JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Article

pubs.acs.org/JACS

Proton Transfer Reactions of Triazol-3-ylidenes: Kinetic Acidities and Carbon Acid pK_a Values for Twenty Triazolium Salts in Aqueous Solution

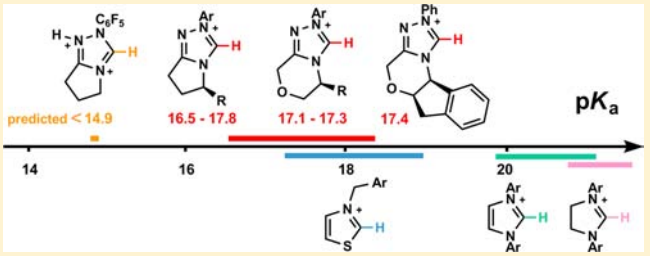
Richard S. Massey,[†,§] Christopher J. Collett,[‡,§] Anita G. Lindsay,[†] Andrew D. Smith,*[,‡] and AnnMarie C. O'Donoghue*[,†]

[†]Department of Chemistry, Durham University, University Science Laboratories, South Road, Durham DH1 3LE, U.K.

[‡]EaStCHEM, School of Chemistry, University of St. Andrews, North Haugh, St. Andrews KY16 9ST, U.K.

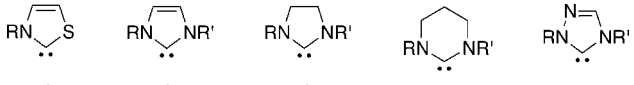
Supporting Information

ABSTRACT: Second-order rate constants have been determined for deuteroxide ion-catalyzed exchange of the C(3)-proton for deuterium, k_{DO} (M^{-1} s^{-1}), of a series of 20 triazolium salts in aqueous solution at 25 °C and ionic strength I = 1.0 (KCl). Evidence is presented that the rate constant for the reverse protonation of the triazol-3-ylidenes by solvent water is close to that for dielectric relaxation of solvent (10^{11} s^{-1}). These data enabled the calculation of carbon acid pK_a values in the range 16.5−18.5 for the 20 triazolium salts. pD rate profiles for deuterium exchange of the triazolium salts reveal that protonation at nitrogen to give *dicationic* triazolium species occurs under acidic conditions, with estimates of pK_a^{N1} = −0.2 to 0.5.



INTRODUCTION

Since the first isolation and characterization of stable *N*-heterocyclic carbenes (NHCs), such species have come to prominence in various fields of chemistry.[1−12] Structural classes embodied within the NHC family include the thiazol-2-ylidenes (**1**), imidazol-2-ylidenes (**2**) and imidazolin-2-ylidenes (**3**), trihydropyrimidin-2-ylidenes (**4**), and triazol-3-ylidenes (**5**). From the early seminal work of Breslow,[13] thiazol-2-ylidenes such as **1** have long been implicated as the catalytically active species in the benzoin condensation; however, until recently, applications beyond this C−C bond-forming reaction were relatively limited. In the past decade, NHCs have proven to be effective organocatalysts of a broad range of synthetic transformations. Initially based upon their established use in polarity reversal or Umpolung techniques,[5,10,14,15] methodologies have been developed for the generation and exploitation of azolium homoenolates[16] and enolates,[17] as well as acylazolium[18] and α,β-unsaturated acylazoliums,[19] leading to remarkable reaction and product diversity within this field. Although many different NHC classes such as **1** and **2** have been employed in organocatalysis, the triazol-3-ylidenes **5** are the most often utilized. It is common in many synthetic transformations to generate the active NHC species in situ from the conjugate acid azolium ion precursor of the NHC by use of an appropriate base.[20] Remarkably, despite the widespread use of azolium ion precursors to NHCs in organocatalysis and elsewhere, there have been relatively few literature reports of the solution kinetic or thermodynamic Brønsted acidities of these precatalysts,[21−32] although there have been studies of NHC nucleophilicities[33] and gas-phase proton affinities.[34−42] Washabaugh and Jencks reported on the C(2)-H/D exchange and aqueous pK_a values of a range of *N*-alkylthiazolium ion analogues of thiamine, that are precursors to thiazol-2-ylidenes **1**.[30−32] Amyes et al. reported aqueous pK_a values for the conjugate acids of imidazol-2-ylidenes **2** (R = R′ = H or Me) and two benzoannelated variants.[22] We recently reported the kinetic acidities toward hydroxide ion, and the aqueous pK_a values, of a broad range of conjugate acid precursors to imidazol-2-ylidenes **2**, imidazolin-2-ylidenes **3**, and trihydropyrimidin-2-ylidenes **4**.[26] In this contribution, we report kinetic acidities and pK_a values in aqueous solution for a large series of synthetically relevant triazolium ion precursors to triazol-3-ylidenes **5**.



A remarkably diverse range of triazol-3-ylidenes has been employed in organocatalytic transformations, with significant variations in both catalytic activities and reactivities being observed within this architecture. For example, *N*-pentafluorophenyl triazolium salts are generally the preferred precatalysts for benzoin and Stetter reaction processes,[43] while *N*-mesityl triazolium precatalysts show remarkably enhanced reactivity in

Received: August 24, 2012
Published: November 22, 2012

   dx.doi.org/10.1021/ja308420c | J. Am. Chem. Soc. 2012, 134, 20421−20432

NHC-catalyzed processes involving enals.[44] Qualitative experiments by Bode and Mahatthananchai have shown that *N*-pentafluorophenyl triazolium salts are more acidic than the corresponding *N*-mesityl salts,[45] implying that more of the corresponding active NHC is likely to be generated under typical reaction conditions in the former case. Further experimentation led them to elegantly ascribe the *N*-mesityl effect to irreversible initial addition of the NHC to the enal. Given these precedents, and the general interest in NHC-mediated catalysis using triazolium precatalysts, we aimed to quantify the effect of variation of the N-substituent, ring-size, and substitution pattern within a series of chiral and achiral triazolium salt, **6**, precursors to singlet NHCs, **7**, upon their kinetic acidities and aqueous pK_a values (Scheme 1).

Scheme 1. Substituent Effects on Kinetic Acidities and pK_a Values of Triazolium Salts

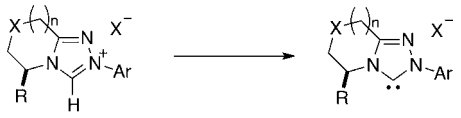


Figure 1 illustrates the specific series of triazolium ions that we have studied and their chloride or tetrafluoroborate counterions (X^-). In each case, the second-order rate constant for deuteroxide ion-catalyzed exchange of the C(3)-proton for deuterium, k_{DO} (M^{-1} s^{-1}) has been determined. Using these values, the carbon acid pK_a values for the triazolium ions in aqueous solution have been calculated. To our knowledge, this is the first report of kinetic acidities and carbon acid pK_a values for a broad range of triazolium ions in any solvent. Analysis of the p*D* rate profiles for deuterium exchange of triazolium ions **6** reveals distinct differences from analogous data for the deprotonations of the conjugate acid precursors to NHCs **1**–**4**. In particular, the data reveal that N(1) protonation to give dicationic triazolium ions can occur under relatively mild acidic conditions, where these species act as precursors to *monocationic* *N*-heterocyclic carbenes.

EXPERIMENTAL SECTION

The syntheses of triazolium salts **8a**–**f**, **9**–**13**, **14b**–**f**, **15a**–**d**, and **16**-X^-, the preparation of solutions, the determination of p*D*, and the NMR methods used to monitor deuterium exchange are described in the Supporting Information.

Deuterium Exchange. All triazolium salts were rigorously dried before use in the deuterium exchange experiments. Typically, reactions were initiated by the addition of the reaction solution, containing internal standard (tetramethylammonium deuterosulfate) and buffer or DCl solution, directly to the triazolium salt. In general, the final substrate and internal standard concentrations in the reaction solutions were 5–10 mM and 0.5–1 mM, respectively. As triazolium salts **10**–**12**, **14b**, **15a**, and **15d** were insoluble in D_2O, perdeuterated acetonitrile (33% v/v) was used as a cosolvent in the exchange reactions of these salts. All H/D exchange reactions were incubated at 25 ± 0.1 °C in a thermostatted water bath. p*D* values were recorded at the beginning and end of each reaction and were found to be constant within error (±0.03).

In general, the reaction progress was monitored over time by withdrawing aliquots (~750 μL) at timed intervals from a reaction solution (~10 mL). These aliquots were quenched to p*D* values 2–3 units below that of the reaction mixture by addition of 1 M DCl solution. The quenched samples were either analyzed immediately, or the capped NMR tubes were placed in sealed bags containing calcium chloride and stored in the freezer for analysis at a later time. Reactions at lower p*D* values (<1.5) were run directly in NMR tubes thermostatted at 25 ± 0.1 °C, without the use of quenching. This was due to the inability to sufficiently quench the reaction through the lowering of p*D*.

Deuterium exchange was followed by ^{1}H NMR spectroscopy during the disappearance of 75–90% of the C(3)-proton signal of each substrate. There was no change in the integrated areas of signals due to all other protons of the triazolium salts **8**–**16**-X^- during this period, and no additional signals appeared. Thus, there was no detectable hydrolysis or decomposition of any of the triazolium salt substrates under the reaction conditions. The observed pseudo first-order rate constants for exchange of the C(3)-proton for deuterium, k_{ex} (s^{-1}), were obtained from the slopes of semilogarithmic plots of reaction progress against time according to eq 1. The values of *f*(s), the fraction of unexchanged substrate, were calculated from eq 2, where A_{C_3H} and A_{std} are the integrated areas of the singlet due to the C(3)-H of the triazolium salt and the broad triplet at 3.3 ppm due to the methyl hydrogens of internal standard, tetramethylammonium deuterosulfate.

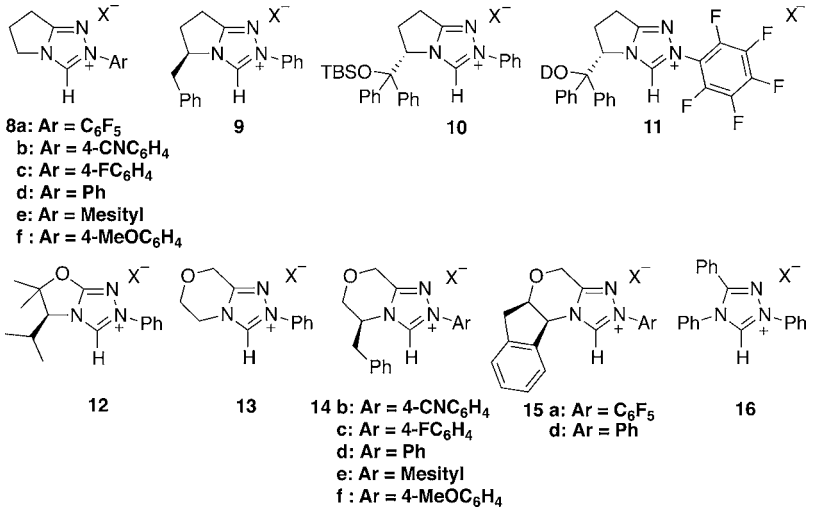


Figure 1. Series of achiral and chiral triazolium salts for which pK_a values in aqueous solution have been determined in this report.

$$\ln f(s) = -k_{ex}t \quad (1)$$

$$f(s) = \frac{(A_{C_3H}/A_{std})_t}{(A_{C_3H}/A_{std})_0} \quad (2)$$

Representative NMR spectra, all first-order kinetic plots and tabulated k_{ex} data are included in the Supporting Information (Figures s1−s86, Tables s1−s24).

