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Review Article

Proton and metal-ion activation of C–H exchange in five-membered azoles

Erwin Buncel[1,*] and Ikenna Onyido[2]
[1] *Department of Chemistry, Queen's University, Kingston, Canada K7L 3N6*
[2] *Department of Chemistry and Center for Agrochemical Technology, University of Agriculture, Makurdi, Nigeria*

Summary

Factors influencing C–H isotopic exchange rates in five-membered azoles, that is imidazoles and thiazoles, under catalysis by H^+ and M^{n+}, especially transition metals, Pt(II) and Co(III) are discussed. Hydrogen ion catalysis through N(3) protonation of azoles **1–3** is generally the most efficient, with rate enhancements in the range 10^2–10^9 over the neutral process being attained. Metal-ion coordination also results in effective catalysis, though less so than catalysis by protons. Catalysis of C–H exchange by M^{n+} can be studied through addition of the metal salts to a buffered solution of the heterocycle in which labile complexes exist, or on synthesized complexes such as **4–13** which are substitution-inert thus precluding complications from unknown dissociation equilibria. A delicate balance of factors influence the ease of C–H exchange, including: (1) the magnitude of the fractional charge located at N(3) of the heterocycle through M^{n+}–N(3) σ bond polarization; (2) metal-to-ligand π back-bonding; (3) the electronic structure of the metal ions. These considerations have obvious consequences for deuterium- and tritium-labelling of a number of biomolecules, e.g. proteins, enzymes, nucleic acids, some vitamins, as well as drugs which incorporate five-membered azoles in their structures. Copyright © 2002 John Wiley & Sons, Ltd.

Key Words: isotopic C–H exchange; catalysis by H^+ and M^{n+}; five-membered azoles

*Correspondence to: Professor E. Buncel, Queen's University, Department of Chemistry, Kingston, Ontario, Canada K7L3N6. E-mail: buncele@chem.queensu.ca

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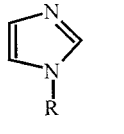
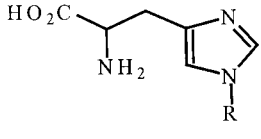
Introduction

Chemists have over the years devoted considerable effort to the investigation of the ionization of carbon acids (C–H bonds).[1a] These studies have furnished acidity scales for diverse families of organic compounds and have found applications in synthetic organic and organometallic chemistry by exploiting the nucleophilic reactivity and kinetic basicity of derived carbanions.[1b–d] Isotopic exchange reactions of C–H have afforded a variety of radioactive and non-radioactive (T or D) labelled compounds which have been used as (radio)tracers in the elucidation of organic and biochemical reaction pathways, exploration of C–H bond activation processes, and investigation of the nature of catalysts.[1e]

The basic structures of several biomolecules which are fundamental to life processes, e.g. proteins, enzymes, nucleic acids, some vitamins, etc. incorporate five-membered azoles such as **1–3** and their derivatives. A common structural feature of these azoles is the presence of heteroatoms (N and S) which ensures the enhanced acidity of C(2)–H over other ring protons, and enables coordination of metal ions to these heteroatomic sites. On the other hand, metal ions have long been recognized to play vital roles in biochemical processes;[2,3] their incorporation into enzymes[4] and their roles as metallopharmaceuticals in medical diagnostics and cancer therapy,[5,6] have received significant attention. At the same time, the environmental effects and toxicity of heavy metals have been well documented.[2,7]



1(a) R = H
(b) R = CH$_3$



2(a) R = H
(b) R = CH$_3$

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Several important biological reactions proceed through H^+ and/or metal ion (M^{n+}) C–H bond activation resulting in coordination to heterocyclic N atoms[8]. The present paper focusses on results obtained in the kinetic investigations of C–H isotopic exchange in **1–3** and the heterocyclic residues of the M^{n+}–azole complexes **7–11** as models for the elucidation of metal ion effects in biological systems. Kinetic data for C(8)–H exchange in the ligand portion of the M^{n+}-purine complexes

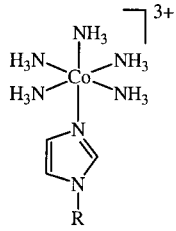
5, **6** and similar structures have been reported and discussed by Jones[9,10] and Martin[11]. The magnitudes of H^+ and M^{n+} activation of the C–H bond towards isotopic exchange are compared and causative factors for observed trends and effects are underlined.

