



# Article Triazolium Salt Organocatalysis: Mechanistic Evaluation of Unusual Ortho-Substituent Effects on Deprotonation

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**Abstract:** Organocatalysis by N-heterocyclic carbenes is normally initiated by the deprotonation of precursor azolium ions to form active nucleophilic species. Substituent effects on deprotonation have an impact on catalytic efficiency and provide insight into general catalytic mechanisms by commonly used azolium systems. Using an NMR kinetic method for the analysis of C(3)-H/D exchange, we determined log  $k_{ex}$ -pD profiles for three *ortho*-substituted *N*-aryl triazolium salts, which enables a detailed analysis of *ortho*-substituent effects on deprotonation. This includes *N*-5-methoxypyrid-2-yl triazolium salt 7 and di-*ortho*-methoxy and di-*ortho-iso*propoxyphenyl triazolium salts 8 and 9, and we acquired additional kinetic data to supplement our previously published analysis of *N*-pyrid-2-yl triazolium salt 6. For 2-pyridyl triazoliums 6 and 7, novel acid catalysis of C(3)-H/D exchange is observed under acidic conditions. These kinetic data were supplemented by DFT analyses of the conformational preferences of 6 upon *N*-protonation. A C(3) deprotonation mechanism involving intramolecular general base deprotonation by the pyridyl nitrogen of the N(1)-deuterated dicationic triazolium salt is most consistent with the data. We also report  $k_{DO}$  values (protofugalities) for deuteroxide-catalyzed exchange for 6–9. The protofugalities for 8 and 9 are the lowest values to date in the *N*-aryl triazolium series.

Keywords: triazolium organocatalysis; H/D exchange; proton transfer; ortho-substituent effects

# 1. Introduction

The organocatalytic properties of N-heterocyclic carbenes (NHCs) are well documented for a broad range of synthetic transformations, including benzoin- and acylointype reactions [1-8], transesterifications [9-19], and annulations [20-28], among many others [29-32]. For the majority of these synthetic procedures, NHCs are typically generated in situ by the deprotonation of a conjugate acid heterocyclic azolium salt. In particular, triazolium salts 1 are widely employed as precatalysts: C(3) deprotonation of 1 generates the NHC, triazolylidene 2, which also has an ylidic/carbanion resonance form 2' (Figure 1) [33]. First described in 1995 by Enders and Teles [34–36], the triazolyl scaffold has been proven to be broadly efficient in a range of NHC-catalyzed transformations [33,37–43]. In particular, the bicyclic pyrrolidine-based triazolyl scaffold 3 reported by Knight and Leeper [44] and related triazolium systems with morpholine- and aminoindane-based structures deliver increased yields and selectivities [45–49]. In addition to the fused ring, the choice of an appropriate N-aryl triazolium substituent is also key to reaction efficiency and product selectivity for a given transformation [50-58]. For example, the N-pentafluorophenyl catalyst 4 designed by Connon and Zeitler still holds the record, to our knowledge, of being the most efficient and stereoselective catalyst for the asymmetric benzoin reaction [47].

As the initial proton transfer step for the formation of triazolylidene **2** is common to a broad range of transformations, we reported both rate constants for deprotonation (kinetic acidities or protofugalities [59]) and carbon acid  $pK_a$  values for a large series of triazolium salts in aqueous solution, which included 36 *N*-aryl examples [60–64]. In addition, there is



Citation: Quinn, P.; Smith, M.S.; Zhu, J.; Hodgson, D.R.W.; O'Donoghue, A.C. Triazolium Salt Organocatalysis: Mechanistic Evaluation of Unusual *Ortho*-Substituent Effects on Deprotonation. *Catalysts* **2021**, *11*, 1055. https://doi.org/10.3390/ catal11091055

Academic Editor: Cristina Trujillo

Received: 7 August 2021 Accepted: 25 August 2021 Published: 30 August 2021

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**Copyright:** © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). an increasingly large body of literature data pertaining to the  $pK_a$  values of the conjugate acids of NHCs in a range of solvents [65–75]. These datasets enable a detailed evaluation of the *N*-aryl substituent effect, which provides useful insight into the catalytic options for these commonly used NHC scaffolds.



**Figure 1.** Triazolium salt precatalysts: C(3) deprotonation to generate NHC (*N*-heterocyclic carbene) and common scaffolds employed in organocatalysis.

As part of these studies, we reported unusual *ortho*-substituent effects on the proton transfer reactions of *N*-aryl triazolium salts [50,51,63]. For triazolium salts without *ortho*-substituents, H/D exchange of C(3)-H in D<sub>2</sub>O solution shows a simple first-order kinetic dependence on the concentration of deuteroxide, evident from a slope of +1 on a plot of log  $k_{ex}$  versus pD and consistent with a base-catalyzed mechanism for H/D exchange (Figure 2a). By contrast, for *ortho*-halo-substituted *N*-aryl triazolium salts (e.g., *N*-pentafluorophenyl triazolium 5 (Figure 2b)), significant changes in slope from log  $k_{ex}$ -pD proportionality were observed at low pDs consistent with H/D exchange via alternative mechanism(s). We previously proposed mechanistic options to explain the altered kinetic behaviors of *ortho*-halo-substituted *N*-aryl triazolium salts [61]. Although there are several potential options consistent with the data, the most likely mechanistic explanation is a pathway via N(1)-deuteration at lower pD values, which facilitates H/D exchange of the resulting N(1)-deuterated dicationic triazolium salt (Figure 2b). To account for the dominance of this altered behavior for *ortho*-halo-substituted triazolium salts 5, an increase in the extent of N(1) deuteration, and hence a more basic N(1), is required.



**Figure 2.** Mechanistic studies of the C(3) H/D exchange reactions of triazolium salts in D<sub>2</sub>O solution: (a) mechanism for DO<sup>-</sup>-catalyzed exchange consistent with a first-order kinetic dependence on deuteroxide ion, (b) potential mechanism for H/D exchange at low pDs accounting for altered dependence of log  $k_{ex}$  on pD for *ortho*-halo *N*-aryl triazolium salts (e.g., **5**), (c) *N*-pyrid-2-yl and *N*-5-methoxypyrid-2-yl triazolium salts **6** and **7** and di-*ortho*-methoxy and di-*ortho*-isopropoxyphenyl triazolium salts **8** and **9**.

