

### Formation and Stability of N-Heterocyclic Carbenes in Water: The Carbon Acid $pK_a$ of Imidazolium Cations in Aqueous Solution

Tina L. Amyes,\* Steven T. Diver,\* John P. Richard, Felix M. Rivas, and  
Krisztina Toth

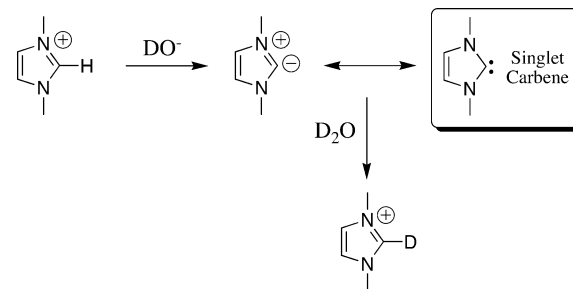
Contribution from the Department of Chemistry, University at Buffalo,  
SUNY, Buffalo, New York 14260

Received December 1, 2003 E-mail: tamyas@chem.buffalo.edu

**Abstract:** We report second-order rate constants  $k_{DO}$  ( $M^{-1} s^{-1}$ ) for exchange for deuterium of the C(2)-proton of a series of simple imidazolium cations to give the corresponding singlet imidazol-2-yl carbenes in  $D_2O$  at 25 °C and  $I = 1.0$  (KCl). Evidence is presented that the reverse protonation of imidazol-2-yl carbenes by solvent water is limited by solvent reorganization and occurs with a rate constant of  $k_{HOH} = k_{reorg} = 10^{11} s^{-1}$ . The data were used to calculate reliable carbon acid  $pK_a$ s for ionization of imidazolium cations at C(2) to give the corresponding singlet imidazol-2-yl carbenes in water:  $pK_a = 23.8$  for the imidazolium cation,  $pK_a = 23.0$  for the 1,3-dimethylimidazolium cation,  $pK_a = 21.6$  for the 1,3-dimethylbenzimidazolium cation, and  $pK_a = 21.2$  for the 1,3-bis-((S)-1-phenylethyl)benzimidazolium cation. The data also provide the thermodynamic driving force for a 1,2-hydrogen shift at a singlet carbene:  $K_{12} = 5 \times 10^{16}$  for rearrangement of the parent imidazol-2-yl carbene to give neutral imidazole in water at 298 K, which corresponds to a favorable Gibbs free energy change of 23 kcal/mol. We present a simple rationale for the observed substituent effects on the thermodynamic stability of N-heterocyclic carbenes relative to a variety of neutral and cationic derivatives that emphasizes the importance of the choice of reference reaction when assessing the stability of N-heterocyclic carbenes.

It is 40 years since the striking report of Olofson and co-workers of facile deuterium exchange of the C(2)-proton of the 1,3-dimethylimidazolium cation (**DMI**) in  $D_2O$  (Scheme 1).<sup>1</sup> The deprotonation of imidazolium cations at C(2) results in the formation of formally neutral carbon bases which are examples of nucleophilic singlet carbenes that are strongly stabilized by the presence of two heteroatoms at the carbenic center (Scheme 1).<sup>2–6</sup> The electron-rich nature of N-heterocyclic carbenes has led to their wide-ranging application in organometallic catalysis,<sup>3,6,7</sup> and they also serve as nucleophilic catalysts in several important reactions such as benzoin condensation<sup>8–12</sup> and acyl transfer.<sup>13,14</sup>

Scheme 1



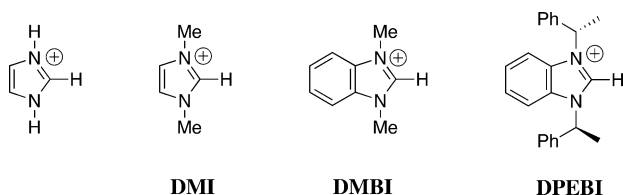
Despite the isolation and characterization of a vast array of stable N-heterocyclic and other diamino carbenes,<sup>2–4</sup> there are no systematic data for the formation and stability of imidazol-2-yl carbenes in aqueous solution at room temperature. Moreover, the kinetic and thermodynamic acidity of the C(2)-proton of simple imidazolium cations has not been examined in the light of modern theories of proton transfer at carbon.

We report here a study of the deuterium exchange reactions of the C(2)-proton for a series of simple imidazolium cations (Chart 1) in  $D_2O$  at 25 °C and  $I = 1.0$  (KCl). The data are used to obtain reliable carbon acid  $pK_a$ s for ionization of these imidazolium cations at C(2) to give the corresponding singlet imidazol-2-yl carbenes in water. We also report the first determination of the thermodynamic driving force for a 1,2-hydrogen shift at a singlet carbene:  $K_{12} = 5 \times 10^{16}$  for rearrangement of

- Olofson, R. A.; Thompson, W. R.; Michelman, J. S. *J. Am. Chem. Soc.* **1964**, *86*, 1865–1866.
- Alder, R. W. In *Carbene Chemistry*; Bertrand, G., Ed.; FontisMedia S. A.; Marcel Dekker Inc.: New York, 2002; pp 153–176.
- Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39–91.
- Arduengo, A. J., III *Acc. Chem. Res.* **1999**, *32*, 913–921.
- Warkentin, J. In *Advances in Carbene Chemistry*; Brinker, U. H., Ed.; JAI Press Inc.: Stamford, CT, 1998; Vol. 2, pp 245–295.
- Herrmann, W. A.; Köcher, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2162–2187.
- Herrmann, W. A. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1290–1309.
- Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726.
- Wanzlick, H. W.; Kleiner, H. J. *Chem. Ber.* **1963**, *96*, 3024–3027.
- Lappert, M. F.; Maskell, R. K. *J. Chem. Soc., Chem. Commun.* **1982**, 580–581.
- Teles, J. H.; Melder, J.-P.; Ebel, K.; Schneider, R.; Gehrler, E.; Harder, W.; Brode, S.; Enders, D.; Breuer, K.; Raabe, G. *Helv. Chim. Acta* **1996**, *79*, 61–83.
- Miyashita, A.; Suzuki, Y.; Kobayashi, M.; Kuriyama, N.; Higashino, T. *Heterocycles* **1996**, *43*, 509–512.
- Grasa, G. A.; Kissling, R. M.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 3583–3586.

- Nyce, G. W.; Lamboy, J. A.; Connor, E. F.; Waymouth, R. M.; Hedrick, J. L. *Org. Lett.* **2002**, *4*, 3587–3590.

Chart 1



the parent imidazol-2-yl carbene to give neutral imidazole in water at 298 K, which corresponds to a favorable Gibbs free energy change of 23 kcal/mol. Finally, we present a simple rationale for the observed substituent effects on the thermodynamic stability of N-heterocyclic carbenes relative to a variety of neutral and cationic derivatives.

### Experimental Section

The syntheses of **DMI**, **DMBI**, and **DPEBI**, the preparation of buffers, and the NMR methods used to monitor deuterium exchange are described in the Supporting Information.

**Determination of  $pD$  and  $pK_{BD}$ .** Solution  $pD$  and the concentration of deuterioxide ion at any  $pD$  were determined as described in our previous work.<sup>15</sup> The apparent value of  $pK_{BD} = 7.72$  for ionization of the imidazolium cation at nitrogen in  $D_2O$  at 25 °C and  $I = 1.0$  (KCl) was determined as the average value of  $pK_{BD} = pD - \log([B]/[BD^+])$  for six different gravimetrically prepared solutions of 30 mM imidazole buffer in  $D_2O$  ( $I = 1.0$ , KCl) at  $[B]/[BD^+] = 0.11$ –19.

**Deuterium Exchange.** All reactions were carried out in  $D_2O$  at 25 °C and  $I = 1.0$  (KCl). The reactions of **DMI**, **DMBI**, and **DPEBI** were initiated by dissolving the crystalline substrate in 2 mL of the appropriate buffer in  $D_2O$  to give a final substrate concentration of 10 mM for **DMI** and **DMBI**, and 5 mM for **DPEBI**. The reactions of imidazole were initiated by bringing a previously frozen solution of 30 or 60 mM imidazole buffer in  $D_2O$  to room temperature. Tetramethylammonium hydrogensulfate, which served as an internal standard, was added by making a  $\geq 200$ -fold dilution of a stock solution in  $D_2O$  into the reaction mixture to give a final concentration of 1–2 mM. 700  $\mu L$  of the reaction mixture was immediately transferred to an NMR tube and incubated at 25 °C. The remainder was incubated at 25 °C and was used to monitor the  $pD$  of the reaction mixture during deuterium exchange. There was no change ( $\pm 0.03$  units) in the  $pD$  of the reaction mixtures during the first two-halftimes for deuterium exchange.

