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**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,^{a, c} Christopher J. Collett,^{b, c} Anita G. Lindsay,^a Andrew D. Smith^{b*}
and AnnMarie C. O'Donoghue^{a*}

^a *Department of Chemistry, Durham University, University Science Laboratories, South
Road, Durham, DH1 3LE, UK
E-mail: annmarie.odonoghue@durham.ac.uk*

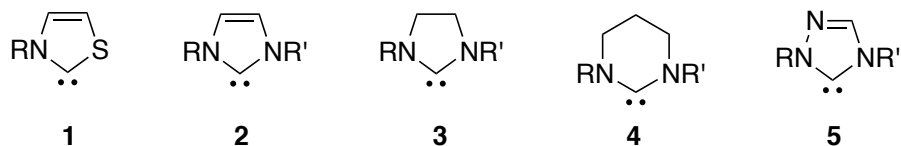
^b *School of Chemistry, University of St Andrews, North Haugh, St Andrews KY16 9ST,
UK
E-mail: ads10@st-andrews.ac.uk*

^c *These authors contributed equally to this work.*

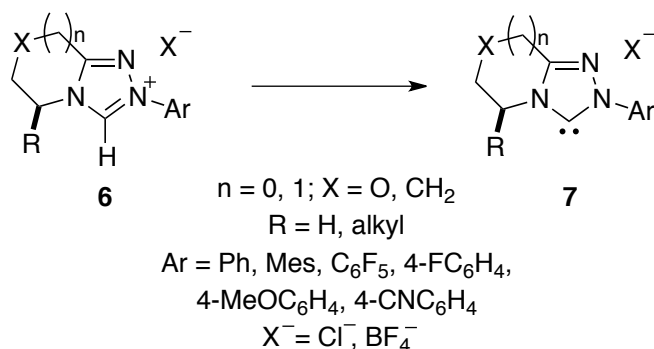
Abstract:

Second order rate constants have been determined for deuteroxide ion-catalyzed exchange of the C(3)-proton for deuterium, k_{DO} ($\text{M}^{-1}\text{s}^{-1}$), of a series of twenty 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}). This data enabled the calculation of carbon acid pK_a values in the range 16.5-18.5 for the twenty 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 $\text{pK}_{\text{a}}^{\text{N1}} = -0.2\text{-}0.5$.

Introduction Since the first isolation and characterisation 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 last 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 homoenolates¹⁶ and enolates,¹⁷ as well as acyl azolium¹⁸ and α,β -unsaturated acylazoliums,¹⁹ leading to remarkable reaction and product diversity within this field. Although many different NHC classes such as **1-2** have been employed in organocatalysis, the triazol-3-ylidenes **5** are the most often utilised. 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 pre-catalysts,²¹⁻³² although there have been studies of NHC nucleophilicities³³ and gas phase proton affinities.³⁴⁻⁴² Washabaugh and Jencks reported on the C2-H/D exchange and aqueous pK_a values of a range of N-alkyl thiazolium 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 benzoannulated variants.²² We recently reported the kinetic acidities towards 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 paper, 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 NHC-catalysed 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 deuterioxide 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 pD -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 reveals 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.

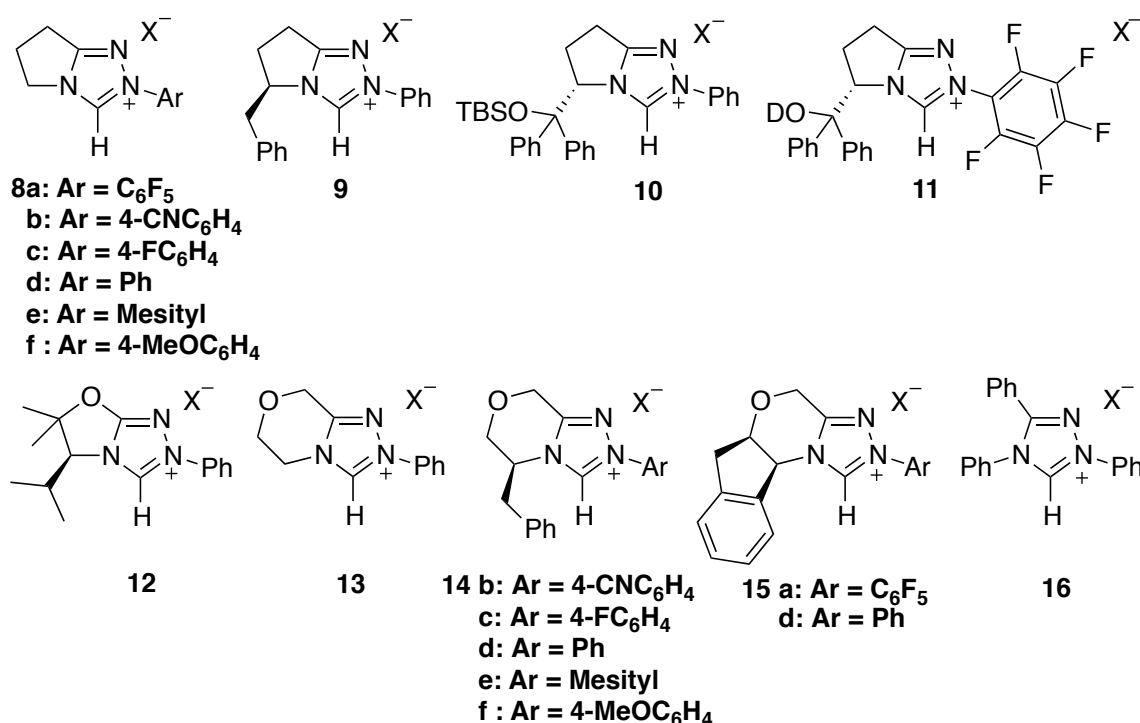


Figure 1. Series of achiral and chiral triazolium salts for which pK_a values in aqueous solution have been determined in this report.

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 pD , 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 deuteriosulfate) 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 D₂O, perdeuterated acetonitrile (33% v/v) was used as a co-solvent in the exchange reactions of these salts. All H/D exchange reactions were incubated at 25 ± 0.1 °C in a thermostated water bath. *pD* 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 *pD* values 2-3 units below that of the reaction mixture by addition of 1 M DCl solution. The quenched samples were either analysed 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 *pD* values (< 1.5) were run directly in NMR tubes thermostated 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 *pD*.

Deuterium exchange was followed by ¹H 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*_{C3H} 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 deuteriosulfate.

