

Intrinsic Barriers for the Reactions of an Oxocarbenium Ion in Water

John P. Richard,*¹ Kathleen B. Williams, and Tina L. Amyes

Contribution from the Department of Chemistry,
University at Buffalo, SUNY, Buffalo New York 14260-3000

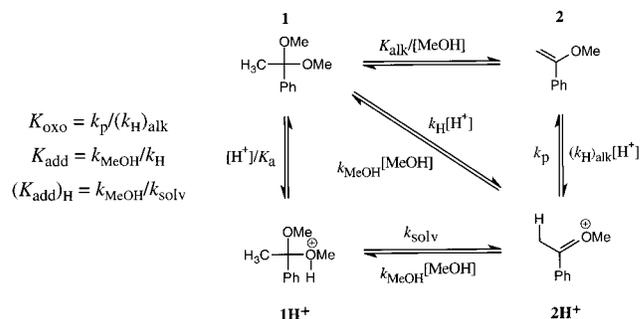
Received May 10, 1999

The nucleophile addition reactions of α -methyl benzyl carbocations with Lewis bases are fast and are generally perceived to be thermodynamically favorable processes.^{2,3} By contrast with proton-transfer reactions at carbon,^{4–6} there has been little consideration of whether these reactions of unstable carbocations are *intrinsically* fast, or whether they are fast simply because they are energetically favorable. This distinction requires a knowledge of the *intrinsic* barrier to the reaction in the absence of a thermodynamic driving force. We report here intrinsic rate constants of $(k_{\text{MeOH}})_o = 1 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ and $(k_p)_o = 450 \text{ s}^{-1}$ for the nucleophilic addition of methanol to the acetophenone oxocarbenium ion 2H^+ and deprotonation of 2H^+ by solvent water, respectively (Scheme 1). These intrinsic rate constants correspond to intrinsic barriers of $\Delta_{\text{MeOH}} = 6.5 \text{ kcal/mol}$ and $\Delta_p = 13.8 \text{ kcal/mol}$ for the nucleophile addition and proton-transfer reactions, respectively.

Table 1 summarizes the rate and equilibrium constants for the formation and reaction of **1**, 1H^+ , **2**, and 2H^+ in water at 25 °C (Scheme 1). The literature values^{7,8} of $k_{\text{MeOH}} = 3 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ and $k_{\text{H}} = 1600 \text{ M}^{-1} \text{ s}^{-1}$ give $K_{\text{add}} = 1900$ for the addition of methanol to 2H^+ to give **1**. The value of $\text{p}K_{\text{a}} = -6.2$ for protonated acetophenone dimethyl ketal 1H^+ was estimated starting from $\text{p}K_{\text{a}} = -2.52$ for protonated dimethyl ether.⁹ The equilibrium constant for the addition of methanol to 2H^+ to give 1H^+ can then be calculated as $(K_{\text{add}})_{\text{H}} = K_{\text{add}}/K_{\text{a}} = 0.0012 \text{ M}^{-1}$ (Scheme 1). The first-order rate constant for the cleavage of 1H^+ to give the oxocarbenium ion 2H^+ can be calculated as $k_{\text{solv}}/K_{\text{a}} = k_{\text{H}}K_{\text{a}} = 2.5 \times 10^9 \text{ s}^{-1}$. This is smaller than the rate constant of $\sim 10^{10} \text{ s}^{-1}$ for the thermodynamically favorable deprotonation of 1H^+ by solvent water to regenerate **1**,¹¹ so that **1** and 1H^+ are essentially at chemical equilibrium during the acid-catalyzed cleavage of **1**. This is in agreement with the conclusions of earlier studies that 1H^+ is an intermediate of the stepwise, specific-acid-catalyzed hydrolysis of ketals,¹² which is the microscopic reverse of nucleophilic addition of methanol to 2H^+ to form **1**.

