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pK_as of the conjugate acids of *N*-heterocyclic carbenes in water†

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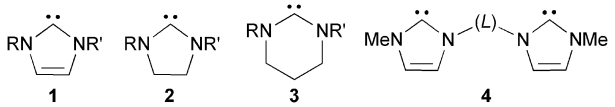
pK_a values of 19.8–28.2 are reported for the conjugate acids of a large series of NHCs in water. The effects of ring size, *N*-substituent and C(4)–C(5) saturation on pK_a are discussed.

There have been many recent reports of the characterisation and application of *N*-heterocyclic carbenes (NHCs) including imidazolyl **1**, imidazolinyl **2**, tetrahydropyrimidinyl **3** and bis-imidazolyl **4** systems.[1]



1 **2** **3** **4**

NHCs have been successfully applied as ligands in organometallic catalysis,[2] and as organocatalysts for many transformations.[3] Key to understanding the action of NHCs in catalysis is a knowledge of their acid–base properties. While there have been reports of pK_as for the conjugate acids of imidazolyl carbenes **1**,[4] there has been no systematic experimental determination of pK_as for a large series of NHCs in water. Herein we report the pK_as for the conjugate acid azolium ions of nineteen NHCs in aqueous solution. These include imidazolium ions **1H$^+$**, 4,5-dihydroimidazolium ions **2H$^+$**, tetrahydropyrimidinium ions **3H$^+$** and bis-imidazolium ions **4H$^+$**.

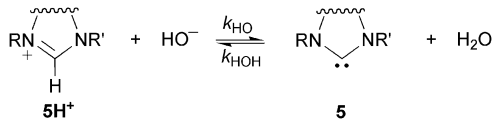
pK_a values for the ionisation of **1H$^+$–4H$^+$** to give NHCs were obtained by a kinetic method developed by Amyes *et al.*[4c,5] The second order rate constant for hydroxide catalysed deprotonation at C(2) of general azolium ion **5H$^+$** k_{HO} (M^{-1} s^{-1}) and the first order rate constant for the reverse protonation of the NHC **5** by water k_{HOH} (s^{-1}) are combined in eqn (1), derived for Scheme 1, with the equilibrium constant for the ion product of water $K_w = 10^{-14}$ to yield the pK_a of **5H$^+$**.

$$pK_a = pK_w + \log\left(\frac{k_{HOH}}{k_{HO}}\right) \quad (1)$$

Values for k_{HO} were determined by a deuterium-exchange method. The exchange of the C(2)–H of azolium ions **5H$^+$** for deuterium in buffered D_2O solutions was monitored by ^{1}H NMR spectroscopy (Scheme 2). Exchange involves the rate-limiting deprotonation of azolium ions **5H$^+$** by deuteroxide to give NHC **5** fully equilibrated with bulk solvent D_2O.

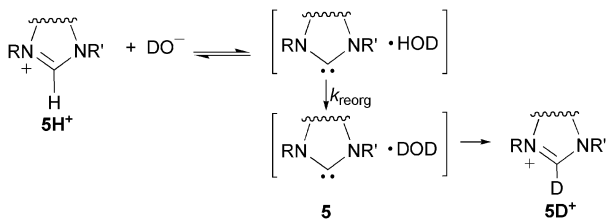
Deuterium exchange resulted in a decrease of the singlet due to the C(2)–H of **5H$^+$** relative to peak(s) due to internal standard. For azolium salts **1H$^+$**, **2H$^+$** and **4H$^+$–X$^-$**, there was no detectable parallel reaction during the time course of deuterium exchange. For tetrahydropyrimidinium salts **3H$^+$–PF$_6^-$**, deuterium exchange was accompanied by a ring-opening hydrolysis reaction. Values for the second order rate constants for deuteroxide-catalyzed exchange, k_{DO}, were obtained as the slopes of linear plots of first order rate constants for exchange as functions of deuteroxide concentration in a given buffer (see ESI†) and are listed in Table 1. By application of the relevant isotope effect correction, as discussed below, k_{HO} values were then obtained from experimental k_{DO} values.[6,7]