Triazolium salt **6** with an *ortho*-nitrogen atom in the *N*-pyrid-2-yl aryl substituent (Figure 2c) uniquely demonstrated formal acid catalysis of H/D exchange at lower pD

values, evident from a slope of close to -1 on a plot of log  $k_{ex}$  versus p*D*, which was not observed for any other triazolium ion [63]. This provided evidence for the potential role of the *N*-pyrid-2-yl substituent as an intramolecular catalyst, although the precise form of catalysis has not been unequivocally established. Related studies involving mechanistic analysis of triazolium-catalyzed benzoin and Stetter-type reactions have highlighted that these *ortho*-substituent effects have also been observed in other steps in addition to the initial NHC-generating step. Rate and equilibrium constants for the formation of the first tetrahedral intermediate from the addition of NHC to aldehyde are substantially altered with *ortho*-heteroatom aryl substituents in both the *N*-aryl of catalyst and aldehyde, in comparison with analogues bearing *para-* or *ortho*-alkyl substitution [51].

To further probe the mechanistic origin of *N*-aryl *ortho*-substituent effects, and in particular to investigate the dominant form of catalysis for the *N*-pyrid-2-yl triazolium salt **6**, we herein report a detailed kinetic evaluation by <sup>1</sup>H NMR of the H/D exchange reactions of three additional triazolium salts, **7**, **8**, and **9**. By tuning the basicity of the pyridyl nitrogen through the introduction of an electron-donating methoxy substituent in **7**, it was postulated that any resulting changes in the log  $k_{ex}$ -pD profile would provide mechanistic insight into the role of the pyridyl substituent. In addition, the study of *ortho*-alkoxy-substituted triazolium salts in **8** and **9** would reveal whether the alternative proton transfer pathways observed for the *ortho*-halo analogues were unique or could extend to other *ortho*-heteroatoms. Our previous results suggest that *ortho*-alkyl substituents do not show any unusual behavior [61]. For *N*-mesityl triazolium salts with *ortho*-methyl substituents, there was no significant deviation from a slope of +1 except for slight upward deviation of one datapoint at the lowest pD value.

Our quantitative kinetic and structure–activity analyses provide useful insight into the mechanistic intricacies of triazolium catalysis. Although triazolium salts are a well-studied NHC organocatalyst class, there remain challenges in their usage in relation to both the stereo- and chemoselectivity of product formation, particularly in more polar media such as water. As one example of the benefits of heteroatom substitution in the NHC scaffold, recent intriguing results from Milo and coworkers demonstrated the importance of secondary sphere interactions in improving enantioselectivity in NHC organocatalysis of the benzoin reaction (as an archetypal NHC-catalyzed process) [76,77]. By invoking dynamic covalent interactions between boronic acid secondary sphere modifiers and the hydroxy substituent on the scaffold of chiral *N*-pentafluorophenyl triazolium salt **4**, enantioselectivities were significantly increased. Thus, we hypothesize that alternative heteroatom substitution in the NHC scaffold, such as the *ortho*-pyridyl nitrogen of **6** and **7**, could facilitate the greater adoption of this approach towards improving enantioselectivity in a broader range of transformations and different solvents.

## 2. Results and Discussion

#### 2.1. Kinetic Analysis of the C(3)-H/D Exchange Reactions of N-Pyridyl Triazolium Salts 6 and 7

*N*-pyrid-2-yl triazolium tetrafluoroborate **6** was prepared as described previously [63]. A synthesis of *N*-5-methoxy-pyrid-2-yl triazolium salt **7** was not reported previously, and we employed the route shown in Scheme 1. A Buchwald–Hartwig amination [78–80] using benzophenone hydrazone **10** and 2-chloro-4-methoxypyridine **11** was employed, which yielded *N*-aryl hydrazone **12**. Subsequent acid-catalyzed hydrolysis, initially to the hydrazinium chloride, followed by neutralization using sodium hydroxide, yielded the aryl hydrazine **13**. Onward conversion to triazolium tetrafluoroborate **7** employed the widely used method reported by Rovis [81]: reaction of aryl hydrazine **13** with 5-methoxy-3,4-dihydro-2*H*-pyrrol-1-ium tetrafluoroborate yielded amidrazone **14** with subsequent cyclization being elicited by triethylorthoformate to afford **7**. The X-ray crystal structures (CCDC 2100846–2100847) obtained in the course of this work of both triazolium tetrafluoroborate salts **6** and **7** are shown in Figure **3**.



Scheme 1. Synthesis of N-5-methoxy-pyrid-2-yl triazolium tetrafluoroborate 7.



**Figure 3.** ORTEP diagrams from X-ray crystal structures of *N*-pyrid-2-yl and *N*-5-methoxy-pyrid-2-yl triazolium tetrafluoroborate salts **6** and **7** (counterions not shown).

The N-5-methoxy-pyrid-2-yl triazolium salt 7 had not been studied previously; thus a log  $k_{ex}$ -pD profile was determined in the pD range 0–4. Exchange reactions were performed in both DCl and formate buffer solutions at 25 °C and ionic strength, I = 1.0 (KCl). For the *N*-pyrid-2-yl analogue **6**, we previously reported a log  $k_{ex}$ -p*D* profile [63]; however, additional data were acquired in the present study in the pD 3-4 region to assist with mechanistic evaluation and more robust kinetic fitting. For both 6 and 7, reactions were too fast above pD 4 for NMR analysis. The kinetic and NMR methods used for the analysis of the C(3)-H/D exchange reactions described herein were identical to those reported by us previously [60,61,63,64]. Over time, the disappearance of the singlet at  $\sim$ 10.3 ppm due to the C(3)-H is observed; however, there is no change in the integrals of all other signals, nor in the appearance of new signals. Figures S1–S2 in Supplementary Materials include representative <sup>1</sup>H NMR spectral overlays at three time points during C(3)-H/D exchange for **6** and **7**, respectively. The observed first-order rate constants for C(3)-H/D exchange at a given pD,  $k_{ex}$  (s<sup>-1</sup>), were obtained as slopes of semilogarithmic plots of the fraction of the remaining unexchanged substrate, f(s), against time according to Equation (1) (Figures S3–S5). Reaction progress was defined by values of f(s) calculated using Equation (2), where  $A_{C(3)-H}$  and  $A_{std}$  are the integrated areas of the singlet at ~10.3 ppm due to the C(3)-H of the substrate and the broad triplet at 3.3 ppm owing to the methyl hydrogens of the internal standard, tetramethylammonium deuteriosulfate. The resulting  $k_{\text{ex}}$  (s<sup>-1</sup>) values obtained at each pD are collected in Tables S1 and S2 for 6 and 7.

