Adjacent Lone Pair (ALP) Effects in Heteroaromatic Systems. 1. Isotope Exchange of Ring Hydrogens in Alkylimidazoles

Yoshio Takeuchi,[1] Herman J. C. Yeh, Kenneth L. Kirk, and Louis A. Cohen*

Laboratory of Chemistry, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20014

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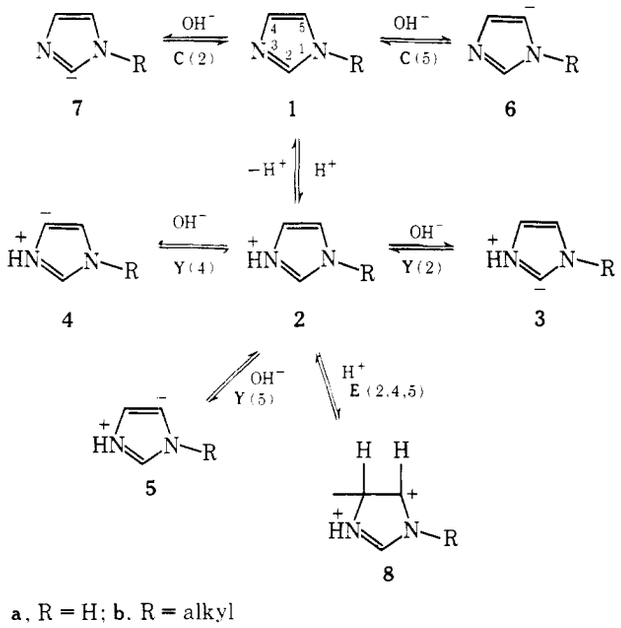
Solvent deuterium isotope exchange (D_2O, 50 °C) is readily observed above pD 5 at C-2 in imidazole and its *C*- or *N*-alkyl derivatives. The intermediate is an ylide, formed by base-catalyzed abstraction of H-2 from the imidazolium ion [path Y(2)]. A similar, but much slower, exchange can be observed at C-4 [Y(4)] or at C-5 [Y(5)] at 100 °C. In strongly alkaline media, NH–imidazoles exchange more rapidly at C-4 or C-5 by a carbanion pathway (C), involving C-proton abstraction from the neutral molecule; in *N*-alkylimidazoles, however, *only* H-5 exchanges by the C pathway [C(5)]. The resistance to carbanion formation at C-4 is ascribed to the *adjacent lone pair* (ALP) effect—a significant electrostatic repulsion between lone pairs in the coplanar, sp^2 orbitals at N-3 and C-4. The partial contributions of the Y and C pathways are evaluated from kinetic data at pD 10–11 and in 1 N NaOD, respectively. For 1-methylimidazole (1 N NaOD, 100 °C), C(5) exchange occurs 15 times faster than Y(5), and Y(5) exchange is three times faster than Y(4). NMR signals for H-4 and H-5 are assigned on the basis of (1) spin-decoupling experiments, (2) nuclear Overhauser enhancements, (3) chemical transformations of 1-methylimidazole-d_2, and (4) $\Delta\delta$ values. It is shown that ring protons adjacent to *N*-methyl can be differentiated from other ring protons by a characteristic shift in δ with variation of solvent ($\Delta\delta$); furthermore, H-5 appears at higher field than H-4 in nonpolar solvents, and this order is reversed for polar solvents.

A number of ring-fluorinated imidazoles have recently become available through a photochemical synthesis developed in this laboratory.[2] In preparation for various biochemical and pharmacological studies with these and related compounds,[3] we explored the possibilities for isotopic labeling of the ring by means of direct exchange with D_2O and T_2O. The initial results were sufficiently at variance with our expectations (based on literature data for imidazole itself)[4] that a more detailed study seemed desirable both for theoretical and practical ends. The study involved an examination of both alkyl- and electronegatively-substituted imidazoles, and led to the formulation of some general concepts regarding C–H acidity in these heteroaromatic systems. In this first paper of the series,[5] we summarize known pathways for exchange in imidazoles, present new data on the exchange of ring hydrogens in both *N*-methyl- and *C*-methylimidazoles, and offer interpretations which may have more general applicability.

Earlier studies on isotope exchange have dealt with imidazole,[4] *N*-methylimidazole,[4] and 4(or 5)-substituted imidazoles such as histidine, histamine, and their derivatives.[6] Information on the effects of an electronegative substituent on rates and sites of exchange has been limited to one report on nitroimidazoles.[7] Detailed kinetic studies with imidazole[4e,f] and with *N*-methylimidazole[4e,f] have demonstrated the existence of three basic pathways for exchange, which we shall designate the ylide (Y), carbanion (C), and electrophilic (E) pathways (Scheme I). Symbols, such as Y(2) and C(5), designate the specific ring positions under discussion. Each pathway prevails in a different pH region, and the pathways show large differences in $\Delta F^{\ddagger}$.