Deuterium exchange was followed by  $^1H$  NMR spectroscopy during the disappearance of 60–85% of the C(2)-proton of the substrate. Values of the reaction progress,  $R$ , were calculated from the integrated areas of the signals due to the C(2)-proton of the substrate ( $A_{C2H}$ ) and the tetramethylammonium ion internal standard ( $A_{IS}$ ) at zero time and time  $t$ , according to eq 1. The observed first-order rate constants for exchange,  $k_{ex}$  ( $s^{-1}$ ), were determined from the slopes of linear semilogarithmic plots of reaction progress against time according to eq 2, which generally covered at least 2 halftimes. The values of  $k_{ex}$  ( $s^{-1}$ ) were reproducible to  $\pm 10\%$ .

$$R = \frac{(A_{C2H}/A_{IS})_t}{(A_{C2H}/A_{IS})_0} \quad (1)$$

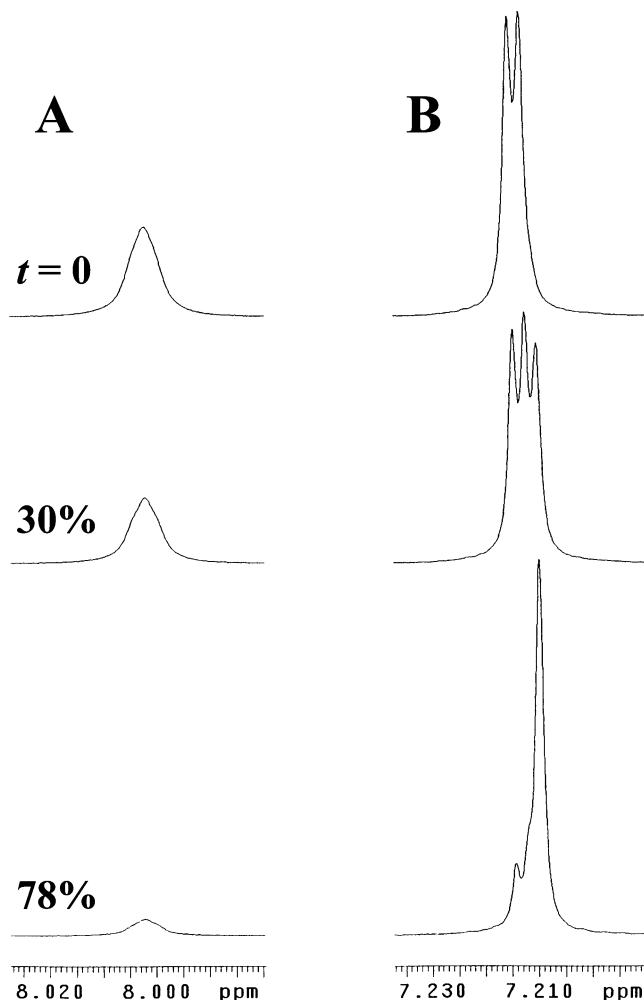
$$\ln R = -k_{ex}t \quad (2)$$

### Results

#### Deuterium Exchange Followed by $^1H$ NMR Spectroscopy.

The exchange for deuterium of the C(2)-proton of imidazole, the 1,3-dimethylimidazolium cation (**DMI**), the 1,3-dimethyl-

benzimidazolium cation (**DMBI**) and the 1,3-bis-((*S*)-1-phenylethyl)benzimidazolium cation (**DPEBI**) in buffered  $D_2O$  ( $pD$  4.3–8.9) at 25 °C and  $I = 1.0$  (KCl) was followed by  $^1H$  NMR spectroscopy at 500 MHz. There was no detectable hydrolysis or decomposition of these substrates during deuterium exchange, monitored for up to 40 days for imidazole, 60 days for **DMI**, 44 days for **DMBI** and 28 days for **DPEBI**.



**Figure 1.** Representative  $^1H$  NMR spectra at 500 MHz of imidazole buffer (30 mM, 80% free base,  $pD$  8.30) obtained during deuterium exchange of the C(2)-proton in  $D_2O$  at 25 °C and  $I = 1.0$  (KCl). (A) Deuterium exchange results in the disappearance of the broad singlet at 8.002 ppm due to the C(2)-proton. The extent of deuterium exchange is indicated above each spectrum. (B) Deuterium exchange results in the disappearance of the doublet ( $J = 1.1$  Hz) at 7.215 ppm due to the C(4,5)-protons and the appearance of an upfield-shifted singlet at 7.210 ppm ( $\Delta\delta = 0.005$  ppm) due to these protons at imidazole containing deuterium at C(2).

Figure 1 shows representative  $^1H$  NMR spectra at 500 MHz of imidazole (30 mM, self-buffered at  $pD$  8.30) obtained during exchange for deuterium of the C(2)-proton in  $D_2O$  at 25 °C. The signal for the C(4,5)-protons at 7.215 ppm appears as a doublet ( $J = 1.1$  Hz) because there is a small long-range coupling to the C(2)-proton (Figure 1B, top spectrum). The signal for the C(2)-proton appears as a broad singlet at 8.002 ppm (Figure 1A, top spectrum). Deuterium exchange at C(2) of imidazole results in the disappearance of the signal for the C(2)-proton and of the doublet at 7.215 ppm due to the C(4,5)-protons, and the appearance of a broad upfield-shifted singlet at 7.210 ppm ( $\Delta\delta = 0.005$  ppm) due to the same protons at imidazole containing deuterium at C(2).

(15) Richard, J. P.; Williams, G.; O'Donoghue, A. C.; Amyes, T. L. *J. Am. Chem. Soc.* **2002**, *124*, 2957–2968.

Figures S1 and S2 of the Supporting Information show the changes in the  $^1\text{H}$  NMR spectra of **DMI** and **DMBI** during deuterium exchange at C(2) in buffered  $\text{D}_2\text{O}$  at 25 °C.

**Rate Constants for Deuterium Exchange.** Deuterium exchange at C(2) of imidazole, **DMI**, **DMBI** and **DPEBI** in the presence of various concentrations of buffer at  $\text{pD}$  4.33–8.88 in  $\text{D}_2\text{O}$  at 25 °C and  $I = 1.0$  (KCl) was followed by monitoring the disappearance of the broad singlet due to the C(2)-proton of the substrate by  $^1\text{H}$  NMR spectroscopy. There was no change in the *total* integrated area for all of the signals due to the other protons of these substrates during deuterium exchange at C(2). The first-order rate constants  $k_{\text{ex}}$  ( $\text{s}^{-1}$ ) for deuterium exchange of the C(2)-proton of these substrates are reported in Tables S1–S4 of the Supporting Information.

The essentially identical values of  $k_{\text{ex}}$  ( $\pm 10\%$ ) for the deuterium exchange reactions of 30 mM imidazole at  $\text{pD}$  7.64 and 60 mM imidazole at  $\text{pD}$  7.69 shows that, under these conditions, the values of  $k_{\text{ex}}$  ( $\text{s}^{-1}$ ) for imidazole are equal to  $k_{\text{o}}$  ( $\text{s}^{-1}$ ) for solvent-catalyzed deuterium exchange. Figure 2 ( $\square$ ) shows the  $\text{pD}$ -rate profile of the values of  $k_{\text{o}}$  for the deuterium exchange reaction of imidazole. There is a downward break at the  $\text{pK}_{\text{a}}$  of N-protonated imidazole which shows that the reactive form of the substrate for the deuteriooxide-ion-catalyzed reaction is the cationic N-protonated imidazole.<sup>16,17</sup> The plot of  $k_{\text{o}}/f_{\text{N}^+}$  against  $[\text{DO}^-]$  according to eq 3 is linear, where  $f_{\text{N}^+}$  is the fraction of the substrate present in the reactive N-protonated form that was calculated from the  $\text{pD}$  and  $\text{pK}_{\text{BD}} = 7.72$  for the apparent  $\text{pK}_{\text{a}}$  of imidazole in  $\text{D}_2\text{O}$  at 25 °C and  $I = 1.0$  (KCl). Figure 2 ( $\blacksquare$ ) shows the  $\text{pD}$ -rate profile of the values of  $k_{\text{o}}/f_{\text{N}^+}$  for the  $\text{DO}^-$ -catalyzed deuterium exchange reaction of N-protonated imidazole.

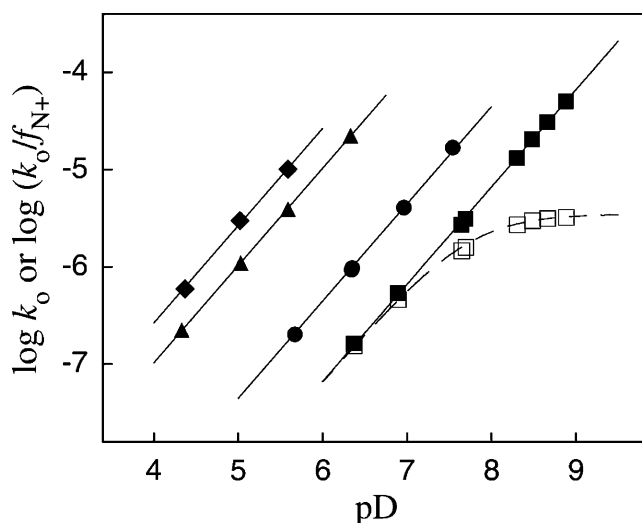
$$\frac{k_{\text{o}}}{f_{\text{N}^+}} = k_{\text{DO}}[\text{DO}^-] \quad (3)$$

$$\log\left(\frac{k_{\text{o}}}{f_{\text{N}^+}}\right) = \log\left(\frac{k_{\text{DO}}K_{\text{w}}}{\gamma_{\text{OL}}}\right) + \text{pD} \quad (4)$$

A 2-fold increase in the concentration of 20% free base phosphate buffer from 50 mM ( $\text{pD}$  6.34) to 100 mM ( $\text{pD}$  6.35) results in no significant change ( $\pm 10\%$ ) in  $k_{\text{ex}}$  ( $\text{s}^{-1}$ ) for **DMI**. Therefore, at these low buffer concentrations, the values of  $k_{\text{ex}}$  ( $\text{s}^{-1}$ ) for **DMI** are equal to  $k_{\text{o}}$  ( $\text{s}^{-1}$ ) for solvent-catalyzed deuterium exchange. Figure 2 ( $\bullet$ ) shows the  $\text{pD}$ -rate profile of the values of  $k_{\text{o}}$  for the  $\text{DO}^-$ -catalyzed deuterium exchange reaction of **DMI** determined in the presence of 25 mM acetate and 50–100 mM phosphate buffer.