$$\ln f(\mathbf{s}) = -k_{\mathrm{ex}} t \tag{1}$$

$$f(s) = (A_{C(3)-H}/A_{std})_t / (A_{C(3)-H}/A_{std})_0$$
(2)

Figure 4a shows the corresponding log  $k_{ex}$ –pD profiles for 6 and 7. Pleasingly, the same overall kinetic behavior is observed for the H/D exchange reactions of the 5-methoxy-2-pyridyl triazolium salt 7, as previously observed for 6. Both profiles show distinct regions of close to –1 and +1 slopes consistent with first-order kinetic dependencies on D<sub>3</sub>O<sup>+</sup> and DO<sup>-</sup>, respectively. The formal dependence on D<sub>3</sub>O<sup>+</sup> is unique to these 2-pyridyl salts, whereas all triazolium salts to date have shown a kinetic dependence on DO<sup>-</sup>. Significantly, log  $k_{ex}$  values in the lower pD region are substantially higher for 7 than for 6, showing that the 5-methoxy substituent on the pyridyl ring has increased reactivity to H/D exchange. For comparison, the plots in Figure 4b include log  $k_{ex}$ –pD data for N-pentafluoroberate 5 and N-phenyl triazolium tetrafluoroborate 15 taken from our previously published studies [61].



**Figure 4.** (a) pD-rate profiles for the C(3)-H/D exchange reactions of *N*-pyrid-2-yl **6** ( $\bigcirc$ ; •, previously published data) and *N*-5-methoxy-pyrid-2-yl triazolium **7** ( $\square$ ) tetrafluoroborate salts in DCl or buffer solutions in D<sub>2</sub>O. The solid and dashed lines show the fits of reaction data to Equations (3) and (4), respectively. (b) Plotted for comparison are log  $k_{ex}$ -pD data taken from R. S. Massey et al. [61] for *N*-pentafluorophenyl triazolium tetrafluoroborate **5** ( $\triangle$ ; **4**, data not included in fitting) and *N*-phenyl triazolium tetrafluoroborate **15** ( $\bigtriangledown$ ; **v**, data not included in fitting).

The solid lines in Figure 4a show the fits of the reaction data to Equation (3) [82], which was used in our previous analysis of reaction data for 6. In this equation, the H/D exchange reaction of the substrate in the region of close to +1 slope is described by the rate constant,  $k_{\text{DO}}$  (M<sup>-1</sup>s<sup>-1</sup>), the second-order rate constant for deuteroxide-catalyzed exchange of the triazolium salts.  $K_{\text{w}} = 10^{-14.87}$  is the ion product of D<sub>2</sub>O at 25 °C, and  $\gamma_{\text{DO}} = 0.73$  is the activity coefficient for deuteroxide ion under our experimental conditions. The H/D exchange reaction of the substrate in the region of close to -1 slope is described by the rate constant,  $k_{\text{H}}$  (s<sup>-1</sup>) [83].

$$\log(k_{\rm ex}) = \log\left[\frac{k_{\rm H}(10^{-pD}) + K_{\rm a}^{\rm N}\left(\frac{k_{\rm DO}K_{\rm W}}{\gamma_{\rm DO}}\right)10^{pD}}{K_{\rm a}^{\rm N} + 10^{-pD}}\right]$$
(3)

This equation allows for speciation between the monocationic triazolium ion (6 or 7) and a conjugate acid dication obtained by protonation at either the triazolyl N(1) or 2-pyridyl N as pD is decreased, and defined by the acid dissociation constant,  $K_a^N$ . Excellent fits of the reaction data are observed for both 6 and 7 at the two ends of the plots, and values obtained from this fitting for both  $k_{DO}$  and  $k_H$  are shown in Table 1. There is more uncertainty associated with a potential value for  $K_a^N$ . The plots do not level to a plateau at the lowest pD values in a manner consistent with full protonation. Linear plots of only log  $k_{ex}$  values at the lowest pDs (Figure S6) yield slopes of -0.73 and -0.93 for 6 and 7, which are slightly below unity, suggesting the beginning of curvature. However, as this curvature is not substantial, there will be large errors associated with the determination of  $K_a^N$ . The fit to Equation (3) yields  $K_a^N = 0.86 (\pm 0.39)$  and 0.57 ( $\pm 0.29$ ) for 6 and 7, respectively. By fixing  $K_a^N$  at defined values of 1, 10, 100, and 1000 (i.e.,  $pK_a^N = 0, -1, -2, -3$ ), both visible inspection and the magnitude of R<sup>2</sup> indicate that the best fit is obtained for  $K_a^N = 1$  in both cases (See Figure S7).

Table 1. Kinetic parameters from fitting of H/D exchange kinetic data for 6–9 and comparison with previous data for 15–17.

Triazolium Salt	$k_{\rm DO}~({\rm M}^{-1}{\rm s}^{-1})$	$k_{ m H}$ (s $^{-1}$ )	$k_{ m in}~({ m s}^{-1})$	Fit	р <i>K</i> <sub>a</sub> [ <i>С</i> (3)-Н] <sup>3</sup>
$ \begin{array}{c}                                     $	$1.01 \ (\pm 0.05) \times 10^8$	$1.35(\pm 0.44)  imes 10^{-4}$	-	Equation (3) $(R^2 = 0.991)$	-
	$8.79~(\pm 0.30)  imes 10^7$	$4.36~(\pm 3.52)  imes 10^{-4}$	$1.97\times10^{-51}$	Equation (4) $(R^2 = 0.998)$	17.4
T N BF4 OMe	$9.57~(\pm 0.84)  imes 10^7$	$2.22 \ (\pm 0.93) \times 10^{-3}$	-	Equation (3) (R <sup>2</sup> = 0.976)	-
	$8.02~(\pm 0.22)  imes 10^7$	$2.30 (\pm 35.9) \times 10^{-1}$	$2.59\times10^{-31}$	Equation (4) $(R^2 = 0.999)$	17.5
	$3.87~(\pm 0.07)  imes 10^7$	-	-	Equation (5) <sup>2</sup> (R <sup>2</sup> = 0.999)	17.8
N <sup>/PrO</sup> N N <sup>+</sup> BF <sub>4</sub> <sup>/PrO</sup> 9	$2.87~(\pm 0.13)  imes 10^7$	-	-	Equation (5) $^{2}$ (R <sup>2</sup> = 0.999)	17.9
$ \begin{array}{c} \searrow = N \\ -N \\ N \\ 15 \end{array} \xrightarrow{BF_4} \\ BF_4 $	$6.82\times10^{74}$	-	-	Equation (5)	17.5 <sup>4</sup>
	$4.20 imes10^{74}$	-	-	Equation (5)	17.8 <sup>4</sup>
$ \begin{array}{c}                                     $	$5.29  imes 10^{74}$	-	-	Equation (5)	17.7 <sup>4</sup>