Formation of solvent-equilibrated NHC **5** involves two distinct steps. Proton transfer from **5H$^+$** to DO^- initially gives NHC **5** in close contact with a molecule of solvent HOD (Scheme 2). This complex can either return to the original reactant state by proton transfer back to the NHC, or solvent reorganization can occur which replaces the HOD molecule by one of bulk solvent DOD. The rate constant for the latter event corresponds to that for dielectric relaxation of solvent ($k_{reorg} = 1 \times 10^{11}$ s^{-1}).[8] Solvent reorganization is essentially irreversible, and only leads to the formation of exchange product **5D$^+$**, as the molecule of HOD is hugely diluted by bulk solvent. The absence of general base catalysis of exchange at a fixed deuteroxide concentration provides evidence that solvent reorganization is rate-limiting for the formation of D_2O-equilibrated NHC **5**.[4c,5] This would imply



5H$^+$ **5**

Scheme 1 Ionization of azolium ions **5H$^+$** at C(2) to yield NHCs **5**.



5H$^+$ **5** **5D$^+$**

Scheme 2 Deuteroxide ion-catalysis of C(2)–H/D exchange in D_2O.

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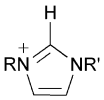
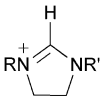
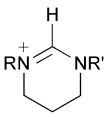
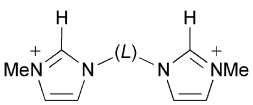
Table 1 Carbon acid pK_a values for azolium salts **1H$^+$**, **2H$^+$** and **3H$^+$–X$^-$**, and **4H$^+$–2X$^-$** in aqueous solution at 25 °C

Azolium ion		Counterion, X^-	k_{DO}[a]/M^{-1} s^{-1}	k_{HO}/M^{-1} s^{-1}	pK_a[b]	F[c]
 **1H$^+$**	**a**: R = R′ = 4-chlorophenyl	Cl^-	3.92×10^5	1.63×10^5	19.8	+0.18
	b: R = R′ = 4-methoxyphenyl	Cl^-	4.80×10^4	2.00×10^4	20.7	+0.13
	c: R = R′ = 2,4,6-trimethylphenyl	Cl^-	4.08×10^4	1.70×10^4	20.8	—
	d: R = R′ = 2,6-di-(*i*-propyl)phenyl	Cl^-	2.00×10^4	8.33×10^3	21.1	—
	e: R = ethyl, R′ = methyl	Cl^-	2.29×10^2	9.54×10^1	23.0[f]	0.00, +0.01
	f: R = *n*butyl, R′ = methyl	PF_6^-	1.07×10^2	4.42×10^1	23.3	—, +0.01
	g: R = *n*hexyl, R′ = methyl	PF_6^-	1.03×10^2	4.25×10^1	23.4	—, +0.01
	h: R = *n*octyl, R′ = methyl	Br^-	1.04×10^2	4.29×10^1	23.4	—, +0.01
	i: R = R′ = *t*-butyl	Cl^-	1.69	7.04×10^{-1}	25.2	−0.02
	j: R = R′ = adamantyl	Cl^-	1.07	4.46×10^{-1}	25.4	−0.07
 **2H$^+$**	**b**: R = R′ = 4-methoxyphenyl	Cl^-	4.26×10^4	1.77×10^4	20.7	+0.13
	c: R = R′ = 2,4,6-trimethylphenyl	Cl^-	1.19×10^4	4.96×10^3	21.3	—
	d: R = R′ = 2,6-di-(*i*-propyl)phenyl	Cl^-	8.37×10^3	3.49×10^3	21.5	—
 **3H$^+$**	**k**: R = R′ = ethyl	PF_6^-	3.48×10^{-3}	1.45×10^{-3}	27.8	0.00
	l: R = R′ = *i*-propyl	PF_6^-	1.48×10^{-3}	6.15×10^{-4}	28.2	+0.04
 **4H$^+$**	**m**: *L* = CH_2	I^-	2.98×10^5[d]	1.24×10^5	19.9	+0.01, —
	n: *L* = $(CH_2)_2$	I^-	5.87×10^3[d,e]	2.45×10^3	21.6	+0.01, —
	o: *L* = $(CH_2)_3$	I^-	1.30×10^3[d]	5.40×10^2	22.3	+0.01, —
	p: *L* = phenyl	I^-	2.03×10^5[d]	8.44×10^4	20.1	+0.01, —