The impetus for the work reviewed in this paper derives from the fact that C–H exchange has found diagnostic applications in the characterization of enzyme mechanisms and assignment of logical functions to metal ions in life processes.[8–13] As well, C–H isotopic exchange constitutes an important synthetic route to radioactive and non-radioactive compounds[14] utilized in medicine, agriculture, industry and other areas critical to human social and economic well-being.

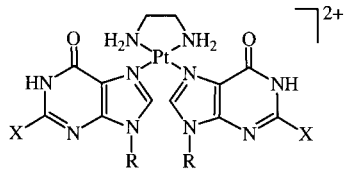
Experimental techniques

A variety of experimental techniques, ranging from IR, NMR (^{1}H and ^{3}H), and Raman spectroscopy to liquid scintillation counting,[9] have been employed in the investigation of C–H isotopic exchange. ^{3}H NMR spectroscopy offers the unique diagnostic advantage of unambiguous assignment of exchange sites in substrates that have multiple exchangeable protons; for preparative purposes this technique provides a check on label specificity in the tritiated product.[15,16] Liquid scintillation counting is an attractive practical method for tritiation/detritiation studies because it combines low levels of radioactivity with very low substrate concentrations, making it convenient for monitoring very slow reactions and to deal with solubility problems posed by organic substrates in aqueous solutions.[9,17]

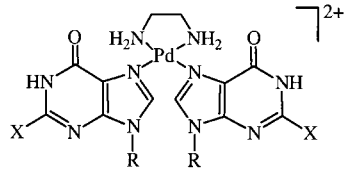
Studies of metal ion effects in C–H exchange have been approached in two ways:[10,18] (a) metal ions are directly introduced as salts into buffered aqueous reaction media containing the ligand with concomitant measurement of exchange rates in the ligand portion of the metal–heterocycle complex formed *in situ* in solution; and (b) **substitution–inert** metal–heterocycle complexes are synthesized, isolated and carefully characterized before isotopic exchange measurements are undertaken. Method (b) ensures that the identity of the reacting species is established under optimized experimental conditions; thus kinetic complications arising from multiple dissociation equilibria involving **kinetically labile** complexes usually encountered in method (a) above are avoided.[18,19]



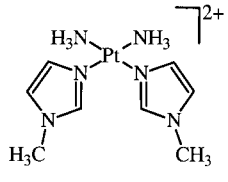
4(a) R = H
(b) R = CH_3



5(a): X = H, R = Ribosyl
(b): X = NH_2, R = Ribosyl



6(a): X = H, R = Ribosyl
(b): X = NH_2, R = Ribosyl



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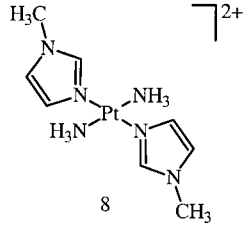

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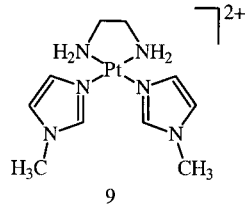

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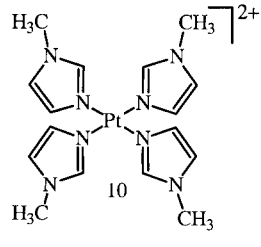

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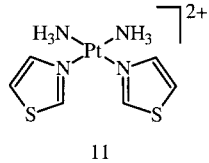