The rate constants for protonation of α -methoxystyrene **2** by hydronium ion and acetic acid in water at 25 °C and $I = 1.0$ (KCl) were determined by published methods¹³ as $(k_{\text{H}})_{\text{alk}} = 80$

Scheme 1



$\text{M}^{-1} \text{ s}^{-1}$ and $k_{\text{AcOH}} = 0.13 \text{ M}^{-1} \text{ s}^{-1}$, respectively. Figure 1 shows the effect of increasing concentrations of acetate ion on the ratio of the yields of α -methoxystyrene **2** and acetophenone from the acid-catalyzed cleavage of acetophenone dimethyl ketal **1** in water at pH 7.0 (10 mM phosphate buffer) at 25 °C and $I = 1.0$ (KCl).¹⁴ The data were fit to eq 1 to give $k_{\text{AcO}}/k_{\text{HOH}} = 0.0034 \text{ M}^{-1}$ for partitioning of 2H^+ between deprotonation by acetate ion to give **2** and nucleophilic addition of solvent water to give, ultimately, acetophenone.¹⁵ This partitioning ratio can be combined with the value of $5 \times 10^7 \text{ s}^{-1}$ for k_{HOH} ,⁷ to give $k_{\text{AcO}} = 1.7 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ as the absolute rate constant for deprotonation of 2H^+ by acetate ion. The acidity of the oxocarbenium ion 2H^+ can then be calculated as $K_{\text{oxo}} = (k_{\text{AcO}}/k_{\text{AcOH}})(K_{\text{a}})_{\text{AcOH}} = 33 \text{ M}$, using $\text{p}(K_{\text{a}})_{\text{AcOH}} = 4.60$ for acetic acid under our experimental conditions. The relationship $K_{\text{oxo}} = k_p/(k_{\text{H}})_{\text{alk}}$ then gives $k_p = 2600 \text{ s}^{-1}$ for deprotonation of 2H^+ by solvent water. The equilibrium constant for elimination of methanol from **1** to give **2** was calculated as $K_{\text{alk}} = K_{\text{oxo}}/K_{\text{add}} = 0.018 \text{ M}$ (Scheme 1).¹⁶

(13) The reactions of **2** were monitored by following the appearance of acetophenone by UV spectroscopy. The protonation of **2** is rate-limiting for its conversion to acetophenone [Loudon, G. M.; Berke, C. *J. Am. Chem. Soc.* **1974**, *96*, 4508–4517].

(14) The products of the cleavage of **1** in water were separated by HPLC and quantified as described in earlier work [Richard, J. P. *J. Am. Chem. Soc.* **1989**, *111*, 1455–1465]. Ratios of product yields $[2]/[\text{acetophenone}]$ were calculated using eq 4 $\{[2]/[\text{acetophenone}] = (A_2/A_{\text{ketone}})(\epsilon_{\text{ketone}}/\epsilon_2)\}$, where A_2/A_{ketone} is the ratio of the peak areas from HPLC analysis and $\epsilon_{\text{ketone}}/\epsilon_2 = 0.46$ is the ratio of the extinction coefficients of the two products at 269 nm. The observed product ratio $[2]/[\text{acetophenone}]$ decreases with time due to acid-catalyzed hydrolysis of **2** to give acetophenone. Therefore, the initial product ratio was determined by extrapolation to zero time of a linear plot of the observed product ratios against time determined during reaction of up to 30% of **1**. During this time, the value of $[2]/[\text{acetophenone}]$ decreases by $\sim 30\%$, but the difference between the ratio obtained by extrapolation to zero time and that obtained at the earliest time point was $\leq 10\%$. The values of A_2/A_{ketone} and the value of $k_{\text{AcO}}/k_{\text{HOH}}$ (M^{-1}) determined from the ratio of product yields were reproducible to better than $\pm 10\%$.

(15) The derivation of eq 1 assumes that there is no catalysis by acetate ion of the nucleophilic addition of water to 2H^+ . An increase in the concentration of acetate ion from 0 to 0.77 M ($I = 1.0$, KCl) results in a 2-fold increase in the observed product rate constant ratio $k_{\text{HOH}}/k_{\text{SO}_3}$ for partitioning of 2H^+ between the addition of solvent water and the diffusion-limited addition of sulfite dianion, which is nominally consistent with catalysis of the addition of water to 2H^+ by acetate ion (ref 8). However, this change in the observed product rate constant ratio is likely a result of a specific acetate ion salt effect on the relative values of k_{SO_3} and k_{HOH} because (a) acetate ion catalysis of the addition of water to 2H^+ ($k_{\text{HOH}} = 5 \times 10^7 \text{ s}^{-1}$, ref 7) should be less important than catalysis of the addition of water to the more stable 1-(4-dimethylaminophenyl)ethyl carbocation ($k_{\text{s}} = 40 \text{ s}^{-1}$ in 50:50 (v/v) trifluoroethanol/water [McClelland, R. A.; Cozens, F. L.; Steenken, S.; Amyes, T. L.; Richard, J. P. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1717–1722]), for which no catalysis by acetate ion was observed.²² (b) The absence of general acid catalysis of the cleavage of **1** to give 2H^+ and methanol (ref 12) requires that there be no general base catalysis of the addition of methanol to 2H^+ in the reverse direction. This suggests that catalysis of the addition of water, whose basicity is similar to that of methanol, is negligible.