Figure 2 also shows the  $\text{pD}$ -rate profiles of the values of  $k_{\text{o}} = k_{\text{ex}}$  ( $\text{s}^{-1}$ ) for the  $\text{DO}^-$ -catalyzed deuterium exchange reactions of **DMBI** in the presence of 50 mM acetate and phosphate buffer ( $\blacktriangle$ ) and of **DPEBI** in the presence of 50 mM acetate buffer ( $\blacklozenge$ ).

The solid lines of unit slope in Figure 2 show the fits of the data to eq 4, where  $K_{\text{w}} = 10^{-14.87}$  is the ion product of  $\text{D}_2\text{O}$  at 25 °C,<sup>18</sup>  $\gamma_{\text{OL}} = 0.75$  is the activity correction for lyoxide ion under our experimental conditions,<sup>15</sup> and  $f_{\text{N}^+} = 1.0$  for **DMI**,



**Figure 2.**  $\text{pD}$ -rate profiles for the deuterium exchange reactions of the C(2)-proton of imidazolium cations in  $\text{D}_2\text{O}$  at 25 °C and  $I = 1.0$  (KCl). Key: ( $\square$ ) Values of  $k_{\text{o}}$  for imidazole; ( $\blacksquare$ ) Values of  $k_{\text{o}}/f_{\text{N}^+}$  for imidazole where  $f_{\text{N}^+}$  is the fraction of the substrate present in the reactive N-protonated form that was calculated from the  $\text{pD}$  and  $\text{pK}_{\text{BD}} = 7.72$  (see text); ( $\bullet$ ) Values of  $k_{\text{o}}$  for **DMI** ( $f_{\text{N}^+} = 1$ ); ( $\blacktriangle$ ) Values of  $k_{\text{o}}$  for **DMBI** ( $f_{\text{N}^+} = 1$ ); ( $\blacklozenge$ ) Values of  $k_{\text{o}}$  for **DPEBI** ( $f_{\text{N}^+} = 1$ ). The solid lines of unit slope show the fits of the data to eq 4 which gave the second-order rate constants  $k_{\text{DO}}$  ( $\text{M}^{-1} \text{s}^{-1}$ ) for  $\text{DO}^-$ -catalyzed exchange of the C(2)-proton listed in Table 1.

**DMBI**, and **DPEBI**. The second-order rate constants  $k_{\text{DO}}$  ( $\text{M}^{-1} \text{s}^{-1}$ ) for  $\text{DO}^-$ -catalyzed exchange of the C(2)-protons of the imidazolium cations obtained from these fits are given in Table 1.

## Discussion

**Isotope Exchange at C(2) of Imidazolium and Benzimidazolium Cations.** The observed changes in the NMR spectra for the imidazolium cation, **DMI** and **DMBI** upon incubation in buffered  $\text{D}_2\text{O}$  ( $\text{pD}$  4.3–8.9) at 25 °C provide direct evidence that disappearance of the C(2)-proton is accompanied by deuterium incorporation at C(2) (Figures 1, S1, and S2). There is no evidence for any hydrolysis of these imidazolium cations or formation of the corresponding carbene dimers<sup>19</sup> during deuterium exchange at C(2) under these conditions.

Deuterium exchange at C(2) of **DMI** in  $\text{D}_2\text{O}$  under a variety of conditions has been reported previously. A value of  $k_{\text{DO}} = 480 \text{ M}^{-1} \text{ s}^{-1}$  at 25 °C can be calculated from the data of Wong and Keck,<sup>17,20</sup> while the observed rate constant for deuterium exchange at  $\text{pD}$  8.9 and ca. 31 °C reported by Olofson et al.<sup>1</sup> can be combined with  $K_{\text{w}} = 10^{-14.70}$  for the ion product of  $\text{D}_2\text{O}$  at 30 °C<sup>18</sup> to give  $k_{\text{DO}} = 1600 \text{ M}^{-1} \text{ s}^{-1}$  at 31 °C. These data are in qualitative agreement with  $k_{\text{DO}} = 247 \text{ M}^{-1} \text{ s}^{-1}$  at 25 °C and  $I = 1.0$  (KCl) determined in this work (Table 1). Deuterium exchange at C(2) of the imidazolium cation in  $\text{D}_2\text{O}$  has been studied at elevated temperatures and values of  $k_{\text{DO}} = 107 \text{ M}^{-1} \text{ s}^{-1}$  at 37 °C,<sup>21</sup>  $360 \pm 120 \text{ M}^{-1} \text{ s}^{-1}$  at 33 °C,<sup>16</sup> and  $1300 \text{ M}^{-1}$

(16) Vaughan, J. D.; Mughrabi, Z.; Wu, E. C. *J. Org. Chem.* **1970**, *35*, 1141–1145.

(17) Wong, J. L.; Keck, J. H., Jr. *J. Org. Chem.* **1974**, *39*, 2398–2403.



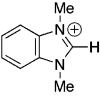
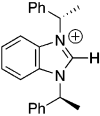
(18) Covington, A. K.; Robinson, R. A.; Bates, R. G. *J. Phys. Chem.* **1966**, *70*, 3820–3824.

(19) Böhm, V. P. W.; Herrmann, W. A. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 4036–4038.

(20) Table 1 of ref 17 reports  $k_{\text{DO}} = 270 \text{ M}^{-1} \text{ s}^{-1}$  for deuterium exchange at C(2) of the 1,3-dimethylimidazolium cation in  $\text{D}_2\text{O}$  at 25 °C. However, an analysis of the experimental data reveals considerable scatter and the fit to eq 4 of this work ( $f_{\text{N}^+} = 1$ ,  $\gamma_{\text{OL}} = 1$ ) gives  $k_{\text{DO}} = 476 \text{ M}^{-1} \text{ s}^{-1}$ .

(21) Bradbury, J. H.; Chapman, B. E.; Pellegrino, F. A. *J. Am. Chem. Soc.* **1973**, *95*, 6139–6140.

**Table 1.** Kinetic and Thermodynamic Acidity of the C(2)–Proton of Substituted Imidazolium Cations in Water at 25 °C and  $I = 1.0$  (KCl)

Carbon Acid	$k_{\text{DO}}$ ( $\text{M}^{-1} \text{s}^{-1}$ ) <sup>a</sup>	$k_{\text{HO}}$ ( $\text{M}^{-1} \text{s}^{-1}$ ) <sup>b</sup>	$\text{p}K_{\text{a}}$ <sup>c</sup>
	36.9	15.4	23.8
 DMI	247	103	23.0
 DMBI	$5.74 \times 10^3$	$2.39 \times 10^3$	21.6
 DPEBI	$1.48 \times 10^4$	$6.17 \times 10^3$	21.2

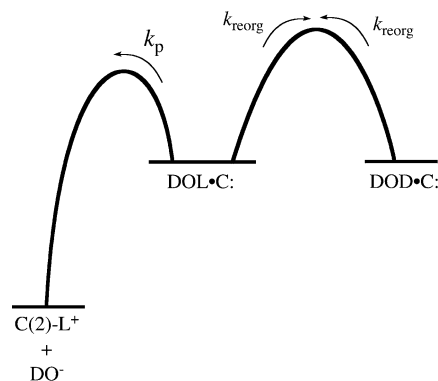
<sup>a</sup> Second-order rate constant for deprotonation of the imidazolium cation at C(2) by deuterioxide ion in  $\text{D}_2\text{O}$  determined by monitoring the disappearance of the C(2)–proton by  $^1\text{H}$  NMR spectroscopy. <sup>b</sup> Second-order rate constant for deprotonation of the imidazolium cation at C(2) by hydroxide ion in  $\text{H}_2\text{O}$ , calculated from the value of  $k_{\text{DO}}$  using a secondary solvent isotope effect of  $k_{\text{DO}}/k_{\text{HO}} = 2.4$  (see text). <sup>c</sup> Carbon acid  $\text{p}K_{\text{a}}$  for ionization of the imidazolium cation at C(2) in  $\text{H}_2\text{O}$ , calculated from  $k_{\text{HO}}$  ( $\text{M}^{-1} \text{s}^{-1}$ ) and  $k_{\text{HOH}} = 10^{11} \text{ s}^{-1}$  for the reverse protonation of the conjugate base (carbene) by solvent water according to eq 5. The estimated uncertainty in these  $\text{p}K_{\text{a}}$  values is  $\pm 0.5$  units (see text).

$\text{s}^{-1}$  at 50 °C<sup>22</sup> have been reported. A temperature correction of these rate constants using an activation energy of 21.4 kcal/mol<sup>23</sup> results in estimated values of  $k_{\text{DO}}$  for the imidazolium cation that are in qualitative agreement with  $k_{\text{DO}} = 36.9 \text{ M}^{-1} \text{ s}^{-1}$  at 25 °C and  $I = 1.0$  (KCl) determined in this work (Table 1). The differences between the earlier literature data and those reported here are likely due to the fact that many of the earlier experiments were conducted with only approximate control of solution  $\text{pD}$ , ionic strength and temperature, and to the improved sensitivity and sophistication of modern NMR spectroscopy which allows for the use of ca. 100-fold lower substrate concentrations.