<sup>1</sup> The error in  $k_{in}$  is high owing, in part, to the limited number of datapoints in this region.<sup>2</sup> See Section 2.2. <sup>3</sup> Calculated as described in Section 2.3. <sup>4</sup> Determined by us previously (see R. S. Massey et al. [61]).

In the middle region of the *pD*-rate profile for the lowest log  $k_{ex}$  values, where the transition occurs between negative and positive slopes, there are several datapoints that deviate above the curve described by Equation (3). This is more significant for the 5-methoxy-2-pyridyl triazolium salt 7 and could potentially be explained by an additional *pD*-independent process. To allow for this third option, we included a *pD*-independent term, defined by the rate constant  $k_{in}$  (s<sup>-1</sup>) in Equation (4) (Figure 4a, dashed line) [82]. The overall fit for **6** is similar, but there is a significant improvement in the overall fit for **7** (R<sup>2</sup> = 0.999 versus 0.976); however, we must caution that the inclusion of an additional

variable will always lead to an improvement in overall kinetic fitting whether its inclusion is mechanistically justified or not. In addition, there is a large increase in the error for  $k_{\rm H}$  when using Equation (4).

$$\log(k_{\rm ex}) = \log\left[\frac{k_{\rm H}(10^{-pD}) + k_{\rm in} + K_{\rm a}^{\rm N}\left(\frac{k_{\rm DO}K_{\rm W}}{\gamma_{\rm DO}}\right)10^{pD}}{K_{\rm a}^{\rm N} + 10^{-pD}}\right]$$
(4)

The following sections will evaluate the potential mechanistic options that can be aligned with the different regions of the log  $k_{ex}$ -pD profiles.

2.1.1. Mechanistic Options for the Region of + 1 Slope in log  $k_{ex}$ -pD Profiles at Higher pD Values (First-Order Dependence on DO<sup>-</sup>)

The first-order dependence on deuteroxide ion in this region of the profile is consistent with a single mechanism for deuteroxide-catalyzed H/D exchange, as shown in Figure 5: C(3) deprotonation of the triazolium salts by deuteroxide results in the formation of a complex between the triazolyl NHCs and a molecule of HOD. Subsequent reorganization of NHC·HOD to NHC·DOL (L = H or D) to allow for the delivery of deuterium, followed by deuteration, leads to a C(3)-deuterated product. Owing to the large excess of bulk solvent over the substrate, the deuteration step is effectively irreversible; thus  $k_{ex}$  reflects a rate-limiting formation of solvent-equilibrated NHC from the triazolium salt and deuteroxide ion at a given pD. By definition, the second-order rate constant,  $k_{DO}$  (M<sup>-1</sup>s<sup>-1</sup>), is the observed  $k_{ex}$  value in 1 M—solution (pD ~ 14). Experimentally, C(3)-H/D exchange for all triazolium ions is orders of magnitude too fast to monitor directly by NMR in 1 M DO<sup>-</sup> (half-lives ~ nanoseconds); thus  $k_{DO}$  values are obtained by the assessment of a range of  $k_{ex}$  values at lower pDs, as described above. The reactivities to deprotonation by a common base,  $k_{DO}$ , allow for the evaluation of the protofugalities of the C(3) hydrogens in the series of triazolium ions.



Figure 5. Mechanism for H/D exchange consistent with first-order dependence on DO<sup>-</sup>.

In our previous studies,  $k_{\text{DO}}$  values for N-aryl triazolium ions spanned a range of ~30 fold across the large series [60–64]. Maximal  $k_{\text{DO}}$  values (~8 × 10<sup>8</sup> M<sup>-1</sup>s<sup>-1</sup>) were observed for N-pentafluorophenyl-substituted triazolium salts, whereas the lowest value to date of  $4.2 \times 10^7 \text{ M}^{-1} \text{s}^{-1}$  was observed for an *N*-4-methoxyphenyltriazolium salt **16**. Typically, values for  $k_{\rm DO}$  were observed to increase for electron-withdrawing N-aryl substituents. In the present study, values of  $k_{\text{DO}} = 8.79 \times 10^7 \,\text{M}^{-1}\text{s}^{-1}$  and  $8.02 \times 10^7 \,\text{M}^{-1}\text{s}^{-1}$  were obtained for 6 and 7 (Table 1), respectively, which fall midway in the range of previously observed values. The extra data obtained herein for 6 in pD regions 3–4 permit a more reliable determination of  $k_{\rm DO}$ . These  $k_{\rm DO}$  values for **6** and **7** are higher than for *N*-phenyl triazolium salt 15, indicating an overall electron-withdrawing effect of both pyridyl substituents. Electron-withdrawing N-aryl substituents will destabilize the cationic triazolium carbon acid relative to the formally neutral NHC conjugate base, thus favoring the deprotonation process. The  $k_{\rm DO}$  values obtained for 6 and 7 are closely similar, suggesting that the electronwithdrawing 2-pyridyl nitrogen dominates the N-aryl substituent effect for deuteroxidecatalyzed exchange. The value for 7 is  $\sim 10\%$  lower than for 6, as would be expected with the additional presence of a donating 5-methoxy substituent. There is no evidence of intramolecular catalysis involving the pyridyl substituent in this region as the  $k_{\rm DO}$  values fall within the normal range observed to date and can be explained by the normal electronwithdrawing substituent effect of the 2-pyridyl group. A substantially higher  $k_{DO}$  value

would have been expected if intramolecular catalysis were operational. Presumably, the intrinsic reactivity to intermolecular deprotonation by  $DO^-$  is so high in this pD region that there is no competition from an intramolecular reaction.