(16) This is in fair agreement with $K_{\text{alk}} = 0.06 \text{ M}$ obtained by combining the value of K_{alk} determined for the elimination reaction in methanol and the free energies of transfer of the reactants and products from methanol to water [Toullec, J. *J. Chem. Soc., Perkin Trans. 2* **1989**, 167–171]. The value of $K_{\text{oxo}} = 33 \text{ M}$ reported here also shows a similar agreement with the value of 65 M determined by a different indirect method in this earlier study.

(1) Tel: (716) 645 6800, ext 2194. Fax: (716) 645 6963. E-mail: jrichard@chem.buffalo.edu.

(2) Richard, J. P. *Tetrahedron* **1995**, *51*, 1535–1573.

(3) McClelland, R. A. *Tetrahedron* **1996**, *52*, 6823–6858.

(4) Bernasconi, C. F. *Tetrahedron* **1985**, *41*, 3219–3234.

(5) Bernasconi, C. F. *Acc. Chem. Res.* **1987**, *20*, 301–308.

(6) Bernasconi, C. F. *Acc. Chem. Res.* **1992**, *25*, 9–16.

(7) Amyes, T. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 7888–7900.

(8) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 8238–8248.

(9) Following the methodologies of Fox and Jencks (ref 10a) and Funderburk et al. (ref 10b), the acidity of 1H^+ can be estimated starting from $\text{p}K_{\text{a}} = -2.52$ for protonated dimethyl ether (ref 10c) and using an average of the values of $\rho_1 = -8.4$ (ref 10a) and $\rho_1 = -9.1$ [Taylor, P. J. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1423–1427], which correlate the $\text{p}K_{\text{a}}$ of alcohols of structure $\text{R}^1\text{R}^2\text{CHOH}$ with the value of σ_1 for the substituents R. The values of $\sigma_1 = 0.12$ for $\text{R}=\text{Ph}$ and 0.30 for $\text{R}=\text{OMe}$ [Charton, M. *Prog. Phys. Org. Chem.* **1981**, *13*, 119–251] then give $\text{p}K_{\text{a}} = -6.2$ for 1H^+ .

(10) (a) Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 1436–1449. (b) Funderburk, L. H.; Aldwin, L.; Jencks, W. P. *J. Am. Chem. Soc.* **1978**, *100*, 5444–5459. (c) Bonvicini, P.; Levi, A.; Lucchini, V.; Modena, G.; Scorrano, G. *J. Am. Chem. Soc.* **1973**, *95*, 5960–5964.

(11) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1–72.

(12) Cordes, E. H.; Bull, H. G. *Chem. Rev.* **1974**, *74*, 581–603.

Table 1. Rate and Equilibrium Constants for the Formation and Reaction of **1**, **1H**⁺, **2** and **2H**⁺ in Water (Scheme 1)^a