RESULTS AND DISCUSSION

Deuterium Exchange Reactions. The deuterium exchange reactions of triazolium salts **8a−f-BF$_4^-$**, **9-Cl$^-$**, **13-BF$_4^-$**, **14c−f Cl$^-$** and **16-BF$_4^-$** were performed in fully aqueous solution at a range of p*D* values and at ionic strength, I = 1.0 (KCl). In all cases, C(3)-H/D exchange was too fast to monitor by ^{1}H NMR spectroscopy above p*D* 4.5 at 25 °C. As some of the deuterium exchange reactions were performed in acetic acid buffer solutions, the contribution of buffer species to the observed rate constant for exchange was assessed. For two representative azolium salts **8c-BF$_4^-$** and **8d-BF$_4^-$**, the effect of an increase in the total buffer concentration by 2.5−10-fold at a fixed buffer ratio resulted in no significant change in k_{ex} at 25 °C (see pp S110−112 in the Supporting Information for results of experiments) once corrections were made for the slight changes in p*D* upon dilution of buffer at constant ionic strength. Buffer catalysis of exchange was also not significant in previous studies of the analogous deuterium exchange reactions of imidazolium, dihydroimidazolium and trihydropyrimidinium ion precursors to carbenes **2**−**4**.[22,26]

For the triazolium salts **8a−f-BF$_4^-$**, **9-Cl$^-$**, **13-BF$_4^-$**, **14c−f Cl$^-$** and **16-BF$_4^-$** studied in fully aqueous solution, values of k_{ex} increase with p*D* in the region from p*D* = 0 to 4.5. Figure 2 shows the p*D* rate profiles of the values of k_{ex} for the deuterium exchange reactions of triazolium salts **8a−f-BF$_4^-$**. Analogous profiles for all salts in Figure 1 are included in the Supporting Information. The solid line through the data for triazolium salts **8b−f-BF$_4^-$** in Figure 2 shows the fit of the log k_{ex} − p*D* data to eq 3, which are derived from eq 4, where k_{DO} (M^{-1} s^{-1}) is the second-order rate constant for deuteroxide-catalyzed exchange, $K_w = 10^{-14.87}$ [46] is the ion product of D_2O at 25 °C, and γ_{DO} is the activity coefficient for deuteroxide ion under our experimental conditions. The good linear fits of the majority of the log k_{ex} − p*D* data for salts **8b−f-BF$_4^-$** to eq 3 are consistent with deuteroxide-catalyzed exchange via Pathway A as the dominant mechanism for H/D-exchange (Scheme 2).

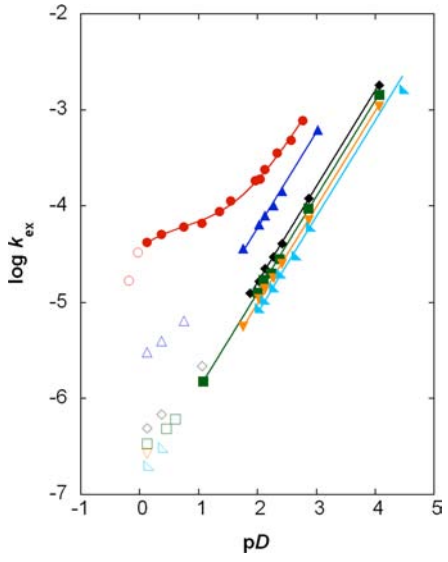


Figure 2. p*D* rate profiles for the deuterium exchange reactions of the C(3)-proton of triazolium salts **8a−f-BF$_4^-$** in D_2O at 25 °C and I = 1.0 (KCl). Key: Values of k_{ex} for **8a** (red ●); **8b** (navy blue ▲); **8c** (black ◆); **8d** (green ■); **8e** (orange ▼); **8f** (light blue ◀).The solid lines show the fits of the data (filled symbols) to eq 6 (**8a**) and eq 3 (**8b−f**). As described in the text, data points indicated by open symbols for **8a−f-BF$_4^-$** were not included in the fits.

$$\log k_{ex} = \log\left(\frac{k_{DO}K_w}{\gamma_{DO}}\right) + pD \quad (3)$$

$$k_{ex} = k_{DO}[DO^-] \quad (4)$$

In Pathway A, deprotonation of the triazolium salt **6** by deuteroxide results in the formation of a complex **7·HOD** between NHC **7** and a molecule of HOD. Subsequent reorganization of complex **7·HOD** to **7·DOL** (L = H or D) to allow delivery of deuterium, followed by deuteration, leads to exchange product **17**. The deuteration step is effectively irreversible, as bulk solvent is present in large excess over substrate, thus k_{ex} reflects rate-limiting formation of NHC **7·DOL** from the triazolium salt and deuteroxide ion.

Upon closer examination of the profiles for **8b−f-BF$_4^-$** in Figure 2, the dependencies of log k_{ex} on p*D* decreases for the 1−3 data points at the lowest p*D* values, and these points deviate upward from the line of unit slope through the remaining log k_{ex} − p*D* data. As discussed in more detail below, the moderate deviation of these data points is likely due to the onset of additional competing pathways for H/D-exchange at lower p*D* values (Pathways B and/or C, Scheme 2). As a result, these data points were omitted from the fits to eq 3 in the determination of the k_{DO} values listed in Table 1. The log k_{ex} − p*D* data for triazolium salts **8d-Cl$^-$**, **9-Cl$^-$**, **13-BF$_4^-$**, **14c−f-Cl$^-$**, and **16-BF$_4^-$** in fully aqueous solution were analyzed in a similar manner by fitting to eq 3 with the omission of the 1−4 data points at lower p*D* values that deviate upward from the lines of unit slope through each set of data. Values of k_{DO} obtained by fitting the data for these salts to eq 3 (Table 1) agree well with those obtained as slopes of linear second-order plots of the same range of k_{ex} values against deuteroxide concentration according to eq 4 (Supporting Information).

For pentafluorophenyl triazolium salt **8a-BF$_4^-$** in Figure 2 (●), the altered dependence on p*D* is more marked and only the data points at the five highest p*D* values fit well to eq 3. In this case, the decreased dependence on p*D* is also followed by a downward break at the lowest p*D* values. This altered dependence on p*D* is not due to a medium effect as the ionic strength was constant for these measurements (I = 1.0 (KCl)). Extra data points were acquired in 1.24 and 2.0 M DCl (Figure 2, ○ plotted for **8a-BF$_4^-$**). Although the ionic strength is higher, these data points further support the existence of the downward break.

The change in the dependence of log k_{ex} values on p*D* suggests competition from additional pathway(s) for deuterium exchange at lower p*D* values (Scheme 2). This could include a p*D*-independent mechanism for H/D exchange with deprotonation by solvent water rather than deuteroxide ion (Pathway B), which initially leads to intermediate **7·HOD$_2^+$**. As these log k_{ex} − p*D* data do not become completely p*D*-independent, the occurrence of Pathways A and B only, without allowing for

dx.doi.org/10.1021/ja308420c | J. Am. Chem. Soc. 2012, 134, 20421−20432

Scheme 2. Potential Competing Pathways for Deuterium Exchange at C(3)-H of Triazolium Salts 6

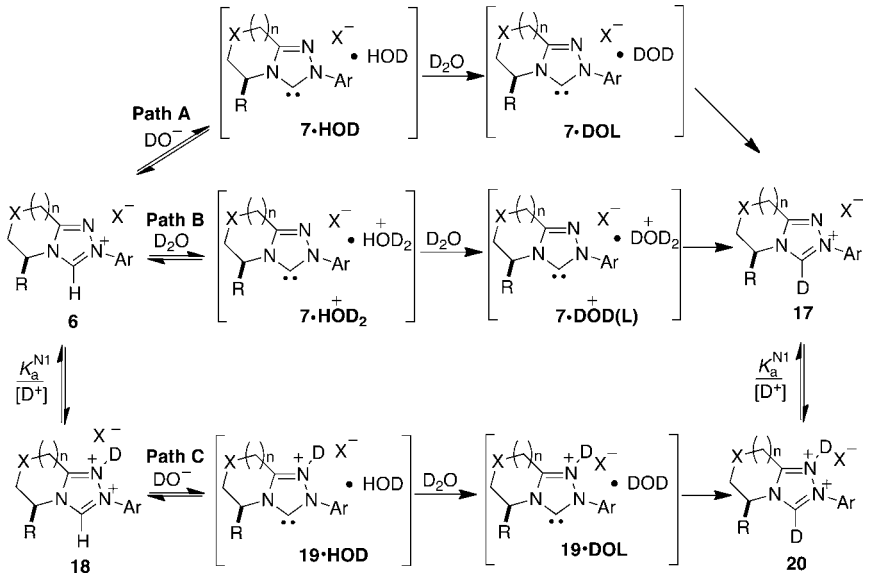


Table 1. Second-Order Rate Constants for Deuteroxide-Catalyzed Exchange, k_{DO} (M^{-1} s^{-1}), and Carbon Acid pK_a Values for Triazolium Salts 8−16-X^- in Aqueous Solution at 25 °C and Ionic Strength, I = 1.0 (KCl)

salt	k_{DO} (M^{-1} s^{-1})	pK_a[d]	salt	k_{DO} (M^{-1} s^{-1})	pK_a[d]
8a-BF_4^-	6.82 (±0.25) × 10^8[b]	16.5	**12-BF_4^-**	4.81 (±0.22) × 10^8[b,c]	17.5[c]
	7.95 (±1.25) × 10^8[b,c]	17.3[c]			
8b-BF_4^-	3.18 (±0.08) × 10^8[a]	16.9	**13-BF_4^-**	2.53 (±0.12) × 10^8[a]	17.0
8c-BF_4^-	8.66 (±0.11) × 10^7[a]	17.4	**14b-Cl^-**	1.36 (±0.17) × 10^9[b,c]	17.1[c]
8d-BF_4^-	6.82 (±0.13) × 10^7[a]	17.5	**14c-Cl^-**	2.17 (±0.13) × 10^8[a]	17.0
	3.70 (±0.15) × 10^8[a,c]	17.6[c]			
8d-Cl^-	5.84 (±0.20) × 10^7[a]	17.6	**14d-Cl^-**	1.59 (±0.08) × 10^8[a]	17.2
8e-BF_4^-	5.29 (±0.07) × 10^7[a]	17.7	**14e-Cl^-**	1.62 (±0.06) × 10^8[a]	17.2
8f-BF_4^-	4.20 (±0.23) × 10^7[a]	17.8	**14f-Cl^-**	1.22 (±0.09) × 10^8[a]	17.3
9-Cl^-	7.05 (±0.25) × 10^7[a]	17.5	**15a-BF_4^-**	1.95 (±0.10) × 10^{13}[c,e]	
10-Cl^-	5.38 (±0.60) × 10^7[b,c]	18.5[c]	**15d-BF_4^-**	7.10 (±0.47) × 10^8[b,c]	17.4[c]
11-BF_4^-	7.05 (±0.63) × 10^8[b,c]	17.4[c]	**16-BF_4^-**	3.61 (±0.16) × 10^8[a]	16.8

