepwise ($D_N{}^{\ddagger} + A_{xh}D_H$) or concerted ($A_{xh}D_HD_N$) mechanism. Hydrogen ion catalysis has been also reported for the reaction of 2,6-dibromo-4-(bromomethylene)cyclohexa-2,5-dienone with Br$^-$ in 95% dioxane/water, but no attempt was made to distinguish between stepwise and concerted mechanisms for this reaction.[5a]

Rate and Equilibrium Constants. The equilibrium constants $K_a{}^P$ and $K_a{}^Q$ from Scheme IV are acid dissociation constants for **1H**$^+$ and 4-HOArC(CF$_3$)$_2$Y, respectively. The rate constants from Scheme IV are defined as follows: $k_{solv}{}^O$ is the rate constant for the cleavage of 4-$^-$OArC(CF$_3$)$_2$Y to form **1** and Y$^-$, k_{Nu} is the rate constant for the capture of 4-HOArC(CF$_3$)$_2^+$ (**1H**$^+$) by halide ion, k_Y is the rate constant for the direct addition of nucleophiles to **1** (Table I), k_{HY} is the third-order rate constant for the hydrogen ion catalyzed addition of Y$^-$ to **1**, and $k_{solv}{}^{OH}$ is the first-order rate constant for the uncatalyzed cleavage of 4-HOArC(CF$_3$)$_2$Y.

Rate constants for the cleavage of 4-HOArC(CF$_3$)$_2$Br were calculated from k_{Br} or k_{HBr} for the reaction in the addition direction (Table I) and K_T, the overall equilibrium constant for the reaction (Table I), by using the relationship $K_T = k_{HBr}/k_{solv}{}^{OH} = k_{Br}/k'_{solv}$. The rate constants calculated for the specific-base-catalyzed and the uncatalyzed cleavage reactions are $k'_{solv} = 3.3 \times 10^{-6}\ M\ s^{-1}$ (Scheme III) and $k_{solv}{}^{OH} = 5.8 \times 10^{-5}\ s^{-1}$, respectively. The value for k'_{solv} is in acceptable agreement with $k'_{solv} = 2.6 \times 10^{-6}\ M\ s^{-1}$, determined from the slope of the plot in Figure 3.

The equilibrium constant K_T for the addition of HI to **1** is 17-fold larger than for the addition of HBr (Table I). Similarly, the equilibrium constant for the addition of I$^-$ to 4-MeOArCH(CF$_3$)$^+$ ($6.8 \times 10^{13}\ M^{-1}$)[17a] is 20-fold larger than for the addition of Br$^-$ ($3.2 \times 10^{12}\ M^{-1}$).[8] These results are consistent with thermodynamic data for the formation of carbon–halide bonds by sequential one-electron transfer steps. The difference between the ionization potentials of I$^-$ and Br$^-$ shows that electron transfer from Y$^-$ to a benzyl carbocation to form a radical pair is more favorable for I$^-$ than Br$^-$ by ca. 16 kcal/mol,[17b] while radical combination to form benzyl bromide is ca. 10 kcal/mol[17c] more favorable than combination to form benzyl iodide.[18] The former effect favors the reaction of I$^-$ with benzyl carbocations, the latter effects favor the reaction of Br$^-$, and the balance of the two effects favors the addition of iodide ion as observed here for the reactions of **1** and 4-MeOArCH(CF$_3$)$^+$.

Table III. Rate and Equilibrium Constants for the Addition of Bromide Ion to 4-XArC(CF$_3$)$_2^{+a}$



	X		
	$^-$O–	H$^+$·$^-$O–^{b}	CH$_3$O–^{c}
k_f	$0.21\ M^{-1}\ s^{-1\,d}$	$3.7\ M^{-1}\ s^{-1}$	$2.3 \times 10^8\ M^{-1}\ s^{-1}$
k_{solv}	$\sim 3 \times 10^3\ s^{-1\,e}$	$5.8 \times 10^{-5}\ s^{-1}$	$3.6 \times 10^{-7}\ s^{-1}$
$K_{add} = k_f/k_{solv}$	$\sim 7 \times 10^{-5}\ M^{-1}$	$6.4 \times 10^4\ M^{-1}$	$6 \times 10^{14}\ M^{-1}$

^{a}At 25 °C in 50:50 (v/v) trifluoroethanol/water (I = 0.50, NaClO$_4$). ^{b}Experimental data for the specific-acid-catalyzed addition of Br$^-$ to **1** (Table I). ^{c}Data from ref 8. ^{d}The value for k_Y from Table I. ^{e}Calculated as described in the text.