2.1.2. Mechanistic Options for the Region of -1 Slope in log  $k_{ex}$ -pD Profile (First-Order Dependence on  $D_3O^+$ )

Formal  $D_3O^+$  catalysis, as observed in this region of the profile, is unique to **6** and **7** and has not been observed to date in proton transfer studies for any other *N*-aryl triazolium salt. For all other triazolium salts, including *N*-pentafluorophenyl triazolium **5**, rate constants for H/D exchange continue to decrease as pD is decreased (e.g., as shown in Figure 4b for **5** and **15**). To account for the increase in  $k_{ex}$  for **6** and **7** at lower pDs, it is necessary to invoke a mechanism that is not possible, or would be substantially slower, for other triazolium ions. Importantly,  $k_{ex}$  rate constants for **7** are at least 15-fold higher than for **6** in this region, and any mechanism should allow for this difference in reactivity.

As both **6** and **7** contain two nitrogen atoms with lone electron pairs, the most logical mechanisms for acid catalysis will involve deuteration at one of these atoms. *N*-deuteration of the triazolium salt will eventually occur as the p*D* decreases, although the precise  $K_a$  is unknown. Possibilities include N(1)-deuteration of the triazolium ring (Option **a** or **d**, Figure 6), deuteration of the 2-pyridyl nitrogen (Option **b**, Figure 6), and shared deuteration between both nitrogens (Option **c**, Figure 6). Mechanisms involving pre-equilibrium *N*-deuteration to any of these three dicationic species, followed by *C*(3) deprotonation by solvent, as shown in Options **a**–**d**, which are kinetically equivalent, would result in formal acid catalysis. Option **d** additionally involves the participation of the 2-pyridyl nitrogen as an intramolecular general base catalyst in the activation of water.



**Figure 6.** Mechanistic options for deprotonation consistent with a formal first-order dependence on  $D_3O^+$ : (a) N(1)-deuteration of triazolium with subsequent C(3)-deprotonation by solvent  $D_2O$ ; (b) N-pyridyl deuteration of triazolium followed by C(3)-deprotonation by solvent  $D_2O$ ; (c) Shared intramolecular deuteration of both N(1) and the 2-pyridyl nitrogen with subsequent C(3)-deprotonation by solvent  $D_2O$ ; (d) N(1)-deuteration of triazolium with subsequent C(3)-deprotonation by solvent  $D_2O$ ; (d) N(1)-deuteration of triazolium with subsequent C(3)-deprotonation by solvent  $D_2O$ ; (d) N(1)-deuteration of triazolium with subsequent C(3)-deprotonation by solvent  $D_2O$  and general base catalysis by 2-pyridyl substituent.

Option **a** can be excluded, as there is no reason why a nonparticipating remote 2pyridyl substituent should result in orders of magnitude increases in rate constants in this region compared with other *N*-aryl substituents. In the DO<sup>-</sup> region of +1 slope, the  $k_{DO}$ values obtained for **6** and **7** fall midway in the range of previously observed rate constants and are not unusually high. It is thus difficult to justify why a remote nonparticipating pyridyl could substantially increase a D<sub>2</sub>O reaction but not a DO<sup>-</sup> reaction.

Option **b** is potentially more chemically reasonable as the range of triazolium salts studied previously did not contain a more basic heteroatom in an *ortho*-position. This option, which involves electrophilic catalysis by an *N*-protonated pyridyl substituent, would be unique to the 2-pyridyl salts **6** and **7**. However, the question then arises as to how protonation on the 2-pyridyl nitrogen could result in an increase in  $k_{ex}$ , whereas with

N(1)-deuteration on the central triazolium ring, as proposed for *ortho*-halo salts (e.g., **5**, Figures 2b and 4b), rate constants continue to decrease with p*D*. A significantly higher  $pK_a^N$  for acid dissociation of the *N*-protonated pyridyl than triazolyl nitrogen could explain this difference in trends. A higher degree of pyridyl *N*-deuteration owing to a higher  $pK_a^N$ , and hence a higher formal cationic charge at this position, would enhance electron deficiency and facilitate the deprotonation at *C*(3) by solvent. As discussed earlier, however, there is no evidence from the *pD* profile that  $pK_a^N$  is significantly greater than zero for **6** or even the more basic 5-methoxypyridyl-substituted **7**. Similar  $pK_a^N$  values ~-0.3 were estimated for *ortho*-halo-substituted salts from reaction data, albeit with relatively large errors in  $K_a^N$ . In a similar manner, Option **c** with a shared intramolecular deuteration would also require an elevated  $pK_a^N$  compared with other triazolium salts in order to account for the substantial increase in rate constants in the –1 region.

Option **d** is not reliant on an elevated  $pK_a^N$  and utilizes the pyridyl nitrogen as an intramolecular general base catalyst (i.e., protonation on the pyridyl nitrogen is not required). In particular, our present results for 7 also add support to this mechanism as intramolecular deprotonation by a more basic 4-methoxyl pyridyl nitrogen would be expected to be close to two orders of magnitude faster than for **6** (note:  $pK_a$  (H<sub>2</sub>O) = 5.17 and 6.62 for pyridinium and 4-methoxypyridinium salts, respectively).

We computationally studied the conformational profiles of both the monocationic and dicationic *N*-2-pyridyl triazolium ion as a function of the change in dihedral angle between the *N*-aryl substituent and central triazolium ring using the B3LYP/6-311++g (d,p) [84–86] level of theory (Supplementary Materials, Section S10). The preferred lowest energy conformation for the monocationic triazolium ion in water (Figure 7, black) has a coplanar *N*-aryl substituent with the pyridyl nitrogen pointing towards the *C*(3)-H, as observed in the experimental X-ray crystal structure for both **6** and **7** (Figure 3).



**Figure 7.** Conformational profiles of monocationic *N*-pyrid-2-yl **6** (—) and the two dicationic forms afforded from *N*-protonation of the triazolyl N(1) (—) or the pyridyl nitrogen (—) obtained by DFT calculations using a B3LYP (6–311G++(d,p) basis set [84–86], PCM water [87]). The inset ball and stick diagrams show the structures corresponding to the lowest energy conformations of *N*-pyrid-2-yl triazolium monocation **6** (—) and the two dicationic forms (—) or (—).