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

$$f(s) = \frac{(A_{\text{C3H}} / A_{\text{std}})_t}{(A_{\text{C3H}} / A_{\text{std}})_0} \quad (2)$$

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-BF₄⁻**, **9-Cl⁻**, **13-BF₄⁻**, **14c-f Cl⁻** and **16-BF₄⁻** were performed in fully aqueous solution at a range of *pD* values and at ionic strength, *I* = 1.0 (KCl). In all cases, C(3)-H/D exchange was too fast to monitor by ¹H NMR spectroscopy above *pD* 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-BF₄⁻** and **8d-BF₄⁻**, 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 p S110-112 for results of experiments) once corrections were made for the slight changes in *pD* 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}

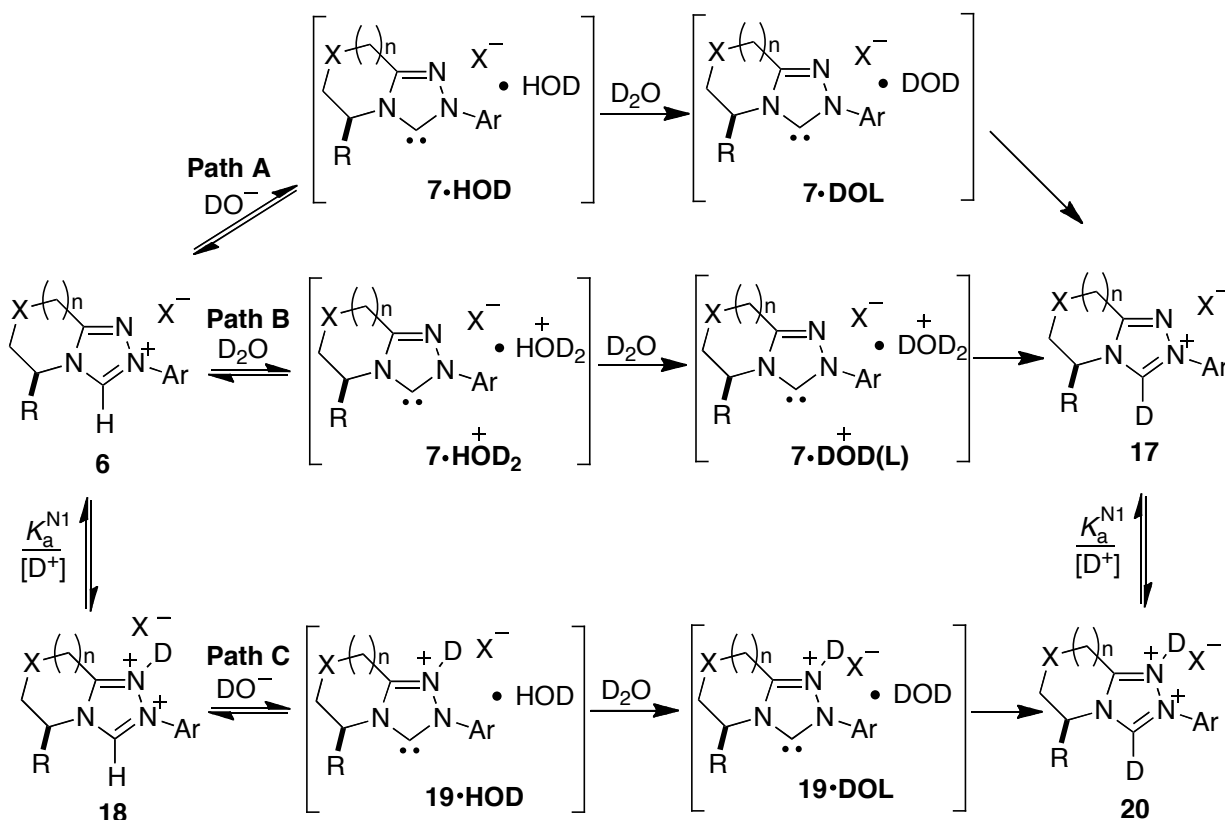
For the triazolium salts **8a-f-BF₄⁻**, **9-Cl⁻**, **13-BF₄⁻**, **14c-f Cl⁻** and **16-BF₄⁻** studied in fully aqueous solution, values of k_{ex} increase with *pD* in the region from *pD* = 0 to 4.5. Figure 2 shows the *pD*-rate profiles of the values of k_{ex} for the deuterium exchange reactions of triazolium salts **8a-f-BF₄⁻**. 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-BF₄⁻** in Figure 2 shows the fit of the log k_{ex} - *pD* data to eq 3, which is derived from eq 4, where k_{DO} (M⁻¹s⁻¹) is the second-order rate constant for deuterioxide-catalyzed exchange, $K_{\text{W}} = 10^{-14.87}$ ⁴⁶ is the ion product of D₂O 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 $\log k_{\text{ex}} - \text{pD}$ data for salts **8b-f-BF₄⁻** to eq 3 is consistent with deuteroxide-catalyzed exchange *via* Pathway A as the dominant mechanism for H/D-exchange (Scheme 2).

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

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

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.



Scheme 2. Potential competing pathways for deuterium exchange at C(3)-H of triazolium salts **6**.

Upon closer examination of the profiles for **8b-f-BF₄⁻** in Figure 2, the dependencies of $\log k_{\text{ex}}$ on pD decreases for the 1-3 data points at the lowest pD values and these points deviate upwards from the line of unit slope through the remaining $\log k_{\text{ex}} - pD$ 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 pD 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 $\log k_{\text{ex}} - pD$ data for triazolium salts **8d-Cl⁻**, **9-Cl⁻**, **13-BF₄⁻**, **14c-f-Cl⁻** and **16-BF₄⁻** in fully aqueous solution were analysed in a similar manner by fitting to eq 3 with the omission of the 1-4 data points at lower pD values that deviate upwards 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 deuterioxide concentration according to eq 4 (supporting information).

For pentafluorophenyl triazolium salt **8a-BF₄⁻** (●), the altered dependence on pD is more marked and only the data points at the five highest pD values fit well to eq 3. In this case, the decreased dependence on pD is also followed by a downward break at the lowest pD values. This altered dependence on pD 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, ○ on plot for **8a-BF₄⁻**). Although the ionic strength is higher, these data points further support the existence of the downward break.

The change in the dependence of $\log k_{\text{ex}}$ values on pD suggests competition from additional pathway(s) for deuterium exchange at lower pD values (Scheme 2). This could include a pD -independent mechanism for H/D exchange with deprotonation by solvent water rather than deuterioxide ion (Pathway B), which initially leads to intermediate

7.HOD₂⁺. As the $\log k_{\text{ex}} - \text{pD}$ data does not become completely pD -independent, the occurrence of Pathways A and B only, without allowing for 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 $\log k_{\text{ex}}$ 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 deuterioxide-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**.

Eq 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 $\log k_{\text{ex}} - \text{pD}$ data for triazolium salt **8a-BF₄⁻** does not fit well at lower pD values to eq 5, which suggests that the combination of one or both of Pathways B and C, together with protonation at N(1), is required to account for the altered dependence of $\log k_{\text{ex}}$ on pD at lower pD values. Eqs 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_{D2O} (s^{-1}) is the first order rate constant for exchange *via* Pathway B, where deprotonation at C(3) is by solvent and k_{DO}' ($\text{M}^{-1}\text{s}^{-1}$) is the second order rate constant for deuterioxide-catalyzed C(3)-H/D exchange of the *N*-protonated azolium ion **18** *via* Pathway C.^{48,49}

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

$$\log k_{\text{ex}} = \log \left[\frac{K_{\text{a}}^{\text{N1}} \left(\left(\frac{k_{\text{DO}} K_{\text{w}}}{\gamma_{\text{DO}}} \right) 10^{\text{pD}} \right) + \left(K_{\text{a}}^{\text{N1}} k_{\text{D2O}} \right)}{\left(K_{\text{a}}^{\text{N1}} + 10^{-\text{pD}} \right)} \right] \quad (6)$$

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

The $\log k_{\text{ex}} - pD$ data for triazolium salt **8a-BF₄⁻** fits 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 $\log k_{\text{ex}} - pD$ data for triazolium salt **8a-BF₄⁻** fit equally well overall to eqs 6 and 7. The solid line through the data for triazolium salt **8a-BF₄⁻** in Figure 2 shows the fit to eq 6. Identical values of k_{DO} ($\text{M}^{-1}\text{s}^{-1}$), 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_{D2O} (s^{-1}) or k_{DO}' ($\text{M}^{-1}\text{s}^{-1}$) 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.