#### Lifetime of Imidazol-2-yl Carbenes in Solvent Water.

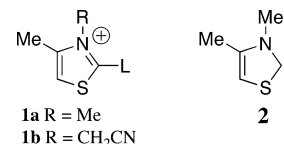
Figure 3 shows the reaction coordinate profile for hydron transfer from C(2) of imidazolium cations  $\text{C}(2)\text{-L}^+$  ( $\text{L} = \text{H}, \text{D}$ ) to deuterioxide ion. Hydron transfer results initially in formation of the corresponding imidazol-2-yl carbene **C**: in close contact with a molecule of DOL. This complex may either collapse with hydron transfer to regenerate the original substrate (“internal return”,  $k_{\text{p}}$ ),<sup>24</sup> or it may undergo reorganization by

dielectric relaxation of the solvent, which occurs with a rate constant of  $k_{\text{reorg}} \approx 1 \times 10^{11} \text{ s}^{-1}$ .<sup>15,25</sup> This solvent reorganization which places a molecule of DOD in a position to deliver a deuteron to C(2) of the carbene is irreversible because it dilutes the molecule of DOL, and so it necessarily results in formation of the isotope exchange product.



**Figure 3.** Reaction coordinate profile for hydron transfer from C(2) of imidazolium and thiazolium cations  $\text{C}(2)\text{-L}^+$  ( $\text{L} = \text{H}, \text{D}$ ) to deuterioxide ion in  $\text{D}_2\text{O}$  to give the free carbene that is limited by solvent reorganization ( $k_{\text{p}} > k_{\text{reorg}}$ ).

The following provide good evidence that the reverse proton transfer from solvent water to C(2) of imidazol-2-yl carbenes to give imidazolium cations is limited by the reorganization of the solvent ( $k_{\text{p}} > k_{\text{reorg}}$ , Figure 3) and occurs with a limiting rate constant of  $k_{\text{HOH}} = k_{\text{reorg}} = 10^{11} \text{ s}^{-1}$ .



(1) There are only small primary isotope effects of  $k_{\text{H}}/k_{\text{T}} = 2.94$  and  $k_{\text{D}}/k_{\text{T}} = 1.58$  for hydron transfer from C(2) of the 3,4-dimethylthiazolium cation **1a** ( $\text{L} = \text{H}, \text{D}, \text{T}$ ) to lyoxide ion at 30 °C and these quantities exhibit a significant deviation from the Swain–Schaad relationship.<sup>24</sup> This shows that there is significant internal return of the transferred hydron to the thiazolium ylide/carbene **2** ( $k_{\text{p}}/k_{\text{reorg}} \approx 3$  for  $\text{L} = \text{H}$ , Figure 3),<sup>24</sup> so that the reverse protonation of **2** by solvent water is limited largely by the physical “encounter” of a molecule of HOH with the carbene. The values of  $k_{\text{DO}}$  ( $\text{M}^{-1} \text{ s}^{-1}$ , Table 1) for C(2) deprotonation of the imidazolium cations studied here, which are structurally similar to thiazolium cations, are 20–8000-fold smaller than that for deprotonation of **1a** ( $\text{L} = \text{H}$ ).<sup>26,27</sup> Therefore, relative to the cationic azolium ion ground state, simple imidazol-2-yl carbenes should be less stable than the thiazol-2-yl carbene **2**, so that their protonation by solvent water should be even more limited by the solvent reorganization step with  $k_{\text{p}} > k_{\text{reorg}}$  and  $k_{\text{HOH}} = k_{\text{reorg}}$ .

(2) There is a systematic increase in the secondary solvent isotope effect for hydron transfer to lyoxide ion from C(2) of N-substituted 4-methylthiazolium cations with their decreasing

(22) Takeuchi, Y.; Kirk, K. L.; Cohen, L. A. *J. Org. Chem.* **1978**, *43*, 3570–3578.

(23) Noszal, B.; Rabenstein, D. L. *J. Phys. Chem.* **1991**, *95*, 4761–4765.

(24) Washabaugh, M. W.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 683–692.

(25) Kaatzte, U. *J. Chem. Eng. Data* **1989**, *34*, 371–374.

(26) A value of  $k_{\text{DO}} = 3.1 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$  for deprotonation of **1a** ( $\text{L} = \text{H}$ ) by deuterioxide ion in  $\text{D}_2\text{O}$  at 25 °C can be estimated from the literature<sup>24</sup> values of  $k_{\text{DO}} = 4.27 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$  and  $\Delta H^\ddagger = 11.7 \text{ kcal/mol}$  ( $E_{\text{a}} = 12.3 \text{ kcal/mol}$ ) at 30 °C ( $I = 2.0$ ).

(27) Haake, P.; Bausher, L. P.; Miller, W. B. *J. Am. Chem. Soc.* **1969**, *91*, 1113–1119.

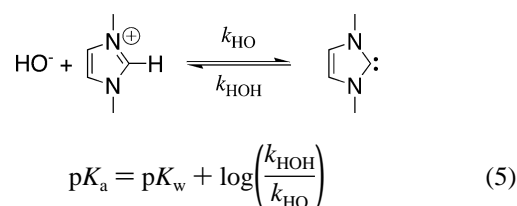
reactivity from  $k_{\text{DO}}/k_{\text{HO}} = 1.30$  for **1b** (L = T) to 2.35 for **1a** (L = T).<sup>24</sup> Therefore, the secondary solvent isotope effect for proton transfer from C(2) of the structurally similar but less reactive (see above) imidazolium cations to lyoxide ion should be essentially equal to the limiting maximum value of  $k_{\text{DO}}/k_{\text{HO}} = 2.4$ .<sup>28</sup> This is consistent with proton transfer that is limited by the physical step of solvent reorganization with  $k_{\text{p}} > k_{\text{reorg}}$  and  $k_{\text{HOH}} = k_{\text{reorg}}$ .<sup>15,29</sup>

(3) The values of  $k_{\text{ex}}$  ( $\text{s}^{-1}$ ) for deuterium exchange at C(2) of **DMI** and **DMBI** in the presence of 1.0 M acetate buffer at *pD* 4.40 or 5.78 are no more than 10% larger than the calculated values of  $k_{\text{o}} = k_{\text{DO}}[\text{DO}^-]$  for the  $\text{DO}^-$ -catalyzed reactions of these substrates at these *pDs* (Tables S2 and S3). This is on the order of the experimental uncertainty in the values of  $k_{\text{ex}}$  ( $\pm 10\%$ ) so that our data provide no evidence for significant Brønsted base catalysis by acetate anion of deuterium exchange at C(2) of simple imidazolium and benzimidazolium cations in  $\text{D}_2\text{O}$ . The absence of detectable buffer catalysis of exchange strongly supports the conclusion that  $k_{\text{HOH}} = k_{\text{reorg}}$  for the protonation of imidazol-2-yl carbenes by solvent water.<sup>15,29,30</sup>

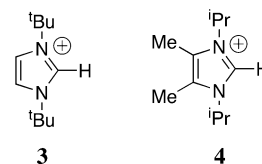
(4) The rate constants for proton transfer from several alcohol solvents to singlet diphenylcarbene  $\text{Ph}_2\text{C}$ : generated by femtosecond laser flash photolysis of diphenyldiazomethane show a good correspondence with the solvation time (dielectric relaxation time) of the solvent.<sup>31</sup> For example,  $k_{\text{MeOH}} = 1.1 \times 10^{11} \text{ s}^{-1}$  ( $\tau = 9 \text{ ps}$ ) for proton transfer to singlet  $\text{Ph}_2\text{C}$ : from solvent methanol is very similar to the solvation time of methanol,  $\tau_{\text{MeOH}} = 6.8 \text{ ps}$ .<sup>31</sup> At the MP2/DZ level the gas-phase proton affinity of singlet diphenylcarbene (275 kcal/mol)<sup>32</sup> is computed to be 18 kcal/mol greater than that of unsubstituted imidazol-2-yl carbene (257 kcal/mol).<sup>33</sup> Therefore, even singlet carbenes with a very highly basic carbon lone pair undergo proton transfer from hydroxylic solvents that is limited by solvent reorganization with a rate constant on the order of  $10^{11} \text{ s}^{-1}$ .

**Carbon Acid  $\text{p}K_{\text{a}}$  of Imidazolium Cations in Water.** Table 1 gives the second-order rate constants  $k_{\text{HO}}$  ( $\text{M}^{-1} \text{ s}^{-1}$ ) for proton transfer from C(2) of the imidazolium cation, **DMI**, **DMBI**, and **DPEBI** to hydroxide ion in water that were calculated from the values of  $k_{\text{DO}}$  ( $\text{M}^{-1} \text{ s}^{-1}$ ) using a secondary solvent isotope effect of  $k_{\text{DO}}/k_{\text{HO}} = 2.4$  for proton transfer that is limited by the solvent reorganization step.<sup>15,29</sup> These values of  $k_{\text{HO}}$  were used to calculate carbon acid  $\text{p}K_{\text{a}}$ s for ionization of the imidazolium cations at C(2) to give imidazol-2-yl carbenes in water (Table 1), using eq 5 derived for Scheme 2, with  $K_{\text{w}} = 10^{-14}$  for the ion product of water at 25 °C and  $k_{\text{HOH}} = 10^{11} \text{ s}^{-1}$  for the reverse protonation of the carbene by solvent water (see above). The range of error in these  $\text{p}K_{\text{a}}$  values is estimated to be  $\pm 0.5$  units and stems largely from the uncertainty in the value of  $k_{\text{HOH}}$  for the reverse protonation of the carbenes by solvent water.