Interestingly, upon *N*-protonation at either N(1) of the triazole or the 2-pyridyl nitrogen to give a dicationic species, the preference for coplanarity remains, however, with a 180° rotation of the pyridyl nitrogen such that it points towards N(1) (Figure 7, red and blue, respectively). Thus, there is a clear difference in the preferred orientation of the pyridyl nitrogen between the monocationic and dicationic triazolium species. The same conformational preferences were observed in both water and methanol as solvents (see Figure S15 for methanol calculations), and also using the M062X/6-311g++ (d,p) [85,86,88] level of theory for the dication calculations in water (Figure S16). In principle, this lends support to mechanistic Option **c** (Figure 7), which requires this preferred lowest energy conformation for the dication, but not to Option **d**. However, the energy barrier for rotation around the N(2)- $C^{ipso}$ (Ar) bond in all three cases (Figure 7) is only 4.0–4.1 kcal mol<sup>-1</sup> at 25 °C, which would permit interconversion between conformers on a subsecond timescale. Thus, all conformations are rapidly accessible on the kinetic timescale of H/D exchange.

2.1.3. Mechanistic Options for the (Potential) Region of Zero Slope in log  $k_{ex}$ -pD Profile (pD-Independent Region)

In the case of 5-methoxy-2-pyridyl triazolium salt 7, there is some evidence for an additional pD-independent process at intermediate pD values. The observed  $k_{ex}$  values at pD 1.7–2.5 are significantly increased above the intersection point of the regions of negative and positive slopes. In the case of **6**, some slight upward deviation of a couple of datapoints is observed, but the changes are smaller. Figure 8 shows a mechanism that could be aligned with this region of the profile: deprotonation at *C*(3) of the monocationic triazolium salt by solvent D<sub>2</sub>O with potential intramolecular assistance from the pyridyl nitrogen. This mechanism also unifies with the mechanism that seems most consistent with the –1 region (i.e., intramolecular deprotonation at *C*(3) by solvent (*c.f.* Figure 8) is facilitated by N(1)-protonation, explaining the large increase in rate constants at lower pDs (*c.f.* Figure 6d)).



Figure 8. Mechanistic option for deprotonation consistent with pD-independent H/D exchange.

2.2. Kinetic Analysis of the C(3)-H/D Exchange Reactions of N-di-Ortho-Alkoxy Triazolium Salts 8 and 9

For the syntheses of *N*-di-*ortho*-methoxy- and *N*-di-*ortho*-isopropoxyphenyl triazolium tetrafluoroborate salts **8** and **9**, we utilized modifications of a previously reported procedure for the preparation of the analogous chloride salt of **8** (Supplementary Materials, Section S9). The C(3)-H/D exchange reactions of **8** and **9** had not been studied previously, and log  $k_{ex}$ -pD profiles were determined in the pD range 0–3. Figures S8 and S9 (Supplementary Materials, Section S7) include representative <sup>1</sup>H NMR spectral overlays at three time points during C(3)-H/D exchange for **8** and **9**, respectively. As for **6** and **7**, no parallel reactions were observed during the timescale for complete deuterium exchange. The observed first-order rate constants for C(3)-H/D exchange at a given pD,  $k_{ex}$  (s<sup>-1</sup>), were obtained as slopes of semilogarithmic plots of the fraction of the remaining unexchanged substrate, *f*(s), against time according to Equation (1) (Figures S10 and S12). As for all previous studies of H/D-deuterium exchange reactions of the conjugate acids of NHCs, buffer catalysis was not significant (Figures S11 and S13, Tables S5 and S6). The resulting  $k_{ex}$  (s<sup>-1</sup>) values obtained at each pD are collected in Tables S3 and S4 for **8** and **9**.

Figure 9 shows the corresponding log  $k_{ex}$ –pD profiles for 8 and 9. For comparison, Figure 9 also includes log  $k_{ex}$ –pD data for *N*-phenyl triazolium tetrafluoroborate 15 taken from our previously published studies [61]. In both cases, the profile is mostly described by a region of +1 slope consistent with the mechanism in Figure 6. There is evidence of some slight upward deviation from the line of +1 slope for a few datapoints at the lowest pD values. Equation (5) is a simplified form of Equations (3) and (4) [82], which only allows for a first-order dependence on DO<sup>-</sup>. To determine a  $k_{DO}$  value, only datapoints that fit a line of unit slope were included (open symbols), and those showing slight upward deviation (filled symbols) were excluded from the kinetic fitting to Equation (5). The slight upward deviation is not significant enough to justify application of Equations (3) or (4) for kinetic fitting.

$$\log(k_{\rm ex}) = \log\left[\left(\frac{k_{\rm DO}K_{\rm W}}{\gamma_{\rm DO}}\right)10^{\rm pD}\right]$$
(5)



**Figure 9.** pD-rate profiles for the *C*(3)-H/D exchange reactions of *N*-di-*ortho*-methoxyphenyl **8** ( $\diamond$ ;  $\blacklozenge$ , data not included in fitting) and *N*-di-*ortho*-isopropoxyphenyl **9** ( $\triangleleft$ ;  $\triangleleft$ , data not included in fitting) tetrafluoroborate salts. The solid lines show the fit of reaction data to Equation (5). Plotted for comparison are log *k*<sub>ex</sub>-pD data taken from R. S. Massey et al. for *N*-phenyl triazolium tetrafluoroborate **15** ( $\bigtriangledown$ ;  $\blacktriangledown$ , data not included in fitting) [61].

The  $k_{\text{DO}}$  values for **8** and **9** (Table 1) are lower than for both *N*-phenyl **15** and *N*-mesityl **17** triazolium salts and also than the lowest  $k_{\text{DO}}$  to date for the *N*-4-methoxyphenyltriazolium salt **16**. Clearly, di-*ortho*-alkoxy substitution is very different from *ortho*-halo substitution in not facilitating alternative pathways for H/D exchange as pD is decreased. Furthermore, opposite effects on deuteroxide-catalyzed exchange are observed at higher pDs. Halo substituents result in increases in protofugality, whereas *ortho*-alkoxy substituents substantially decrease  $k_{\text{DO}}$ , consistent with a net electron-donating substituent effect for the latter-reducing *C*(3) carbon acidity.