As chiral triazolium salts **10-12-BF₄⁻**, **14b-Cl⁻**, **15a-BF₄⁻** and **15d-BF₄⁻** were insoluble in D₂O, perdeuterated acetonitrile (33% v/v) was used as a co-solvent in the exchange reactions of these salts. The deuterium exchange reactions of triazolium salts **8a-BF₄⁻** and **8d-BF₄⁻** were studied both in D₂O, and in 2:1 D₂O:CD₃CN, so that the effect of acetonitrile co-solvent on k_{DO} could be assessed. The appearance of the pD -rate profiles for **10-12-BF₄⁻**, **14b-Cl⁻**, and **15d-BF₄⁻** in 2:1 D₂O:CD₃CN 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 $\log k_{\text{ex}}$

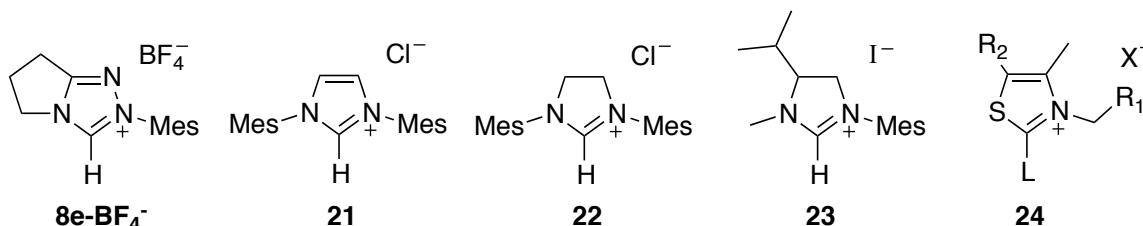
values on pD occurs at higher pD values than for the salts studied in fully aqueous solution likely a result of the combined effect of solvent on pK_a^{N1} , k_{D2O} (s^{-1}) or $k_{DO'}$ values. The exchange data for the salts studied in 2:1 $D_2O:CD_3CN$ were fitted to eqs 6/7 rather than eq 3 in each case as this resulted in lower errors in k_{DO} values (Table 1). As discussed above for *N*-pentafluorophenyl salt **8a-BF₄⁻** assuming either extreme of Pathways B or C, values for the constants k_{D2O} (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-BF₄⁻** in 2:1 $D_2O:CD_3CN$ was too fast to follow by 1H 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-BF₄⁻**, deuterium exchange data were acquired in 1-3 M DCl in 2:1 $D_2O:CD_3CN$ ($pDs \sim -0.42 - 0.06$). The pD -rate profile of the values of k_{ex} for the deuterium exchange reaction for triazolium salt **15a-BF₄⁻** (Figure s83) shows an increase in k_{ex} with pD in this range. This increase could either be due to deuterioxide catalysis of C(3)-H/D exchange for the triazolium salt **15a-BF₄⁻** or the N1-deuterated conjugate acid. A plot of k_{ex} values for salt **15a-BF₄⁻** against deuterioxide concentration (Figure s82) gave k_{DO}^* ($M^{-1}s^{-1}$) as its slope (Table 1).

Substituent Effects on Kinetic Acidities towards Deuterioxide Ion (k_{DO})

The kinetic acidities towards deprotonation of all triazolium ions by deuterioxide ion *via* Pathway A (k_{DO} , Table 1) are significantly higher than for analogous imidazolium,^{22,26} 4,5-dihydroimidazolium²⁶ and thiazolium ions³⁰ 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-BF₄⁻** 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** ($k_{DO} = 4.08 \times 10^4 M^{-1}s^{-1}$ and $1.19 \times 10^4 M^{-1}s^{-1}$)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 $3.45 \times 10^2 M^{-1}s^{-1}$ for 1-mesityl-3-methyl-4-*i*-propyl-4,5-dihydroimidazolium iodide **23**,⁵⁰ which has alkyl substituents at N(3) and C(4) as for triazolium ion **8e-BF₄⁻**. 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 destabilise the parent triazolium ion relative to the formally neutral transition state, thereby increasing the observed rate constant for exchange.

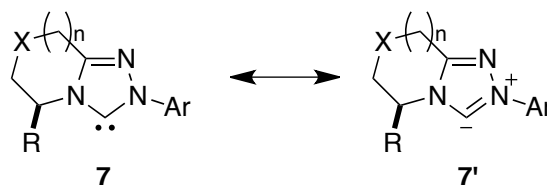


The triazolium salts in Table 1 are also substantially more acidic than any thiazolium salt studied to date under similar reaction conditions, although the latter experiments have been limited to *N*-alkyl substituted examples.³⁰ We have measured a k_{DO} value of $3.28 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ for thiazolium salt **24** ($\text{L} = \text{H}$; $\text{R}_1 = \text{Ph}$; $\text{R}_2 = \text{CH}_2\text{CH}_2\text{OD}$; $\text{X}^- = \text{Cl}^-$) 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, pS72-S74). Washabaugh and Jencks reported similar k_{DO} values in the range $3.23 \times 10^5 \text{ M}^{-1} \text{ s}^{-1} - 2.14 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ for the deuterium exchange reactions of a series of thiazolium salts **24** ($\text{L} = \text{H}$; $\text{R}_1 = \text{neutral alkyl or aryl}$; $\text{R}_2 = \text{H}$), 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-BF₄⁻** from the most reactive *N*-pentafluorophenyl- to the least reactive 4-methoxyphenyltriazolium 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 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-di-*i*propylphenyl, 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 co-planarity 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 deuterioxide, 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



The effect of acetonitrile co-solvent on k_{DO} was assessed for triazolium salts **8a**- and **8d-BF₄⁻**, which were studied both in 100% D₂O, and 2:1 D₂O:CD₃CN. The effect of the addition of acetonitrile co-solvent is a 5.4 fold increase in k_{DO} for **8d-BF₄⁻** (Table 1). A small 1.2-fold increase is observed for **8a-BF₄⁻**, although the k_{DO} value in 2:1 D₂O:CD₃CN in this case is less accurate as there are only 2 data points in the region of the *pD* 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 deuterioxide in the mixed solvent relative to fully aqueous solution.