Oxygen Substituent Effects. Table III gives the changes in the rate and equilibrium constants for the addition of bromide ion to **1** that occur upon protonation and methylation of the oxygen substituent at **1**. The value of $k_{solv}{}^O \approx 3 \times 10^3\ s^{-1}$ (Table III) for the reaction of 4-$^-$OArC(CF$_3$)$_2$Br to form **1** was calculated from $K_T = 64\,000\ M^{-2}$, $K_a{}^P = 10^{-9}$ M,[19] and the relationship $k_{solv}{}^O = k_{Br}/K_TK_a{}^P$ derived for Scheme IV.[19] K_{add} for the addition of Br$^-$ to **1** to form 4-$^-$OArC(CF$_3$)$_2$Br was then calculated as $k_{Br}/k_{solv}{}^O$. The second column of Table III gives data for the reaction of **1** with bromide ion at a standard state of 1.0 M acid (Table I). The third column of Table III lists data for the reaction of 4-MeOArC(CF$_3$)$_2^+$ with bromide ion. The value of k_{solv} was determined as the first-order rate constant for the solvolysis of 4-MeOArC(CF$_3$)$_2$Br by an S$_N$1 ($D_N + A_N$)[40a] mechanism. The rate constant for the capture of 4-MeOArC(CF$_3$)$_2^+$ by bromide ion was taken from earlier work.[8]

There is a ~10^{19}-fold difference between K_{add} for the reaction of **1** and K_{add} for the reaction of 4-MeOArC(CF$_3$)$_2^+$ (first and third columns of Table III). This difference reflects the large destabilization of **1** by methylation of the oxygen ring substituent. 4-$^-$OArC(CF$_3$)$_2$Br is highly unstable, with an estimated rate constant of $k_{solv}{}^O \approx 3 \times 10^3\ s^{-1}$ for cleavage to form **1** and Br$^-$ (Scheme IV). The cleavage reaction is strongly favored; $K_{add} \approx 7 \times 10^{-5}$ M. These data are consistent with the earlier observations that **1** is stable at neutral pH in the presence of bromide ion and that 4-HOArC(CF$_3$)$_2$Br breaks down rapidly on an HPLC column to form **1**.[8]

There is a ~10^9-fold difference between K_{add} for the addition of bromide ion to **1** to form 4-$^-$OArC(CF$_3$)$_2$Br and K_{add} for the addition of bromide ion to **1** to form 4-HOArC(CF$_3$)$_2$Br at a standard state of 1 M acid (first and second columns of Table III). Protonation of **1** at the oxygen ring substituent gives **1H**$^+$ ($K_a{}^Q$, Scheme IV), which is expected to show an affinity for bromide ion similar to that observed for 4-MeOArC(CF$_3$)$_2^+$. Therefore, if 1 M acid protonated a significant fraction of **1** (log $K_a{}^Q \approx 0$), then K_{add} for the reaction of **1** in 1 M acid and K_{add} for the reaction of 4-MeOArC(CF$_3$)$_2^+$ would be similar. However, the value of K_{add} for the reaction of **1** in 1.0 M acid is 10^{10}-fold smaller than K_{add} for the reaction of 4-MeOArC(CF$_3$)$_2^+$. This

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(16) Diffusion-limited rate constants of (4–7) × $10^9\ M^{-1}\ s^{-1}$ have been measured directly for the reaction of azide ion with unstable carbocations in water or predominately aqueous solutions: McClelland, R. A.; Kanagasabapathy, V. M.; Steenken, S. *J. Am. Chem. Soc.* **1988**, *110*, 6913–6914.