Scheme I



a, R = H; b, R = alkyl

The most facile exchange, which occurs at C-2, has been studied at 25–80 °C and follows the rate expressions

$$\text{rate} = k_Y[\text{ImH}^+][\text{OH}^-]$$

$$k_{obsd} = k_Y K_w/(K_1 + [\text{H}^+]) \quad (1)$$

in which K_1 is the dissociation constant for the imidazolium ion ($\text{ImH}^+ \rightarrow \text{Im}$) and K_w is the ion product for water. This rate law is consistent with the log k_{obsd}/pH profile,[8] and is supported by the demonstration of an even more facile exchange in 1,3-dimethylimidazolium ion (in which the positive charge cannot be lost by dissociation).[4f] For *N*-alkylimidazoles (**1b**), the constancy of k_{obsd} in the alkaline region (Figure 1, curve B) results from the fact that an increase in $[\text{OH}^-]$ is directly offset by a decrease in $[\text{ImH}^+]$ (**2b**). For imidazole itself, however (Figure 1, curve A), k_{obsd} decreases again at high pH due to the formation of the (presumably unreactive) Im^- species. In both compounds, at moderate temperatures and at pH values between 7 and 11, total exchange at C-2 can be achieved conveniently without measurable exchange at C-4 or C-5 (Table I).

Exchange at C-4 or C-5 is very much slower than at C-2 (Table I), earlier experimental data having been obtained at 160–190 °C;[4e,f] yet, the log k_{obsd}/pH profiles suggest exchange mechanisms, Y(4) and Y(5), analogous to Y(2). At 50 °C and neutral or mildly alkaline pH, exchange at C-2 (in 1-methylimidazole) occurs 10^4–10^5 as rapidly as at C-4 or C-5. This relatively high kinetic acidity of H-2 ($t_{1/2}$ = 42 min), and its strikingly greater reactivity than that of H-4 or H-5, may be the combined result of several phenomena: (1) the inductive influence of two nitrogen atoms on C-2 vs. one on C-4 or C-5; (2) the effect of a full positive charge on C-2 vs. a partial charge on C-4 or C-5; (3) the possibility of slightly greater s character

Table I. Solvent Deuterium Exchange of Ring Protons in Alkylimidazoles[a]

imidazole	registry no.	Y(2),[b] 10^2k_{obsd}	C(5),[c] 10^3k_{obsd}	Y(4), 10^5k_{obsd}	Y(5),[d] 10^5k_{obsd}
1-methyl	616-47-7	1.65	1.67	4.13[c,d]	11.3
1,2-dimethyl	1739-84-0		0.42	4.13[c,d]	4.13
1,4-dimethyl	6338-45-0	0.92	0.36		1.49
1,5-dimethyl	10447-93-5	1.43		3.72[c,d]	
imidazole	288-32-4	0.58	6.47	3.85[d]	3.85
2-methyl	693-98-1		1.07	3.85[d]	3.85
4-methyl	822-36-6	0.50	23.1		3.50

[a] All rates are min^{-1}. [b] At 50 °C, pD 10–11; under these conditions, no exchange is observed at H-4 or H-5 for any compound in 720 h. [c] At 100 °C, 1 N NaOD. [d] At 100 °C, pD 10–11.

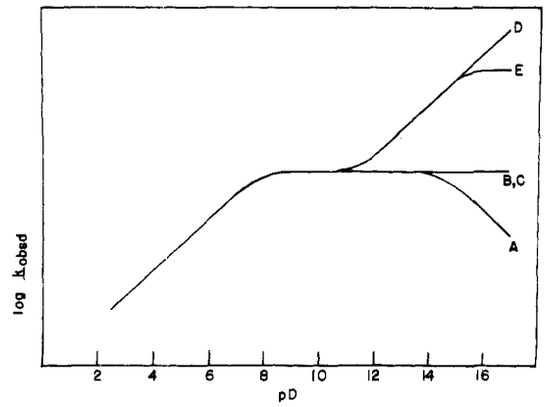
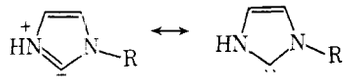


Figure 1. Theoretical curves illustrating the several pathways for exchange of imidazole ring protons, and the effect of pD and change in the state of ionization: A, path Y(2) for imidazole; B, path Y(2) for 1-methylimidazole; C, path Y(4) for 1-methylimidazole; D, exchange of H-5 in 1-methylimidazole [Y(5) below and C(5) above, pD 11]; E, exchange of H-4 and H-5 in imidazole [Y(4,5) below and C(4,5) above, pD 11]. No numerical relationships are implied by the coincidence of the curves.

in the C(2)–H bond; and (4) enhanced stabilization of the ylide intermediate (**3**) through resonance with a neutral carbene form (**9**), which resonance stabilization is not available to **4** or **5**.