[a] Kinetic data were obtained at 25 °C. [b] Estimated errors in pK_a values are ±0.5 units. [c] Field/inductive substituent parameter for R and R′ taken from Hansch *et al.*[9] '—' indicates no available F value. [d] k_{DO} values are based on total disappearance of the NMR singlet due to the *two* equivalent C(2)–H's of **4-H$^+$**. [e] From data at pD 5.94 only. [f] An identical pK_a value (23.0) was determined by Amyes *et al.*[4c] in water for dimethylimidazolium iodide.

that the reverse protonation of NHC **5** by water is also solvent reorganization-limited *i.e.* $k_{HOH} = k_{reorg} = 1 \times 10^{11}$ s^{-1}.

The effect of an increase in the concentration of the basic component of buffer on first order rate constants for exchange at fixed pD was investigated for a range of representative azolium salts. In all cases a 2–9 fold increase in the total buffer concentration resulted in no significant change (±10%) in rate constant at 25 °C (see ESI†). This is in agreement with the results of Amyes *et al.* for the deuteroxide-catalysed exchange reactions of dimethylimidazolium and dimethylbenzylimidazolium iodide.[4c]

Values for k_{HO} (M^{-1} s^{-1}) for deprotonation of azolium ions at C2 by hydroxide ion were calculated from corresponding k_{DO} values using a secondary solvent isotope effect of $k_{DO}/k_{HO} = 2.4$ for proton transfer that is limited by solvent reorganisation.[6,7] These k_{HO} values may be combined in eqn (1) with the rate constant for the reverse protonation of the NHC by water using $k_{HOH} = 1 \times 10^{11}$ s^{-1} and the resulting azolium salt pK_a values are given in Table 1.

The k_{DO} values of azolium salts **1H$^+$–4H$^+$–X$^-$** in Table 1 span 10^8-fold, and the pK_as vary by 8.4 units. *N*,*N*-diarylimidazolium salts **1H$^+$a–d–Cl$^-$** are the most acidic with pK_as from 19.8–21.1. Experimental k_{DO} values for **1H$^+$a–d–Cl$^-$** vary by only 20-fold despite significant changes in the electronic properties of the *N*-aryl substituents in this series. X-Ray crystal structures of *N*,*N*-diarylimidazolium salts and corresponding NHCs show that the aryl and imidazole rings are not coplanar.[1] Thus, the *N*-aryl substituent effects are mainly steric and field/inductive because inter-ring conjugation is restricted. Inductively electron-withdrawing substituents are expected to stabilise the formally neutral carbene-like transition state for deuteroxide-catalyzed exchange relative to the cationic azolium ion and increases in k_{DO} and decreases in pK_a are expected. The greater electron-withdrawing field/inductive effect of a 4-chlorophenyl substituent (F = + 0.18)[9] compared to the other aryl substituents is consistent with the 10-fold greater k_{DO} value and lower pK_a for **1H$^+$a–Cl$^-$**. Values of k_{DO} for **1H$^+$b–d–Cl$^-$** only vary by 2-fold in agreement with the similar inductive/field effects of 4-methoxy and 4-alkylphenyl substituents (F = + 0.12 − 0.13).[9]

The *N*,*N*-dialkylimidazolium salts **1H$^+$e–j–X$^-$** are up to 10^5 fold less reactive towards deuteroxide ion than the diaryl series **1H$^+$a–d–Cl$^-$** and the resulting pK_a values are up to 5.6 units higher. There is a greater span of k_{DO} values within the dialkyl imidazolium ion series of 230-fold. Keeping one *N*-methyl substituent whilst varying the second *N*-substituent from ethyl, *n*-butyl, *n*-hexyl to *n*-octyl decreases the k_{DO} value by a maximum of 2-fold and the change in pK_a value is <0.4 units. This small effect is consistent with the observations of Chu *et al.* in a study of the pK_as of 1,3-dialkylimidazolium salts in DMSO.[4e] By contrast, changing both *N*-substituents to bulky *t*-butyl or adamantyl substituents decreases the k_{DO} value by 200–300 fold and the pK_a increases by 2 units. Based on F values, the field/inductive electron donating effect of alkyl groups lies in the order: adamantyl (−0.07) > *t*-butyl (−0.02) > ethyl (0.00) > methyl (0.01) > *i*-propyl (0.04). Decreases in k_{DO} values are observed with more negative *N*-substituent F values consistent with the better stabilization

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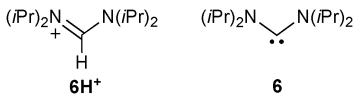
of the cationic parent azolium ion by more electron-donating substituents. As *t*-butyl and adamantyl substituents have different F values yet very similar k_{DO} values, this suggests that steric effects are also important in these cases.