(17) (a) The ratio of the rate constants for the capture of 4-MeOArCH(CF$_3$)$^+$ by iodide ion ($5 \times 10^9\ M^{-1}\ s^{-1}$) and for the ionization of 4-MeOArCH(CF$_3$)I to form 4-MeOArCH(CF$_3$)$^+$ and I$^-$ ($7.3 \times 10^{-5}\ s^{-1}$).[9a] (b) Pearson, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 6109–6114. (c) McMillan, D. F.; Golden, D. M. *Annu. Rev. Phys. Chem.* **1982**, *33*, 493–532.

(18) I am grateful to a reviewer for suggesting this analysis of the difference in halide ion affinities for addition to benzyl carbocations.

(19) The pK_a's of substituted phenols in trifluoroethanol/water have not been determined. The value of 9.0 for the ionization of 4-HOArC(CF$_3$)$_2$Br is an estimate that has been made in order to illustrate the great instability of 4-$^-$OArC(CF$_3$)$_2$Br.

shows that only a small fraction of **1** is protonated in a 1 M solution of $HClO_4$ ($\log K_a^Q \gg 0$).

Equation 6 and the data in Table III can be used to calculate an estimated pK_a^Q of -8.1 for deprotonation of **1H$^+$** ($-\log K_a^Q$, Scheme IV). The following values were used in this calculation:

$$pK_a^Q(\mathbf{1H^+}) = \log K_T - [\log (K_{add})_{OMe} - \Delta\log (K_{add})_{OMe}] \quad (6)$$

$K_T = 64.000\ M^{-1}$ is the equilibrium constant for the addition of H^+ and Br^- to **1** in the presence of 1.0 M acid, $(K_{add})_{OMe} = 6 \times 10^{14}\ M^{-1}$ is the equilibrium constant for the addition of bromide ion to 4-MeOArC$(CF_3)_2^+$ (Table III), and $\Delta\log (K_{add})_{OMe} = 1.9$ is an estimate of the effect on $\log (K_{add})_{OMe}$ of a change from a 4-MeO to a 4-HO substituent.[20]

1H$^+$, with an estimated pK_a of -8.1, is considerably more acidic than protonated acetone ($pK_a = -3.1$).[23] The large negative pK_a for **1H$^+$** reflects the destabilization of this benzyl cation by the strongly electron withdrawing α-CF_3 substituents.

Uncatalyzed Reactions. The solvent deuterium isotope effect (DIE) of $(k_o)_{HOH}/(k_o)_{DOD} = 2.0$ for the uncatalyzed addition of solvent to **1** (Table II) is larger than the values of 1.2 and 1.17, respectively, observed for the addition of water to the trianisylmethyl cation[24a] and a ferrocenylalkyl cation.[24b] The small isotope effects for the latter reactions are consistent with rate-determining carbon-oxygen bond formation. The larger solvent DIE observed for the addition of solvent to **1** shows that, in comparison to carbocation addition reactions, there is a significantly greater weakening of bonds between hydrogen and solvent on moving to the reaction transition state. This may be explained by one or more of the following changes: (A) a shift to a later transition state for the solvent addition reaction leading to an increase in the acidity of hydrogens attached to the water nucleophile and a strengthening of their hydrogen bonds to solvent,[25,26] (B) stabilization of the developing negative charge at the quinone oxygen by hydrogen bonds to solvent,[26] and (C) a primary solvent deuterium isotope effect on the reaction resulting from the appearance of general-base catalysis of the water addition reaction by a second molecule of water.[27]

The solvent deuterium isotope effect decreases from 2.0 to 1.0 when the nucleophile is changed from solvent to bromide ion (Table II). This decrease can be explained by the difference in the changes in the solvent-nucleophile interactions that occur on moving from the ground state to transition state for the two reactions. The acidity of the hydrogens attached to the water nucleophile increases on moving to the reaction transition state, and this may cause changes in the interactions of these hydrogens with solvent, which contribute to the normal isotope effect [(A) and (B) above]. On the other hand, the reaction of bromide ion as a nucleophile must be preceded by partial desolvation of the ion. This will contribute to an inverse solvent DIE, because the solvation of halide ions in H_2O is stronger than in D_2O.[28]