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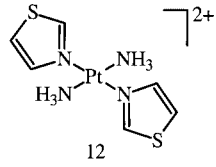

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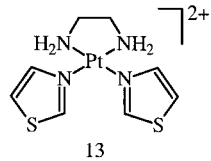

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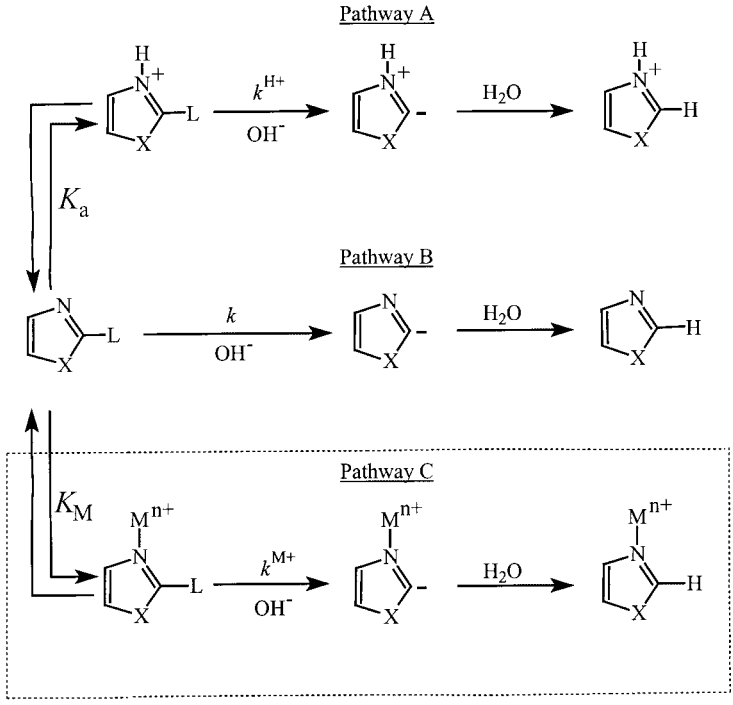
Exchange mechanism and rate equations

The generalized mechanism[9,20,21] for C–H isotopic exchange in **1–3** and their derivatives in aqueous buffers are given in Scheme 1 which is



Scheme 1.

specific for exchange at C(2). When exchange occurs at C(4) or C(5), the ylide intermediate shown in Path A, which results in C(2)–H abstraction from the protonated substrate, is replaced by an intermediate bearing localized charge, i.e. a higher energy process. Path B is the pathway for exchange of the neutral substrate; discussion of the boxed-in portion of Scheme 1 (i.e. Path C) is deferred till later. When X = N–H on Scheme 1, deprotonation of N–H occurs at high pH to form unreactive pools of the anionic form of the substrate. In purines where N–H deprotonation occurs at a site remote from the exchange site, the resulting anionic species have been shown to undergo exchange at high pH.[9]

Equations (1) and (2) give the kinetic expressions for reaction via Paths A and B; SH_2^+ and SH refer to protonated and neutral forms of the substrate, respectively, while K_a is the dissociation constant for N (3)

protonation and K_w is the ionic product of water.

$$\text{rate} = k^{H+}[SH_2^+][OH^-] + k[SH][OH^-] \quad (1)$$

$$k_{obs} = \frac{k^{H+}K_w + kK_a[OH^-]}{K_a + [H^+]} \quad (2)$$

Simplification of Equation (2) to reflect values of $[H^+]$ and $[OH^-]$ in the different pH regions[22] yields kinetic equations consistent with pH-rate profiles which generally provide unambiguous information regarding the identities of exchanging species as well as unreactive species along the reaction coordinate.[9,22]