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The protons at C-4 and C-5 of 1-methylimidazole show relatively little difference in rate of exchange by the Y pathway up to pH ~12 (Table I and ref 4f); curiously, however, one of these hydrogens exchanges much more rapidly than the other at higher pH (Figure 1, curves C and D), with a linear dependence of k_{obsd} on base concentration.

$$\text{rate} = k_C[\text{Im}][OH^-]$$

$$k_{obsd} = k_C[OH^-] \quad (2)$$

The data are consistent with path C, involving the slow formation of an sp^2 carbanion (**6**) from the neutral imidazole species. Presumably, H-2 in 1-methylimidazole could also undergo exchange by a carbanion (**7**) pathway [C(2)], if the much more facile Y(2) pathway did not exist.[5] For imidazole itself, k_{obsd} for the C(5) pathway approaches a constant value at high pH (Figure 1, curve E), because the increase in $[OH^-]$ is offset by a decrease in [Im]. In the present study, we demonstrate that the more acidic proton in 1-methylimidazole is H-5, and not H-4 as previously assigned.[4f]

A third pathway for exchange (E) is found in strongly acidic media.[4f] At all three ring-carbon positions, log k_{obsd} increases directly with H_0, suggesting proton attack on **2**

Table II. NMR Signal Assignments for *N*-Methylimidazole Ring Protons

ref	solvent	δ, ppm H-2	H-4	H-5
10a	$CDCl_3$	7.41	6.86	7.05
4c		7.41	6.86	7.05
10b		7.47	7.08	6.88
10c,f		7.43	7.05	6.90
a		7.41	7.03	6.87
10d	C_6D_{12}	7.41	7.05	6.88
4f	D_2O	7.63	7.13	7.03
10e		7.60	7.08	7.00
a		7.57	7.00	7.07

[a] Present investigation.

$$\text{rate} = k_E[\text{ImH}^+][H_0]$$

$$k_{obsd} = k_E[H_0] \quad (3)$$

and the intermediacy of species such as **8**. In this case, H-2 is ~100-fold less reactive to exchange than H-4 or H-5, presumably because amidine resonance must be lost in the course of proton attack at C-2.

Since the carbanion pathway (C) has been observed only in very strongly alkaline media and at high temperature, it has received relatively little attention.[4f] As the basicity of the imidazole ring is reduced, and the acidities of the ring hydrogens are enhanced, by the introduction of electronegative groups, exchange by path C becomes significant at lower pH and lower temperature and may, in fact, replace path Y in importance.[5] Accordingly, we found it necessary to explore the chemistry of path C more fully and, in particular, to account for the differences in reactivity at C-4 and C-5.

Results and Discussion

NMR Assignments. In *N*-alkylimidazoles, H-4 and H-5 generally have different δ values. Since the kinetics of solvent deuterium isotope exchange are most conveniently followed by NMR changes, there must be an unequivocal correlation of the two protons with their NMR signals. In Table II are summarized the δ assignments given to the ring protons of *N*-methylimidazole in previous studies;[10] in general, these assignments were based on a qualitative evaluation of electronic effects and are inconsistent with respect to H-4 and H-5. The signal at lowest field is unquestionably that for H-2.[11] On the basis of three experimental criteria, we have concluded that the ring proton signal at highest field (in nonpolar solvents) corresponds to H-5, and that H-5 is much more acidic than H-4. The order of the H-4 and H-5 signals is reversed in shifting from solvent $CDCl_3$ to D_2O. In earlier work,[4f] path C has been ascribed to exchange at C-4; as a result of our demonstration of this solvent reversal, however, the explanation offered by Wong and Keck for the order of acidities of H-4 and H-5 becomes invalid. The same NMR criteria were

Table III. NMR Solvent Shifts ($\Delta\delta$) for *N*-Methylimidazoles

imidazole	position	δ, ppm			Δδ, ppm	
		$CDCl_3$	Me_2SO-d_6	D_2O[a]	Δ_1[b]	Δ_2[c]
1-methyl	H-2	7.41	7.55	7.57	−0.14	−0.16
	H-4	7.03	6.88	6.99	+0.15	+0.04
	H-5	6.87	7.08	7.07	−0.21	−0.20
1,2-dimethyl	H-4	6.87	6.68	6.84	+0.19	+0.04
	H-5	6.77	6.97	6.97	−0.20	−0.20
1,4-dimethyl	H-2	7.25	7.37	7.45	−0.12	−0.20
	H-5	6.55	6.75	6.82	−0.20	−0.27
1,5-dimethyl	H-2	7.35	7.45	7.48	−0.10	−0.13
	H-4	6.74	6.59	6.73	+0.15	+0.01

[a] Adjusted to pD 10 to exclude partial ring protonation. [b] $\Delta_1 = \delta_{CDCl_3} - \delta_{Me_2SO\text{-}d_6}$. [c] $\Delta_2 = \delta_{CDCl_3} - \delta_{D_2O}$.

applied to several other *N*-methylimidazoles, both to confirm the validity of the methods and to extend their applicability.