As mentioned above, the deuterium exchange reaction of the *N*-pentafluorophenyl

catalyst **15a-BF₄⁻** in 2:1 D₂O:CD₃CN was too fast to measure above pD 0.06, and the estimated k_{DO}^* value of $\sim 2 \times 10^{13} \text{ M}^{-1} \text{ s}^{-1}$ in Table 1 is 25000-fold higher than the k_{DO} value for achiral analogue **8a-BF₄⁻** 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-BF₄⁻** is unfeasibly high and clearly exceeds the bimolecular diffusional limit for small molecules in solution ($\sim 5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$). This outcome is likely because the data for **15a-BF₄⁻** is 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-BF₄⁻**, 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-BF₄⁻** is surprising. By contrast, the k_{DO} value for the corresponding *N*-phenyl catalyst **15d-BF₄⁻** is only 1.9-fold larger than for analogous achiral *N*-phenyl triazolium salt **8d-BF₄⁻** in the same solvent and k_{ex} values could be acquired up to pD 3.8 in both cases. One possible explanation is a significantly higher $\text{p}K_{\text{a}}^{\text{N1}}$ for **15a-BF₄⁻** with the reaction of N-protonated **15a-BF₄⁻** providing a greater contribution to k_{ex} at higher pDs than for the other triazolium salts. The N-protonated dicationic triazolium ions are predicted to have greater kinetic acidities towards deprotonation by deuterioxide 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 $\text{p}K_{\text{a}}^{\text{N1}}$ in 2:1 D₂O:CD₃CN solutions were unsuccessful due to insufficient changes in the spectral data for **15a-BF₄⁻** and other salts upon variation of pD (see pS113-115 supporting information). A higher $\text{p}K_{\text{a}}^{\text{N1}}$ for **15a-BF₄⁻** seems counter-intuitive 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-BF₄⁻** and **15d-BF₄⁻**, shows the non-planar 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 unfavourable electrostatic interaction between the lone pair on N1 and those on the *ortho*-halogen atom. This could also be the case for *N*-pentafluorophenyltriazolium salt **15a-BF₄⁻** and would account for a

higher pK_a for N1-protonation. To the best of our knowledge, crystal structures of **15a-BF₄⁻** and **15d-BF₄⁻** have not been published.

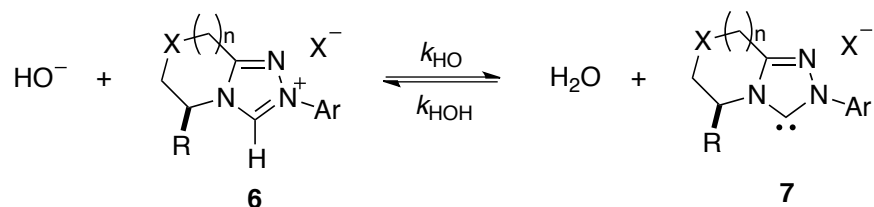
Our suggestion of an increase in pK_a^{N1} for **15a-BF₄⁻** due to the spacial influence of *ortho*-halogen atoms on the N-aryl ring on N1-basicity is supported by the significant difference between the *pD*-profile for **8a-BF₄⁻** versus the other triazolium salts **8b-f-BF₄⁻** in Figure 1. Of this series of triazolium salts, only the *N*-pentafluorophenyl triazolium salt **8a-BF₄⁻** has *ortho*-halogen rather than hydrogen atoms on the *N*-aryl ring. The k_{DO} values for **8a-f-BF₄⁻** 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 *pD* occurs at significantly higher *pD* values for **8a-BF₄⁻** compared with the other triazolium salts **8b-f-BF₄⁻**, and a higher pK_a^{N1} for the former salt. For example, the onset of the altered dependence on *pD* occurs over 1 *pD* unit higher for *N*-pentafluorophenyl triazolium salt **8a-BF₄⁻** compared with *N*-*para*-cyanophenyl salt **8b-BF₄⁻**, however, their corresponding $\log k_{DO}$ values only differ by 0.3 units.

Effect of Counterion on Kinetic Acidities towards 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 = BF₄⁻ and Cl⁻ in fully aqueous solution. A 1.2-fold increase in k_{DO} is observed upon changing from X = Cl⁻ to BF₄⁻, 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 counter anions are known to form hydrogen bonds both in the solid state and in concentrated solutions in non-hydroxylic 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 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 deuterioxide-catalyzed C(3)-H/D exchange *via* Pathway A (Scheme 2).

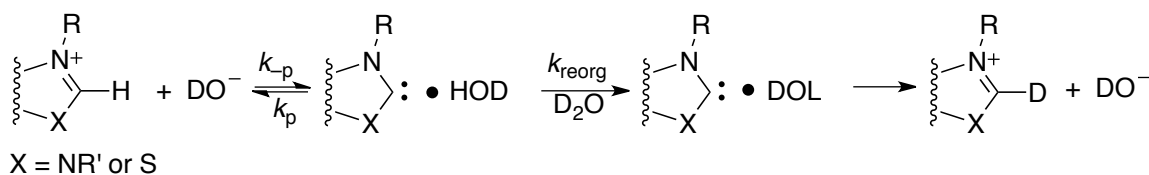


Scheme 3. Ionization of triazolium ion salt **6** at C(3) to yield NHCs **7**.

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

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 us²⁶ 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 pD 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 deuterioxide 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 deuterioxide 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 $k_{\text{HOD}} = k_{\text{reorg}} = 1 \times 10^{11} \text{ s}^{-1}$ for the dielectric relaxation of water^{62,63} could be assumed.



Scheme 4. Mechanism for deuterioxide-catalyzed azolium ion H/D-exchange.

Washabaugh and Jencks reported rate constants for C(2)-hydron exchange catalyzed by deuterioxide ion for a range of thiazolium ions **24** ($\text{L} = \text{H}, \text{D}$ or T ; $\text{R}_1 = \text{Me}, \text{Ph}, \text{CN}$; $\text{R}_2 = \text{H}$).³⁰⁻³² These reactions showed primary kinetic isotope effects that increase over the range $(k_{\text{H}}/k_{\text{T}})_{\text{obs}} = 2.9\text{--}14.7$ with increasing acidity of the thiazolium ion.³² These varying primary kinetic isotope effects, and the observation of significant deviations of $(k_{\text{D}}/k_{\text{T}})_{\text{obs}}$ and $(k_{\text{H}}/k_{\text{T}})_{\text{obs}}$ values from the Swain-Schaad relationship, shows that there is significant internal return of the transferred hydron to the thiazolyl carbene from water.³² This is consistent with an Eigen mechanism⁶⁴ 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 ($k_{\text{p}}/k_{\text{reorg}} \sim 3.3$) was largest for the least acidic thiazolium ion **24** ($\text{R}_1 = \text{Me}$; $\text{R}_2 = \text{H}$) with $k_{\text{DO}} = 4.27 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ and $\text{pK}_{\text{a}} = 18.9$ at 30°C and ionic strength 2.0 M (NaCl). For the more acidic *N*-cyanomethylthiazolium ion **24** ($\text{R}_1 = \text{CN}$; $\text{R}_2 = \text{H}$) with $k_{\text{DO}} = 4.62 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ and $\text{pK}_{\text{a}} = 16.9$, the internal return ratio decreases to $k_{\text{p}}/k_{\text{reorg}} \sim 0.3$.