## 2.3. Estimation of Carbon Acid C(3)-H pKa Values

In the determination of aqueous  $pK_a$  values of weak carbon acids, the main problem is the levelling effect and the quantitative deprotonation of water. Owing to the greater basicities of most NHCs relative to hydroxide ion, quantitative deprotonation of water occurs, which prevents the determination of  $pK_a$  values by direct quantification of the relative concentrations of acid and conjugate base species at equilibrium. We previously employed an alternative kinetic approach by using the rate constants for the forward and reverse directions of the proton transfer equilibrium in the calculation of  $pK_a$  using Equation (6) derived for Scheme 2 [60,61,63–65]. In this equation,  $k_{HO}$  (M<sup>-1</sup>s<sup>-1</sup>) is the second-order rate constant for deprotonation at *C*(3) by hydroxide ion, which may be calculated from the corresponding  $k_{DO}$  value using a value of  $k_{DO}/k_{HO} = 2.4$  for the secondary solvent isotope effect on the basicity of HO<sup>-</sup> in H<sub>2</sub>O versus DO<sup>-</sup> in D<sub>2</sub>O. As discussed previously [61], the absence of significant general base catalysis of deuterium exchange provides good evidence that the reverse protonation of the triazol-3-ylidene NHC by water is equal or close to the limiting rate constant for the physical process of solvent reorganization ( $k_{\text{HOH}} \le k_{\text{reorg}} = 10^{11} \text{ s}^{-1}$ ). The main error in  $pK_a$  determination using this method is associated with the value assumed for  $k_{\text{HOH}}$ ; hence these  $pK_a$  values provide upper limit estimations. Using this same approach, C(3)-H  $pK_a$  values were calculated for triazolium tetrafluoroborate salts **6–9**, which range from 17.4 to 17.9 (Table 1). Given that values of  $k_{\text{DO}}$  for **6–9** only vary by threefold ( $2.87 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ – $8.79 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ ), and the logarithmic relationship of  $k_{\text{HO}}$  and  $pK_a$  in Equation (6), the resulting C(3)-H  $pK_a$  values vary by less than 1 unit. Consistent with our previous work, *N*-aryl substituent effects on  $pK_a$  are relatively small. As commented previously [61], the main factor influencing the  $pK_a$ s of the conjugate acids of NHCs is the nature of the ring heteroatoms in the central heterocycle, while the effects of N-aryl substituent are substantially smaller.

$$pK_{a} = pK_{w} + \log \frac{k_{\text{HOH}}}{k_{\text{HO}}}$$
(6)

$$HO^{-} + \bigvee_{H}^{N^{+}} Ar \xrightarrow{k_{HO}} H_{2}O + \bigvee_{N}^{N^{+}} Ar$$

**Scheme 2.** Determination of C(3)-H p $K_a$  using a kinetic approach.

#### 3. Conclusions

The *C*(3) deprotonation of 1,2,4-triazolium salts is the first key step in all organocatalysis processes involving NHC catalysis by triazolylidenes. Structure–reactivity studies of substituent effects on this proton transfer step can provide valuable insight into the modes of catalysis possible for a given *N*-aryl substituent. In order to mechanistically interrogate *ortho*-substituent effects on proton transfer, we reported detailed hydrogen–deuterium kinetic studies of *N*-5-methoxypyrid-2-yl triazolium salt 7 and di-*ortho*-methoxy and di*ortho-iso*propoxyphenyl triazolium salts 8 and 9. In each case, we evaluated the effect of a change in reaction pD on the rate constant for exchange,  $k_{ex}$ , and performed a detailed kinetic evaluation of the log  $k_{ex}$ –pD profiles.

In common with all triazolyl NHCs studied to date, the profiles for **7–9** all included a region of +1 slope consistent with a first-order dependence on deuteroxide ion. The second-order rate constants for deuteroxide-catalyzed exchange,  $k_{DO}$  (also known as the protofugality), could be measured as  $8.02 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ ,  $3.87 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ , and  $2.87 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$  for **7–9**, respectively. Relative to *N*-phenyl triazolium tetrafluoroborate **15**, the 5-methoxy-2-pyridyl substituent of **7** increases  $k_{DO}$ , whereas the di-*ortho*-alkoxy substituents of **8** and **9** decrease  $k_{DO}$  consistent with electron-withdrawing and electron-donating substituent effects on protofugality, respectively. Using the values for  $k_{DO}$ , we also estimated upper limits on  $pK_a$  values for deprotonation at C(3).

The log  $k_{ex}$ –pD profile for the N-5-methoxypyrid-2-yl triazolium salt 7 also demonstrated an extensive region of close to –1 slope, which had only been observed previously for N-pyrid-2-yl analogue **6**, but not for any other triazolium salt. Significantly, the effect of a 5-methoxy substituent in the pyridyl ring of 7 is to increase rate constants in this region by at least 15-fold compared with **6**. As there is no evidence for significant protonation of the pyridyl substituent above pD 0 for either **6** or **7**, we propose that a H/D exchange mechanism involving intramolecular general base deprotonation at C(3) by the pyridyl nitrogen of the N(1)-deuterated dicationic triazolium salt is more consistent with the data than one involving electrophilic catalysis with protonation on the pyridyl nitrogen.

**Supplementary Materials:** The following are available online at https://www.mdpi.com/article/10 .3390/catal11091055/s1: Figure S1—Representative <sup>1</sup>H NMR spectra between 11.2 and 6.8 ppm at 500 MHz of 6 (10 mM, pD 3.07) during exchange of C(3)-H (s, 8.33 ppm) for deuterium in D<sub>2</sub>O at 25 °C and I = 1.0 (KCl). [internal standard, tetramethylammonium deuteriosulphate (s, 3.17 ppm)].