Addition of M^{n+} to the reaction medium maintained at a pH in which the substrate is completely protonated ensures exchange only via Paths A and C (Scheme 1),[9] such that Equation (3) obtains when both protonated and metal-coordinated substrate forms are the reactive species in H/D or H/T exchange. Formation of kinetically unproductive metal–azole complexes (i.e. $k^{M+} = 0$ in Scheme 1) leads to Equation (4) which manifestly assigns an inhibitory role to the metal ion.[23]

$$k_{obs}^{M+} = \frac{K^{H+}K'_M K_W + k^{M+}K_a[M^{n+}][OH^-]}{K'_M[H^+] + K_a K'_M + K_a[M^{n+}]} \quad (3)$$

$$k_{obs}^{M+} = \frac{K^{H+}K'_M K_W}{K'_M[H^+] + K_a K'_M + K_a[M^{n+}]} \quad (4)$$

The quantity K'_M (Equations 3 and 4) $= 1/K_M$, where K_M is the stability constant of the M^{n+}-azole complex.

The simplest kinetic scenario for H/D or H/T exchange involving M^{n+} intervention is presented by **substitution–inert** M^{n+}–azole complexes,[18] e.g. **4–13**, as well as 1,3-dialkylated imidazoles[24] and 3-alkylated thiazoles.[25] Such M^{n+}–azole complexes obey the simple second-order rate expression of Equation (5); the mechanism of C–H exchange in the ligand portion of these complexes simplifies to the boxed-in portion of Scheme 1.

$$k_{obs}^{M+} = k^{M+}[OH^-] \quad (5)$$

In Table 1 we have assembled available rate data for C–H (H/D or H/T) exchange in azoles coordinated to different electrophiles which provide information on the relative magnitudes of k^{H+} and k^{M+} (Scheme 1) as well as positional reactivities, for subsequent discussion.

Table 1. Rate constants[a] for H/D and H/T exchange of ring hydrogens in 1–3 under catalysis by various electrophiles (H^+, R^+, M^{n+})

Substrate (Reference)[b]	Exchange (T/°C)	$k^{H+}(M^{-1}s^{-1})$[c]			$k^{M+}(M^{-1}s^{-1})$[d]		
		C(2)	C(4)	C(5)	C(2)	C(4)	C(5)
1a (26)	H/T(85)	6.0×10^3					
(27)	H/D(37)	6.4×10^3					
4a (18)	H/T(60)				1.24		
(28)	H/D(60)				0.27		
1b (22)	H/T(85)	1.0×10^4					
(29)	H/D(163)	9.0×10^{6e}	1.7×10^{2f}	2.6×10^{2f}			
Me^+-MeIm[g] (29)	H/D(163)	$\sim 1.3 \times 10^{7h}$	3.4×10^2	3.4×10^2			
4b (18)	H/T(60)				0.15		
9[i] (19)	H/D(60)				3.5×10^{-2i}	1.7×10^{-5j}	1.0×10^{-4k}
2a (30)	H/T(85)	6.1×10^3					
(27)	H/D(37)	2.9×10^3					
2b (21)	H/T(85)	1.0×10^4			$\geqslant 0.1$,CH_3Hg(II)		
(11)	H/D(61)	3.2×10^3			1.3×10^{-2}, Pd(II)		
3(26,34)	H/T(85)	3.5×10^6			$\sim 1 \times 10^4$,Cu(II)		
(25)	H/D(60)	4.2×10^{6i}			~ 7, Ag(I)		
Et^+Thz[g] (25)	H/D(60)	$1.9 \times 10^{7l,m}$					
13(31)	H/D(60)				9.2×10^{2n}	2.54[o]	4.83[p]

Table 1. (*continued*)

Substrate (Reference)[b]	Exchange (T/°C)	k^{H+} ($M^{-1}s^{-1}$)[c]			k^{M+} ($M^{-1}s^{-1}$)[d]		
		C(2)	C(4)	C(5)	C(2)	C(4)	C(5)
BzImH[g] (26)	H/T(85)	6.2×10^4			~0.21, Ag(I)		
BzMe-Im[g](22)	H/T(85)	2.0×10^5					
BzThz[g] (26,34)	H/T(85)	1×10^8			$\sim 3 \times 10^2$,Ag(I)		