For the structurally similar imidazolium, 4,5-dihydroimidazolium and

trihydropyrimidinium ions, values of k_{DO} ($\text{M}^{-1}\text{s}^{-1}$) at 25 °C and ionic strength 1.0 M (KCl) range from $3.92 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ to $1.48 \times 10^3 \text{ M}^{-1}\text{s}^{-1}$,²⁶ which are $1.1 - 6.9 \times 10^8$ fold smaller than corresponding values for the thiazolium ion **24** ($\text{L}=\text{H}$; $\text{R}_1 = \text{Me}$; $\text{R}_2 = \text{H}$) for which solvent reorganization is largely rate-limiting ($k_{\text{p}}/k_{\text{reorg}} \sim 3.3$). Therefore, relative to their azolium 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, and so their protonation by water should be even more limited by the solvent reorganization step ($k_{\text{p}} \gg k_{\text{reorg}}$).

The k_{DO} values in Table 1 for triazolium salts **8a-f-BF₄⁻**, **9-Cl⁻**, **13-BF₄⁻**, **14c-f Cl⁻** and **16-BF₄⁻** in aqueous solution at 25 °C and ionic strength 1.0 M (KCl) range from $4.20 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ to $6.82 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$, and are no greater than 14.7-fold different from the value determined for the *N*-cyanomethylthiazolium salt **24** ($\text{R}_1 = \text{CN}$; $\text{R}_2 = \text{H}$) under similar reaction conditions ($k_{\text{DO}} = 4.62 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$). For thiazolium ions **24**, the change of *N*-substituent from methyl to cyanomethyl increases k_{DO} by 109-fold, and the internal return ratio, $k_{\text{p}}/k_{\text{reorg}}$, decreases by 10-fold from 3.3 to 0.3. Therefore, the $k_{\text{p}}/k_{\text{reorg}}$ 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** ($\text{R}_1 = \text{CN}$; $\text{R}_2 = \text{H}$). On this basis, rate constants for protonation of the corresponding triazolyliidenes **7** by water should be the same, and no more than ~6-fold lower than, the rate constant for reorganization of solvent ($k_{\text{reorg}} = 1 \times 10^{11} \text{ s}^{-1}$).

Although the $k_{\text{p}}/k_{\text{reorg}}$ ratios clearly illustrate that re-protonation of thiazolyliidenes 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 $\pm 30\%$ or more.³² For the determination of a pK_{a} value for *N*-cyanomethylthiazolium salt **24** ($\text{R}_1 = \text{CN}$; $\text{R}_2 = \text{H}$) 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 re-protonation of triazolyliidenes **7** is limited by reorganization of solvent and that $k_{\text{HOH}} = k_{\text{reorg}} = 1 \times 10^{11} \text{ s}^{-1}$. Furthermore, significant general base catalysis of exchange was not observed for two representative

salts **8c**- and **8d-BF₄⁻**, which have larger k_{DO} values than for the N-cyanomethylthiazolium salt **24** ($R_1 = \text{CN}$; $R_2 = \text{H}$). It was not possible to probe for buffer catalysis of exchange in the case of triazolium salts more acidic than **8c-BF₄⁻**, as deuterium exchange in acetic acid buffers was too fast to monitor by ¹H NMR spectroscopy. The absence of significant general base catalysis of exchange supports the conclusion that re-protonation of triazolylienes and solvent reorganization occur at the similar rates.

For the triazolium salts studied in 2:1 D₂O:CD₃CN, the same value of $k_{\text{HOH}} = k_{\text{reorg}}$ = $1 \times 10^{11} \text{ s}^{-1}$ 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 water at 25 °C, and added electrolytes have been shown to increase this value by up to 2-fold.⁶⁵ As 2:1 D₂O:CD₃CN 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} ($\text{M}^{-1}\text{s}^{-1}$) 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 $k_{\text{DO}}/k_{\text{HO}} = 2.4^{66}$ 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 $k_{\text{HOH}} = 1 \times 10^{11} \text{ s}^{-1}$. The resulting $\text{p}K_{\text{a}}$ values for all triazolium salts are listed in Table 1 and range from 16.6 – 18.5. For those salts with k_{DO} values $\leq 8.66 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ in fully aqueous solution, the value for *N*-(4-fluorophenyl)-triazolium salt **8c-BF₄⁻**, the error in $\text{p}K_{\text{a}}$ is ≤ 0.08 units (supporting information pS109-110). General base catalysis of C(3)-H/D-exchange was not significant for **8c-BF₄⁻**, which strongly supports the claim that $k_{\text{HOH}} = k_{\text{reorg}}$ for this and less reactive salts. For salts with k_{DO} values greater than for **8c-BF₄⁻**, 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 ~six-fold lower than k_{reorg} and the true $\text{p}K_{\text{a}}$ 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 towards deuterioxide ion as the same k_{HOH} value for reprotonation is used in each case. By contrast, a comparison of acidities of 1-mesityl-3-methyl-4-*i*propyl-4,5-dihydroimidazolium iodide **23**⁵⁰ and N-mesityl triazolium salt **8e-BF₄⁻** reveals that the pK_a values for the triazolium salts are 5 units lower than for analogous imidazolium salts, and demonstrates the large influence of the extra ring nitrogen atom on acidity.

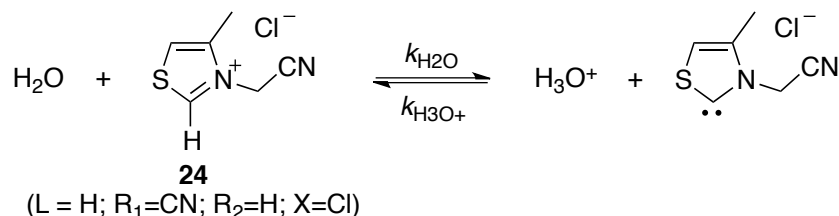
Additional Pathways for Deuterium Exchange

One of the notable effects of the additional ring nitrogen of the triazolium ions **6** is the change in dependence of $\log k_{\text{ex}}$ values on pD 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 pD -rate profiles, which involves an increase in $\log k_{\text{ex}}$ with pD , and is consistent with deuterioxide-catalyzed exchange *via* Pathway A only. Washabaugh and Jencks observed the onset of a clear pD -independent region in the pD -rate profile for C(2)-proton exchange of thiazolium salt **24** ($L=H$; $R_1 = 2\text{-methyl-4-aminopyrimidinyl}$; $R_2 = \text{CH}_2\text{CH}_2\text{OD}$; $X^- = \text{Cl}^-$) but only in 2-4 M DCl solution at D_0 values less than -1.0 .³⁰ This was ascribed to pD independent C(2)-H/D exchange by a mechanism analogous to Pathway B in Scheme 1, and a value of $k_{\text{D}_2\text{O}} = 1.5 \times 10^{-8} \text{ s}^{-1}$ was estimated. Similarly, the onset of a pD -independent region was observed for the 3-cyanomethyl-4-methylthiazolium salt **24** ($R_1 = \text{cyano}$; $R_2 = H$; $X^- = \text{Cl}^-$) in 0.8-2.7 M DCl yielding $k_{\text{D}_2\text{O}} = 9.4 \times 10^{-8} \text{ s}^{-1}$.³¹ Further decreases in $\log k_{\text{ex}}$ 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 ($> 1 \text{ M}$) would be expected to shift the equilibrium in Scheme 5 to the left.