[a]Values of k_{DO} (M^{-1} s^{-1}) obtained by fitting log k_{ex} − pD data to eq 3. [b]Values of k_{DO} (M^{-1} s^{-1}) obtained by fitting log k_{ex} − pD data to eq 6 or eq 7. [c]Deuterium exchange data acquired in 33 v/v% CD_3CN/D_2O. [d]pK_a values obtained by application of eq 8 as described in the text using k_{DO} values obtained from fitting log k_{ex} − pD data to either eq 3 or eqs 6 and 7. [e]Value of k^*_{DO} (M^{-1} s^{-1}) obtained as slope of second-order plot of k_{ex} (s^{-1}) against deuteroxide concentration.

protonation at N(1), are not sufficient to explain the data. Protonation of triazolium ion **6** at N(1) would decrease the fraction of monocationic substrate available for deuterium exchange via Pathways A and B, and could account for the continued decrease in log k_{ex} values with pD.[47] Additionally, the initial protonation of the triazolium ion **6** at N(1) to give dicationic azolium ion **18** could be followed by deuteroxide-catalyzed exchange (Pathway C). In this mechanism, deprotonation by DO^- at C(3) would give a monocationic NHC−HOD complex **19·HOD**, and the subsequent formation of dicationic exchange product **20**.

Equation 5 allows for the additional dependence of Pathway A on K_a^{N1}, the acidity constant for ionization at N(1), however, does not allow for Pathway B or C. The log k_{ex} − pD data for triazolium salt **8a-BF_4^-** do not fit well at lower pD values to eq 5, which suggests that the combination of one or both of Pathways B and C with protonation at N(1) is required to account for the altered dependence of log k_{ex} on pD at lower pD values. Equations 6 and 7 allow for the dependence of k_{ex} (s^{-1}) on Pathways A and B, or Pathways A and C, respectively, with protonation at N(1) at lower pD values in each case. In these kinetically indistinguishable equations, k_{D_2O} (s^{-1}) is the first-order rate constant for exchange via Pathway B, where deprotonation at C(3) is by solvent and k'_{DO} (M^{-1} s^{-1}) is the second-order rate constant for deuteroxide-catalyzed C(3)-H/D exchange of the *N*-protonated azolium ion **18** via Pathway C.[48,49]

$$\log k_{ex} = \log\left[\frac{K_a^{N1}\left(\left(\frac{k_{DO}K_w}{\gamma_{DO}}\right)10^{pD}\right)}{(K_a^{N1} + 10^{-pD})}\right] \quad (5)$$

$$\log k_{ex} = \log\left[\frac{K_a^{N1}\left(\left(\frac{k_{DO}K_w}{\gamma_{DO}}\right)10^{pD}\right) + (K_a^{N1}k_{D_2O})}{(K_a^{N1} + 10^{-pD})}\right] \quad (6)$$

dx.doi.org/10.1021/ja308420c | J. Am. Chem. Soc. 2012, 134, 20421−20432

$$\log k_{ex} = \log\left[\frac{K_a^{N1}\left(\left(\frac{k_{DO}K_w}{\gamma_{DO}}\right)10^{pD}\right) + \left(\frac{k'_{DO}K_w}{\gamma_{DO}}\right)}{(K_a^{N1} + 10^{-pD})}\right] \quad (7)$$

The log k_{ex} − pD data for triazolium salt **8a-BF$_4^-$** fit well to eqs 6 and 7, which confirms that Pathway A occurs at higher pD values and that one of Pathways B and C, together with protonation at N(1), could account for the data at lower pD values. On the basis of overall kinetic fitting to eqs 6 and 7, it is not possible to distinguish whether Pathway B or C, or both, occur at lower pD's. Owing to the two equations being kinetically indistinguishable, the log k_{ex} − pD data for triazolium salt **8a-BF$_4^-$** fit equally well overall to eqs 6 and 7. The solid line through the data for triazolium salt **8a-BF$_4^-$** in Figure 2 shows the fit to eq 6. Identical values of k_{DO} (M^{-1} s^{-1}), for deuterium exchange via Pathway A, are obtained from either fit and these are included in Table 1.

Assuming protonation at N(1) and either Pathway B or C, we can extract values for the other unknown constants in eqs 6 and 7. Consideration of the magnitude of kinetic constants obtained by assuming either extreme of Pathway B or C, enables us to probe the likelihood of either pathway, and this will be discussed further below. Fitting to both equations yields identical values for K_a^{N1}, whereas assuming eq 6 or 7, respectively, the rate constants, k_{D_2O} (s^{-1}) or k'_{DO} (M^{-1} s^{-1}) are obtained, and these values are included in Table 2. The kinetic data in both Tables 1 and 2 will be discussed in the following sections.

Table 2. Kinetic Analysis of Deuterium Exchange Data for Triazolium Salts Showing an Altered Dependence on pD in Aqueous Solution at 25 °C and Ionic Strength, I = 1.0 (KCl)

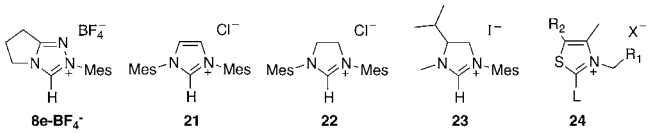
salt	K_a^{N1} (M)[c]	k_{D_2O} (s^{-1})[d]	k'_{DO} (M^{-1} s^{-1})[e]
8a-BF$_4^-$[a]	1.5 (±0.4)	6.1×10^{-5} ($\pm 3.6 \times 10^{-6}$)	3.3×10^{10} ($\pm 2.0 \times 10^{9}$)
8a-BF$_4^-$[b]	0.5 (±0.1)	1.4×10^{-4} ($\pm 5.9 \times 10^{-6}$)	1.1×10^{12} ($\pm 4.5 \times 10^{10}$)
10-Cl$^-$[b]	0.6 (±0.3)	9.2×10^{-7} ($\pm 1.7 \times 10^{-7}$)	7.0×10^{9} ($\pm 1.3 \times 10^{9}$)
11-BF$_4^-$[b]	0.6 (±0.2)	5.6×10^{-5} ($\pm 3.4 \times 10^{-6}$)	4.3×10^{11} ($\pm 2.6 \times 10^{10}$)
12-BF$_4^-$[b]	0.4 (±0.1)	9.3×10^{-6} ($\pm 6.3 \times 10^{-7}$)	7.1×10^{10} ($\pm 4.8 \times 10^{9}$)
14b-Cl$^-$[b]	0.5 (±0.1)	6.8×10^{-5} ($\pm 5.0 \times 10^{-6}$)	5.2×10^{11} ($\pm 3.8 \times 10^{10}$)
15d-BF$_4^-$[b]	0.3 (±0.1)	2.1×10^{-5} ($\pm 1.8 \times 10^{-6}$)	1.6×10^{11} ($\pm 1.4 \times 10^{10}$)

[a]Deuterium exchange data acquired in D_2O. [b]Deuterium exchange data acquired in 33 v/v% CD_3CN/D_2O. [c]Values of K_a^{N1} (M) obtained by fitting log k_{ex} − pD data to eq 6 or eq 7. [d]Values of k_{D_2O} (s^{-1}) obtained by fitting log k_{ex} − pD data to eq 6 [e]Values of k'_{DO} (M^{-1} s^{-1}) obtained by fitting log k_{ex} − pD data to eq 7.

As chiral triazolium salts **10**−**12-BF$_4^-$**, **14b-Cl$^-$**, **15a-BF$_4^-$**, and **15d-BF$_4^-$** were insoluble in D_2O, perdeuterated acetonitrile (33% v/v) was used as a cosolvent in the exchange reactions of these salts. The deuterium exchange reactions of triazolium salts **8a-BF$_4^-$** and **8d-BF$_4^-$** were studied both in D_2O, and in 2:1 D_2O/CD_3CN, so that the effect of acetonitrile cosolvent on k_{DO} could be assessed. The appearance of the pD rate profiles for **10**−**12-BF$_4^-$**, **14b-Cl$^-$**,and **15d-BF$_4^-$** in 2:1 D_2O/CD_3CN can also be explained by the occurrence of parallel pathways for deuterium exchange as in Scheme 2 (see Supporting Information for pD rate profiles); however, the altered dependence of log k_{ex} values on pD occurs at higher pD values than for the salts studied in fully aqueous solution, likely a result of the combined effect of solvent on pK_a^{N1}, k_{D_2O} (s^{-1}), or k'_{DO} values. The exchange data for the salts studied in in 2:1 D_2O/CD_3CN were fitted to eq 6 or 7 rather than eq 3 in each case as this resulted in smaller errors in k_{DO} values (Table 1). As discussed above for *N*-pentafluorophenyl salt **8a-BF$_4^-$** assuming either extreme of Pathway B or C, values for the constants k_{D_2O} (s^{-1}) or k'_{DO} (M^{-1} s^{-1}) could be obtained and these are also included for the salts studied in 2:1 D_2O/CD_3CN in Table 2.

The C(3)-H/D deuterium exchange reaction of the *N*-pentafluorophenyl triazolium salt **15a-BF$_4^-$** in 2:1 D_2O/CD_3CN was too fast to follow by ^{1}H NMR spectroscopy above pD 0.06. By contrast, the deuterium exchange reactions of all other triazolium salts in Figure 1 could be followed up to pD 3.5. For triazolium salt **15a-BF$_4^-$**, deuterium exchange data were acquired in 1−3 M DCl in 2:1 D_2O/CD_3CN (pD's ≈ −0.42−0.06). The pD rate profile of the values of k_{ex} for the deuterium exchange reaction for triazolium salt **15a-BF$_4^-$** (Figure s83, Supporting Information) shows an increase in k_{ex} with pD in this range. This increase could either be due to deuteroxide catalysis of C(3)-H/D exchange for the triazolium salt **15a-BF$_4^-$** or the N1-deuterated conjugate acid. A plot of k_{ex} values for salt **15a-BF$_4^-$** against deuteroxide concentration (Figure s82, Supporting Information) gave k^*_{DO} (M^{-1} s^{-1}) as its slope (Table 1).