[a] Rate constants are defined in Scheme 1.
[b] See references for original data.
[c] H/D exchange reactions were carried out in D_2O solutions (pD = pH + 0.4).
[d] Metal ions following k^{M+} values were studied by competitive method (see text).
[e] A value of $k^{H+} = 1.1 \times 10^2\,M^{-1}s^{-1}$ was obtained at 25°C (see Reference 29a).
[f] Assignment of values of rate constants to C(4)–H and C(5)–H exchange is based on work reported in Reference 29b.
[g] Abbreviations: Me^+-MeIm = 1,3-dmethylimidazole; Et^+-Thz = 3-ethylthiazole; BzImH = benzimidazole; BzMeIm = 1-methylbenzimidazole.
[h] The relevant rate constant is k^{R+}, in which case there is CH_3^+ coordination at N(3); a value of $k^{R+} = 2.7 \times 10^2\,M^{-1}s^{-1}$ was obtained at 25°C (see Ref. 29a).
[i] Values of k^{M+} for C(2)–H exchange in **7**, **8**, and **10** are not significantly different.
[j] C(4)–H exchange was not observed in **7**, **8**, and **10**.
[k] Value of k^{M+} for C(5)–H exchange in 7 = $1.8 \times 10^{-5}\,M^{-1}s^{-1}$; C(5)–H exchange was not observed in **8** and **10**.
[l] Calculated from data at pD = 2.80 and T = 60.7°C (see Refs. 25b and 31).
[m] The relevant rate constant is k^{R+}, in which case there is $CH_3CH_2^+$ coordination at N(3) of **3** (see text).
[n] Similar results were obtained for **11** and **12**.
[o] C(4)–H exchange was not observed in **11** and **12**.
[p] The values for C(5)–H exchange in **11** and **12** are $k^{M+} = 3.69$ and $4.22\,M^{-1}s^{-1}$, respectively.

Proton activation

C(2)–H in the neutral substrate is generally more acidic than other ring hydrogens. The reactivity order C(2)–H $\gg$ C(5)–H > C(4)–H, and C(2)–H > C(5)–H have been reported for **1**[29] and **3**[25], respectively. The reactivity sequence for **1** is attributed to a combination of C(2) flanking by heteroatoms[22,29] and the adjacent lone pair (ALP) phenomenon.[29b] The same order of reactivity is obtained in protonated **1** as in the neutral substrate; conceivably **2** follows the same trend.

The superiority of Path A over Path B has been demonstrated in several studies.[9,21,22,29] The ratio k^{H+}/k, otherwise known as the *proton activating factor* (paf)[12], is typically in the range 10^2–10^9, reflecting the combined effects of ground-state acidification of ring hydrogens consequent upon N(3) protonation and transition state stabilization in the formation of the derived intermediate which overwhelmingly favour exchange from the protonated azole over the neutral substrate.[9,18,21.26,29] The same magnitude of rate enhancement obtained upon protonation at N(3) is also induced by N(3) methylation (alkylation). Hence N(3)–CH_3^+ coordination is a good model for the electrostatic effects of N(3) protonation on exchange rates of azoles; complications arise, however, upon alkylation of **3**, to the extent that hydrolytic ring cleavage predominates over exchange at (especially) C(4) and C(5).[25]