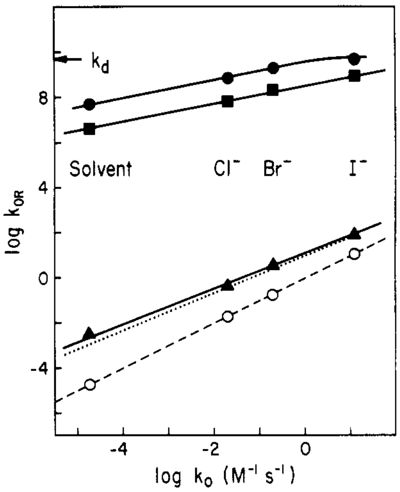

Figure 4. Logarithmic plot of the rate constants, k_O, for the reaction of solvent and halide ions with **1** against the following: (▲) rate constants for the hydrogen ion catalyzed addition of nucleophiles to **1**, dotted line shows the correlation using data for halide ions only; (■) rate constants for the addition of nucleophiles to 4-MeOArC$(CF_3)_2^+$; (●) rate constants for the addition of nucleophiles to 4-MeOArCH$(CF_3)^+$; (○) rate constants k_O for the addition of nucleophiles to **1**, dashed line shows the slope expected for an electrophile with the same nucleophile selectivity as **1**. The rate constants have the following units: s^{-1} (●, ■, ○) or $M^{-1}\ s^{-1}$ (▲) for the addition of solvent and $M^{-1}\ s^{-1}$ (●, ■, ○) or $M^{-2}\ s^{-1}$ (▲) for the addition of halide ions. The estimated rate constant for a diffusion-limited reaction, $k_d = 5 \times 10^9\ M^{-1}\ s^{-1}$, is also labeled.

Hydrogen Ion Catalyzed Reactions. Stepwise or Concerted Catalysis? The reactions of solvent and halide ions that are catalyzed by the hydrogen ion may follow either a stepwise mechanism (A_HD_{xh} + $A_N{}^*$)[40a,b] or a concerted mechanism ($A_NA_HD_{xh}$) in which proton transfer and formation of a carbon-halide bond occur in a single step (Scheme IV). The following experimental observations are consistent with a concerted mechanism for the reaction of halide ions.

(1) 4-HOArC$(CF_3)_2$Br breaks down to give **1**, Br^- and H^+ with a rate constant ($k_{solv}{}^{OH} = 5.8 \times 10^{-5}\ s^{-1}$) that is 160-fold larger than k_{solv} for the reaction of 4-MeOArC$(CF_3)_2$Br (Table III). This difference could be due either to stabilization of the transition state for a stepwise mechanism by solvation of the positive charge that develops at the oxygen ring substituent or to the kinetic advantage for reaction by the concerted mechanism (Scheme IV). It is not likely that solvation at the 4-HO substituent could account for the faster cleavage of 4-HOArC$(CF_3)_2$Br, because stabilization by solvation of a transition state that resembles a protonated carbonyl group is small for the hydrogen ion catalyzed cleavage of ring-substituted acetophenone-bisulfite addition compounds. These reactions proceed through O-protonated acetophenone intermediates, and they are no more than 10-fold faster than the cleavage of the corresponding O-methyl compounds to form oxocarbenium ion intermediates.[29] The difference in substituent constants $\sigma^+{}_{OH} - \sigma^+{}_{OMe} = -0.12$,[21] and $\rho_{solv} = -10.7$[22] for the ionization of 4-XArC$(CF_3)_2$Br gives a ~20-fold effect for this substitution on k_{solv} for reaction to form 4-HOArC$(CF_3)_2^+$ (**1H$^+$**). The larger (160-fold) effect observed is consistent with a kinetic advantage for the reaction of 4-HOArC$(CF_3)_2$Br by a concerted mechanism that bypasses **1H$^+$**, the intermediate of the stepwise reaction.