Substituent Effects on Kinetic Acidities toward Deuteroxide Ion (k_{DO}). The kinetic acidities toward deprotonation of all triazolium ions by deuteroxide ion via Pathway A (k_{DO}, Table 1) are significantly higher than for analogous imidazolium,[22,26] 4,5-dihydroimidazolium[26] and thiazolium ions[30] studied in fully aqueous solution at 25 °C. As one representative comparison, the presence of the additional ring nitrogen increases the k_{DO} value for *N*-mesityl triazolium salt **8e-BF$_4^-$** by 1.3 × 10^3 and 4.4 × 10^3-fold, respectively, relative to the values for *N*,*N*-dimesitylimidazolium and 4,5-dihydroimidazolium salts **21** and **22** (k_{DO} = 4.08 × 10^4 M^{-1} s^{-1} and 1.19 × 10^4 M^{-1} s^{-1}).[26] A better measure of the true effect of the additional ring nitrogen atom can be gleaned by comparison with the k_{DO} value of 3.45 × 10^2 M^{-1} s^{-1} for 1-mesityl-3-methyl-4-isopropyl-4,5-dihydroimidazolium iodide **23**,[50] which has alkyl substituents at N(3) and C(4) as for triazolium ion **8e-BF$_4^-$**. The effect of the additional ring nitrogen is to increase k_{DO} by over 1.5 × 10^5-fold. The mechanism for deuterium exchange via Pathway A, involves the uphill deprotonation of the cationic triazolium ion by deuteroxide to give a formally neutral carbene intermediate **7**. The presence of the additional electron-withdrawing ring nitrogen atom will destabilize the parent triazolium ion relative to the formally neutral transition state, thereby increasing the observed rate constant for exchange.



8e-BF$_4^-$ **21** **22** **23** **24**

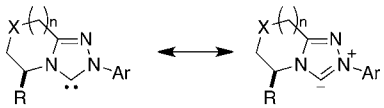
The triazolium salts in Table 1 are also substantially more acidic than any thiazolium salt studied to date under similar reaction conditions, although the latter experiments have been

dx.doi.org/10.1021/ja308420c | J. Am. Chem. Soc. 2012, 134, 20421−20432

limited to *N*-alkyl-substituted examples.[30] We have measured a k_{DO} value of 3.28×10^5 M^{-1} s^{-1} for thiazolium salt **24** (L = H; R_1 = Ph; R_2 = CH_2CH_2OD; X^- = Cl^-) under our experimental conditions in D_2O at 25 °C and I = 1.0 (KCl), which is at least 120-fold smaller than values for any of the triazolium ions in Table 1 (Supporting Information, pp S72−S74). Washabaugh and Jencks reported similar k_{DO} values in the range 3.23×10^5−2.14×10^6 M^{-1} s^{-1} for the deuterium exchange reactions of a series of thiazolium salts **24** (L = H; R_1 = neutral alkyl or aryl; R_2 = H), in D_2O at 30 °C and I = 2.0 (NaCl).[30]

In contrast with the large 10^5-fold effect of the additional ring nitrogen, the result of varying the N-substituent on k_{DO} values is small. The span of kinetic acidities obtained by comparing k_{DO} values for all triazolium salts in Figure 1 is only 37-fold. The k_{DO} values change by only 16.2-fold across the series **8a−f-BF$_4^-$** from the most reactive *N*-pentafluorophenyl triazolium to the least reactive 4-methoxyphenyl triazolium salt.[51] Within this series, our results agree with qualitative experiments by Bode and Mahatthananchai that suggested that the more electron withdrawing *N*-pentafluorophenyl triazolium salts are more acidic than the corresponding *N*-mesityl salts.[45] An even smaller *N*-aryl substituent effect on k_{DO} is observed across the morpholinyl series of triazolium salts **14c−f** in water. All of the series **14c−f** have higher k_{DO} values by 2.4−2.9-fold compared to those of analogous pyrrolidine-derived salts **8c−f** due to the presence of the electron-withdrawing oxygen ring atom in the fused morpholinyl ring; however, the *N*-aryl substituent effect is less than 2-fold.

Similarly small *N*-aryl substituent effects were observed on k_{DO} values for the *N*,*N*-diarylimidazolium and 4,5-dihydroimidazolium series.[26] Despite having two *N*-aryl substituents, variation of these substituents (4-chlorophenyl, mesityl, 2,6-diisopropylphenyl, 4-methoxyphenyl) only altered k_{DO} by less than 20-fold. The small effect of the *N*-aryl substituent in the imidazolium and dihydroimidazolium series was partly ascribed to the difficulty in achieving coplanarity of both aryl rings with the central imidazole or dihydroimidazole; however, this is not likely to be a major contributing factor for the triazolium salts in Figure 1 with just one *N*-aryl substituent. Alternatively, there could be a change in the nature of the transition state for proton transfer to deuteroxide, from resembling carbene **7** for more electron-withdrawing *N*-aryl substituents to zwitterionic ylide **7′** as the substituent becomes more electron-donating. The alteration of charge density between species **7** and **7′**, depending on the electronic effect of the *N*-aryl substituent, could reduce the overall observed N-substituent effect.[52]



7 **7′**

The effect of acetonitrile cosolvent on k_{DO} was assessed for triazolium salts **8a-** and **8d-BF$_4^-$**, which were studied both in 100% D_2O, and 2:1 D_2O/CD_3CN. The effect of the addition of acetonitrile cosolvent is a 5.4-fold increase in k_{DO} for **8d-BF$_4^-$** (Table 1). A small 1.2-fold increase is observed for **8a-BF$_4^-$**, although the k_{DO} value in 2:1 D_2O/CD_3CN in this case is less accurate as there are only two data points in the region of the p*D* profile due to Pathway A. Possible explanations for the observed increases in k_{DO} could be the decreased stabilities of the parent triazolium cations and the increased basicity of deuteroxide in the mixed solvent relative to fully aqueous solution.

As mentioned above, the deuterium exchange reaction of the *N*-pentafluorophenyl catalyst **15a-BF$_4^-$** in 2:1 D_2O/CD_3CN was too fast to measure above p*D* 0.06, and the estimated k_{DO}^* value of $\sim 2 \times 10^{13}$ M^{-1} s^{-1} in Table 1 is 25000-fold higher than the k_{DO} value for achiral analogue **8a-BF$_4^-$** in the same solvent. Both of these salts have a *N*-pentafluorophenyl substituent, however, differ by the fused ring systems attached to the central triazole. The value for k_{DO}^* for **15a-BF$_4^-$** is unfeasibly high and clearly exceeds the bimolecular diffusional limit for small molecules in solution ($\sim 5 \times 10^9$ M^{-1} s^{-1}). This outcome is likely because the data for **15a-BF$_4^-$** are not adequately described by eq 4 alone. Due to the limited data set and large variation in ionic strength and viscosity in the 1−3 M DCl solutions that were required to enable monitoring of the fast exchange reactions of **15a-BF$_4^-$**, further fitting was not attempted. Given the small span of k_{DO} values of 37-fold for all other triazolium salts in Figure 1, this large rate enhancement of H/D exchange for **15a-BF$_4^-$** is surprising. By contrast, the k_{DO} value for the corresponding *N*-phenyl catalyst **15d-BF$_4^-$** is only 1.9-fold larger than for analogous achiral *N*-phenyl triazolium salt **8d-BF$_4^-$** in the same solvent and k_{ex} values could be acquired up to p*D* 3.8 in both cases. One possible explanation is a significantly higher pK_a^{N1} for **15a-BF$_4^-$** with the reaction of N-protonated **15a-BF$_4^-$** providing a greater contribution to k_{ex} at higher p*D*'s than for the other triazolium salts. The N-protonated dicationic triazolium ions are predicted to have greater kinetic acidities toward deprotonation by deuteroxide ion than monocationic analogues (see k'_{DO} values in Table 2 and later discussion). UV−vis spectrophotometric and NMR spectroscopic attempts at the determination of pK_a^{N1} in 2:1 D_2O/CD_3CN solutions were unsuccessful due to insufficient changes in the spectral data for **15a-BF$_4^-$** and other salts upon variation of p*D* (see pp S113−115 Supporting Information). A higher pK_a^{N1} for **15a-BF$_4^-$** seems counterintuitive as the electron withdrawing *N*-pentafluorophenyl group would be expected to decrease the basicity of N1. The recent crystal structure of an aza-Breslow intermediate analogue,[53] which was prepared from the *N*-(2,4,6)-tribromophenyl analogue of **15a-BF$_4^-$** and **15d-BF$_4^-$**, shows the nonplanar orientation of the *N*-tribromophenyl substituent relative to the central triazole with one of the ortho bromine atoms on this ring in close spacial proximity to N1. Protonation at N1 might decrease an unfavorable electrostatic interaction between the lone pair on N1 and those on the ortho halogen atom. This could also be the case for *N*-pentafluorophenyl triazolium salt **15a-BF$_4^-$** and would account for a higher pK_a for N1-protonation. To the best of our knowledge, crystal structures of **15a-BF$_4^-$** and **15d-BF$_4^-$** have not been published.

Our suggestion of an increase in pK_a^{N1} for **15a-BF$_4^-$** due to the spacial influence of ortho halogen atoms on the *N*-aryl ring on N1-basicity is supported by the significant difference between the p*D*-profile for **8a-BF$_4^-$** vs the other triazolium salts **8b−f-BF$_4^-$** in Figure 1. Of this series of triazolium salts, only the *N*-pentafluorophenyl triazolium salt **8a-BF$_4^-$** has an ortho halogen rather than hydrogen atoms on the *N*-aryl ring. The k_{DO} values for **8a−f-BF$_4^-$** only differ by 16.2 fold across the series and this reflects the electronic effect of the *N*-aryl substituent. However, the onset of the altered dependence of log k_{ex} values on p*D* occurs at significantly higher p*D* values for **8a-BF$_4^-$** compared with the other triazolium salts **8b−f-BF$_4^-$**,

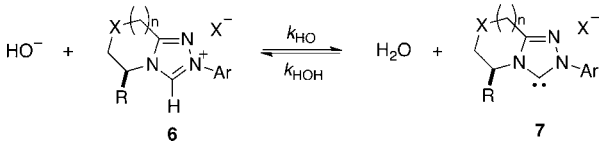
dx.doi.org/10.1021/ja308420c | J. Am. Chem. Soc. 2012, 134, 20421−20432

and a higher pK_a^{N1} for the former salt. For example, the onset of the altered dependence on p*D* occurs over 1 p*D* unit higher for *N*-pentafluorophenyl triazolium salt **8a**-BF_4^- compared with *N*-*p*-cyanophenyl salt **8b**-BF_4^-, however, their corresponding log k_{DO} values only differ by 0.3 units.

Effect of Counterion on Kinetic Acidities toward Deuteroxide Ion. The effect of a change in counterion on kinetic acidity could be assessed by comparing k_{DO} values for triazolium salt **8d** with two different counterions, $X^- = BF_4^-$ and Cl^- in fully aqueous solution. A 1.2-fold increase in k_{DO} is observed upon changing from $X^- = Cl^-$ to $X^- = BF_4^-$, which is just outside of the error range of these measurements. The small effect is unsurprising as the exchange reactions are performed using dilute millimolar solutions of the triazolium salts in a highly ionizing aqueous solvent at saturating ionic strength (I = 1.0 (KCl)). One could suggest different extents of assistance by the two counterions in the deprotonation step. However, general base catalysis by the more basic acetate ion is not significant, which would suggest that similar catalysis by the weakly basic tetrafluoroborate or chloride ions is unlikely in aqueous solution. By contrast, azolium cations and counteranions are known to form hydrogen bonds both in the solid state and in concentrated solutions in nonhydroxylic solvents, which often results in the observation of large anion effects.[54−59] Under the present fully aqueous conditions, hydrogen bonding with solvent clearly outcompetes any interactions between the triazolium cation and counteranion.

