

## Intrinsic Barriers for the Reactions of an Oxocarbenium Ion in Water

John P. Richard,\*<sup>1</sup> Kathleen B. Williams, and Tina L. Amyes

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

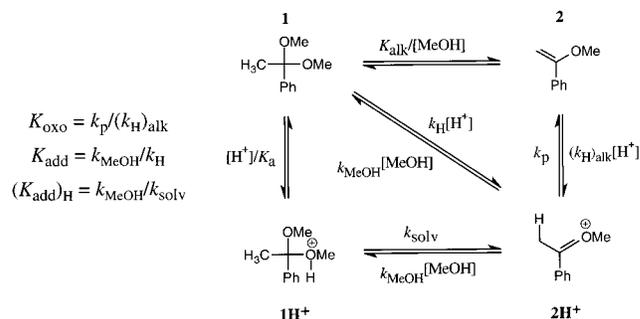
Received May 10, 1999

The nucleophile addition reactions of  $\alpha$ -methyl benzyl carbocations with Lewis bases are fast and are generally perceived to be thermodynamically favorable processes.<sup>2,3</sup> By contrast with proton-transfer reactions at carbon,<sup>4–6</sup> 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  $(k_{\text{MeOH}})_0 = 1 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$  and  $(k_{\text{p}})_0 = 450 \text{ s}^{-1}$  for the nucleophilic addition of methanol to the acetophenone oxocarbenium ion  $2\text{H}^+$  and deprotonation of  $2\text{H}^+$  by solvent water, respectively (Scheme 1). These intrinsic rate constants correspond to intrinsic barriers of  $\Delta_{\text{MeOH}} = 6.5 \text{ kcal/mol}$  and  $\Delta_{\text{p}} = 13.8 \text{ kcal/mol}$  for the nucleophile addition and proton-transfer reactions, respectively.

Table 1 summarizes the rate and equilibrium constants for the formation and reaction of **1**,  $1\text{H}^+$ , **2**, and  $2\text{H}^+$  in water at 25 °C (Scheme 1). The literature values<sup>7,8</sup> 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  $2\text{H}^+$  to give **1**. The value of  $\text{p}K_{\text{a}} = -6.2$  for protonated acetophenone dimethyl ketal  $1\text{H}^+$  was estimated starting from  $\text{p}K_{\text{a}} = -2.52$  for protonated dimethyl ether.<sup>9</sup> The equilibrium constant for the addition of methanol to  $2\text{H}^+$  to give  $1\text{H}^+$  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  $1\text{H}^+$  to give the oxocarbenium ion  $2\text{H}^+$  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  $1\text{H}^+$  by solvent water to regenerate **1**,<sup>11</sup> so that **1** and  $1\text{H}^+$  are essentially at chemical equilibrium during the acid-catalyzed cleavage of **1**. This is in agreement with the conclusions of earlier studies that  $1\text{H}^+$  is an intermediate of the stepwise, specific-acid-catalyzed hydrolysis of ketals,<sup>12</sup> which is the microscopic reverse of nucleophilic addition of methanol to  $2\text{H}^+$  to form **1**.

The rate constants for protonation of  $\alpha$ -methoxystyrene **2** by hydronium ion and acetic acid in water at 25 °C and  $I = 1.0$  (KCl) were determined by published methods<sup>13</sup> 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  $\alpha$ -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).<sup>14</sup> The data were fit to eq 1 to give  $k_{\text{AcO}}/k_{\text{HOH}} = 0.0034 \text{ M}^{-1}$  for partitioning of  $2\text{H}^+$  between deprotonation by acetate ion to give **2** and nucleophilic addition of solvent water to give, ultimately, acetophenone.<sup>15</sup> This partitioning ratio can be combined with the value of  $5 \times 10^7 \text{ s}^{-1}$  for  $k_{\text{HOH}}$ ,<sup>7</sup> to give  $k_{\text{AcO}} = 1.7 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$  as the absolute rate constant for deprotonation of  $2\text{H}^+$  by acetate ion. The acidity of the oxocarbenium ion  $2\text{H}^+$  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  $K_{\text{oxo}} = k_{\text{p}}/(k_{\text{H}})_{\text{alk}}$  then gives  $k_{\text{p}} = 2600 \text{ s}^{-1}$  for deprotonation of  $2\text{H}^+$  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).<sup>16</sup>

(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  $A_2/A_{\text{ketone}}$  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  $A_2/A_{\text{ketone}}$  and the value of  $k_{\text{AcO}}/k_{\text{HOH}}$  ( $\text{M}^{-1}$ ) 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  $2\text{H}^+$ . 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  $2\text{H}^+$  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  $2\text{H}^+$  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  $k_{\text{SO}_3}$  and  $k_{\text{HOH}}$  because (a) acetate ion catalysis of the addition of water to  $2\text{H}^+$  ( $k_{\text{HOH}} = 5 \times 10^7 \text{ s}^{-1}$ , 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.<sup>22</sup> (b) The absence of general acid catalysis of the cleavage of **1** to give  $2\text{H}^+$  and methanol (ref 12) requires that there be no general base catalysis of the addition of methanol to  $2\text{H}^+$  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  $K_{\text{alk}}$  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  $1\text{H}^+$  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  $\sigma_1$  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  $1\text{H}^+$ .