Scheme 2



The values of  $\text{p}K_{\text{a}} = 21.2\text{--}23.8$  for the C(2)-proton of simple imidazolium cations show that these cations are relatively weak carbon acids whose carbon acidities in water are intermediate between those of the prototypical neutral carbonyl carbon acids acetone ( $\text{p}K_{\text{a}} = 19.3$ )<sup>34</sup> and ethyl acetate ( $\text{p}K_{\text{a}} = 25.6$ ).<sup>35</sup>

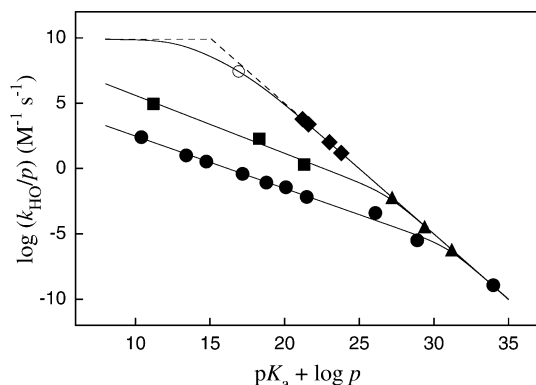


The value of  $\text{p}K_{\text{a}} = 23.0$  for the C(2)-proton of **DMI** in water (Table 1) is substantially higher than the previous estimate of  $\text{p}K_{\text{a}} \approx 17$  for the very similar 1,3,4-trimethylimidazolium cation<sup>27</sup> that has been propagated in the contemporary literature.<sup>36</sup> However, it is very similar to the values of  $\text{p}K_{\text{a}} = 22.7$  for **3**<sup>37</sup> and  $\text{p}K_{\text{a}} = 24.0$  for **4**<sup>38</sup> determined in DMSO. This is consistent with the small solvent effect on the acidities of a variety of thiazolium and alkylammonium cations, for which the  $\text{p}K_{\text{a}}$ s in DMSO and water lie within 1  $\text{p}K$  unit of each other.<sup>39</sup>

**Intrinsic Reactivity of Imidazol-2-yl Carbenes in Water.** Figure 4 shows Brønsted-type rate-equilibrium correlations of rate constants for deprotonation of several classes of carbon acids by hydroxide ion in water,  $\log k_{\text{HO}}$ , with the  $\text{p}K_{\text{a}}$  of the carbon acid, with statistical corrections for the number of protons  $p$  at the carbon acid. The extended linear correlation with a slope of  $-0.40$  for proton transfer from neutral monocarbonyl carbon acids over a range of 20  $\text{p}K_{\text{a}}$  units (Figure 4, ●) was discussed in our earlier work.<sup>15,35,40</sup> This correlation was expected to exhibit a downward break to a slope of  $-1.0$  at  $\text{p}K_{\text{a}} = 31$  where the reverse protonation of the carbanion by solvent water is limited equally by  $k_{\text{reorg}}$  for solvent reorganization and  $k_{\text{p}}$  for the proton-transfer step (Figure 3), so that  $k_{\text{HOH}} = k_{\text{reorg}}/2 = 5 \times 10^{10} \text{ s}^{-1}$ . The downward break was verified for acetate anion ( $\text{p}K_{\text{a}} = 33.5$ ), whose dianionic enolate undergoes protonation by solvent water with  $k_{\text{HOH}} = k_{\text{reorg}} = 10^{11} \text{ s}^{-1}$ .<sup>15</sup> The more limited data for proton transfer from a series of cationic monocarbonyl carbon acids (Figure 4, ■) define a linear correlation of slope  $= -0.44$  that lies ca. 3.5 log units above that for neutral monocarbonyl carbon acids, and which is expected to exhibit a downward break to a slope of  $-1.0$  at around  $\text{p}K_{\text{a}} = 27$ .<sup>41–43</sup>

- (28) Gold, V.; Grist, S. *J. Chem. Soc., Perkin Trans. 2* **1972**, 89–95.  
 (29) Richard, J. P.; Williams, G.; Gao, J. *J. Am. Chem. Soc.* **1999**, *121*, 715–726.  
 (30) Fishbein, J. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1988**, *110*, 5087–5095.  
 (31) Peon, J.; Polshakov, D.; Kohler, B. *J. Am. Chem. Soc.* **2002**, *124*, 6428–6438.  
 (32) Pliego, J. R., Jr.; De Almeida, W. B. *J. Chem. Soc., Faraday Trans.* **1997**, *93*, 1881–1883.  
 (33) Dixon, D. A.; Arduengo, A. J., III *J. Phys. Chem.* **1991**, *95*, 4180–4182.

- (34) Keeffe, J. R.; Kresge, A. J. In *The Chemistry of Enols*; Rappoport, Z., Ed.; John Wiley and Sons: Chichester, 1990; pp 399–480.  
 (35) Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 3129–3141.  
 (36) Sauer, R. R. *Tetrahedron Lett.* **1996**, *37*, 149–152.  
 (37) Kim, Y.-J.; Streitwieser, A. *J. Am. Chem. Soc.* **2002**, *124*, 5757–5761.  
 (38) Alder, R. W.; Allen, P. R.; Williams, S. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1267–1268.  
 (39) Bordwell, F. G.; Satish, A. V. *J. Am. Chem. Soc.* **1991**, *113*, 985–990.  
 (40) Richard, J. P.; Amyes, T. L.; Toteva, M. M. *Acc. Chem. Res.* **2001**, *34*, 981–988.  
 (41) Rios, A.; Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 9373–9385.

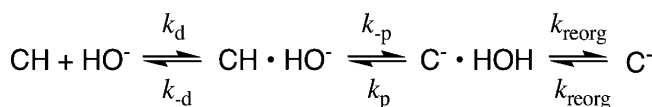


**Figure 4.** Rate-equilibrium correlations of  $k_{\text{HO}}$  ( $\text{M}^{-1} \text{s}^{-1}$ ) for deprotonation of carbon acids by hydroxide ion with the  $\text{p}K_{\text{a}}$  of the carbon acid in water at 25 °C. The values of  $k_{\text{HO}}$  and  $\text{p}K_{\text{a}}$  were statistically corrected for the number of acidic protons  $p$  at the carbon acid. (●) Correlation for neutral monocarbonyl carbon acids.<sup>15,35,41,43</sup> (■) Correlation for cationic monocarbonyl carbon acids.<sup>41–43</sup> (▲) Data for cyanoalkanes which define a slope of  $-1.0$ .<sup>29</sup> (◆) Data for simple imidazolium cations from this work which define a slope of  $-1.0$  (Table 1). (○) Data for the 3-cyanomethyl-4-methylthiazolium cation **1b** ( $L = \text{H}$ ),  $\text{p}K_{\text{a}} = 16.9$ .<sup>24,77</sup> The Eigen/Marcus curve through the data for the imidazolium (◆) and 3-cyanomethyl-4-methylthiazolium (○) cations was constructed using an estimated Marcus intrinsic barrier of 5.0 kcal/mol, as described in ref 47.

Figure 4 (◆) shows the linear correlation with a slope of  $-1.0$  for proton transfer to hydroxide ion from C(2) of the simple imidazolium cations studied here (Table 1), whose conjugate bases undergo protonation by solvent water with  $k_{\text{HOH}} = k_{\text{reorg}} = 10^{11} \text{ s}^{-1}$ . Therefore, the downward break for proton transfer from C(2) of simple imidazolium cations is anticipated to occur at  $\text{p}K_{\text{a}} < 21.2$  determined for **DPEBI**. Our earlier data<sup>29</sup> for proton transfer from simple cyanoalkanes (Figure 4, ▲), whose conjugate bases also undergo protonation by solvent water with  $k_{\text{HOH}} = k_{\text{reorg}} = 10^{11} \text{ s}^{-1}$ ,<sup>29</sup> necessarily lie on the same “limiting” correlation of slope  $-1.0$  defined by the data for imidazolium cations.

Scheme 3 shows the Eigen mechanism<sup>44</sup> for proton transfer from a carbon acid to hydroxide ion, where  $k_{\text{reorg}}$  ( $\text{s}^{-1}$ ) is the *first-order* rate constant for “encounter” of the conjugate base of the carbon acid with water by solvent reorganization that places a molecule of HOH in a “reactive” position (see Figure 3). The solid curve through the data for simple imidazolium cations in Figure 4 (◆) shows the calculated fit to this mechanism obtained using  $k_{\text{d}} = k_{\text{HO}} = 10^{9.9} \text{ M}^{-1} \text{ s}^{-1}$  for the thermodynamically favorable diffusion-limited proton transfer between HCN ( $\text{p}K_{\text{a}} = 9.0$ ) and hydroxide ion,<sup>45</sup>  $k_{\text{reorg}} = 10^{11} \text{ s}^{-1}$ , and an estimated Marcus intrinsic barrier<sup>46</sup> for the actual proton-transfer step ( $k_{-p}$  or  $k_p$ ) of 5.0 kcal/mol.<sup>47</sup> This Eigen/Marcus curve shows that the downward break in the correlation for proton transfer between C(2) of imidazolium and thiazolium cations and hydroxide ion is expected to occur at around  $\text{p}K_{\text{a}} = 18.4$ .

### Scheme 3



(42) Rios, A.; Crueiras, J.; Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **2001**, *123*, 7949–7950.

(43) Rios, A.; Richard, J. P.; Amyes, T. L. *J. Am. Chem. Soc.* **2002**, *124*, 8251–8259.