Estimation of pK_a. The carbon acid pK_a values for triazolium salts **6** in water may be obtained from the rate constants for deprotonation by hydroxide ion (k_{HO}) and for the reverse protonation of NHC **7** by water (k_{HOH}) according to eq 8 derived for Scheme 3.[22,26] In eq 8, K_w is the equilibrium

Scheme 3. Ionization of Triazolium Ion Salt, 6, at C(3) to Yield NHCs, 7



constant for autoionization of water. Values for k_{HO} (M^{-1} s^{-1}) for deprotonation of triazolium ions **6** at C(3) by hydroxide ion can be calculated from corresponding experimental k_{DO} values for deuteroxide-catalyzed C(3)-H/D exchange via Pathway A (Scheme 2).

$$pK_a = pK_w + \log \frac{k_{HOH}}{k_{HO}} \quad (8)$$

In related studies, the rate of proton transfer from neat alcohol solvents to singlet diphenylcarbene has been shown by femtosecond transient absorption spectroscopy to be controlled by solvent reorganization.[60] Evidence was presented in earlier work by Amyes et al.[22] and us[26] supporting the hypothesis that the reverse protonation of imidazol-2-ylidenes **2**, imidazolin-2-ylidenes **3**, and trihydropyrimidin-2-ylidenes **4** is also limited by reorganization of solvent, and occurs with a limiting rate constant of $k_{HOH} = 1 \times 10^{11}$ s^{-1}. The k_{ex} values for deuterium exchange at C(2) of the corresponding imidazolium, 4,5-dihydroimidazolium, and trihydropyrimidinium ions were found to be unaltered by an increase in the concentration of acetate, phosphate, or quinuclidine buffers at fixed p*D* values in D_2O solution. The absence of detectable general base catalysis of exchange strongly supports the conclusion that proton transfer of the C(2)-H to deuteroxide is not rate-limiting in the overall deuterium exchange mechanism. Instead the rate-limiting step is the reorganization of the initially formed complex **7**·**HOD** via dielectric relaxation of solvent to **7**·**DOL** (k_{reorg}, Scheme 4).[61] Thus, in the overall mechanism for deuterium exchange, non-rate-limiting proton transfer to deuteroxide ion from the imidazolium, 4,5-dihydroimidazolium, or trihydropyrimidinium ion is followed by irreversible solvent reorganization due to the large dilution of the molecule of HOD by bulk solvent. In this case, general base catalysis of exchange is not possible because there is no mechanism by which buffer bases can lower the barrier to the physical transport step of solvent reorganization. Therefore, the microscopic reverse protonation of the corresponding NHCs **2**−**4** by water is also limited by reorganization of solvent, and a limiting rate constant of $k_{HOH} = k_{reorg} = 1 \times 10^{11}$ s^{-1} for the dielectric relaxation of water[62,63] could be assumed.

Washabaugh and Jencks reported rate constants for C(2)-hydron exchange catalyzed by deuteroxide ion for a range of thiazolium ions **24** (L = H, D, or T; R_1 = Me, Ph, CN; R_2 = H).[30−32] These reactions showed primary kinetic isotope effects that increase over the range $(k_H/k_T)_{obs}$ = 2.9−14.7 with increasing acidity of the thiazolium ion.[32] These varying primary kinetic isotope effects, and the observation of significant deviations of $(k_D/k_T)_{obs}$ and $(k_H/k_T)_{obs}$ values from the Swain−Schaad relationship, show that there is significant internal return of the transferred hydron to the thiazolyl carbene from water.[32] This is consistent with an Eigen mechanism[64] for proton transfer (Scheme 4), in which both proton transfer (k_p) and reorganization of the NHC·water complex (k_{reorg}) are partially rate limiting, and a small intrinsic barrier for proton transfer.[32] The extent of internal return ($k_p/k_{reorg} \approx 3.3$) was largest for the least acidic thiazolium ion **24** (R_1 = Me; R_2 = H) with $k_{DO} = 4.27 \times 10^5$ M^{-1} s^{-1} and pK_a = 18.9 at 30 °C and ionic strength 2.0 M (NaCl). For the more acidic *N*-cyanomethylthiazolium ion **24** (R_1 = CN; R_2 = H) with $k_{DO} = 4.62 \times 10^7$ M^{-1} s^{-1} and pK_a = 16.9, the internal return ratio decreases to $k_p/k_{reorg} \approx 0.3$.

For the structurally similar imidazolium, 4,5-dihydroimidazolium, and trihydropyrimidinium ions, values of k_{DO} (M^{-1} s^{-1}) at 25 °C and ionic strength 1.0 M (KCl) range from 3.92×10^5 to 1.48×10^{-3} M^{-1} s^{-1},[26] which are 1.1−6.9 × 10^8-fold smaller than corresponding values for the thiazolium ion **24** (L = H; R_1 = Me; R_2 = H) for which solvent reorganization is largely rate limiting ($k_p/k_{reorg} \approx 3.3$). Therefore, relative to their azolium

Scheme 4. Mechanism for Deuteroxide-Catalyzed Azolium Ion H/D-Exchange

dx.doi.org/10.1021/ja308420c | J. Am. Chem. Soc. 2012, 134, 20421−20432

ion ground state, imidazol-2-ylidenes **2**, imidazolin-2-ylidenes **3**, and trihydropyrimidin-2-ylidenes **4** should be less stable than the corresponding thiazol-2-ylidenes, so that their protonation by water should be even more limited by the solvent reorganization step ($k_p \gg k_{reorg}$).

The k_{DO} values in Table 1 for triazolium salts **8a−f-BF$_4^-$**, **9-Cl$^-$**, **13-BF$_4^-$**, **14c−f Cl$^-$**, and **16-BF$_4^-$** in aqueous solution at 25 °C and ionic strength 1.0 M (KCl) range from 4.20×10^7 to 6.82×10^8 M^{-1} s^{-1} and are no greater than 14.7-fold difference from the value determined for the *N*-cyanomethylthiazolium salt **24** (R_1 = CN; R_2 = H) under similar reaction conditions ($k_{DO} = 4.62 \times 10^7$ M^{-1} s^{-1}). For thiazolium ions **24**, the change of N-substituent from methyl to cyanomethyl increases k_{DO} by 109-fold, and the internal return ratio, k_p/k_{reorg}, decreases by 10-fold from 3.3 to 0.3. Therefore, the k_p/k_{reorg} values for triazolium salts **8**, **9a−f**, **10**, **14** and **15c−f** are expected to be the same or, at most, 2-fold lower than for the *N*-cyanomethylthiazolium salt **24** (R_1 = CN; R_2 = H). On this basis, rate constants for protonation of the corresponding triazolylidenes **7** by water should be the same and no more than ∼6-fold lower than the rate constant for reorganization of solvent ($k_{reorg} = 1 \times 10^{11}$ s^{-1}).

Although the k_p/k_{reorg} ratios clearly illustrate that reprotonation of thiazolylidenes and solvent reorganization occur at similar rates, Washabaugh and Jencks state that the extent of internal return should be interpreted conservatively because the errors are ±30% or more.[32] For the determination of a pK_a value for *N*-cyanomethylthiazolium salt **24** (R_1 = CN; R_2 = H) using eq 8, these authors have assumed the limiting k_{HOH} value for the protonation of the *N*-cyanomethylthiazolylidene by water.[30] For the determination of triazolium ion pK_a's, we have also assumed that the reprotonation of triazolylidenes **7** is limited by reorganization of solvent and that $k_{HOH} = k_{reorg} = 1 \times 10^{11}$ s^{-1}. Furthermore, significant general base catalysis of exchange was not observed for two representative salts **8c**- and **8d-BF$_4^-$**, which have k_{DO} values larger than those of the *N*-cyanomethylthiazolium salt **24** (R_1 = CN; R_2 = H). It was not possible to probe for buffer catalysis of exchange in the case of triazolium salts more acidic than **8c-BF$_4^-$**, as deuterium exchange in acetic acid buffers was too fast to monitor by ^{1}H NMR spectroscopy. The absence of significant general base catalysis of exchange supports the conclusion that reprotonation of triazolylidenes and solvent reorganization occur at similar rates.

For the triazolium salts studied in 2:1 D_2O/CD_3CN, the same value of $k_{HOH} = k_{reorg} = 1 \times 10^{11}$ s^{-1} has been assumed for the reverse protonation of the corresponding NHCs by water. To our knowledge, rate constants for dielectric relaxation of acetonitrile−water mixtures have not been determined to date. The dielectric relaxation of pure acetonitrile is only 2.5-fold slower than that of water at 25 °C, and added electrolytes have been shown to increase this value by up to 2-fold.[65] As 2:1 D_2O/CD_3CN solutions are largely aqueous, it is reasonable to assume that the rate constant for solvent reorganization by dielectric relaxation of solvent is similar to that in fully aqueous solution.

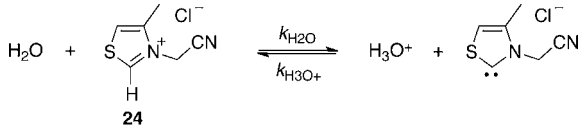
Values for k_{HO} (M^{-1} s^{-1}) for deprotonation of triazolium salts **8−16** at C(3) by hydroxide ion could then be calculated from corresponding k_{DO} values using a secondary solvent isotope effect of $k_{DO}/k_{HO} = 2.4$[66] for proton transfer that is largely limited by solvent reorganization. These k_{HO} values may be combined in eq 8 with the rate constant for the reverse protonation of the NHC by water using $k_{HOH} = 1 \times 10^{11}$ s^{-1}. The resulting pK_a values for all triazolium salts are listed in Table 1 and range from 16.6 to 18.5. For those salts with k_{DO} values ≤8.66×10^7 M^{-1} s^{-1} in fully aqueous solution, such as the value for *N*-(4-fluorophenyl)triazolium salt **8c-BF$_4^-$**, the error in pK_a is ≤0.08 units (pp S109−110, Supporting Information). General base catalysis of C(3)-H/D exchange was not significant for **8c-BF$_4^-$**, which strongly supports the claim that $k_{HOH} = k_{reorg}$ for this and less reactive salts. For salts with k_{DO} values greater than those for **8c-BF$_4^-$**, deuterium exchange reactions in buffers were too fast to enable assessment of the presence/absence of general base catalysis of exchange. As discussed above, in these cases k_{HOH} could be up to ∼6-fold lower than k_{reorg}, and the true pK_a values could be up to one unit lower than the values quoted in Table 1.

This small span of pK_a values reflects the small substituent effects on kinetic acidities toward deuteroxide ion as the same k_{HOH} value for reprotonation is used in each case. A comparison of acidities of 1-mesityl-3-methyl-4-isopropyl-4,5-dihydroimidazolium iodide **23**[50] and *N*-mesityl triazolium salt **8e-BF$_4^-$** reveals that the pK_a values for the triazolium salts are 5 units lower than those for analogous imidazolium salts and demonstrates the large influence of the extra ring nitrogen atom on acidity.