The 4,5-dihydroimidazolium salts **2H$^+$b–d–Cl$^-$** have lower k_{DO} values, and higher pK_a values, than analogous imidazolium salts **1H$^+$b–d–Cl$^-$** although the differences are small. The largest effect of saturation of the C(4)–C(5) double bond is an increase in pK_a by 0.5 units for **2H$^+$c** compared to **1H$^+$c**.

The k_{DO} values for tetrahydropyrimidinium salts **3H$^+$k–l–PF$_6^-$** are substantially smaller than for **1H$^+$** and **2H$^+$**.[10] The k_{DO} values decrease by up to 10^8-fold, and the pK_as increase by 8.4 units to 27.8–28.2 as a result of the one-carbon increase in ring size. The increased pK_as for **3H$^+$k–l–PF$_6^-$** correlate with the greater N–C–N angles in these systems compared to the five-membered ring series. Diaminocarbenes prefer unusually small N–C–N angles, *e.g.* that in **1i** is 102.2°[11] compared with an N–C(H)–N angle of 109.6° in **1H$^+$i**.[12] Any structural change that enforces a larger angle will favour the protonated ion and increase the pK_a. In **3H$^+$k–PF$_6^-$**, the N–C(H)–N angle is 125.3°,[13] while the N–C–N angle in the KN(SiMe$_2$)$_2$ complex of **3l** is 116.3°.[14]

Methylene-linked bis-imidazolium ion **4H$^+$m–2I$^-$** is significantly more acidic than analogous dialkylimidazolium ion **1H$^+$e–Cl$^-$**. The effect of a cationic imidazolium substituent is a 240-fold increase in k_{DO} and decrease in pK_a by 3 units in a manner similar to that of changing from two *N*-alkyl to *N*-aryl substituents. This effect decreases as the length of the alkyl linker increases. Bis-imidazolium salt **4H$^+$p–2I$^-$** with an aryl linker has a similar acidity to **4H$^+$m–2I$^-$**.

Deuterium exchange of the C(2)–H of acyclic formamidinium salt **6H$^+$–PF$_6^-$** does not compete with hydrolysis. The second order rate constant for deuteroxide-catalysed hydrolysis for acyclic salt **6H$^+$–PF$_6^-$** (k_{HYD} = 3.02 × 10^{-4} M^{-1} s^{-1}) is similar to that for tetrahydropyrimidinium analogue **3H$^+$l–PF$_6^-$**.[10] For the latter, deuterium exchange competes with hydrolysis, thus the deuterium exchange reaction for **6H$^+$–PF$_6^-$** must be significantly slower. On the basis that we could detect ≥ 10% exchange in competition with hydrolysis, a lower limit of pK_a > 29.9 may be established for **6H$^+$–PF$_6^-$**. Acyclic carbene **6** has a N–C–N angle of 121.1°,[15] while the precursor **6H$^+$–OTf$^-$** has a N–C(H)–N angle of 133.2°.[13] This much larger N–C–N angle favours acyclic ion **6H$^+$** resulting in a higher pK_a value.



6H$^+$ **6**

Counterion effects on k_{DO} and pK_a values are negligible, as clearly seen by comparing data for imidazolium ions **1H$^+$f–h**, which have almost identical k_{DO} and pK_a values despite having different counterions. As the azolium ion salts will be fully dissociated in water, this small counterion effect is unsurprising.

In summary, we have determined pK_as for the conjugate acids of a large series of NHCs in water. The largest effects on pK_a are observed by varying *N*-substituent or ring size, while the effects of C(4)–C(5) saturation are small.