The continued decrease in the $\log k_{\text{ex}}$ data for **8a-BF₄⁻** in aqueous solution at lower pD values is not likely due to acidity function effects as these measurements were conducted in more dilute DCl solutions ($< 1 \text{ M DCl}$). Furthermore, such acid inhibition

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

Washabaugh and Jencks calculated a $\text{p}K_{\text{a}}$ value of 16.9 for the 3-cyanomethyl-4-methylthiazolium salt **24** ($\text{L} = \text{H}$; $\text{R}_1 = \text{cyano}$; $\text{R}_2 = \text{H}$; $\text{X}^- = \text{Cl}^-$) in aqueous solution at 30 °C by application of eq 8 using $k_{\text{DO}} = 4.68 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$, $k_{\text{DO}}/k_{\text{HO}} = 2.4$, and by assuming reprotonation of the thiazolyl carbene is at the diffusional limit.³⁰ Using the pD -independent value of $k_{\text{D2O}} = 9.4 \times 10^{-8} \text{ s}^{-1}$, they obtained the same $\text{p}K_{\text{a}}$ value by application of eq 9, derived for Scheme 5, using an experimental value of $k_{\text{H2O}}/k_{\text{D2O}} = 2.6$ and by assuming that reprotonation of the thiazolyl carbene by hydronium ion is also diffusion controlled ($k_{\text{H3O}^+} = 2 \times 10^{10} \text{ M}^{-1}\text{s}^{-1}$).³⁰ The excellent agreement obtained using two different kinetic estimations of $\text{p}K_{\text{a}}$ strongly supports the assignment of the pD -independent region to a mechanism analogous to Pathway B (Scheme 2).



Scheme 5. Ionization of thiazolium salts **24** at C(2) to yield corresponding thiazolyl carbenes.

$$\text{p}K_{\text{a}} = -\log \frac{k_{\text{H2O}}}{k_{\text{H3O}^+}} \quad (9)$$

By contrast the C(3)-carbon acid $\text{p}K_{\text{a}}$ value in aqueous solution calculated for the triazolium salt **8a-BF₄⁻** obtained by application of eq 9 using the k_{D2O} 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 $\text{p}K_{\text{a}}$ values calculated using eq 8 and 9 are obtained for the other salts listed in Table 2. Conversely, using the k_{D2O} values in Table 2 and an experimental value of $k_{\text{H2O}}/k_{\text{D2O}} = 2.6$, requires an impossibly large reverse rate constant of $k_{\text{H3O}^+} > 5 \times 10^{12} \text{ M}^{-1}\text{s}^{-1}$ in order to obtain the

C(3)-carbon acid pK_a value for the triazolium salt **8a-BF₄⁻** in Table 1. Further support of substantial k_{D2O} overestimation comes from a comparison of deuterium exchange data for the *N*-pentafluorophenyltriazolium salt **8a-BF₄⁻** (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-BF₄⁻** is higher by 14.7-fold than the corresponding value for the thiazolium salt **24** whereas the calculated k_{D2O} value is higher by over 5000-fold. Although over-estimation of k_{D2O} values could partly result from 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 pD -rate profile for triazolium salt **8a-BF₄⁻** at lower pD 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 pDs for exchange *via* Pathway A or levelling 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} – pD data for triazolium salt **8a-BF₄⁻** to eq 6 or 7 yields an estimate of $pK_a^{N1} \sim -0.2$. Fitting of data for the other triazolium salts **10-12-BF₄⁻**, **14b-Cl**, and **15d-BF₄⁻** yields similar pK_a^{N1} values in the range -0.2-0.5 in 2:1 D₂O:CD₃CN. 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 = NH₂ 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 characterisation 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

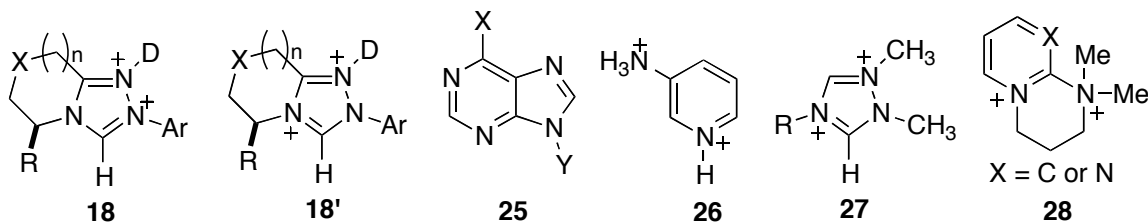


Table 2 additionally includes estimates of second order rate constants, k_{DO}' ($\text{M}^{-1}\text{s}^{-1}$) for deuterioxide-catalyzed exchange of the C(3)-H of N-protonated triazolium ions **8a-BF₄⁻**, **10-12-BF₄⁻**, **14b-Cl⁻**, and **15d-BF₄⁻** obtained by fitting the $\log k_{\text{ex}} - \text{pD}$ 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 $k_{\text{d}} = 5 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$, and in the case of facilitated diffusion, as observed for hydronium ion, $k_{\text{d}} = 2 \times 10^{10} \text{ M}^{-1}\text{s}^{-1}$. In general, bimolecular rate constants should not exceed these diffusional limits. The k_{DO}' value estimated for triazolium salt **8a-BF₄⁻** 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 - $10^8 \text{ M}^{-1}\text{s}^{-1}$ 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 $\log k_{\text{ex}}$ data for triazolium salt **8a-BF₄⁻** on pD as the acidity of the medium is increased. All except one of the other estimated k_{DO}' values in Table 2 for **10-12-BF₄⁻**, **14b-Cl⁻**, and **15d-BF₄⁻** studied in 2:1 $\text{D}_2\text{O}:\text{CD}_3\text{CN}$ 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 $\text{D}_2\text{O}:\text{CD}_3\text{CN}$, although the data does fit well to eq 6/7. An alternative explanation, that would show the same kinetic dependence on pD , is that N-protonation is followed by a concerted process that avoids the formation of a monocationic NHC where deprotonation by deuterioxide 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-BF₄⁻**. This calculation assumes that the reverse rate of protonation of the monocationic NHC by solvent is limited by dielectric relaxation of solvent ($k_{HOH} = \times 10^{11} \text{ s}^{-1}$). 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 $1 \times 10^{11} \text{ s}^{-1}$. 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 pK 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 pD under acidic conditions. The data requires that protonation at N(1) occurs to give *dicationic triazolium ions* at lower pD 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-BF₄⁻, we have also estimated upper limit C(3)-H pK_a value that is *at least* 1.7 units lower than for the non-protonated 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.

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Supporting Information Available

The syntheses of triazolium salts **8a-f**, **9-13**, **14b-f**, **15a-d** and **16-X**, the preparation of solutions, the determination of pD, and the NMR methods used to monitor deuterium exchange are described in the Supporting Information. Representative NMR spectra, all first order kinetic plots, tabulated *k*_{ex} data and log *k*_{ex} – pD profiles are included in the supporting information for all triazolium salts **8-16**. Second order plots of *k*_{ex} values against deuterioxide concentration are also included where relevant. Kinetic data obtained in studies of the effect of general base concentration on deuterioxide-catalyzed exchange is provided. Experimental data obtained in attempts towards the independent determination of pK_a^N are also included. This information is available free of charge via the internet at <http://pubs.acs.org>.