Additional Pathways for Deuterium Exchange. One of the notable effects of the additional ring nitrogen of the triazolium ions **6** is the change in dependence of log k_{ex} values on p*D* as the acidity of the medium is increased. Analogous exchange reactions of the significantly less reactive *N*,*N*-disubstituted imidazolium, dihydroimidazolium, and trihydropyrimidinium ions show just a single region in the p*D* rate profiles, which involves an increase in log k_{ex} with p*D*, and is consistent with deuteroxide-catalyzed exchange via Pathway A only. Washabaugh and Jencks observed the onset of a clear p*D*-independent region in the p*D* rate profile for C(2)-proton exchange of thiazolium salt **24** (L = H; R_1 = 2-methyl-4-aminopyrimidinyl; R_2 = CH_2CH_2OD; X^- = Cl^-) but only in 2−4 M DCl solution at D_0 values less than −1.0.[30] This was ascribed to p*D*-independent C(2)-H/D exchange by a mechanism analogous to Pathway B in Scheme 1, and a value of $k_{D_2O} = 1.5 \times 10^{-8}$ s^{-1} was estimated. Similarly, the onset of a p*D*-independent region was observed for the 3-cyanomethyl-4-methylthiazolium salt **24** (R_1 = cyano; R_2 = H; X^- = Cl^-) in 0.8−2.7 M DCl yielding $k_{D_2O} = 9.4 \times 10^{-8}$ s^{-1}.[31] Further decreases in log k_{ex} values for this salt were observed in DCl solutions of greater than 5 M, and this was ascribed to modest acid inhibition of ionization in strong acid media because of acidity function effects. The large increase in the activity of hydronium ion in strong acid solutions (>1 M) would be expected to shift the equilibrium in Scheme 5 to the left.

The continued decrease in the log k_{ex} data for **8a-BF$_4^-$** in aqueous solution at lower p*D* values is not likely due to acidity function effects as these measurements were conducted in more dilute DCl solutions (<1 M DCl). Furthermore, such acid

Scheme 5. Ionization of Thiazolium Salts 24 at C(2) to Yield Corresponding Thiazolyl Carbenes



24
(L = H; R_1=CN; R_2=H; X=Cl)

dx.doi.org/10.1021/ja308420c | J. Am. Chem. Soc. 2012, 134, 20421−20432

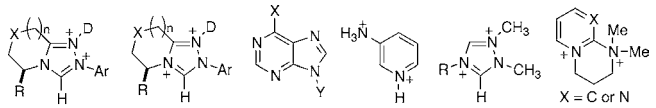
inhibition effects would be expected to be similar for the closely related thiazolium and triazolium carbon acids, and further decreases in log k_{ex} values are only observed for DCl concentrations greater than 5 M in the former case.

Washabaugh and Jencks calculated a pK_a value of 16.9 for the 3-cyanomethyl-4-methylthiazolium salt **24** (L = H; R_1 = cyano; R_2 = H; X^- = Cl^-) in aqueous solution at 30 °C by application of eq 8 using k_{DO} = 4.68 × 10^7 M^{-1} s^{-1}, k_{DO}/k_{HO} = 2.4, and by assuming reprotonation of the thiazolyl carbene is at the diffusional limit.[30] Using the p*D*-independent value of k_{D_2O} = 9.4 × 10^{-8} s^{-1}, they obtained the same pK_a value by application of eq 9, derived for Scheme 5, using an experimental value of k_{H_2O}/k_{D_2O} = 2.6 and by assuming that reprotonation of the thiazolyl carbene by hydronium ion is also diffusion controlled ($k_{H_3O^+}$ = 2 × 10^{10} M^{-1} s^{-1}).[30] The excellent agreement obtained using two different kinetic estimations of pK_a strongly supports the assignment of the p*D*-independent region to a mechanism analogous to Pathway B (Scheme 2).

$$pK_a = -\log \frac{k_{H_2O}}{k_{H_3O^+}} \qquad (9)$$

By contrast the C(3)-carbon acid pK_a value in aqueous solution calculated for the triazolium salt **8a-BF$_4^-$** obtained by application of eq 9 using the k_{D_2O} value in Table 2, with the same assumptions as Washabaugh and Jencks, is 2.5 units lower than when estimated using eq 8. Similar decreases of 2.6−3.3 units in C(3)-carbon acid pK_a values calculated using eqs 8 and 9 are obtained for the other salts listed in Table 2. Conversely, using the k_{D_2O} values in Table 2 and an experimental value of k_{D_2O}/k_{D_2O} = 2.6, requires an impossibly large reverse rate constant of $k_{H_3O^+}$ > 5 × 10^{12} M^{-1} s^{-1} in order to obtain the C(3)-carbon acid pK_a value for the triazolium salt **8a-BF$_4^-$** in Table 1. Further support of substantial k_{D_2O} overestimation comes from a comparison of deuterium exchange data for the *N*-pentafluorophenyl triazolium salt **8a-BF$_4^-$** (Tables 1 and 2) and the 3-cyanomethyl-4-methylthiazolium salt **24** (R_1 = cyano; R_2 = H; X = Cl^-) studied by Washabaugh and Jencks. The k_{DO} value for **8a-BF$_4^-$** is higher by 14.7-fold than the corresponding value for the thiazolium salt **24**, whereas the calculated k_{D_2O} value is higher by over 5000-fold. Although overestimation of k_{D_2O} values could partly result from an error in the fitting to eq 6, these observations most likely infer that Pathway B is not occurring.

As mentioned previously, the appearance of the p*D* rate profile for triazolium salt **8a-BF$_4^-$** at lower p*D* values requires that protonation at N(1) occurs. If protonation at N(1) did not occur, then either the log k_{ex} data would continue to linearly decrease at lower p*D*'s for exchange via Pathway A, or leveling would occur for exchange via Pathway B as was observed for thiazolium ions **24**. Protonation at N(1) is required to explain the kinetic data. The fitting of log k_{ex} − p*D* data for triazolium salt **8a-BF$_4^-$** to eq 6 or 7 yields an estimate of $pK_a^{N1} \approx -0.2$. Fitting of data for the other triazolium salts **10−12-BF$_4^-$**, **14b-Cl**, and **15d-BF$_4^-$** yields similar pK_a^{N1} values in the range −0.2−0.5 in 2:1 D_2O/CD_3CN. There is no available literature pK_a value for the dicationic parent triazolium ion in water; however, aqueous pK_a values of −0.43 and −1.66 have been determined for the second ring protonations of adenine and purine **25** (X = NH_2 or H; Y = H), and of −1.23 for diprotonated 3-aminopyridine **26** using the Cox−Yates excess acidity method.[67] These authors also reported that a pK_a value could not be determined for diprotonated imidazole using the same method due to insufficient changes in NMR spectral data upon variation of acid concentration. The charge separation in triazolium ion **18**, when drawn alternatively as **18′**, is similar to that in diprotonated adenine and purine **25** and diprotonated-3-aminopyridine **26**.[67] There have also been two literature reports of the syntheses and spectral characterization of trialkylated triazolium ions **27** (R = Me or ^{i}Pr)[68,69] with triflate or tetrafluoroborate counterions, which also support the existence of dicationic triazolium ions **18**/**18′** under acidic conditions. Dicationic amidinium ions **28** have been prepared by Murphy and co-workers, which proved to be more reactive as methylating agents than dimethylsulfate.[70] Furthermore, recent work by Keitz et al. implicates Brønsted acid protonation of the unsubstituted triazole nitrogen of a 1,2,3-triazolylidene bound to a ruthenium catalyst in the protonolysis of the Ru−carbene bond in the generation of the metathesis-active species.[71]



18 **18'** **25** **26** **27** **28**

Table 2 additionally includes estimates of second-order rate constants, k'_{DO} (M^{-1} s^{-1}) for deuteroxide-catalyzed exchange of the C(3)-H of N-protonated triazolium ions **8a-BF$_4^-$**, **10−12-BF$_4^-$**, **14b-Cl$^-$**, and **15d-BF$_4^-$** obtained by fitting the log k_{ex} − p*D* data for the relevant salts to eq 7 with the assumption that only Pathways A and C occur. Bimolecular diffusion of small molecules in solution has an associated rate constant of k_d = 5 × 10^9 M^{-1} s^{-1}, and in the case of facilitated diffusion, as observed for hydronium ion, k_d = 2 × 10^{10} M^{-1} s^{-1}. In general, bimolecular rate constants should not exceed these diffusional limits. The k'_{DO} value estimated for triazolium salt **8a-BF$_4^-$** is just greater than these limits; however, allowing for the errors in both k'_{DO} and K_a^{N1} could be considered as diffusion-limited. This observation is not unreasonable as the dicationic salts would be expected to have similar or greater kinetic acidities than monocationic analogues which have k_{DO} values in the range 10^7−10^8 M^{-1} s^{-1} in aqueous solution. Thus, Pathway C is the more likely of the two kinetically equivalent scenarios in Scheme 2 to account for the altered dependence of log k_{ex} data for triazolium salt **8a-BF$_4^-$** on p*D* as the acidity of the medium is increased. All except one of the other estimated k'_{DO} values in Table 2 for **10−12-BF$_4^-$**, **14b-Cl$^-$**, and **15d-BF$_4^-$** studied in 2:1 D_2O/CD_3CN are significantly greater than the limiting diffusional rate constant in water. Thus, the occurrence of Pathway C is not likely for these salts studied in 2:1 D_2O/CD_3CN, although the data do fit well to eq 6/7. An alternative explanation, that would show the same kinetic dependence on p*D*, is that N-protonation is followed by a concerted process that avoids the formation of a monocationic NHC where deprotonation by deuteroxide occurs at the same time as protonation by solvent.

Using the estimated k'_{DO} value in Table 2 assuming the occurrence of Pathway 3, and by application of eq 8 as described above, an upper limit on the C(3)-H carbon acid pK_a value of 14.9 may be predicted for the N(1)-protonated dicationic triazolium ion **8a-BF$_4^-$**. This calculation assumes that the reverse rate of protonation of the monocationic NHC by

dx.doi.org/10.1021/ja308420c | J. Am. Chem. Soc. 2012, 134, 20421−20432

solvent is limited by dielectric relaxation of solvent (k_{HOH} = × 10^{11} s^{-1}). As the deprotonation of this N-protonated dicationic triazolium ion by deuteroxide ion is at the diffusional limit, the reverse rate constant for protonation of the corresponding monocationic NHC by water is likely to be no longer limited by dielectric relaxation of solvent and would be expected to be substantially lower than 1 × 10^{11} s^{-1}. Thus, this predicted pK_a value for the dicationic N-protonated triazolium ion is an upper limit and is lower by *at least* 1.7 units than the corresponding pK_a in Table 1 for the monocationic triazolium ion in aqueous solution. In reality, the effect of N-protonation on the C(3)-H carbon acid pK_a value would be expected to be similar to the substantial 5 unit effect observed upon replacement of a ring carbon by nitrogen. Thus, the predicted kinetic and thermodynamic acidities of the dicationic triazolium precursors **18** to monocationic NHCs **19** are higher than for the conjugate acids of all other NHC families **1**−**5**.