reaction	equilibrium constant	rate constants
$\mathbf{1} \xrightleftharpoons{K_{\text{alk}}/[\text{MeOH}]} \mathbf{2}$	$K_{\text{alk}} = 0.018 \text{ M}^b$	
$\mathbf{1H}^+ \xrightleftharpoons{K_a/[\text{H}^+]} \mathbf{1}$	$K_a = 1.6 \times 10^6 \text{ M}^c$	
$\mathbf{2H}^+ \xrightleftharpoons{K_{\text{oxo}}/[\text{H}^+]} \mathbf{2}$	$K_{\text{oxo}} = 33 \text{ M}^d$	$k_p = 2600 \text{ s}^{-1} \text{ }^e$
$\mathbf{2H}^+ \xrightleftharpoons{K_{\text{add}}/[\text{MeOH}]/[\text{H}^+]} \mathbf{1}$	$K_{\text{add}} = 1900^f$	$(k_{\text{H}})_{\text{alk}} = 80 \text{ M}^{-1} \text{ s}^{-1} \text{ }^g$
$\mathbf{2H}^+ \xrightleftharpoons{(K_{\text{add}})_{\text{H}}/[\text{MeOH}]} \mathbf{1H}^+$	$(K_{\text{add}})_{\text{H}} = 0.0012 \text{ M}^{-1} \text{ }^i$	$k_{\text{MeOH}} = 3 \times 10^6 \text{ M}^{-1} \text{ s}^{-1} \text{ }^g$
		$k_{\text{H}} = 1600 \text{ M}^{-1} \text{ s}^{-1} \text{ }^h$
		$k_{\text{MeOH}} = 3 \times 10^6 \text{ M}^{-1} \text{ s}^{-1} \text{ }^g$
		$k_{\text{solv}} = 2.5 \times 10^9 \text{ s}^{-1} \text{ }^j$

^a At 25 °C and $I = 1.0$ (KCl), unless noted otherwise. A discussion of the uncertainties and standard errors in the rate and equilibrium constants reported in this table is given in the Supporting Information. ^b Calculated as $K_{\text{alk}} = K_{\text{oxo}}/K_{\text{add}}$. ^c Estimated from $\text{p}K_a = -2.52$ for dimethyl ether, as described in ref 9. ^d Calculated as $K_{\text{oxo}} = (k_{\text{AcO}}/k_{\text{AcOH}})(K_a)_{\text{AcOH}}$, see text. ^e Calculated as $k_p = K_{\text{oxo}}(k_{\text{H}})_{\text{alk}} = (k_{\text{AcO}}/k_{\text{AcOH}})(K_a)_{\text{AcOH}}(k_{\text{H}})_{\text{alk}}$. ^f Calculated as $K_{\text{add}} = k_{\text{MeOH}}/k_{\text{H}}$. ^g Data from ref 7. ^h Data from ref 8. ⁱ Calculated as $(K_{\text{add}})_{\text{H}} = K_{\text{add}}/K_a$. ^j Calculated as $k_{\text{solv}} = k_{\text{H}}K_a$.

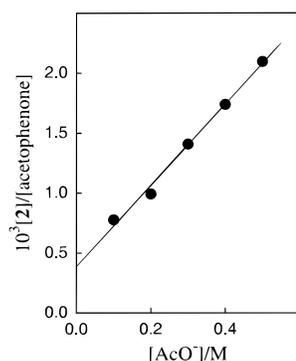


Figure 1. The effect of increasing concentrations of acetate ion on the ratio of the yields of α -methoxystyrene and acetophenone, $[2]/[\text{acetophenone}]$, from the acid-catalyzed cleavage of acetophenone dimethyl ketal **1** in water at pH 7.0 (10 mM phosphate buffer) at 25 °C and $I = 1.0$ (KCl). The solid line shows the least-squares fit of the data to eq 1 of the text. The slope of this line is $k_{\text{AcO}}/k_{\text{HOH}} = 0.0034 \text{ M}^{-1}$ for partitioning of the oxocarbenium ion **2H**⁺ between deprotonation by acetate ion and nucleophilic addition of solvent water.

$$[2]/[\text{acetophenone}] = \frac{k_o}{k_{\text{HOH}}} + \frac{k_{\text{AcO}}}{k_{\text{HOH}}}[\text{AcO}^-] \quad (1)$$

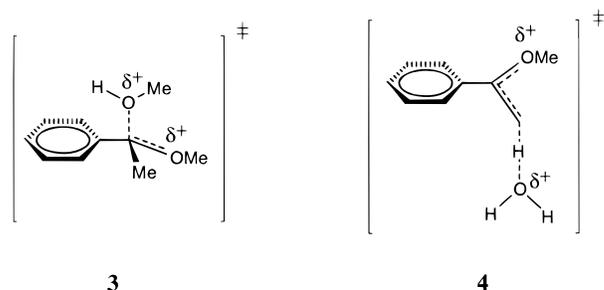
$$\log k = \frac{1}{1.36} \left\{ 17.44 - \Lambda \left(1 - \frac{1.36 \log K}{4\Lambda} \right)^2 \right\} \quad (2)$$