(2) Values of $\log k_{OR}$ for the addition of nucleophiles to 4-MeOArC$(CF_3)_2^+$ and for the acid-catalyzed addition of nucleophiles to **1** have each been plotted against $\log k_O$ for the direct addition of nucleophiles to **1** (Figure 4). The data for the reaction of 4-MeOArC$(CF_3)_2^+$, the acid-catalyzed addition of nucleophiles to **1**, and the direct addition of nucleophiles to **1** (dashed line,

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[20] The 1.9-unit difference in $\log K_{add}$ for the addition bromide ion to **1H$^+$** and 4-MeOArC$(CF_3)_2^+$ was calculated from eq 8 and values of $\sigma^+{}_{OMe} = -0.79$, $\sigma^+{}_{OH} = -0.91$,[21] and $\rho_{add} = (\rho_f - \rho_{solv}) = 16$.[22]

$$\Delta\log (K_{add})_{OMe} = (\sigma_{OH} - \sigma_{OMe})\rho_{add} \quad (8)$$

[21] Hine, J. *Structural Effects on Equilibria in Organic Chemistry*; Wiley: New York, 1975; p 72.

[22] $\rho_{solv} = -10.7$, measured for the ionization of ArC$(CF_3)_2$OTs in trifluoroacetic acid,[10] is an estimate of ρ_{solv} for ionization of ArC$(CF_3)_2$Br. $\rho_f = 5.3$ is calculated with the assumption that the ratio ρ_f/ρ_{solv} for this reaction is the same as the value of $\rho_f/\rho_{solv} = 4.8/-9.7$ determined for the ionization of ArCH(CF_3)OTs and the capture of ArCH$(CF_3)^+$ by solvent.[9]

[23] Bagno, A.; Lucchini, V.; Scorrano, G. *Bull. Soc. Chim. Fr.* **1987**, 563-572.

[24] (a) Bunton, C. A.; Carrasco, N.; Watts, W. E. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1267-1273. (b) Hill, E. A.; Mueller, W. J. *Tetrahedron Lett.* **1968**, *9*, 2565-2569.

[25] (a) Stahl, N.; Jencks, W. P. *J. Am. Chem. Soc.* **1986**, *108*, 4196-4205.

[26] The net bonding to hydrogen is weakened upon hydrogen bond formation, which consequently is more favorable in H_2O than D_2O: Schowen, R. L. *Prog. Phys. Org. Chem.* **1972**, *9*, 275-332. Gold, V.; Grist, S. *J. Chem. Soc. B* **1971**, 2282-2285. Winey, D. A.; Thornton, E. R. *J. Am. Chem. Soc.* **1975**, *97*, 3102-3108.

[27] Studies on general-base catalysis of the addition of water to carbenium ions have shown that these reactions may proceed by stepwise or concerted mechanisms, depending on the carbenium ion. These results are summarized in Gandler, J. R. *J. Am. Chem. Soc.* **1985**, *107*, 8218-8223.

[28] Swain, C. G.; Bader, R. F. W. *Tetrahedron* **1960**, *10*, 182-199.

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Scheme V

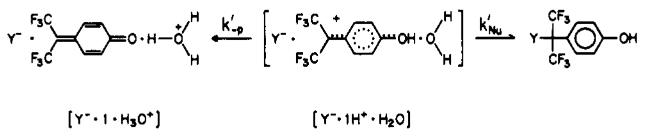

Figure 3) are correlated with slopes of 0.42, 0.78,[30] and 1.00, respectively. These slopes correspond to the selectivity of halide ions and solvent in the different reactions. The slope of 0.78 for the acid-catalyzed reaction is inconsistent with a stepwise mechanism and trapping of the intermediate **1H**$^+$ by halide ions. The selectivity of **1H**$^+$ (4-HOArC$(CF_3)_2^+$) toward halide ions should be close to that of 4-MeOArC$(CF_3)_2^+$, because the two cations are expected to have comparable chemical stabilities. However, the observed selectivity for the acid-catalyzed reaction (0.78) is closer to that for the reaction of the stable electrophile **1** (1.00) than for the reaction of 4-MeOArC$(CF_3)_2^+$ (0.42).