■ CONCLUSIONS

In conclusion, studies of the proton transfer reactions of a range of triazolyl carbenes indicate that triazolium precatalysts are more acidic by 5 p*K* units than analogous imidazolium and 4,5-dihydroimidazolium architectures. Our results show that the incorporation of electron-withdrawing *N*-aryl substituents on the triazolium ring and an electronegative oxygen atom within the fused ring increase the kinetic acidity (k_{DO}) and decrease the pK_a. The presence of the additional ring nitrogen atom in triazolium ions compared with imidazolium and thiazolium counterparts results in an altered dependence of first-order rate constants for deuterium exchange on p*D* under acidic conditions. The data require that protonation at N(1) occurs to give *dicationic triazolium ions* at lower p*D* values with estimates of pK_a^{N1} = −0.2−0.5. Our results suggest that the presence of an ortho halogen on the *N*-aryl substituent could potentially increase pK_a^{N1}, and work in our laboratories is focused on acquiring additional proof of this hypothesis. Assuming the occurrence of deuteroxide-catalyzed exchange for N-protonated dicationic triazolium ion **8a-BF$_4^-$**, we have also estimated an upper limit C(3)-H pK_a value that is *at least* 1.7 units lower than that for the nonprotonated monocationic analogue. Work from our laboratories is also directed toward the implications of these more acidic dicationic triazolium species in catalysis and their use in the possible extension of NHC-mediated transformations.

■ ASSOCIATED CONTENT

Supporting Information

The syntheses of triazolium salts **8a**−**f**, **9**−**13**, **14b**−**f**, **15a**−**d**, and **16-X**$^-$, the preparation of solutions, the determination of p*D*, and the NMR methods used to monitor deuterium exchange are described. Representative NMR spectra, all first-order kinetic plots, tabulated k_{ex} data, and log k_{ex} − p*D* profiles for all triazolium salts **8**−**16**. Relevant second-order plots of k_{ex} values against deuteroxide concentration. Kinetic data obtained in studies of the effect of general base concentration on deuteroxide-catalyzed exchange. Experimental data obtained in attempts toward the independent determination of pK_a^N. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

ads10@st-andrews.ac.uk; annmarie.odonoghue@durham.ac.uk

Author Contributions

[§]R.S.M and C.J.C. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Royal Society for a University Research Fellowship (A.D.S.) and the EPSRC (C.J.C, R.S.M., and A.G.L.) for funding, and the EPSRC National Mass Spectrometry Service Centre (Swansea). We also thank Stuart Leckie (A.D.S.) for his assistance in synthesis of triazolium salts.

■ REFERENCES

(1) Alder, R. W.; Blake, M. E.; Chaker, L.; Harvey, J. N.; Paolini, F.; Schutz, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5896.
(2) Arduengo, A. J. *Acc. Chem. Res.* **1999**, *32*, 913.
(3) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39.
(4) de Fremont, P.; Marion, N.; Nolan, S. P. *Coord. Chem. Rev.* **2009**, *253*, 862.
(5) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606.
(6) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117.
(7) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290.
(8) Kirmse, W. *Angew. Chem., Int. Ed.* **2004**, *43*, 1767.
(9) Kuhl, O. *Chem. Soc. Rev.* **2007**, *36*, 592.
(10) Marion, N.; Diez-Gonzalez, S.; Nolan, I. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988.
(11) Perry, M. C.; Burgess, K. *Tetrahedron: Asymmetry* **2003**, *14*, 951.
(12) Vignolle, J.; Cattoen, X.; Bourissou, D. *Chem. Rev.* **2009**, *109*, 3333.
(13) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.
(14) Campbell, C. D.; Duguet, N.; Gallagher, K. A.; Thomson, J. E.; Lindsay, A. G.; O'Donoghue, A. C.; Smith, A. D. *Chem. Commun.* **2008**, 3528.
(15) Glorius, F.; Hirano, K. *Organocatalysis* **2008**, *2*, 159.
(16) For reviews see: (a) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691. (b) Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. *Chem. Soc. Rev.* **2011**, *40*, 5336. For selected examples see: (c) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205. (k) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370. (d) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905. (e) He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131. (f) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5334. (g) Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2416. (h) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2740. (i) Rommel, M.; Fukuzumi, T.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 17266. (j) Liu, Q.; Rovis, T. *Org. Lett.* **2009**, *11*, 2856. For the use of α′-hydroxyenones as α,β-unsaturated aldehyde surrogates see (k) Chiang, P.-C.; Rommel, M.; Bode, J. W. *J. Am. Chem. Soc.* **2009**, *131*, 8714.
(17) For selected examples see: (a) Zhang, Y. R.; He, L.; Wu, X.; Shao, P. L.; Ye, S. *Org. Lett.* **2008**, *10*, 277. (b) Lv, H.; Zhang, Y.-R.; Huang, X.-L.; Ye, S. *Adv. Synth. Catal.* **2008**, *350*, 2715. (c) He, L.; Lv, H.; Zhang, Y.-R.; Ye, S. *J. Org. Chem.* **2008**, *73*, 8101. (d) Zhang, Y.-R.; Lv, H.; Zhou, D.; Ye, S. *Chem.—Eur. J.* **2008**, *14*, 8473. (e) Wang, X.-N.; Shao, P.-L.; Lv, H.; Ye, S. *Org. Lett.* **2009**, *11*, 4029. (f) Huang, X.-L.; He, L.; Shao, L. P.-L.; Ye, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 192. (g) Lv, H.; You, L.; Ye, S. *Adv. Synth. Catal.* **2009**, *351*, 2822. (h) Wang, X.-N.; Lv, H.; Huang, X.-L.; Ye, S. *Org. Biomol. Chem.* **2009**, *7*, 346. (i) Lv, H.; Chen, X.-Y.; Sun, L.-H.; Ye, S. *J. Org. Chem.* **2010**, *75*, 6973. (j) Shao, P.-L.; Chen, X.-Y.; Ye, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 8412. (k) Duguet, N.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1108. (l) Concellón, C.; Duguet, N.; Smith, A. D. *Adv. Synth. Catal.* **2009**, *351*, 3001. (m) Duguet, N.; Donaldson, A.; Leckie, S. M.; Douglas, J.; Shapland, P.; Brown, T. B.; Churchill, G.; Slawin, A. M. Z.; Smith, A. D.

Tetrahedron: Asymmetry **2010**, *21*, 582. (n) Duguet, N.; Donaldson, A.; Leckie, S. M.; Kallström, E. A.; Campbell, C. D.; Shapland, P.; Brown, T. B.; Slawin, A. M. Z.; Smith, A. D. *Tetrahedron: Asymmetry* **2010**, *21*, 601. (o) Douglas, J.; Ling, K.; Concellon, C.; Slawin, A. M. Z.; Churchill, G.; Smith, A. D. *Eur. J. Org. Chem.* **2010**, 5863. (p) Reynolds, J. T.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 16406. (q) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 2860. (r) He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15088. (s) Kaeobamrung, J.; Kozlowski, M. C.; Bode, J. W. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20661. (t) Kobayashi, S.; Kinoshita, T.; Uehara, H.; Sudo, T.; Ryu, I. *Org. Lett.* **2009**, *11*, 3934. (u) Kawanaka, Y.; Phillips, E. M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 18028. (v) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418. (w) Phillips, E. M.; Wadamoto, M.; Chan, A.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3107. (x) Li, Y.; Wang, X.-Q.; Zheng, C.; You, S.-L. *Chem. Commun.* **2009**, 5823. (y) Lv, H.; Mo, J.; Fang, X.; Chi, Y. R. *Org. Lett.* **2011**, *13*, 5366. (z) Ling, K. B.; Smith, A. D. *Chem. Commun.* **2011**, *47*, 373.

(18) For selected examples see: (a) Bakhtiar, C.; Smith, E. H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 239. (b) Grasa, G. A.; Kissling, R. M.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 3583. (c) Grasa, G. A.; Güveli, T.; Singh, R.; Nolan, S. P. *J. Org. Chem.* **2003**, *68*, 2812. (d) Connor, E. F.; Nyce, G. W.; Myers, M.; Möck, A.; Hedrick, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 914. (e) Nyce, G. W.; Lamboy, J. A.; Connor, E. F.; Waymouth, R. M.; Hedrick, J. L. *Org. Lett.* **2002**, *4*, 3587. (f) Nyce, G. W.; Glauser, T.; Connor, E. F.; Möck, A.; Waymouth, R. M.; Hedrick, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 3046. (g) Suzuki, Y.; Yamauchi, K.; Muramatsu, K.; Sato, M. *Chem. Commun.* **2004**, 2770. (h) Kano, T.; Sasaki, K.; Maruoka, K. *Org. Lett.* **2005**, *7*, 1347. (i) Suzuki, Y.; Muramatsu, K.; Yamauchi, K.; Morie, Y.; Sato, M. *Tetrahedron* **2006**, *62*, 302. (j) Movassaghi, M.; Schmidt, M. A. *Org. Lett.* **2005**, *7*, 2453. (k) Schmidt, M. A.; Müller, P.; Movassaghi, M. *Tetrahedron Lett.* **2008**, *49*, 4316. (l) Thomson, J. E.; Rix, K.; Smith, A. D. *Org. Lett.* **2006**, *8*, 3785. (m) Thomson, J. E.; Campbell, C. D.; Concellón, C.; Duguet, N.; Rix, K.; Slawin, A. M. Z.; Smith, A. D. *J. Org. Chem.* **2008**, *73*, 2784. (n) Thomson, J. E.; Kyle, A. F.; Concellón, C.; Gallagher, K. A.; Lenden, P.; Morrill, L. C.; Miller, A. J.; Joannesse, C.; Slawin, A. M. Z.; Smith, A. D. *Synthesis* **2008**, *40*, 2805. (o) Thomson, J. E.; Kyle, A. F.; Ling, K. B.; Smith, S. R.; Slawin, A. M. Z.; Smith, A. D. *Tetrahedron* **2010**, *66*, 3801. (p) Campbell, C. D.; Collett, C. J.; Thomson, J. E.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2011**, *9*, 4205. (q) Campbell, C. D.; Concellón, C.; Smith, A. D. *Tetrahedron: Asymmetry* **2011**, *22*, 797. (r) Smith, A. D. *Synthesis* **2012**, *44*, 1182. (s) Rovis, T. *Adv. Synth. Catal.* **2012**, *354*, 1617.

(19) For selected examples see: (a) Ryan, S. J.; Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 14176. (b) Mahatthananchai, J.; Zheng, P.; Bode, J. W. *Angew. Chem., Int. Ed.* **2011**, *50*, 1673. (c) Zhu, Z.-Q.; Xiao, J.-C. *Adv. Synth. Catal.* **2010**, *352*, 2455. (d) De Sarkar, S.; Studer, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9266. (e) Guin, J.; De Sarkar, S.; Grimme, S.; Studer, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8727. (f) Rong, Z.-Q.; Jia, M.-Q.; You, S.-L. *Org. Lett.* **2011**, *13*, 4080. (g) Zhu, Z.-Q.; Zheng, X.-L.; Jiang, N.-F.; Wang, X.; Xiao, J.-C. *Chem. Commun.* **2011**, *47*, 8670.