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

The systematic shift in the position of the downward break to a slope of  $-1.0$  for the correlations shown in Figure 4 to lower carbon acid  $\text{p}K_{\text{a}}$  on moving from neutral to cationic monocarbonyl compounds and to azolium cations is a direct consequence of the increasing intrinsic reactivity and decreasing Marcus intrinsic barrier to proton transfer along this series of carbon acids.<sup>15</sup> It shows a strong correspondence with the expected increasing extents of localization of negative charge at the central carbon of the conjugate base.<sup>48</sup> The tendency toward a greater localization of negative charge at the  $\alpha$ -carbon of the formally neutral enolates of cationic monocarbonyl compared with those of neutral monocarbonyl carbon acids has been discussed in our earlier work.<sup>40,41</sup> The small Marcus intrinsic barrier to proton transfer from C(2) of imidazolium cations is consistent with evidence for a high degree of localization of the lone pair at the in-plane  $sp^2$ -orbital of the carbene conjugate base.<sup>33,49,50</sup>

Figure 4 illustrates the kinetic and thermodynamic acidity of carbon acids of varying structure over a wide range of carbon acid  $\text{p}K_{\text{a}}$  and substrate reactivity. It serves to emphasize the *extremely low* intrinsic reactivity of neutral carbonyl compounds as carbon acids. For example, a neutral monocarbonyl carbon acid of  $\text{p}K_{\text{a}} = 15.74$  for water undergoes proton transfer to hydroxide ion  $10^8$ -fold more slowly than an imidazolium cation of the same  $\text{p}K_{\text{a}}$ .<sup>51</sup> Therefore, imidazol-2-yl carbenes are expected to be up to  $10^8$ -fold more reactive toward water than a typical enolate carbanion of the same thermodynamic basicity, which implies a difference in the Marcus intrinsic barriers to proton transfer of around 11 kcal/mol. The large intrinsic reactivity of imidazol-2-yl carbenes toward proton donors such as water suggests that their addition and expulsion from carbonyl electrophiles is also intrinsically fast, which is consistent with

(45) Bednar, R. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1985**, *107*, 7117–7126.

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

(47) Proton transfer from C(2) of the 3-cyanomethyl-4-methylthiazolium cation **1b** ( $L = \text{H}$ ,  $\text{p}K_{\text{a}} = 16.9$ ) to lyoxide ion is limited in part by proton transfer with  $k_p/k_{\text{reorg}} = 0.29$  (Figure 3).<sup>24</sup> The value of  $k_{\text{reorg}} = 10^{11} \text{ s}^{-1}$  then gives  $k_p = 2.9 \times 10^{10} \text{ s}^{-1}$ . This value of  $k_p$  was substituted into the Marcus expression of eq 7 derived at 298 K ( $K_w = 10^{-14} \text{ M}^2$ ,  $K_{\text{a}} = 10^{-16.9} \text{ M}$ ) to give an estimated Marcus intrinsic barrier<sup>46</sup> for proton transfer between C(2)

$$\log k_p = \frac{1}{1.36} \left\{ 17.44 - \Lambda \left( 1 - \frac{1.36 \log(K_w/K_{\text{a}})}{4\Lambda} \right)^2 \right\} \quad (7)$$

$$k_{\text{HO}} = \frac{k_d k_{-p} k_{\text{reorg}}}{k_{-p} k_{\text{reorg}} + k_{-d} k_{\text{reorg}} + k_{-d} k_p} \quad (8)$$

$$k_{-p} = \left( \frac{k_{-d}}{k_d} \right) \left( \frac{K_{\text{a}}}{K_w} \right) k_p \quad (9)$$

of azolium cations and hydroxide ion of  $\Lambda = 5.0$  kcal/mol. The solid curve through the data for imidazolium cations in Figure 4 (◆) was calculated according to eq 8, which is the steady-state equation for the Eigen mechanism shown in Scheme 3, with values of  $k_p$  and  $k_{-p}$  calculated using eq 7 ( $\Lambda = 5.0$  kcal/mol) and eq 9, respectively,  $k_{\text{reorg}} = 10^{11} \text{ s}^{-1}$ ,  $k_d = 10^{9.9} \text{ M}^{-1} \text{ s}^{-1}$  and  $k_{-d} = 10^{9.9} \text{ s}^{-1}$  (we assume no work term for the encounter of hydroxide ion and the carbon acid so that  $k_d = k_{-d}$ ).

(48) Bernasconi, C. F. *Adv. Phys. Org. Chem.* **1992**, *27*, 119–238.

(49) Heinemann, C.; Mueller, T.; Apeloig, Y.; Schwarz, H. *J. Am. Chem. Soc.* **1996**, *118*, 2023–2038.

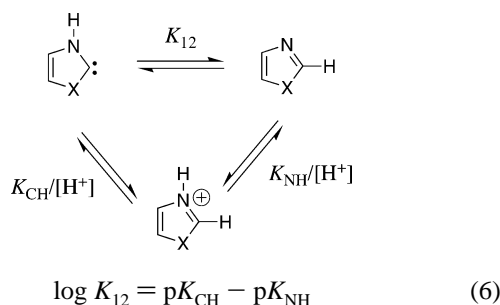
(50) Arduengo, A. J., III; Dias, H. V. R.; Dixon, D. A.; Harlow, R. L.; Klooster, W. T.; Koetzle, T. F. *J. Am. Chem. Soc.* **1994**, *116*, 6812–6822.

(51) The linear correlation for proton transfer from neutral monocarbonyl carbon acids (Figure 4, ●) is given by  $\log(k_{\text{HO}}/p) = 6.496 - 0.401(\text{p}K_{\text{a}} + \log p)$ ,<sup>15,43</sup> which gives  $k_{\text{HO}} = 1.53 \text{ M}^{-1} \text{ s}^{-1}$  for proton transfer from a carbon acid of  $\text{p}K_{\text{a}} = 15.74$ . Interpolation of the calculated Eigen/Marcus curve<sup>47</sup> for proton transfer from C(2) of imidazolium cations (Figure 4, ◆) gives  $k_{\text{HO}} = 1.51 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$  for proton transfer from C(2) of a hypothetical imidazolium cation of  $\text{p}K_{\text{a}} = 15.74$ .

their efficacy as nucleophilic catalysts of benzoin condensation<sup>8–12</sup> and acyl transfer.<sup>13,14</sup>

**1,2-Hydrogen Shift at Imidazol-2-yl Carbene.** A signature reaction channel of singlet carbenes is the 1,2-hydrogen shift in which the carbenic carbon is converted to an olefinic carbon at the product.<sup>52,53</sup> The thermodynamic cycle in Scheme 4 (X = NH) shows that the equilibrium constant for the 1,2-hydrogen shift at singlet imidazol-2-yl carbene to give neutral imidazole can be obtained directly from the acidity constants for ionization of the imidazolium cation at nitrogen ( $K_{\text{NH}}$ ) and at C(2) ( $K_{\text{CH}}$ ), according to eq 6.

Scheme 4

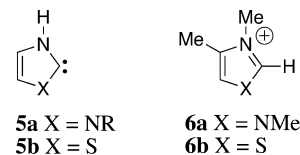


The values of  $\text{p}K_{\text{CH}} = 23.8$  (Table 1) and  $\text{p}K_{\text{NH}} = 7.1$ <sup>54</sup> for ionization of the imidazolium cation at carbon and nitrogen, respectively, were substituted into eq 6 to obtain  $K_{12} = 5.0 \times 10^{16}$  as the equilibrium constant for the 1,2-H shift at the parent imidazol-2-yl carbene to give imidazole in water at 25 °C. This corresponds to a favorable Gibbs free energy change of  $\Delta G_0 = -22.7$  kcal/mol and it represents the first determination of the thermodynamic driving force for a 1,2-H shift at a singlet carbene.<sup>55</sup> The concerted 1,2-H shift at singlet imidazol-2-yl carbene is symmetry-forbidden<sup>3</sup> and the kinetic barrier to this reaction in the gas phase has been calculated to be in the range  $\Delta E^\ddagger = 40$  to 47 kcal/mol<sup>56–59</sup> so that this reaction cannot occur directly. Rather, the 1,2-H shift at imidazol-2-yl carbene to give imidazole in water occurs by proton transfer to the carbenic carbon to give the imidazolium cation followed by loss of a proton from nitrogen to give the neutral imidazole product (Scheme 4).

**Substituent Effects on the Stability of N-Heterocyclic Carbenes.** The literature on the stability of N-heterocyclic carbenes **5** presents conflicting conclusions about the effect of a change from a nitrogen to a sulfur substituent X on the stability of these species. Along with the classic report of Haake et al. that  $\text{DO}^-$ -catalyzed deuterium exchange at C(2) of the thiazolium cation **6b** in  $\text{D}_2\text{O}$  is ca. 3000-fold faster than for the imidazolium cation **6a**,<sup>27</sup> there have been several attempts to

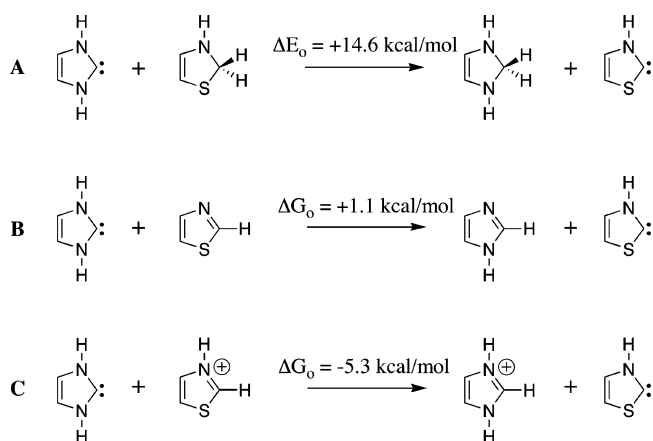
rationalize the apparent greater stability of thiazolium than of imidazolium ylides/carbenes.<sup>36,60–63</sup>