1. Spin-Decoupling and NOE Experiments. While the NMR signals for H-4 and H-5 are primarily triplets (in *N*-methylimidazole),[12] the signal which occurs at higher field in $CDCl_3$ shows significant fine structure, which we attribute to four-bond coupling ($J < 0.3$ Hz) with the protons of the *N*-methyl group. Irradiation at the *N*-methyl frequency results in sharpening of the triplet at δ 6.87 and loss of fine structure; no change is seen in the signal at δ 7.03. Assignment of the higher field signal to H-5 receives further support from nuclear Overhauser enhancement (NOE) experiments: saturation of the *N*-methyl protons by double resonance produced a 13% increase in peak intensity for the signal at δ 6.87 and a 3% increase for that at δ 7.03. The validity of these criteria was confirmed by examination of 1,4- and 1,5-dimethylimidazole, whose structures had been established by chemical degradation[13b] and by unequivocal synthesis.[13c,d]

2. Solvent Effects on δ Values. In a variety of azole systems, δ values for ring protons adjacent to *N*-alkyl groups have been found to have a solvent dependence which distinguishes them from other ring protons. In the original study,[10c] *N*-methylimidazole was the only imidazole system subjected to this analysis; we have extended the method to a variety of substituted *N*-methylimidazoles and, on the basis of 20 compounds examined to date, have found no exceptions[14] to the following rule: for protons adjacent to the *N*-methyl group, $\delta_{CDCl_3} - \delta_{Me_2SO\text{-}d_6}$ (= Δ_1) or $\delta_{CDCl_3} - \delta_{D_2O}$ (= Δ_2) have significant negative values (−0.1 to −0.6); for any remaining ring protons, these Δ values are either close to zero or are positive (Table III). The Δδ test provides the same proton assignments for *N*-methylimidazole as were obtained by spin-decoupling and NOE techniques. The reliability of this analytical tool is strengthened by the consistency of the results for the known 1,4- and 1,5-dimethylimidazoles (Table III).

3. Chemical Transformation. *N*-Methylimidazole was subjected to exchange in 1 N NaOD at 100 °C; after 16 h, H-2 and one of the remaining protons had exchanged completely, while the third proton (at δ 6.99 in D_2O and 7.03 in $CDCl_3$) had exchanged only to a negligible extent. This product, *N*-methylimidazole-d_2, was nitrated[13a] to give a mixture containing 90% 1-methyl-4-nitroimidazole-d_2 and 10% 1-methyl-5-nitroimidazole-d_1. Since the structures of the isomeric nitro derivatives had been established by chemical degradation[13a] and since all proton signals for the two isomers show uniquely different δ values,[10b] it was relatively simple to use NMR not only to determine the ratio of the isomers following nitration, but also to demonstrate that the proton surviving exchange in *N*-methylimidazole is H-4 (δ 7.03 in $CDCl_3$). Furthermore, spin decoupling has no effect on the single ring proton signal of *N*-methylimidazole-d_2. On the basis of the NMR assignments and the nitration results, we conclude that H-5 had exchanged in preference to H-4.

Basis for Selective Exchange in *N*-Methylimidazoles. The carbanion intermediates necessary for exchange at C-4 or C-5 by path C are **10** and **11**, respectively. It is evident that **10** contains lone pairs in *adjacent*, coplanar, sp^2 orbitals, while the same lone pairs in **11** are *nonadjacent*. Thus, electrostatic

10

11

repulsion alone may be sufficient to render **10** energetically less favorable than **11**. The energy difference between these two carbanions must be significant since, at 100 °C, H-5 can be exchanged completely by path C without measurable C exchange at H-4 over 90–100 h; even at 163 °C, there is no evidence for the formation of **10**.[15] This selectivity in carbanion formation, which we find to be general for *N*-alkylimidazoles, we have named the *adjacent lone pair* (ALP) effect.[16]

Unusual exchange properties of pyridine and diazine rings have been interpreted on the basis of such electrostatic interaction.[17] In *N*-alkylpyridinium ions and in pyridine *N*-oxide, the order of base-promoted hydrogen exchange is H-2 > H-3 > H-4;[18] this order is consistent with labilization of the ring hydrogens via a combination of σ-, π-, and field-inductive transmission from the positively-charged ring nitrogen atom, and with damping of the effect with increasing distance. In pyridine itself, however, H-2 is the least acidic proton;[18] it is reasonable that the sp^2 lone pair on nitrogen would resist strongly the creation of an sp^2 carbanion at the most proximate ring carbon atom. The ALP effect is eliminated as soon as the lone pair on nitrogen is utilized in covalent bonding, even by protonation.[19]