(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.

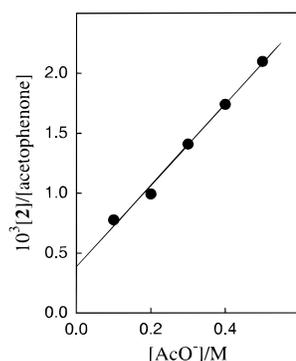
(11) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1–72.

(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**<sup>+</sup>, **2** and **2H**<sup>+</sup> in Water (Scheme 1)<sup>a</sup>

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

<sup>a</sup> 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. <sup>b</sup> Calculated as  $K_{\text{alk}} = K_{\text{oxo}}/K_{\text{add}}$ . <sup>c</sup> Estimated from  $\text{p}K_a = -2.52$  for dimethyl ether, as described in ref 9. <sup>d</sup> Calculated as  $K_{\text{oxo}} = (k_{\text{AcO}}/k_{\text{AcOH}})(K_a)_{\text{AcOH}}$ , see text. <sup>e</sup> Calculated as  $k_p = K_{\text{oxo}}(k_{\text{H}})_{\text{alk}} = (k_{\text{AcO}}/k_{\text{AcOH}})(K_a)_{\text{AcOH}}(k_{\text{H}})_{\text{alk}}$ . <sup>f</sup> Calculated as  $K_{\text{add}} = k_{\text{MeOH}}/k_{\text{H}}$ . <sup>g</sup> Data from ref 7. <sup>h</sup> Data from ref 8. <sup>i</sup> Calculated as  $(K_{\text{add}})_{\text{H}} = K_{\text{add}}/K_a$ . <sup>j</sup> 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  $\alpha$ -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**<sup>+</sup> between deprotonation by acetate ion and nucleophilic addition of solvent water.

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

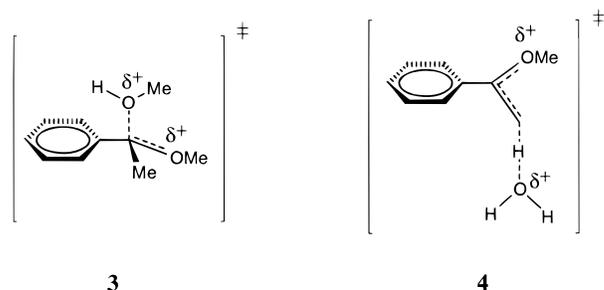
$$\log k = \frac{1}{1.36} \left\{ 17.44 - \Lambda \left( 1 - \frac{1.36 \log K}{4\Lambda} \right)^2 \right\} \quad (2)$$

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

Table 1 shows that, despite the 6 kcal/mol larger thermodynamic driving force for the deprotonation of **2H**<sup>+</sup> to give **2** ( $\Delta G^\circ = -2.1$  kcal/mol) than for the nucleophilic addition of methanol to give **1H**<sup>+</sup> ( $\Delta G^\circ = 4.0$  kcal/mol), there is a 1200-fold larger rate constant for the latter reaction. The rate and equilibrium constants for these reactions of **2H**<sup>+</sup> were substituted into the Marcus equation<sup>17</sup> (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**<sup>+</sup>, and  $\Lambda_p = 13.8 \pm 0.1$  kcal/mol as the intrinsic barrier for the hypothetical thermoneutral deprotonation of **2H**<sup>+</sup> 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).<sup>18</sup>

The value of  $(k_{\text{MeOH}})_o$  for addition of methanol to **2H**<sup>+</sup> 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,<sup>4</sup> 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.<sup>19</sup> We conclude that the thermoneutral nucleophilic addition of methanol to the oxocarbenium ion **2H**<sup>+</sup> is an intrinsically *fast* reaction. By contrast, the deprotonation of **2H**<sup>+</sup> 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**<sup>+</sup>, 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  $\alpha$ -oxygen and  $\alpha$ -phenyl groups to the benzylic carbon.<sup>2</sup> The falloff in stabilizing electron donation to the benzylic carbon of carbocations such as **2H**<sup>+</sup> on proceeding to the transition state **3** may be relatively large because<sup>2,3,20</sup> (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  $\pi$ -overlap with  $\alpha$ -substituents is further reduced by the movement away from a planar geometry at the partly  $sp^3$ -hybridized benzylic carbon of **3**.<sup>20,21</sup> 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**<sup>+</sup> 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  $\Lambda_{\text{MeOH}}$ ,  $\Lambda_p$ ,  $(k_{\text{MeOH}})_o$ , 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  $\Lambda_{\text{MeOH}}$ ,  $\Lambda_p$ ,  $(k_{\text{MeOH}})_o$ , and  $(k_p)_o$  is discussed in the Supporting Information.