Certain reactivity trends are obvious from Table 1. Exchange rate of C(2)–H is the same in **1** and **2** under catalysis by H^+; it thus appears that the alkyl fragment at C(4) which bears ionizable acidic and basic functions in **2** exerts little or no effect on the exchange process at C(2). Benzo annelation increases the rate of C(2)–H exchange in **1** and **2** by a factor of 10 or more. Furthermore, CH_3 substitution in **1a** and **2a** to give **1b** and **2b**, respectively, results in 2–3-fold increase in C(2)–H exchange rate. Interestingly, the results of benzo annelation and CH_3 substitution run contrary to expectations based solely on the inductive/field effects of these groups but have been satisfactorily explained by Buncel and co-workers[21,22] using FMO–PMO theory. The ratio of 1.6 obtained when C(2)–H exchange rates in histamine and **1a** are compared,[26,30] favouring the former, is amenable to a similar interpretation.[21] Replacement of N–H/N–CH_3 in **1** by S to give **3** results with a significant (10^2–10^3-fold) increase in C(2)–H exchange rate, suggesting better stabilization of the ylide intermediate formed from **3** than from **1**. This observation points to the importance of d–σ

orbital overlap-stabilization in the thiazolium system[32] and highlights the importance of the thiazolium structure in the function of thiamin.[8] Ground- and transition-state effects in neutral and protonated azoles which determine observed reactivity trends, positional reactivities, and preferential exchange at C(2) have received considerable attention.[18,19,21–23,31,32]

Metal-ion activation

A rational expectation, based on the effect of H^+ on C–H exchange, is that large rate enhancements would result upon placement of multiple positive charges at N(3) of azoles through M^{n+} ($n > 1$) coordination.[11,23,33,34] Literature results, however, show that relative to the proton, metal ions actually depress C–H exchange rates in these substrates. Thus in H/T exchange at C(2) of **1a**, retardation of exchange rates by metal ions was observed[35] according to the order: Cu(II) > Zn(II) ~ Ni(II) ≫ CH_3Hg(II). Similar trends have been reported for **1b**,[23,34] **2b**,[21] **3**,[23,34] and benzothiazole.[23,34] Pd(II) depresses C(2)–H exchange in **2b** by 2.5×10^5-fold relative to the reaction of the protonated substrate.[11] The results cited above were obtained by competitive addition of metal ions to buffered solutions of the ligand, in which case the kinetics were often complicated by the presence of **kinetically liable** metal–azole complexes (*vide supra*).

The Co(III)-bound imidazoles $[Co(NH_3)_5$imidazole$]^{3+}$ $[Co(en)_2(OH)$imidazole$]^{2+}$ and $[Co(en)_2(OH)$1-methyl imidazole$]^{2+}$ (en = ethylenediamine) were found[33] to be either resistant or sluggish to deuteriation. Quantitative data for C–H exchange in other **substitution–inert** complexes, e.g. Co(III) complexes[18] **4a** and **4b**, and Pt(II) complexes[19,31] **7–13**, are given in Table 1, along with other literature data on metal-ion activation of C–H exchange in azoles **1–3**.

The data in Table 1 reveal a number of interesting reactivity trends in the catalytic action of M^{n+} in C–H exchange. (i) H^+ is generally a better catalyst than M^{n+}, i.e. the kinetic condition $k^{H+} > k^{M+}$ (Scheme 1) generally holds. (ii) M^{n+}-coordinated azoles react faster than their neutral counterparts (see Refs. 18, 19, 21–23, 30 and 31 for detailed quantitative data on reactions of neutral substrates); k^{M+}/k (so-called *metal-activating* factor, maf[9]) ≫ 1, being generally of the order of 10^3–10^6. (iii) CH_3Hg(II) and Co(III) activate only C(2)–H towards isotopic exchange; no evidence of C(4,5)–H exchange was found.[18,21]

On the other hand, C(4,5)–H exchange was observed, in addition to C(2)–H exchange, with Pt(II)[19,31] as catalyst. (iv) Data for **1b** and **2b** present the order of the catalytic effectiveness of the different electrophiles as $H^+(CH_3^+) \gg Co(III) > CH_3H_g(II) \geqslant Pd(II) \sim Pt(II)$. Although the mediating metal ions incorporate a wide diversity of metal-ion characteristics, the significance of the above order with respect to the relative efficacy of H^+ and M^{n+} in promoting C–H exchange is worth noting and will be highlighted subsequently.