For an N-alkylimidazole, the rate of exchange by path Y(4) or Y(5) is independent of pD at any value at least 1.5 units higher than its p*K* (Figure 1, curve C). Accordingly, paths Y and C can be differentiated by comparison of exchange rates at pD 10–11, in which range the base-dependent path C makes a negligible contribution, and in 1 N NaOD, in which medium exchange by path C greatly overwhelms that by path Y. For 1-methylimidazole in 1 N NaOD at 100 °C, C(5) is 15 times as fast as Y(5) and 40 times as fast as Y(4) (Table I). A very slow C(4) pathway is ruled out by the fact that exchange at this position is no faster than 1 N NaOD than at pD 10–11.

Exchange in *C,N*-Dimethylimidazoles. The ALP effect was subjected to further validation by study of the isomeric *C,N*-dimethylimidazoles. In the case of 1,2-dimethylimidazole, δ values for H-4 and H-5 were assigned on the basis of spin-decoupling experiments and Δδ values (Table III). In 1 N NaOD at 100 °C, C(5) exchange occurs ca. tenfold as fast as Y(5) or Y(4), the latter exchanges showing essentially the same rate (Table I). As in the case of 1-methylimidazole, no C(4) exchange can be detected (cf. **12**) after 5 days at 100 °C. The 2-methyl group, by virtue of its electron-releasing ability,

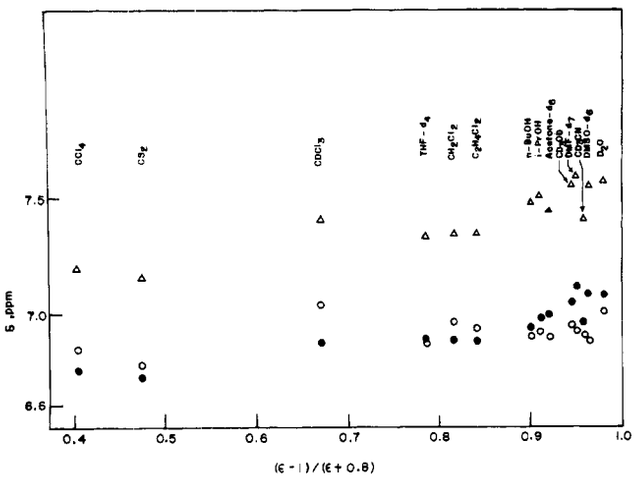
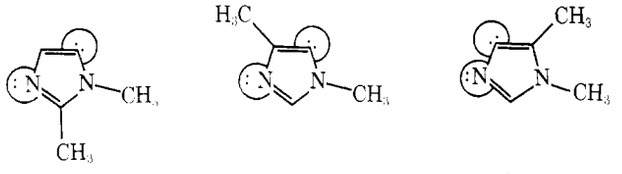


Figure 2. Plot of NMR δ values for ring protons of *N*-methylimidazole vs. a function of ϵ, the solvent dielectric constant: △, H-2; ○, H-4; ●, H-5. For each solvent, assignments of H-4 and H-5 were made on the basis of spin-decoupling experiments.

exerts a three- to fourfold decrease in the rate of C(5) or Y(5) exchange relative to 1-methylimidazole, but has practically no effect on Y(4).



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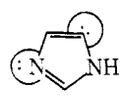
The ALP effect is seen again in a comparison of 1,4- and 1,5-dimethylimidazoles (Table I) and their respective carbanions (**13** and **14**). In 1 N NaOD at 100 °C, C(5) exchange in 1,4-dimethylimidazole occurs 24 times as fast as Y(5) exchange, and 10 times as fast as Y(4) exchange in 1,5-dimethylimidazole.[20] In the latter compound, the rate of C-4 exchange is the same at pD 11 as in 1 N NaOD; thus, exchange at this position occurs only by path Y. The energetically unfavorable carbanion (**14**) may be capable of generation in the presence of a strong, nonaqueous base; this possibility is under investigation.

Exchange in NH–Imidazoles. As already indicated, the rate of Y(2) exchange in imidazole falls off in strong base (Figure 1, curve A) due to the formation of the Im^- species. A similar decrease in rate is to be expected for Y(4) and Y(5) exchange and, thus, k_Y for NH–imidazoles is best evaluated only at the lower pD (10–11). In fact, however, exchange at C-4 or C-5 in imidazole is considerably *faster* in 1 N NaOD than at lower [OD^-]. Based on an estimated $pK_2(D_2O) = 15.2$,[21] imidazole should be only partially in the Im^- form in this medium,[22] and the C–H bonds in imidazole may be sufficiently acidic to permit the transient existence of carbanion **15**; this species, as in the cases of **11**, **12**, or **13**, would not be



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subject to the ALP effect at C-5. Since path C(5) is 170 times as fast as path Y(5) for imidazole (Table I), the effect of a high concentration of base in decreasing the rate of the Y(5) pathway is easily overwhelmed by its favorable effect on the C(5) pathway. A plot of log $k_{C(obsd)}$ vs. pD should follow the pK_2 titration curve (analogously to curve E of Figure 1), leveling off at base concentrations which are experimentally unattainable in D_2O. In accordance with the ALP effect, carbanion **15** has been formulated in the lower energy form; because of tautomerism, however, C-4 and C-5 are experimentally indistinguishable.