(3) The increase in the solvent DIE, from $k_H/k_D = 0.68$ for the acid-catalyzed addition of water to **1** to $k_{HBr}/k_{DBr} = 1.0$ for the acid-catalyzed addition of bromide ion to **1** (Table III), is inconsistent with a stepwise mechanism for the reaction of bromide ion. If catalysis of both the solvent and bromide ion reactions involved stepwise protonation of **1**, then the difference in solvent deuterium isotope effects for the reaction of the two nucleophiles would depend upon changes in the interaction of these nucleophiles with solvent on moving to the reaction transition state. When water reacts as a nucleophile, a charged oxonium ion develops at the transition state, which will be stabilized by hydrogen bonds to solvent; however, at least one hydrogen bond between solvent and bromide ion must be cleaved before this ion can react as a nucleophile to form a bond to carbon. Hydrogen bonds are stronger in H_2O than in D_2O.[26,28] Therefore, the change in hydrogen bonding interactions at the water and bromide ion nucleophiles will lead to normal and inverse isotope solvent DIEs, respectively, so that k_H/k_D would be greater than k_{HBr}/k_{DBr}. The larger solvent DIE observed for the hydrogen ion catalyzed addition of Br⁻ to **1** is consistent with a significant contribution of a primary solvent DIE for a mechanism in which carbon–bromine bond formation and proton transfer to **1** take place in a single step.

(4) Equation 7, derived for Scheme IV, can be used to calculate the rate constant k_{Nu} for trapping of **1H**$^+$, if this species is assumed to be an intermediate of the hydrogen ion catalyzed addition of halide ions to **1**. A rate constant of $k_{Nu} = 1 \times 10^{10}$ M^{-1} s^{-1} for the reaction of iodide ion with **1H**$^+$ is calculated from eq 7, with use of the observed rate constant $k_{HI} = 81$ M^{-2} s^{-1} (Table I) and the estimated value of $K_a{}^Q = 10^{8.1}$ M. However, **1H**$^+$ is not a

$$k_{Nu} = k_{HI}K_a{}^Q \qquad (7)$$

sufficiently reactive carbocation to undergo capture by iodide ion with $k_I = 10^{10}$ M^{-1} s^{-1}: The rate constant for the capture of the slightly more unstable cation 4-MeOArC$(CF_3)_2^+$ is only $k_I = 1 \times 10^9$ M^{-1} s^{-1}. This calculation suggests that either there is a large error in the estimate of $K_a{}^Q$ for the deprotonation of **1H**$^+$ or the hydrogen ion catalyzed reaction of iodide ion follows a concerted pathway that bypasses **1H**$^+$.

Enforced or Nonenforced? I now consider the question of whether the concerted mechanism for the acid-catalyzed addition of halide ions to **1** is enforced by the lifetime of the unstable intermediate **1H**$^+$. The relevant pathways for the breakdown of this intermediate [Y⁻·**1H**$^+$·OH$_2$] are shown in Scheme V. A concerted mechanism will be enforced if this species cannot exist as an intermediate in a potential energy well, that is, if the barrier to the collapse of **1H**$^+$ in the presence of bromide ion (k'_{Nu}) or water (k'_{-p}) is smaller than that for a bond vibration.[31]

There must be a significant barrier to k'_{Nu} for the addition of halide ions to **1H**$^+$, because the more unstable carbocation 4-MeOArC$(CF_3)_2^+$ is captured by halide ions in *activation*-limited reactions ($k_{Nu} \leq 1 \times 10^9$ M^{-1} s^{-1}, Figure 4). It is less clear whether the concerted mechanism may be enforced by the absence of a barrier to proton transfer from **1H**$^+$ to water (k'_{-p}). Proton transfer reactions occur along hydrogen bonds, usually with double potential wells in which there is a barrier to transfer from the hydrogen bond donor to the acceptor.[32,33] However, a single potential structure is possible for the hydrogen bond between **1** and H_3O^+ in which the proton lies at the minimum of an energy well centered close to water, which is a considerably stronger base than **1** ($pK_a{}^Q \approx -8.1$).[32,33]

UV and NMR spectral data for acetone in concentrated solutions of mineral acids are consistent with the formation of a stable complex containing H_3O^+ in a hydrogen bond to the carbonyl group.[23] This complex may represent a hydrogen bond with a single potential energy minimum, and by analogy a similar structure is possible for the hydrogen bond between H_3O^+ and **1**.