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Notes and references

1 For reviews see: A. J. Arduengo, *Acc. Chem. Res.*, 1999, **32**, 913–921; D. Bourissou, O. Guerret, F. P. Gabbai and G. Bertrand, *Chem. Rev.*, 2000, **100**, 39–91; R. W. Alder, M. E. Blake, L. Chaker, J. N. Harvey, F. Paolini and J. Schutz, *Angew. Chem., Int. Ed.*, 2004, **43**, 5896–5911; W. Kirmse, *Angew. Chem., Int. Ed.*, 2004, **43**, 1767–1769; O. Kuhl, *Chem. Soc. Rev.*, 2007, **36**, 592–607; J. Vignolle, X. Cattoen and D. Bourissou, *Chem. Rev.*, 2009, **109**, 3333–3384.

2 For reviews see: W. A. Herrmann, *Angew. Chem., Int. Ed.*, 2002, **41**, 1290–1309; M. C. Perry and K. Burgess, *Tetrahedron: Asymmetry*, 2003, **14**, 951–961; R. H. Grubbs, *Tetrahedron*, 2004, **60**, 7117–7140; P. de Fremont, N. Marion and S. P. Nolan, *Coord. Chem. Rev.*, 2009, **253**, 862–892.

3 For reviews see: D. Enders, O. Niemeier and A. Henseler, *Chem. Rev.*, 2007, **107**, 5606–5655; N. Marion, S. Diez-Gonzalez and I. P. Nolan, *Angew. Chem., Int. Ed.*, 2007, **46**, 2988–3000.

4 For previous pK_a determinations see: (*a*) R. W. Alder, P. R. Allen and S. J. Williams, *Chem. Commun.*, 1995, 1267–1268; (*b*) Y. J. Kim and A. Streitwieser, *J. Am. Chem. Soc.*, 2002, **124**, 5757–5761; (*c*) T. L. Amyes, S. T. Diver, J. P. Richard, F. M. Rivas and K. Toth, *J. Am. Chem. Soc.*, 2004, **126**, 4366–4374; (*d*) A. M. Magill, K. J. Cavell and B. F. Yates, *J. Am. Chem. Soc.*, 2004, **126**, 8717–8724; (*e*) Y. Chu, H. Deng and J. P. Cheng, *J. Org. Chem.*, 2007, **72**, 7790–7793.

5 T. L. Amyes and J. P. Richard, *J. Am. Chem. Soc.*, 1996, **118**, 3129–3141; J. P. Richard, G. Williams and J. L. Gao, *J. Am. Chem. Soc.*, 1999, **121**, 715–726; J. P. Richard, G. Williams, A. C. O'Donoghue and T. L. Amyes, *J. Am. Chem. Soc.*, 2002, **124**, 2957–2968.

6 V. Gold and S. Grist, *J. Chem. Soc., Perkin Trans. 2*, 1972, 89–95.

7 A. J. Kresge, R. A. More O'Ferrall and M. F. Powell, in *Isotopes in Organic Chemistry*, ed. E. Buncel and C. C. Lee, Elsevier, New York, 1987, vo1. 7.

8 U. Kaatze, R. Pottel and A. Schumacher, *J. Phys. Chem.*, 1992, **96**, 6017–6020.

9 C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165–195.

10 Under our experimental conditions, competing deuteroxide-catalyzed hydrolysis was observed for tetrahydropyrimidinium ions **3H$^+$** (k_{HYD} = 2.83 × 10^{-2} and 2.21 × 10^{-4} M^{-1} s^{-1} for **3H$^+$k–PF$_6^-$** and **3H$^+$l–PF$_6^-$**).

11 A. J. Arduengo, H. Bock, H. Chen, M. Denk, D. A. Dixon, J. C. Green, W. A. Herrmann, N. L. Jones, M. Wagner and R. West, *J. Am. Chem. Soc.*, 1994, **116**, 6641–6649.

12 P. A. Chase and D. W. Stephan, *Angew. Chem., Int. Ed.*, 2008, **47**, 7433–7437.

13 R. W. Alder, M. E. Blake, S. Bufali, C. P. Butts, A. G. Orpen, J. Schutz and S. J. Williams, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1586–1593.

14 R. W. Alder, M. E. Blake, C. Bortolotti, S. Bufali, C. P. Butts, E. Linehan, J. M. Oliva, A. G. Orpen and M. J. Quayle, *Chem. Commun.*, 1999, 241–242.

15 R. W. Alder, P. R. Allen, M. Murray and A. G. Orpen, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1121–1123.