For 2-methylimidazole, pK_2 is ~0.6 unit higher than for imidazole;[23] accordingly, C(5) exchange should be favored by the greater concentration of neutral species present in 1 N NaOD, but retarded by the electron-releasing ability of the methyl group. As shown in Table I, 2-methylimidazole exchanges at C-5 ca. sixfold more slowly than does imidazole, suggesting the latter factor to be the more significant.

In 4-methylimidazole, C(5) exchange is much faster than for any other compound examined in this study. The result is surprising, since pK_2 for the compound is probably comparable to that for 2-methylimidazole and since the 4-methyl group should be somewhat more effective than 2-methyl in retarding carbanion formation at C-5 (cf. k_{obsd} values for 1,2- and 1,4-dimethylimidazole). At the present time, we cannot offer a reasonable explanation for this phenomenon.[5] Both 2- and 4-methylimidazole undergo C(5) exchange faster than their 1-methyl derivatives. Although deactivation by the 1-methyl group may be due simply to electron release, it is possible that this substituent offers significant steric hindrance to the formation of a solvated carbanion at the adjacent C-5 position.

In principle, the ALP effect should also exist between C-2 and N-3. Its occurrence or nonoccurrence cannot be determined with the present series of compounds, however, since Y(2) exchange may be 500–1000 times as fast as C(2) exchange (based on C(5) data). As demonstrated in the following paper,[5] studies with electronegatively-substituted imidazoles show that the ALP effect at C-2 is either much weaker than at C-4 or is absent entirely.

Buffer Catalysis. In principle, a proton exchange dependent on hydroxide ion should also be subject to catalysis by weaker general bases, although the magnitude of the catalysis may be immeasurably small. Since the ylide pathway for exchange requires proton abstraction from an already protonated species, this pathway should show particular sensitivity to buffer catalysis over a wide pH range. Relatively few attempts to demonstrate buffer catalysis of exchange in heteroaromatic systems have been recorded, with inconclusive results;[4g] in particular, Wong and Keck[4f] found no measurable phosphate buffer catalysis in Y(2) exchange in imidazole or *N*-methylimidazole. Preliminary to a more extensive investigation of this question, we have found that exchange of H-2 in *N*-methylimidazole at pD 4.9 *is* enhanced 4.3-fold in the presence of 1 M acetate buffer (0.2 M substrate, 50 °C). General base catalysis of the carbanion pathway should also be demonstrable and is described in the following paper.[5]

Solvent Effects (Δδ Values). We have shown that comparison of δ values for the C-4 and C-5 protons of 1-methyl- and 1,2-dimethylimidazole in several solvents offers a convenient and reliable means for assignment of the proton signals. The data of Table III demonstrate the need for caution, inasmuch as the order of these signals in $CDCl_3$ is reversed in D_2O for both compounds. As an extension of these observations, we have obtained δ values for *N*-methylimidazole protons in 14 solvents (Figure 2). The δ values do not provide a statistically acceptable correlation when plotted against solvent parameters such as E_T[24] or various functions of the dielectric constant (ϵ).[25] These δ values were obtained at a single concentration of *N*-methylimidazole; a more complete analysis would require extrapolation to zero concentration, although the effect of concentration may be too small[10e] to account for the several serious deviations in Figure 2. The basis for the overall effect of solvent polarity, as well as the differential effects at the several ring positions (Δδ values), are not

clear and are still under investigation. In any case, it is obvious from Figure 2 that the order of δ values for H-4 and H-5 in *N*-methylimidazoles is reversed in shifting from a nonpolar to a polar solvent, and that signal assignments cannot be made on the basis of electron density considerations alone.

Experimental Section[26]

Materials. 1-Methylimidazole, 2-methylimidazole, and 1,2-dimethylimidazole were obtained from commercial sources; NMR spectra showed these compounds to be of acceptable purity. Commercial samples of 4(5)-methylimidazole could not be freed of unidentified contaminants. This compound was prepared from acetol acetate, formaldehyde, and ammonia,[27] and purified by distillation: bp 90–92 °C (0.35 mm); NMR ($CDCl_3$), δ 2.25 (3 H, d, CH_3), 6.76 (1 H, m, H-4(5)), 7.55 (1 H, d, H-2).