Proton versus metal ion activation

As pointed out earlier, *paf* and *maf* values for C–H exchange **1** and **3** are in the range 10^2–10^9 and 10^3–10^6, respectively. Comparing the relative effectiveness of H^+ and M^{n+} in these processes, the kinetic condition $k^{H+}/k^{M+} \gg 1$ has been consistently demonstrated,[9,18,24] the ratio being usually of the order of 10^3–10^5. Consequently, the generally observed trend in C–H exchange is protonated $\gg$ metallated $\gg$ neutral substrate. The relative order of catalytic effectiveness of the different metal ions given above for **1b** and **2b** suggests an interplay of several factors, presumably operating in a delicate balance, which determine the relative reactivities of H^+ and M^{n+}. Exploring and understanding the range and importance of these underlying factors should aid in interpretation of the roles and mechanisms of intervention of metal ions in living systems.

The simple but semi-quantitative model of Norris, Buncel and Taylor,[37] which correlates the magnitude of positive charge placed at N(3) of azoles by electrophile coordination with C(2)–H acidity, has sought to explain the degree of electrophile (H^+, R^+, M^{n+})-induced activation of C(2)–H, and possibly other ring hydrogens, towards isotopic exchange. However, data in Table 1 manifestly provide evidence that while the influence of H^+ and R^+ can be satisfactorily explained by the amount of charge located at N(3) and the extent of stabilization of the transition state, the effect of M^{n+} results from an interplay of several factors. Thus, it is important to evaluate the extent of M^{n+}–N(3) σ bond polarization along with other metal ion variables like electronic structure and the extent of metal-ligand π back-bonding, emphasizing the complex nature of the physiological chemistry of (especially) transition metal ions.

Under catalysis by H^+, the ratio for C(2)–H over C(4,5)–H exchange in **1a** is calculated[29a] as 3.5×10^4. The same ratio is found to be *ca.*$\mathbf{2} \times 10^2$ for Pt(II)[30] catalysis in **9–13**. These data underline the superiority of resonance stabilization of the ylide intermediate obtained on C(2)–H abstraction under catalysis by H^+, over inductive stabilization of the localized charge placed at C(4,5) when M^{n+} is the catalyst. For the imidazoles, the order C(2)–H $\gg$ C(5)–H > C(4)–H is found whether the catalyst is H^+[29b]or Pt(II).[19] In the former case, the order results from the combined effects of resonance stabilization of the ylide intermediate consequent upon C(2)–H deprotonation and the ALP phenomenon.[29b] On the other hand, the reactivity order for **11–13** with Pt(II) as catalyst reflects the involvement of S in stabilizing the negative charge at C(2) as well as the preferential placement of a partial positive charge at N(1)–CH_3 through resonance which stabilizes the negative charge at C(5).[30] Thus, in the thiazole series, e.g. **13**, the order C(5)–H > C(4)–H obtained with Pt(II) as catalyst largely mirrors the effect of α-carbanion stabilization by the adjacent S.[30]

Concluding remarks

Coordination of H^+ and M^{n+} at N(3) of azoles **1–3** enhances ring C–H exchange rates relative to the reactions of the neutral substrates. The generally observed order of catalytic effectiveness of $H^+ > M^{n+}$ in C–H exchange processes is confirmed in all cases investigated. Data for the imidazoles and histidines extrapolate to the order $H^+(CH_3^+) \gg$ Co(III) > CH_3H_g(II) > Pd(II) ~ Pt(II) for the catalytic effectiveness of the different electrophiles.