Figure S2—Representative <sup>1</sup>H NMR spectra between 11.2 and 6.8 ppm at 500 MHz of 7 (10 mM, pD 1.08) during exchange of C(3)-H (s, 10.39 ppm) for deuterium in DCl solution in  $D_2O$  at 25 °C and I = 1.0 (KCl). [internal standard, tetramethylammonium deuteriosulphate (s, 3.17 ppm)]. Figure S3—Semilogarithmic plots of the fraction of unexchanged substrate against time for the C(3)-H/D exchange reaction of 6 in solutions of DCl in D<sub>2</sub>O at 25 °C and I = 1.0 (KCl). The majority of the data for 6 (for lower pD values) has been previously reported. Figure S4—Semilogarithmic plots between pD = 0.42 and pD = 1.73 of the fraction of unexchanged substrate against time for the C(3)-H/D exchange reaction of 7 in solutions of DCl in  $D_2O$  at 25 °C and I = 1.0 (KCl). Figure S5—Semilogarithmic plots between pD = 2.03 and pD = 3.66 of the fraction of unexchanged substrate against time for the C(3)-H/D exchange reaction of 7 in solutions of DCl in D<sub>2</sub>O at 25  $^{\circ}$ C and I = 1.0 (KCl). Table S1—First order rate constants for exchange of the C3-H of triazolium salt 6 for deuterium, in solutions of DCl in  $D_2O$  at 25 °C and I = 1.0 (KCl). Data for pD values of 3.07—3.66 were obtained as part of this work. Table S2—First order rate constants for exchange of the C(3)-H of triazolium salt 7 for deuterium in solutions of DCl in D<sub>2</sub>O at 25 °C and I = 1.0 (KCl). Figure S6—Linear plot of log  $k_{\text{ex}}$  against pD for the H/D exchange of triazolium salt 6 (•) and 7 (•) at pD values  $\leq 1.1, 25 \,^{\circ}\text{C}$  and I = 1.0 (KCl). Figure S7—Plot of log  $k_{ex}$  versus pD for the C(3)-H/D exchange of 6 (•) and 7 (•) using eqn. 3 (main text), with  $K_a^N$  fixed to different values. Figure S8—Representative <sup>1</sup>H NMR at 400 MHz of 8 (10 mM, pD 1.08) during exchange of C(3)-H (s, 9.76 ppm) for deuterium in DCl solution in D<sub>2</sub>O at 25 °C and I = 1.0 (KCl). [internal standard, tetramethylammonium deuteriosulphate (s, 3.17 ppm)]. Figure S9—Representative <sup>1</sup>H NMR at 400 MHz of **9** (10 mM, pD 1.08) during exchange of C(3)-H (s, 9.82 ppm) for deuterium in DCl solution in  $D_2O$  at 25 °C and I = 1.0 (KCl). [internal standard, tetramethylammonium deuteriosulphate (s, 3.17 ppm)]. Figure S10—Semilogarithmic plot of the fraction of unexchanged substrate against time for the deuterium exchange reaction of 8 in solutions of DCl in D<sub>2</sub>O at 25 °C and I = 1.0 (KCl). Figure S11—Semilogarithmic plot of the fraction of unexchanged substrate against time for the deuterium exchange reaction of 8 in solutions of varying formate buffer concentration in D<sub>2</sub>O at 25 °C and I = 1.0 (KCl). Figure S12—Semilogarithmic plots of the fraction of unexchanged substrate against time for the deuterium exchange reaction of 9 in solutions of DCl in  $D_2O$  at 25 °C and I = 1.0 (KCl). Figure S13—Semilogarithmic plots of the fraction of unexchanged substrate against time for the deuterium exchange reaction of 9 in solutions of varying formate buffer concentration in  $D_2O$  at 25 °C and I = 1.0 (KCl). Table S3—First order rate constants for exchange of the C(3)-H of triazolium salt 8 for deuterium in solutions of DCl in  $D_2O$  at 25 °C and I = 1.0 (KCl). Table S4—First order rate constants for exchange of the C(3)-H of triazolium salt 9 for deuterium in solutions of DCl in  $D_2O$  at 25 °C and I = 1.0 (KCl). Table S5—First order rate constants for exchange of the C(3)-H of triazolium salt 8 for deuterium, with varying formate buffer concentration, in solutions of DCl in D<sub>2</sub>O at 25 °C and I = 1.0 (KCl). Table S6—First order rate constants for exchange of the C(3)-H of triazolium salt 9 for deuterium, with varying formate buffer concentration, in solutions of DCl in D<sub>2</sub>O at 25 °C and I = 1.0 (KCl). Figure S14 – Structures of pyrid-2-yl triazolium salts for which DFT calculations were undertaken of energies as a function of dihedral angle of the monocation, dication from N1 protonation (N1 dication) and dication from protonation of the pyrid-2-yl nitrogen (pyridyl dication). Figure S15-Conformational profiles of monocationic N-5-methoxypyrid-2-yl 7 (----) and the two dicationic forms afforded from *N*-protonation of the triazolyl N(1) (—) or the pyridyl nitrogen (—) obtained by DFT calculations using B3LYP (6-311G++(d,p) basis set, PCM methanol). Figure S16—The effect of dihedral angle between N-aryl and triazolium ring on the calculated energy of the dication of 6 resulting from pyrid-2-yl nitrogen protonation obtained using B3LYP/6-311g++ (d,p) or M062X/6-311g++ (d,p) with PCM (water). Points are calculated energies with the solid curve an interpolation between the data points.

Author Contributions: Conceptualization, A.C.O. and P.Q.; methodology, A.C.O. and P.Q.; kinetic experiments, P.Q.; synthesis, P.Q.; computational modelling, M.S.S., J.Z., and P.Q.; writing—original draft preparation, A.C.O. and M.S.S.; writing—review and editing, D.R.W.H.; supervision, A.C.O. and D.R.W.H. All authors have read and agreed to the published version of the manuscript.

**Funding:** We thank the EPSRC (PQ, EP/M506321/1; MSS, EP/S022791/1; JZ, EP/S020713/1) for funding.

**Data Availability Statement:** All kinetic data are contained within the article or Supplementary Materials.

**Acknowledgments:** We are grateful to the Durham Chemistry NMR service for their ongoing help and support. We also thank Dmitry S. Yufit of the Durham Chemistry Crystallography Service for X-ray crystallography for **6** and **7**.

Conflicts of Interest: The authors declare no conflict of interest.

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- 82. As  $pD = -\log a_{D^+}$  therefore  $10^{-pD} = a_{D^+} = \gamma^{D_+}[D^+]$ .

- 83. In our previous publication in relation to **6**, we used a rate constant k' (s<sup>-1</sup>) rather than  $k_{\rm H}$  (s<sup>-1</sup>) to describe the H/D-exchange reaction of substrate in the region of close to -1 slope. Owing to the consideration of an additional pD-independent region in the present manuscript, and the need for a third rate constant to describe this region, we have changed k' (s<sup>-1</sup>) to  $k_{\rm H}$  (s<sup>-1</sup>) for the -1 region. The latter more clearly denotes a region involving formal acid catalysis.
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