1,4- and 1,5-Dimethylimidazoles. A solution of 4(5)-methylimidazole (2.46 g, 0.03 mol) in 3 mL of benzene was stirred at 5 °C while a solution of methyl iodide (4.68 g, 0.033 mol) in 2 mL of benzene was added over 10 min; the mixture was then heated at reflux for 30 min. Evaporation of the solvent gave a yellow oil which was dissolved in 20 mL of water. The solution was adjusted to pH 9.5 and was extracted with five 30-mL portions of chloroform. The combined extracts were washed with saturated brine and dried (Na_2SO_4). Evaporation of solvent gave 2.41 g of yellow oil which, according to its NMR spectrum, was composed mainly of ca. equal parts of the desired isomers. Separation was effected by chromatography on 320 g of neutral alumina and elution with chloroform–1% methanol, the 1,4 isomer emerging first in 32% yield; slower fractions provided the 1,5 isomer in 27% yield. Both compounds were obtained as oils, and were identified by mass spectra and by comparison of their NMR spectra with those of materials prepared by unequivocal synthesis.[13d]

Nitration of *N*-Methylimidazole-d_2. A solution of 1.0 g of *N*-methylimidazole in 10 mL of 1 N NaOD was heated at 100 °C for 16 h. The solution, after cooling, was extracted with five 15-mL portions of ethyl acetate. The combined extracts were washed with a small amount of saturated brine and dried (Na_2SO_4). Evaporation of the solvent gave a colorless oil (0.83 g); its NMR spectrum in both D_2O and $CDCl_3$ showed only one proton peak in the aromatic region, whose area was slightly less than one-third that of the *N*-methyl peak.

A solution of 0.50 g of this material in 1 mL of concentrated nitric acid was stirred at 0 °C while 2 mL of concentrated sulfuric acid was added in portions over 30 min. The mixture was boiled gently for 2 h, poured into 5 mL of cold water, and brought to pH 5 with 10% sodium hydroxide. A precipitate was collected (0.36 g), which was characterized by NMR and mass spectra as 2,5-dideuterio-1-methyl-4-nitroimidazole. Extraction of the filtrate provided an additional 0.16 g of nitrated material which, according to its NMR spectrum, was composed of the above compound and 2-deuterio-1-methyl-5-nitroimidazole in a 2:1 ratio. NMR spectral analysis was based on comparison with the spectra of the nondeuterated isomers,[7,10b] prepared by published procedures[13a] and separated by chromatography. 1-Methyl-4-nitroimidazole: NMR ($CDCl_3$) δ 3.76 (3 H, s, N-CH_3), 7.44 (1 H, br, H-2), 7.78 (1 H, d, J = 1.5 Hz, H-5). 1-Methyl-5-nitroimidazole: NMR ($CDCl_3$) δ 3.98 (3 H, s, N-CH_3), 7.59 (1 H, br, H-2), 8.05 (1 H, d, J = 1.2 Hz, H-4).

NMR Spectra. Values of δ and J were measured on a Varian HA-100 spectrometer relative to internal (or external) tetramethylsilane or to sodium 3-(trimethylsilyl)propionate-d_4 for D_2O solutions. Room temperature was maintained at 25 °C while the probe temperature was measured at 30 °C. Spin-decoupling and NOE experiments were performed in the usual manner.[28] A Varian A-60 spectrometer was used for kinetic measurements.

Kinetic Measurements. Sodium deuterioxide (40%) was obtained from BioRad Laboratories and D_2O from Aldrich Chemical Co. Solutions of the imidazoles in D_2O (0.2 M) were brought to the desired pD at a Corning pH meter (Model 101). Measured pD values were adjusted by addition of the correction factor 0.40.[29] NMR sample tubes containing the imidazole solutions were maintained at the desired temperature ±0.5 °C in a thermostatically controlled bath or by immersion in a steam cone. At various intervals, the tubes were plunged into an ice bath to quench the exchange reaction and then brought back to 25 °C for NMR measurement. Each signal was integrated four to six times and the results were averaged; deviations never exceeded 5%. Nonexchanging *C*- or *N*-methyl groups were used as internal integration standards. In the case of imidazole itself, the signal for sodium 3-(trimethylsilyl)propionate-d_4 was used as an integration standard; in parallel runs, internal sodium trimethylacetate was used with essentially the same results. No decomposition was observed for any of the compounds. Pseudo-first-order rate constants were determined graphically over two or more half-lives for Y(2) and C(5) exchanges, and over 1–2 half-lives for Y(4,5) exchanges. The values of k_{obsd} in Table I are averages of two to three runs, with deviations of 5–10%.