More recently, the isolation of a wide variety of imidazol-2-yl and other diamino carbenes as stable species<sup>2–4</sup> has fuelled computational investigations of their stability.<sup>33,36,49,56–59,64</sup> One conclusion from this work is that N-substituted imidazol-2-yl carbenes **5a** are *more* stable than their S-substituted thiazol-2-yl counterparts **5b**.<sup>36,58</sup>



The data obtained in this work allow for the first comparison of the *thermodynamic* acidities of imidazolium and thiazolium cations in water. Table 2 gives the kinetic and thermodynamic acidities of the C(2)-proton of several simple azolium cations in water at 25 °C that were determined in this work or calculated from literature data. The thermodynamic cycle in Scheme 4 shows that the substituent effect on the carbon basicity of N-heterocyclic carbenes is the sum of the substituent effects on the 1,2-H shift at the carbene to give the corresponding neutral azole and on N-protonation of the neutral azole to give the azolium cation. The difference in the  $\text{p}K_{\text{a}}$ s for ionization of the unsubstituted imidazolium cation (Scheme 4, X = NH) and the thiazolium cation (Scheme 4, X = S) at C(2),  $\Delta \log K_{\text{CH}} = 3.9$  (Table 2), and at nitrogen,  $\Delta \log K_{\text{NH}} = 4.7$ ,<sup>65</sup> then gives  $\Delta \log K_{12} = -0.8$  as the *difference* in the equilibrium constants for the 1,2-H shift at the parent imidazol-2-yl and thiazol-2-yl carbenes to give the corresponding azoles in water. This is illustrated in Figure 5 which shows that the 3.9 pK unit (5.3 kcal/mol) smaller C(2) carbon acidity of the imidazolium cation than of the thiazolium cation in water reflects the 6.4 kcal/mol greater stabilization of the imidazolium than of the thiazolium cation relative to the neutral azole, and the *offsetting* 1.1 kcal/mol greater stability of the imidazol-2-yl carbene than of the thiazol-2-yl carbene relative to the neutral azole.

Scheme 5

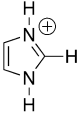

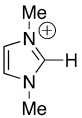




Scheme 5 shows a series of isodesmic reactions that result in the interconversion of imidazol-2-yl and thiazol-2-yl carbenes

- (52) Bonneau, R.; Liu, M. T. H. In *Advances in Carbene Chemistry*; Brinker, U. H., Ed.; JAI Press Inc.: Stamford, CT, 1998; Vol. 2, pp 1–28.
- (53) Moss, R. A. In *Advances in Carbene Chemistry*; Brinker, U. H., Ed.; JAI Press Inc.: Stamford, CT, 1994; Vol. 1, pp 59–88.
- (54) Catalan, J.; Claramunt, R. M.; Elguero, J.; Laynez, J.; Menendez, M.; Anvia, F.; Quiñan, J. H.; Taagepera, M.; Taft, R. W. *J. Am. Chem. Soc.* **1988**, *110*, 4105–4111.
- (55) To the best of our knowledge, the only other thermodynamic data for such a process is  $\Delta H = -42.1$  kcal/mol for the 1,2-H shift at methylchlorocarbene to give vinyl chloride in heptane at 295 K, determined using photoacoustic calorimetry.<sup>75</sup>
- (56) Heinemann, C.; Thiel, W. *Chem. Phys. Lett.* **1994**, *217*, 11–16.
- (57) Boehme, C.; Frenking, G. *J. Am. Chem. Soc.* **1996**, *118*, 2039–2046.
- (58) Maier, G.; Endres, J. *Eur. J. Org. Chem.* **1998**, 1517–1520.
- (59) McGibbon, G. A.; Heinemann, C.; Lavorato, D. J.; Schwarz, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1478–1481.

- (60) Olofson, R. A.; Landesberg, J. M. *J. Am. Chem. Soc.* **1966**, *88*, 4263–4265.

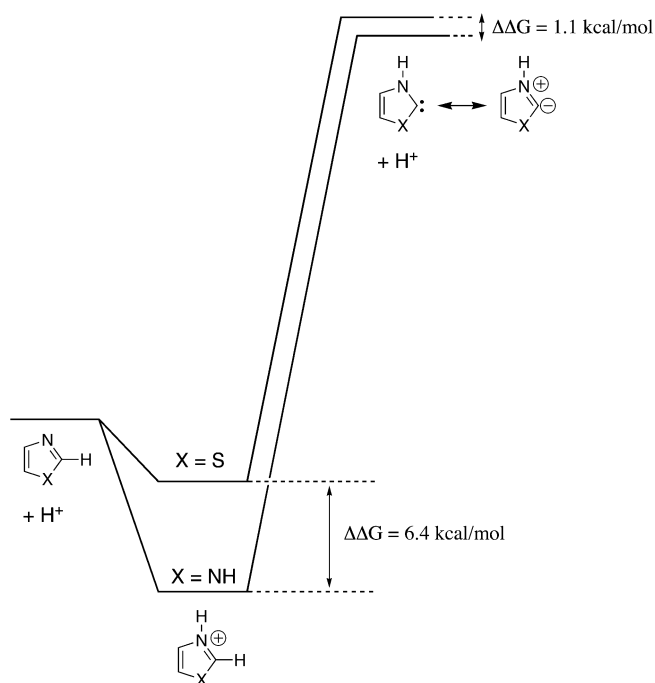
**Table 2.** Effect of Nitrogen, Sulfur and Oxygen Heteroatom Substituents on the Kinetic and Thermodynamic Acidity of the C(2)–Proton of Simple Azolium Cations in Water at 25 °C

Carbon Acid	$k_{\text{HO}}$ ( $\text{M}^{-1} \text{s}^{-1}$ ) <sup>a</sup>	$\text{p}K_{\text{a}}$ <sup>b</sup>
	15.4 <sup>c</sup>	23.8 <sup>c</sup>
	$1.3 \times 10^5$ <sup>d</sup>	19.9 <sup>e</sup>
	103 <sup>c</sup>	23.0 <sup>c</sup>
	$3.4 \times 10^5$ <sup>f</sup>	19.5 <sup>e</sup>
	$3 \times 10^7$ <sup>g</sup>	16.9 <sup>h</sup>

<sup>a</sup> Second-order rate constant for deprotonation of the azolium cation at C(2) by hydroxide ion in  $\text{H}_2\text{O}$ . <sup>b</sup> Carbon acid  $\text{p}K_{\text{a}}$  for ionization of the azolium cation at C(2) in  $\text{H}_2\text{O}$  to give the corresponding N-heterocyclic carbene. <sup>c</sup> Data from Table 1. <sup>d</sup> Calculated from  $k_{\text{DO}} = 3.1 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$  for the 3,4-dimethylthiazolium cation at 25 °C [ref 26] using a secondary solvent isotope effect of  $k_{\text{DO}}/k_{\text{HO}} = 2.35$  [ref 24] with the assumption that the combined effects of N-methylation (2.6-fold increase in  $k_{\text{DO}}$  per N-methyl group observed for the imidazolium cation, Table 1) and 4-methylation (2–4-fold decrease in  $k_{\text{DO}}$  at 50 °C, ref 22) result in essentially no change in  $k_{\text{HO}}$  for azolium cations. <sup>e</sup> Calculated from  $k_{\text{HO}}$  ( $\text{M}^{-1} \text{ s}^{-1}$ ) and  $k_{\text{HOH}} = 10^{11} \text{ s}^{-1}$  for the reverse protonation of the conjugate base (carbene) by solvent water according to eq 5. <sup>f</sup> Calculated from  $k_{\text{HO}} = 1.3 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$  for the thiazolium cation (Table 2) and the 2.6-fold increase in  $k_{\text{DO}}$  per N-methyl group observed for the imidazolium cation (Table 1). <sup>g</sup> Calculated from  $k_{\text{HO}} = 103 \text{ M}^{-1} \text{ s}^{-1}$  for the 1,3-dimethylimidazolium cation (Table 1) and the  $3 \times 10^5$ -fold greater value of  $k_{\text{DO}}$  for the 3,4-dimethyl-2-oxazolium cation than for the 1,3,4-trimethylimidazolium cation at 34 °C [ref 27]. <sup>h</sup> Estimated from  $k_{\text{HO}} = 2.73 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$  for the 3-cyanomethyl-4-methylthiazolium cation **1b** (L = H) at 25 °C [ref 77] for which  $\text{p}K_{\text{a}} = 16.9$  [ref 24], with the assumption that proton transfer from oxazolium cations to hydroxide ion follows the same Eigen correlation as that shown in Figure 4 for the closely related imidazolium and thiazolium cations.

and the products of their hydrogenation (Scheme 5A), 1,2-hydrogen shift (Scheme 5B) and proton transfer (Scheme 5C) reactions.

The value of  $\Delta E_{\text{o}} = +14.6 \text{ kcal/mol}$  in the gas phase for Scheme 5A was calculated as the difference in the energies of

**Figure 5.** Effect of a change from a nitrogen to a sulfur heteroatom substituent on the Gibbs free energy change for the 1,2-hydrogen shift reaction of N-heterocyclic carbenes to give the neutral azole ( $|\Delta\Delta G| = 1.1 \text{ kcal/mol}$ ) and for proton transfer to C(2) to give the azolium cation ( $|\Delta\Delta G| = 6.4 - 1.1 = 5.3 \text{ kcal/mol}$ ) in water at 298 K.

hydrogenation of the two carbenes computed at the B3LYP/6-311G(d,p) level.<sup>58</sup> It shows that, relative to the corresponding hydrogen adduct, an imidazol-2-yl carbene is substantially *more stable* than a thiazol-2-yl carbene. This reflects the greater  $\pi$ -donating ability to carbon of nitrogen than of sulfur<sup>66,67</sup> and the greater stabilization of the carbene by electron donation of the lone pair at nitrogen than of that at sulfur to the  $p$ -orbital at C(2). By contrast, no such  $\pi$ -stabilization is possible at the hydrogen adducts where C(2) is  $sp^3$ -hybridized, so that the large positive value of  $\Delta E_{\text{o}}$  reflects the *complete* loss of  $\pi$ -interactions of the lone pair(s) at the N or S heteroatom substituent with C(2) on moving from the carbene to the hydrogen adduct.