These results highlight the fact that reactivities in electrophile-activated C–H exchange in **1–3** result from the operation of a diversity of factors. The magnitude of ground- and transition-state stabilization, extent of N(3)-electrophile σ bond polarization and the electronic structure of metal ions, as well as the degree of metal-ligand π back-bonding, are factors which need be considered in assessing metal-ion activation of C–H exchange. The foregoing therefore emphasizes a holistic approach in the interpretation of the biochemistry of metal ions.

An interesting juxtaposition arises between the present work and the recent review by Davies[38] entitled 'Metals as surrogates for hydrogen' which highlights the H/M equivalence in a variety or organic reactions. The general analogy between protic acids and Lewis acids is, of course,

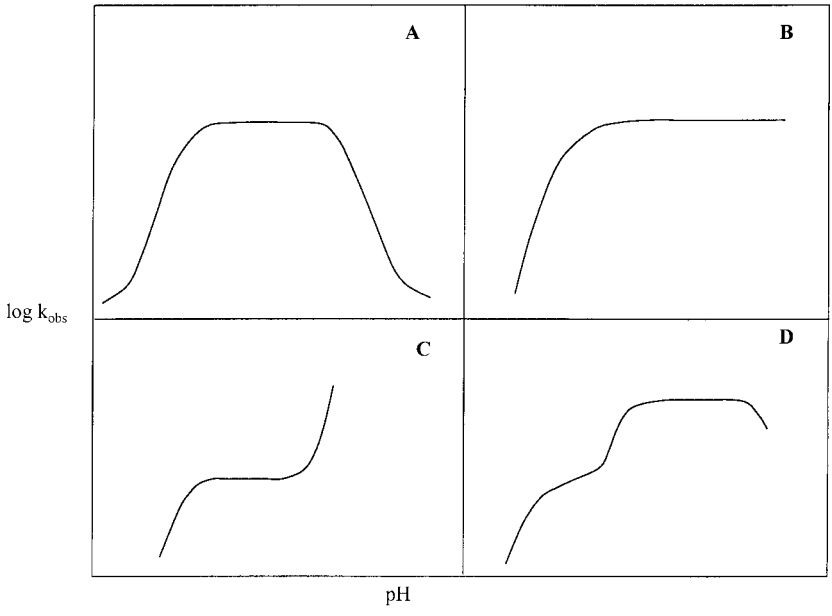


Figure 1. Generic rate-pH profiles encountered in C(2)–H exchange in azoles: (A) e.g. 1a[26] and benzimidazole[24]; (B) e.g. 1b[22], 1-methylbenzimidazole[24] and complex 4a[28]; (C) e.g. 3 and benzothiazole[23,34]; and (D) e.g. 2a[27,30], 2b[20], and histamine[30]

central in our Scheme 1. It follows also that the exchange of the L moiety, i.e. H, D or T, should occur as well when L is a metal or organometallic group, e.g. Bu_3Sn, etc.[†] While this was implicit in our earlier finding[37] that CH_3Hg^+ coordination by CH_3Hg^+ at N(1) of **1b** gave rise to substitution by CH_3Hg^+ at C(2), and similarly coordination by CH_3Hg^+ at N(7) was followed by facile methylmecuriation at C(8) in several nucleosides (inosine, guanosine, xanthosine)[39], this extension of the H/M principle in Scheme 1 should greatly broaden the scope of the C–H exchange process.

Finally, it is pointed out that the rate of C–H exchange is often pH-dependent. This generally is the case when the substrate contains an ionizable group, e.g. **1a**, **2a**, **2b**, **4a**. The pH-rate profile in such systems is characteristic of both structure and mechanism. From a practical viewpoint, the chemist interested in preparing a labelled compound should appreciate that in some cases it would be advantageous to carry

[†]We thank Professor Davies for bringing to our attention this extension of the H/M principle.

out the exchange in basic medium, while in others a neutral or acidic medium would be appropriate. Some generic-rate pH profiles encountered in C(2)–H exchange in azoles are shown in Figure 1 (see also reference 9).

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