Registry No.—2,5-Dideuterio-1-methyl-4-nitroimidazole, 66769-96-8; 2-deuterio-1-methyl-5-nitroimidazole, 66769-97-9; 1-methyl-4-nitroimidazole, 3034-41-1; 1-methyl-5-nitroimidazole, 3034-42-2.

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and, based on pK_1 for 2-methylimidazole as 7.85 (H_2O), estimate pK_2 = 15.1 (H_2O) or 15.8 (D_2O).
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Adjacent Lone Pair (ALP) Effects in Heteroaromatic Systems. 2. Isotope Exchange of Ring Hydrogens in Nitro- and Fluoroimidazoles

Yoshio Takeuchi,[1] Kenneth L. Kirk, and Louis A. Cohen*

Laboratory of Chemistry, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20014

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The ring protons of nitro- and fluoroimidazoles (and their *N*-methyl derivatives) undergo base-catalyzed exchange in D_2O by a combination of carbanion (C) and ylide (Y) pathways. In the C pathway, a proton is abstracted from the neutral imidazole species, and in the Y pathway, from the imidazolium ion. In 4-X-imidazoles, C exchange occurs more readily at C-5 than at C-2, log k_C correlating with σ_o^0 for the NH– and with σ_p^0 for the *N*-methyl series. For 1-methyl-4-nitroimidazole, $t_{1/2}$ = 2 min at C-5 (50 °C, 0.2 N NaOD). In 1-methyl-5-X-imidazoles, exchange at C-4 occurs only by the Y pathway, carbanion formation in the neutral species being retarded by the *adjacent lone pair* (ALP) effect at N-3. The same effect is seen in the lack of C exchange at C-4 in 1-methyl-2-X-imidazoles. The ALP effect is considerably weaker or nonexistent at C-2. Most exchanges *across* the ring show correlations of log *k* with σ_m^0. 4-Alkylimidazoles (but not 1,4-dialkylimidazoles) show enhanced C exchange at C-5, which may result from the existence of a trace concentration of the ketimine tautomer. Enhanced exchange at C-5 in 2-fluorohistidine is ascribed to a combination of the ketimine effect, C exchange involving catalysis by hydroxide ion *and* intramolecular general base catalysis by the side-chain primary amine function. The use of buffer catalysis for the tritium labeling of poorly reactive imidazoles is described.

In the first paper of this series,[2] we summarized present knowledge on pathways for isotopic exchange of ring hydrogens in imidazole, *N*-methylimidazole, and their *C*-methyl derivatives (Scheme I of preceding paper):[2] base-catalyzed exchange occurs by a carbanion (C) pathway, in which a proton is abstracted from the *neutral* imidazole species in the rate-limiting step, and/or an ylide (Y) pathway, involving base attack on the imidazolium *ion*. In addition, we established unequivocal assignments for the NMR signals of these hydrogens, presented new data on the rates of solvent–deuterium exchange, and demonstrated that considerable differences in proton acidity are observed at C-4 and C-5, positions which should be fairly equivalent in electron density. These differences were interpreted on the basis of the *adjacent lone pair* (ALP) effect: a ring-nitrogen atom bearing an sp^2 lone pair provides a sizable electrostatic obstacle to the generation of an sp^2 carbanion at an adjacent ring-carbon atom. While operation of the ALP effect is readily demonstrable at C-4 (adjacent to the lone pair at N-3), the magnitude of the effect at C-2 could not be evaluated because ylide exchange (Y) at the latter position may be 500–1000-fold faster than carbanion (C) exchange. Ylide exchange is not subject to the ALP effect because the lone pair at N-3 is utilized in formation of the imidazolium ion. We had hoped, therefore, that electronegative substituents at C-4 or C-5 might retard the Y pathway at C-2 and permit an evaluation of C exchange at the latter position. Further, it was conceivable that an electronegative group at C-5 might reduce or negate the ALP effect at C-4.

For various biological studies, we also needed practical routes to tritium-labeled fluoroimidazoles, as well as data on tritium loss from the labeled materials.[3] Initial studies had already indicated that the apparent acidities[4] of the ring hydrogens in these compounds are inconsistent with expectations based on nonfluorinated imidazoles. Thus, at pD 11 and 50 °C, $t_{1/2}$ = 7 h for exchange of H-2 in histidine,[5] while H-2 in 4(5)-fluorohistidine fails to exchange over a wide range in temperature or pD.[6] In contrast, H-5 in 2-fluorohistidine exchanges with $t_{1/2}$ = 20 h under the stated conditions, while H-5 in histidine is totally inert to exchange (except at very high temperatures). In our attempt to rationalize the behavior of the fluoroimidazoles, we were also led to examine imidazoles containing nitro[7] and several other substituents. Since alkylation of the imidazole NH eliminates complications due to ionization in basic media, 1-methyl-X-imidazoles (series **1–3**) were examined first. The principal compounds investigated are summarized in Chart I.

Chart I