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- (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-triazolyliidenes, referred to as mesionic carbenes, showed N2 to have the second highest proton affinity after the carbene itself (J. Bouffard *et al*, *Organometallics*, **2011**, *30*, 2617.).
- (48) A pathway involving the C(3)-deprotonation of the dicationic triazolium ion **18** by D₂O 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^- versus D_2O is the dominating factor ($\text{p}K_{\text{a}}(\text{D}_2\text{O}) = 16.6$ versus $\text{p}K_{\text{a}}(\text{D}_3\text{O}^+) \sim -2$).
- (49) Including the two data points obtained for **8a-BF₄⁻** 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 datapoints at the lowest pD s, although including just the datapoint in 1.24 M DCl clearly gives a slope of 1. A referee 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 ^1H NMR spectra at any pD that could be consistent with hydrate formation from the reaction of water with triazolium salt **8a-BF₄⁻** (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 ^1H NMR spectra (see *Ref.* 26). UV-Vis spectra for **8a-BF₄⁻** (Fig s89) retain a strong absorbance at 230 nm, which increases in 4M HCl and is not consistent with a saturated triazacyclopentane ring. An additional peak at 205 nm also increases with acid concentration, however, to a lesser extent than 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 $\log k_{\text{ex}}$ 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.
- (51) The standard error in k_{DO} values obtained from fitting to eq 3 or 6/7 ranged from 2-8%. 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 6/7.
- (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: $k_{\text{ex}} = (k_{\text{p}}k_{\text{reorg}})/(k_{\text{p}} + k_{\text{reorg}})$
Based on 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.
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- (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 D₂O resulting in the formation of complex **7.DOL** (L = D). Both processes are extremely fast and could adequately describe limiting dielectric relaxation of solvent.
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Table 1 Second order rate constants for deuterioxide-catalysed exchange, k_{DO} ($\text{M}^{-1}\text{s}^{-1}$), and carbon acid $\text{p}K_{\text{a}}$ values for triazolium salts **8-16-X⁻** in aqueous solution at 25°C and ionic strength, $I = 1.0$ (KCl).

Salt	k_{DO} ($\text{M}^{-1}\text{s}^{-1}$)	$\text{p}K_{\text{a}}^{\text{d}}$	Salt	k_{DO} ($\text{M}^{-1}\text{s}^{-1}$)	$\text{p}K_{\text{a}}^{\text{d}}$
8a-BF₄⁻	$6.82 (\pm 0.25) \times 10^8{}^{\text{b}}$ $7.95 (\pm 1.25) \times 10^8{}^{\text{b,c}}$	16.5 17.3 ^c	12-BF₄⁻	$4.81 (\pm 0.22) \times 10^8{}^{\text{b,c}}$	17.5 ^c
8b-BF₄⁻	$3.18 (\pm 0.08) \times 10^8{}^{\text{a}}$	16.9	13-BF₄⁻	$2.53 (\pm 0.12) \times 10^8{}^{\text{a}}$	17.0
8c-BF₄⁻	$8.66 (\pm 0.11) \times 10^7{}^{\text{a}}$	17.4	14b-Cl⁻	$1.36 (\pm 0.17) \times 10^9{}^{\text{b,c}}$	17.1 ^c
8d-BF₄⁻	$6.82 (\pm 0.13) \times 10^7{}^{\text{a}}$ $3.70 (\pm 0.15) \times 10^8{}^{\text{a,c}}$	17.5 17.6 ^c	14c-Cl⁻	$2.17 (\pm 0.13) \times 10^8{}^{\text{a}}$	17.0
8d-Cl⁻	$5.84 (\pm 0.20) \times 10^7{}^{\text{a}}$	17.6	14d-Cl⁻	$1.59 (\pm 0.08) \times 10^8{}^{\text{a}}$	17.2
8e-BF₄⁻	$5.29 (\pm 0.07) \times 10^7{}^{\text{a}}$	17.7	14e-Cl⁻	$1.62 (\pm 0.06) \times 10^8{}^{\text{a}}$	17.2
8f-BF₄⁻	$4.20 (\pm 0.23) \times 10^7{}^{\text{a}}$	17.8	14f-Cl⁻	$1.22 (\pm 0.09) \times 10^8{}^{\text{a}}$	17.3
9-Cl⁻	$7.05 (\pm 0.25) \times 10^7{}^{\text{a}}$	17.5	15a-BF₄⁻	$1.95 (\pm 0.10) \times 10^{13}{}^{\text{e,c}}$	
10-Cl⁻	$5.38 (\pm 0.60) \times 10^7{}^{\text{b,c}}$	18.5 ^c	15d-BF₄⁻	$7.10 (\pm 0.47) \times 10^8{}^{\text{b,c}}$	17.4 ^c
11-BF₄⁻	$7.05 (\pm 0.63) \times 10^8{}^{\text{b,c}}$	17.4 ^c	16-BF₄⁻	$3.61 (\pm 0.16) \times 10^8{}^{\text{a}}$	16.8

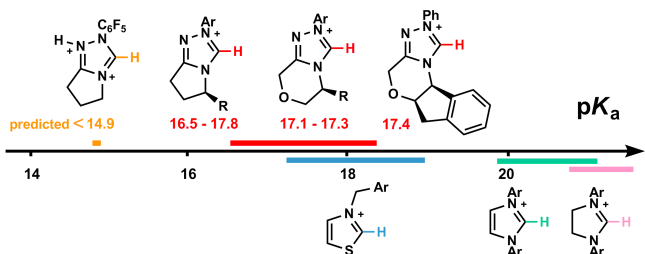
^aValues of k_{DO} ($\text{M}^{-1}\text{s}^{-1}$) obtained by fitting $\log k_{\text{ex}} - \text{p}D$ data to eq 3. ^bValues of k_{DO} ($\text{M}^{-1}\text{s}^{-1}$) obtained by fitting $\log k_{\text{ex}} - \text{p}D$ data to eq 6 or eq 7. ^cDeuterium exchange data acquired in 33 v/v% $\text{CD}_3\text{CN}:\text{D}_2\text{O}$. ^d $\text{p}K_{\text{a}}$ values obtained by application of eq 8 as described in the text using k_{DO} values obtained from fitting $\log k_{\text{ex}} - \text{p}D$ data to either eq 3 or eq 6-7. ^eValue of k_{DO}^* ($\text{M}^{-1}\text{s}^{-1}$) obtained as slope of second order plot of k_{ex} (s^{-1}) against deuterioxide concentration.