$$\log k_o = 12.8 - \frac{\Lambda}{1.36} \quad (3)$$

Table 1 shows that, despite the 6 kcal/mol larger thermodynamic driving force for the deprotonation of **2H**⁺ to give **2** ($\Delta G^\circ = -2.1$ kcal/mol) than for the nucleophilic addition of methanol to give **1H**⁺ ($\Delta G^\circ = 4.0$ kcal/mol), there is a 1200-fold larger rate constant for the latter reaction. The rate and equilibrium constants for these reactions of **2H**⁺ were substituted into the Marcus equation¹⁷ (eq 2, derived at 298 K) to give $\Lambda_{\text{MeOH}} = 6.5 \pm 0.5$ kcal/mol as the intrinsic barrier for the hypothetical thermoneutral nucleophilic addition of methanol to **2H**⁺, and $\Lambda_p = 13.8 \pm 0.1$ kcal/mol as the intrinsic barrier for the hypothetical thermoneutral deprotonation of **2H**⁺ by solvent water. These intrinsic barriers correspond to intrinsic rate constants of $(k_{\text{MeOH}})_o = (1.1 \pm 0.9) \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ and $(k_p)_o = 450 \pm 60 \text{ s}^{-1}$ (eq 3).¹⁸

The value of $(k_{\text{MeOH}})_o$ for addition of methanol to **2H**⁺ is larger than $k_o = 1 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ for thermoneutral protonation of the dicyanomethyl carbanion by secondary amines, a prototypical *fast* proton transfer at carbon,⁴ and only ~60-fold smaller than $k_d \approx$

$(5-7) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ for the diffusion-limited reactions of carbocations.¹⁹ We conclude that the thermoneutral nucleophilic addition of methanol to the oxocarbenium ion **2H**⁺ is an intrinsically *fast* reaction. By contrast, the deprotonation of **2H**⁺ by solvent water through transition state **4** is a much slower process.



A qualitative explanation for the existence of a significant intrinsic barrier for carbocation–nucleophile combination reactions such as the addition of methanol to **2H**⁺, is that the stabilization of the transition state **3** due to the developing C–O bond is *smaller* than the opposing increase in energy from the *loss* of stabilizing electron donation from the α -oxygen and α -phenyl groups to the benzylic carbon.² The falloff in stabilizing electron donation to the benzylic carbon of carbocations such as **2H**⁺ on proceeding to the transition state **3** may be relatively large because^{2,3,20} (a) there is a fractional loss of stabilization from electron donation that is roughly equal to the fraction of C–O bond formation at **3**; and (b) stabilization of the carbocation from π -overlap with α -substituents is further reduced by the movement away from a planar geometry at the partly sp^3 -hybridized benzylic carbon of **3**.^{20,21} Whatever the explanation for the magnitude of $\Lambda_{\text{MeOH}} = 6.5$ kcal/mol, this experimental intrinsic barrier for the addition of methanol to **2H**⁺ will serve as a benchmark against which to test developing theoretical work to model these intrinsic barriers.

Acknowledgment. We acknowledge the National Institutes of Health Grant GM 39754 for its generous support of this work.

Supporting Information Available: A discussion of the uncertainties and standard errors in the rate and equilibrium constants reported in Table 1, and in the intrinsic barriers and rate constants Λ_{MeOH} , Λ_p , $(k_{\text{MeOH}})_o$, and $(k_p)_o$. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA9915293

(19) McClelland, R. A.; Kanagasabapathy, V. M.; Banait, N. S.; Steenken, S. *J. Am. Chem. Soc.* **1991**, *113*, 1009–1014.

(20) Kresge, A. J. *Can. J. Chem.* **1974**, *52*, 1897–1903.

(21) Bernasconi, C. F.; Wenzel, P. J. *J. Am. Chem. Soc.* **1994**, *116*, 5405–5413.

(22) (a) Ta-Shma, R.; Jencks, W. P. *J. Am. Chem. Soc.* **1986**, *108*, 8040–8050. Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1396–1401.

(17) Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 891–899.

(18) The quoted errors are standard errors. The calculation of the standard errors in the values of Λ_{MeOH} , Λ_p , $(k_{\text{MeOH}})_o$, and $(k_p)_o$ is discussed in the Supporting Information.