The following results from this work are consistent with a stepwise ($A_HD_{xh} + A_N{}^*$)[40a,b] mechanism for H$^+$-catalyzed addition of solvent to **1**, where the reactant is first protonated to form **1H**$^+$, which is then captured by water (Scheme IV). If **1H**$^+$ forms as an intermediate of this reaction, then the concerted addition reaction of HY cannot be enforced and there must be a barrier to proton transfer from **1H**$^+$ to water.

(1) The inverse solvent DIE of $k_H/k_D = 0.68$ (Table II) for the acid-catalyzed reaction of **1** is consistent with stepwise, preequilibrium, protonation of **1** followed by addition of solvent to **1H**$^+$, because D_3O^+ is a stronger acid than H_3O^+.[26,34] The observation of a smaller solvent DIE on the H$^+$-catalyzed addition of solvent than on the H$^+$-catalyzed addition of bromide ion suggests that the two reactions occur by stepwise and concerted mechanisms, respectively.

(2) $K_a{}^Q = 10^{8.1}$ M, $k_H = 0.0032$ M^{-1} s^{-1}, and eq 7 for Scheme IV give $k_{Nu} = 4 \times 10^5$ s^{-1} for the trapping of the putative intermediate **1H**$^+$ by solvent. This is 10-fold smaller than $k_s = 4.5 \times 10^6$ s^{-1} for the capture of 4-MeOArC$(CF_3)_2^+$ by solvent,[8] a difference that is in keeping with the lower reactivity expected for **1H**$^+$. In contrast with the hydrogen ion catalyzed addition of halide ions to **1**, it is not necessary to propose a concerted mechanism for the solvent reaction in order to explain the observed rate of the reaction.

(3) Figure 4 (▲) shows the correlation between the rate constants for the direct addition of nucleophiles to **1** and rate constants for reactions catalyzed by hydrogen ion. If only data for halide ion reactions are used (dotted line), then a small, 0.22 log unit, positive deviation is observed for the hydrogen ion catalyzed addition of water. This deviation is consistent with an upward break in the structure–reactivity plot due to the appearance of a stepwise mechanism for this reaction.

Structure–Reactivity Relationships. The correlation between log k_{OR} for the addition of nucleophiles to 4-MeOArC$(CF_3)_2^+$ and log k_O for the reaction of **1** (Figure 4) has a slope of 0.42, which is much smaller than the value of 1.0 that would have been observed if the two electrophiles showed the same selectivity toward nucleophilic reagents (dashed line, Figure 4). The smaller selectivity of 4-MeOArC$(CF_3)_2^+$ does not arise from a rate-limiting step for the reaction that is *independent of the electrophile* (e.g., desolvation of the nucleophile),[35,36] because the values of k_{OR} for the addition of nucleophiles to 4-MeOArC$(CF_3)_2^+$ are at least 5-fold smaller than those for the addition to 4-MeOArCH$(CF_3)^+$

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(30) When data for halide ions only are used, a slope of 0.82 is obtained (dotted line, Figure 4). This may be a slightly more accurate measure of the selectivity for the reaction of halide ions by a concerted reaction mechanism. There is evidence that the addition of water proceeds by a different, stepwise, reaction mechanism.

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(Figure 4). We conclude that the destabilization of **1** by methylation of the oxygen ring substituent causes a large decrease in the chemical selectivity of the electrophile for reaction with halide ions and solvent.