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^{NI} (M) ^c	k_{D2O} (s ⁻¹) ^d	$k_{DO}^{'}$ (M ⁻¹ s ⁻¹) ^e
8a-BF₄⁻ ^a	1.5 (± 0.4)	6.1×10^{-5} (± 3.6×10^{-6})	3.3×10^{10} (± 2.0×10^9)
8a-BF₄⁻ ^b	0.5 (± 0.1)	1.4×10^{-4} (± 5.9×10^{-6})	1.1×10^{12} (± 4.5×10^{10})
10-Cl⁻ ^b	0.6 (± 0.3)	9.2×10^{-7} (± 1.7×10^{-7})	7.0×10^9 (± 1.3×10^9)
11-BF₄⁻ ^b	0.6 (± 0.2)	5.6×10^{-5} (± 3.4×10^{-6})	4.3×10^{11} (± 2.6×10^{10})
12-BF₄⁻ ^b	0.4 (± 0.1)	9.3×10^{-6} (± 6.3×10^{-7})	7.1×10^{10} (± 4.8×10^9)
14b-Cl⁻ ^b	0.5 (± 0.1)	6.8×10^{-5} (± 5.0×10^{-6})	5.2×10^{11} (± 3.8×10^{10})
15d-BF₄⁻ ^b	0.3 (± 0.1)	2.1×10^{-5} (± 1.8×10^{-6})	1.6×10^{11} (± 1.4×10^{10})

^aDeuterium exchange data acquired in D₂O. ^bDeuterium exchange data acquired in 33 v/v% CD₃CN:D₂O. ^cValues of K_a^{NI} (M) obtained by fitting log $k_{ex} - pD$ data to eq 6 or eq 7. ^dValues of k_{D2O} (s⁻¹) obtained by fitting log $k_{ex} - pD$ data to eq 6. ^eValues of $k_{DO}^{'}$ (M⁻¹s⁻¹) obtained by fitting log $k_{ex} - pD$ data to eq 7.

TOC Graphic:



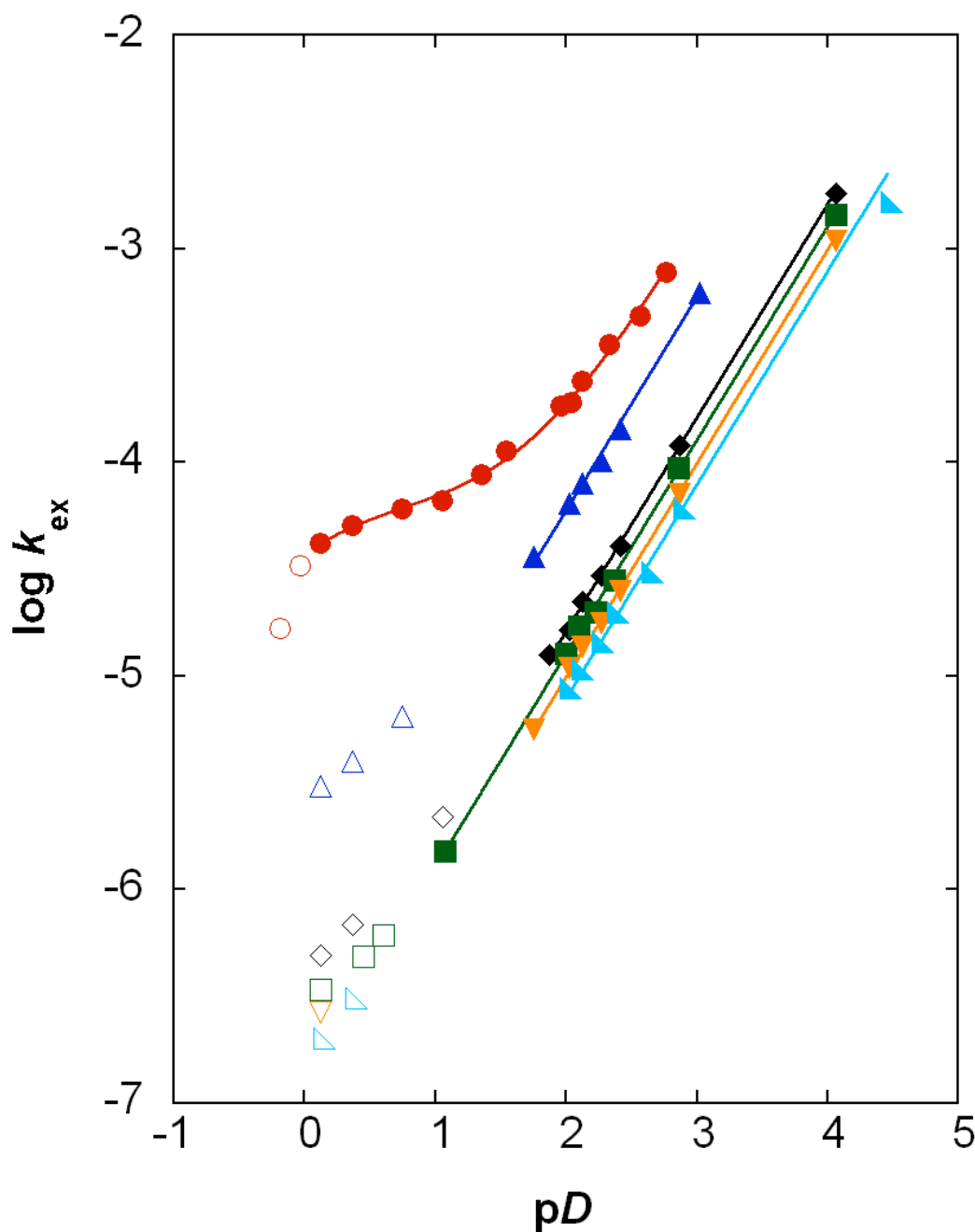
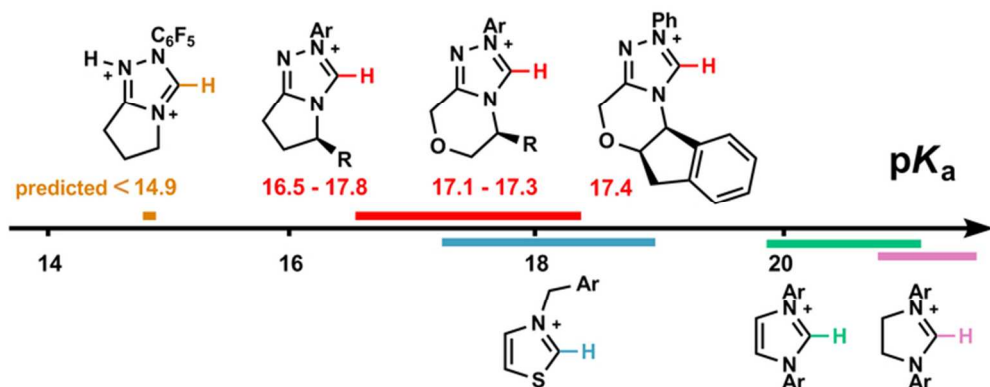


Figure 2. pD -rate profiles for the deuterium exchange reactions of the C(3)-proton of triazolium salts **8a-f**-BF₄⁻ in D₂O at 25 °C and $I = 1.0$ (KCl). Key: Values of k_{ex} for **8a** (●); **8b** (▲); **8c** (◆); **8d** (■); **8e** (▼); **8f** (▲). The solid lines show the fits of the data (filled symbols) to eq 6 (**8a**) and eq 3 (**8b-f**). As described in the text, data points indicated by open symbols for **8a-f**-BF₄⁻ were not included in the fits.



33x13mm (600 x 600 DPI)