(20) Limited examples of NHC-catalyzed processes proceeding without added base have been reported. See: (a) Ciganek, E. *Synthesis* **1995**, 1311. (b) Kaeobamrung, J.; Mahatthananchai, J.; Zheng, P.; Bode, J. W. *J. Am. Chem. Soc.* **2010**, *132*, 8810. (c) Zhu, Z.-Q.; Zheng, X.-L.; Jiang, N.-F.; Wang, X.; Xiao, J.-C. *Chem. Commun.* **2011**, *47*, 8670.

(21) Alder, R. W.; Allen, P. R.; Williams, S. J. *Chem. Commun.* **1995**, *12*, 1267.

(22) Amyes, T. L.; Diver, S. T.; Richard, J. P.; Rivas, F. M.; Toth, K. *J. Am. Chem. Soc.* **2004**, *126*, 4366.

(23) Bordwell, F. G.; Satish, A. V. *J. Am. Chem. Soc.* **1991**, *113*, 985.

(24) Chu, Y.; Deng, H.; Cheng, J. P. *J. Org. Chem.* **2007**, *72*, 7790.

(25) Guthrie, J. P.; O'Ferrall, R. A. M.; O'Donoghue, A. C.; Waghorne, W. E.; Zrinski, I. *J. Phys. Org. Chem.* **2003**, *16*, 582.

(26) Higgins, E. M.; Sherwood, J. A.; Lindsay, A. G.; Armstrong, J.; Massey, R. S.; Alder, R. W.; O'Donoghue, A. C. *Chem. Commun.* **2011**, *47*, 1559.

(27) Kim, Y. J.; Streitwieser, A. *J. Am. Chem. Soc.* **2002**, *124*, 5757.

(28) Magill, A. M.; Cavell, K. J.; Yates, B. F. *J. Am. Chem. Soc.* **2004**, *126*, 8717.

(29) Pezacki, J. P. *Can. J. Chem.* **1999**, *77*, 1230.

(30) Washabaugh, M. W.; Jencks, W. P. *Biochemistry* **1988**, *27*, 5044.

(31) Washabaugh, M. W.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 674.

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

(33) Maji, B.; Breugst, M.; Mayr, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 6915.

(34) Bouffard, J.; Keitz, B. K.; Tonner, R.; Guisado-Barrios, G.; Frenking, G.; Grubbs, R. H.; Bertrand, G. *Organometallics* **2011**, *30*, 2617.

(35) Gronert, S.; Keeffe, J. R.; O'Ferrall, R. A. M. *J. Org. Chem.* **2009**, *74*, 5250.

(36) Gronert, S.; Keeffe, J. R.; O'Ferrall, R. A. M. *J. Am. Chem. Soc.* **2011**, *133*, 3381.

(37) Huber, S. M.; Heinemann, F. W.; Audebert, P.; Weiss, R. *Chem.—Eur. J.* **2011**, *17*, 13078.

(38) Kassaee, M. Z.; Shakib, F. A.; Momeni, M. R.; Ghambarian, M.; Musavi, S. M. *J. Org. Chem.* **2010**, *75*, 2539.

(39) Lai, C. L.; Guo, W. H.; Lee, M. T.; Hu, C. H. *J. Organomet. Chem.* **2005**, *690*, 5867.

(40) Lee, M. T.; Hu, C. H. *Organometallics* **2004**, *23*, 976.

(41) Lo, R.; Ganguly, B. *Chem. Commun.* **2011**, *47*, 7395.

(42) Tian, Z. X.; Kass, S. R. *Int. J. Mass Spectrom.* **2007**, *267*, 288.

(43) For select examples see: (a) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem.* **2005**, *70*, 5725. (b) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876. (c) Baragwanath, L.; Rose, C. A.; Zeitler, K.; Connon, S. J. *J. Org. Chem.* **2009**, *74*, 9214. For the effect of different aryl substituents on triazolium salts for the intramolecular Stetter reaction see (d) Rovis, T. *Chem. Lett.* **2008**, *37*, 2.

(44) For select examples see: (a) Sohn, S. S.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3873. (b) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418. (c) Struble, J. R.; Bode, J. W. *Org. Synth.* **2010**, *87*, 362.

(45) Mahatthananchai, J.; Bode, J. W. *Chem. Sci.* **2012**, *3*, 192.

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

(47) We are assuming that N1 is the atom of highest proton affinity on the monocationic 1,2,4-triazolium salt. Previous density functional calculations for 1,2,3-triazolylidenes, referred to as mesionic carbenes, showed N2 to have the second highest proton affinity after the carbene itself Bouffard, J.; Keitz, B. K.; Tonner, R.; Guisado-Barrios, G.; Frenking, G.; Grubbs, R. H.; Bertrand, G. *Organometallics* **2011**, *30*, 2617.

(48) A pathway involving the C(3)-deprotonation of the dicationic triazolium ion **18** by D_2O would require an increase in log k_{ex} with decreasing p*D* as the acid concentration is increased, i.e. a linear region of slope −1 at lower p*D* values. As this is not observed, we can rule out this mechanistic option. Thus, despite the extremely low concentrations of deuteroxide in dilute acid solution (10^{-13}–10^{-16} M), the 10^{19}-fold higher basicity of DO^- vs D_2O is the dominating factor (pK_a (D_2O) = 16.6 vs pK_a (D_3O^+) ≈ −2).

(49) Including the two data points obtained for **8a-BF$_4^-$** at higher ionic strength in 1.24 and 2.0 M DCl (open circles in Figure 1), a line of slope greater than one could fit through the three data points at the lowest p*D*'s, although including just the data point in 1.24 M DCl clearly gives a slope of 1. A reviewer has kindly suggested a good alternative mechanism consistent with a slope of 2 where initial protonation on nitrogen is immediately followed by addition of water at C(3), then an additional protonation and a second hydration leading to a tricationic triazacyclopentane (two protons more than the reactive species). There are no additional peaks observed in ^{1}H NMR spectra at any p*D* that could be consistent with hydrate formation

from the reaction of water with triazolium salt **8a-BF$_4^-$** (e.g., Figure s1, Supporting Information). We have previously observed hydration of the conjugate acids of trihydropyrimidin-2-ylidenes **4**, which was evident from the additional peaks in the ^{1}H NMR spectra (see ref 26). UV−vis spectra for **8a-BF$_4^-$** (Figure s89, Supporting Information) retain a strong absorbance at 230 nm, which increases in 4 M HCl and is not consistent with a saturated triazacyclopentane ring. An additional peak at 205 nm also increases with acid concentration to a lesser extent, however, than that observed at 230 nm. On the basis of this spectroscopic data, we do not have compelling evidence to support this mechanism. The more marked decrease in log k_{ex} observed in the case of the extra data point in 2 M DCl could also be explained by the higher ionic strength, and substantially higher viscosity, of this DCl solution.

(50) Higgins, E. M.; O'Donoghue, A. C. Ph.D. Thesis, Durham University: Durham, U.K., 2007.

(51) The standard error in k_{DO} values obtained from fitting to eq 3 or to eqs 6 and 7 ranged from 2 to 8%. Any pair of k_{DO} values for two different triazolium salts in Table 1 that differ by greater than 1.1-fold may be regarded as different, when comparing values obtained by fitting to eq 3 or to eqs 6 and 7.

(52) A steady-state treatment of the mechanism shown in Scheme 4, which describes Pathway A in Scheme 2, gives the following equation for the observed rate constant for exchange: $k_{ex} = (k_{-p}k_{reorg})/(k_p + k_{reorg})$ On the basis of estimated internal return ratios as described in the text, k_p and k_{reorg} values are of comparable magnitude; thus, the nature of the transition state for proton transfer will also influence the observed rate constant for exchange even if the solvent reorganization process is the marginally limiting process.

(53) DiRocco, D. A.; Oberg, K. M.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 6143.

(54) Abdulsada, A. K.; Greenway, A. M.; Hitchcock, P. B.; Mohammed, T. J.; Seddon, K. R.; Zora, J. A. *J. Chem. Soc., Chem. Commun.* **1986**, *24*, 1753.

(55) Fannin, A. A.; King, L. A.; Levisky, J. A.; Wilkes, J. S. *J. Phys. Chem.* **1984**, *88*, 2609.

(56) Grasa, G. A.; Singh, R.; Scott, N. M.; Stevens, E. D.; Nolan, S. P. *Chem. Commun.* **2004**, *24*, 2890.

(57) Headley, A. D.; Jackson, N. M. *J. Phys. Org. Chem.* **2002**, *15*, 52.

(58) Holloczki, O.; Gerhard, D.; Massone, K.; Szarvas, L.; Nemeth, B.; Veszpremi, T.; Nyulaszi, L. *New J. Chem.* **2010**, *34*, 3004.

(59) Wei, S. P.; Wei, X. G.; Su, X. Y.; You, J. S.; Ren, Y. *Chem.—Eur. J.* **2011**, *17*, 5965.

(60) Peon, J.; Polshakov, D.; Kohler, B. *J. Am. Chem. Soc.* **2002**, *124*, 6428.

(61) Dielectric relaxation of solvent to allow delivery of a deuteron to NHC **7** could simply involve the independent rotation of the initially formed HOD molecule within the complex to give **7·DOL** (L = H). Alternatively, rotation could be accompanied by proton transfer with bulk solvent D_2O, resulting in the formation of complex **7·DOL** (L = D). Both processes are extremely fast and could adequately describe limiting dielectric relaxation of solvent.

(62) Kaatze, U. *J. Chem. Eng. Data* **1989**, *34*, 371.

(63) Kaatze, U.; Pottel, R.; Schumacher, A. *J. Phys. Chem.* **1992**, *96*, 6017.

(64) Eigen, M. *Angew. Chem., Int. Ed.* **1964**, *3*, 1.

(65) Barthel, J.; Kleebauer, M.; Buchner, R. *J. Solution Chem.* **1995**, *24*, 1.

(66) Kresge, A. J.; O'Ferrall, R. A. M.; Powell, M. F. In *Isotopes in Organic Chemistry*; Buncel, E., Lee, C. C., Eds.; Elsevier: New York, 1987; Vol. 7.

(67) Benoit, R. L.; Frechette, M. *Can. J. Chem.* **1984**, *62*, 995.

(68) Curphey, T. J.; Prasad, K. S. *J. Org. Chem.* **1972**, *37*, 2259.

(69) Guerret, O.; Sole, S.; Gornitzka, H.; Trinquier, G.; Bertrand, G. *J. Organomet. Chem.* **2000**, *600*, 112.

(70) Corr, M. J.; Roydhouse, M. D.; Gibson, K. F.; Zhou, S. Z.; Kennedy, A. R.; Murphy, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 17980.

(71) Keitz, B. K.; Bouffard, J.; Bertrand, G.; Grubbs, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 8498.