The value of  $\Delta G_{\text{o}} = +1.1 \text{ kcal/mol}$  in water for Scheme 5B ( $\Delta\log K_{12} = -0.8$ , this work) is close to the value of  $\Delta E_{\text{o}} = +2.5 \text{ kcal/mol}$  in the gas phase calculated as the difference in the energy changes for the 1,2-H shift at the two carbenes computed at the B3LYP/6-31G\*\* level.<sup>59,68</sup> It shows that, relative to the corresponding neutral azole, an imidazol-2-yl carbene is of *similar stability* to a thiazol-2-yl carbene (Figure 5). This is consistent with a similar stabilization of the carbene and the neutral azole, both of which are formally aromatic, by  $\pi$ -interactions of the lone pair(s) at the N or S heteroatom substituent.<sup>56</sup>

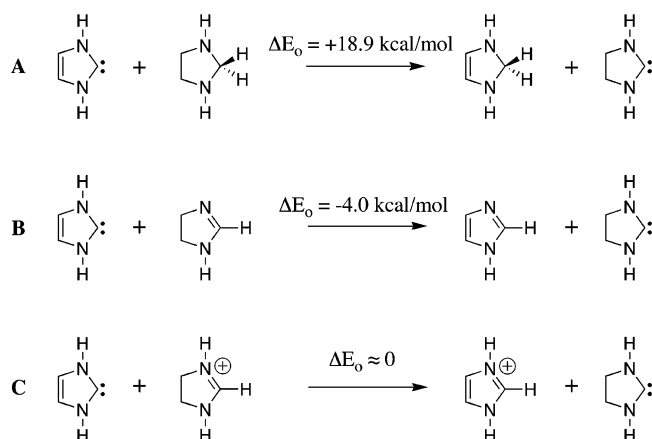
Finally, the value of  $\Delta G_{\text{o}} = -5.3 \text{ kcal/mol}$  in water for Scheme 5C ( $\Delta\log K_{\text{CH}} = 3.9$ , Table 2) shows that, relative to the corresponding azolium cation, an imidazol-2-yl carbene is substantially *less stable* than a thiazol-2-yl carbene. This is

- (61) Olofson, R. A.; Landesberg, J. M.; Houk, K. N.; Michelman, J. S. *J. Am. Chem. Soc.* **1966**, *88*, 4265–4266.  
 (62) Aldrich, H. S.; Alworth, W. L.; Clement, N. R. *J. Am. Chem. Soc.* **1978**, *100*, 2362–2366.  
 (63) Scheffers-Sap, M. M. E.; Buck, H. M. *J. Am. Chem. Soc.* **1979**, *101*, 4807–4811.  
 (64) Alder, R. W.; Blake, M. E.; Oliva, J. M. *J. Phys. Chem. A* **1999**, *103*, 11 200–11 211.

- (65) Calculated using the statistically corrected value of  $\text{p}K_{\text{a}} = 7.41$  for the imidazolium cation in water at  $I = 0.1$  and 25 °C<sup>54</sup> and  $\text{p}K_{\text{a}} = 2.68$  for the thiazolium cation in water at 25 °C.<sup>76</sup>  
 (66) Kapp, J.; Schade, C.; El-Nahasa, A. M.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2236–2238.  
 (67) Bernardi, F.; Bottoni, A.; Venturini, A. *J. Am. Chem. Soc.* **1986**, *108*, 5395–5400.  
 (68) McGibbon, G. A.; Hrusak, J.; Lavorato, D. J.; Schwarz, H.; Terlouw, J. K. *Chem. Eur. J.* **1997**, *3*, 232–236.



Scheme 6



consistent with the conclusion that imidazol-2-yl carbenes are strongly stabilized by  $\pi$ -interactions, but that this stabilization is even more important at the imidazolium cation.<sup>49</sup> These data serve to emphasize that substituent effects on organic reactions depend not only on the stability of reactive intermediates (e.g., carbenes), but that they can also exhibit a very strong dependence on the stability of the reacting ground state.<sup>69,70</sup>

The above discussion emphasizes the importance of the choice of reference reaction when assessing the “stability” of N-heterocyclic carbenes. For example, the value of  $\Delta E_0 = +18.9$  kcal/mol for the reaction shown in Scheme 6A,<sup>71</sup> which has been taken as a measure of the relative stability of the formally aromatic imidazol-2-yl carbenes and their saturated imidazolin-2-yl counterparts,<sup>57,72</sup> can be attributed to the greater stabilization of the former carbenes by cyclic electron delocalization.<sup>49,57</sup> However, this difference in thermodynamic stability is largely eradicated when the reference reaction is the 1,2-H shift to give the neutral azole (Scheme 6B,  $\Delta E_0 = -4.0$  kcal/mol<sup>73</sup>), or proton transfer to give the azolium cation (Scheme 6C,  $\Delta E_0 \approx 0$  kcal/mol<sup>74</sup>), both of which are  $sp^2$ -hybridized at C(2) and can therefore derive stabilization from cyclic electron delocalization.<sup>49,56</sup>

(69) Richard, J. P.; Amyes, T. L.; Rice, D. J. *J. Am. Chem. Soc.* **1993**, *115*, 2523–2524.

(70) Apeloig, Y.; Biton, R.; Abu-Freih, A. *J. Am. Chem. Soc.* **1993**, *115*, 2522–2523.

(71) Calculated as the difference in the energies of hydrogenation of the two carbenes computed at the MP4/6-311G(d,p)//MP2/6-31G(d) level.<sup>57</sup> A value of  $\Delta E_0 = +14.4$  kcal/mol has been computed at the B3LYP/6-31G(d)//B3LYP/6-31G(d) level.<sup>72</sup>

(72) Denk, M. K.; Rodezno, J. M.; Gupta, S.; Lough, A. J. *J. Organomet. Chem.* **2001**, *617–618*, 242–253.

**Summary.** (1) The determination of reliable values of  $pK_a = 21.2–23.8$  for ionization of the C(2)-proton of simple imidazolium and benzimidazolium cations in water reveal these cations to be relatively weak carbon acids whose acidities are intermediate between those of the prototypical neutral carbonyl carbon acids acetone and ethyl acetate.

(2) Imidazol-2-yl carbenes exhibit a high intrinsic reactivity toward protonation by solvent water and the Marcus intrinsic barrier to this reaction is estimated to be ca. 11 kcal/mol smaller than that for protonation of the enolates of simple monocarbonyl carbon acids.

(3) A thermodynamic cycle gives the thermodynamic driving force for the 1,2-hydrogen shift at singlet imidazol-2-yl carbene to give imidazole in water as  $\Delta G_0 = -22.7$  kcal/mol (298 K).

(4) An analysis of substituent effects on the hydrogenation, 1,2-hydrogen shift and proton transfer reactions of simple N-heterocyclic carbenes emphasizes the importance of the choice of reference reaction when assessing the stability of N-heterocyclic carbenes relative to a variety of neutral and cationic derivatives.

**Acknowledgment.** We acknowledge the National Science Foundation (CHE-0092434 to S. T. Diver) and the National Institutes of Health (GM 39754 to J. P. Richard) for generous support of this work.

**Supporting Information Available:** Details of the syntheses of **DMI**, **DMBI**, and **DPEBI**, the preparation of buffers and the NMR methods. Tables S1–S4: Rate Constants  $k_{ex}$  ( $s^{-1}$ ) for deuterium exchange at C(2) of imidazole, **DMI**, **DMBI**, and **DPEBI** in buffered  $D_2O$  at 25 °C. Figures S1–S2:  $^1H$  NMR spectra of **DMI** and **DMBI** obtained during deuterium exchange in buffered  $D_2O$  at 25 °C. Figure S3: Representative semilogarithmic plots of reaction progress against time. (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA039890J

(73) Calculated as the difference in the energy changes for the 1,2-H shift at the two carbenes computed at the MP4/6-311G(d,p)//MP2/6-31G(d) level.<sup>57</sup>

(74) At the B3LYP/6-31G\* level the 1,3-dimethylimidazol-2-yl carbene and the corresponding saturated 1,3-dimethylimidazolin-2-yl carbene are computed to have identical proton affinities of 266.0 kcal/mol.<sup>2</sup>

(75) LaVilla, J. A.; Goodman, J. L. *J. Am. Chem. Soc.* **1989**, *111*, 6877–6878.

(76) Barszcz, B.; Gabryszewski, M.; Kulig, J.; Lenarcik, B. *J. Chem. Soc., Dalton Trans.* **1986**, 2025–2028.

(77) A value of  $k_{HO} = 2.73 \times 10^7 M^{-1} s^{-1}$  for deprotonation of **1b** (L = H) by hydroxide ion in  $H_2O$  at 25 °C was calculated from the following literature data<sup>24</sup> at 30 °C ( $I = 2.0$ ):  $k_{DO} = 4.62 \times 10^7 M^{-1} s^{-1}$ , a secondary solvent isotope effect of  $k_{DO}/k_{HO} = 1.3$ , and  $\Delta H^\ddagger = 7.9$  kcal/mol ( $E_a = 8.5$  kcal/mol).