There are many examples of carbocation addition reactions in which nucleophile selectivity is independent of electrophile reactivity.[11a,b] Data from these reactions were used to develop the N_+ scale for the reactivity of nucleophiles toward carbocations and related electrophiles. By contrast, methylation of the carbonyl oxygen of **1** causes a significant decrease in the selectivity of the electrophile toward reaction with halide ions. The change in substituent at **1** from 4-$^-$O to 4-MeO particularly favors the observation of a decrease in selectivity, because the difference in the reactivity of **1** and 4-MeOArC$(CF_3)_2{}^+$ is extremely large (10^{11}-fold). Further, there is only a small chemical barrier to the capture of 4-MeOArC$(CF_3)_2{}^+$, and the following recent studies suggest that Hammond effects begin to become significant when the carbocation lifetime is decreased to 10^{-5} s or shorter. (1) β_{nuc} for the reaction of ring-substituted 1-phenylethyl carbocations with alcohols decreases from 0.50 (4-N$(CH_3)_2$) to 0.22 (4-OPh) for an increase in k_s for carbocation capture by 50:50 (v/v) trifluoroethanol/water from ≤ 2000 s^{-1} to 3×10^8 s^{-1}.[35a] (2) A large number of substituted triarylmethyl carbocations obey the N_+ equation; however, a breakdown of the N_+ scale has been noted for the triphenylmethyl cation, which is captured by water with a rate constant of 1.5×10^5 s^{-1}.[11c,36] By contrast, there are a number of reactions of cations with nucleophiles in which nucleophile selectivities remain constant as the rate constants for nucleophile addition increase up to the diffusion limit.[11b] I can offer no simple explanation to reconcile the differences in these results. This laboratory is in the process of collecting more extensive data for the addition of anionic and neutral nucleophiles to benzyl carbocations in order to determine whether the N_+ scale is generally applicable to the reactions of these highly unstable carbocations.

Biological Relevance. The results of these chemical studies on a simple quinone methide lead to the following generalizations about the biological activity of more elaborate quinone methides.[1-4]

(1) The efficiency with which an electrophilic reagent will label a nucleophilic site in a cell depends on the rate constant ratio k_{Nu}/k_s (M^{-1}) for reaction of the electrophile with the nucleophile and solvent. Efficient labeling is favored by a large value of k_{Nu} and a small value of k_s, so that the electrophile will have a long lifetime in which to encounter and react with the nucleophilic reagent. By this criteria, quinone methides are very well suited to the role of electrophilic labels of biological molecules. The selectivities of **1** for reaction with azide ion ($k_{az}/k_s > 4 \times 10^8$ M^{-1})[37] and bromide ion ($k_{Br}/k_s = 12000$ M^{-1}) are far larger than the values of 10^6 and 33 M^{-1},[36,38] respectively, for the capture of the more reactive substituted triarylmethyl carbocations.

(2) The results reported in this work show that the addition of nucleophiles to **1** is catalyzed by protonation of the quinone oxygen. Similarly, biologically important quinone methides may react preferentially with "hot" spots along the DNA chain[39] where a general acid is properly aligned to catalyze the nucleophilic addition reaction.

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Remote Control of Stereogenicity Transfer by Ring-Generated Anisotropic Orbital Overlap. Stereochemistry of Hydrogen Shift in the Intramolecular Reverse Ene Reaction of a *cis*-2-Alkyl-1-alkenylcyclopropane

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Abstract: The thermal rearrangement of *cis*-2-(2-propyl)-1(*E*)-propenylcyclopropane at temperatures near 230 °C in the gas phase occurs with activation parameters of $E_a = 35.5 \pm 0.6$ kcal/mol and log $A = 12.05 \pm 0.5$ (A, s^{-1}). The optically active isotopically doubly labeled analogue (*cis*-2(*S*)-(2(*S*)-propyl-*1*-d_3)-1(*S*)-(1(*E*)-propenyl-*2*-*d*)cyclopropane **5** was synthesized in 12 steps from dicyclopentadiene. Pyrolysis of **5** gave only 2-methyl-octa-2(*Z*),5(*Z*)-diene-*1*-d_3-*7*(*S*)-*d*, with high stereospecificity at each of the three sites of stereogenicity. This result is the one predicted if the reaction is controlled by optimal overlap of the reacting C–H and π bond orbitals with the C_s symmetric component of the degenerate $3E'$ highest occupied orbital of the cyclopropane ring.

Introduction

The orbital symmetry rules[1] designate the stereochemical course of pericyclic reactions as allowed or forbidden from the properties of *orbital phases*. Relatively little attention has been directed to the more subtle factor of *orbital overlap*, whose requirements can determine which of several formally allowed pathways will be preferred. We suggest that the structural replacement of a double bond by an alicyclic ring will cause one of two orbital-symmetry-allowed reaction pathways of the derived homologue to enjoy better orbital overlap. The present group of papers[2,3]

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