Acid-Catalyzed Isotope Exchange of Ring Hydrogens in Fluoroimidazoles

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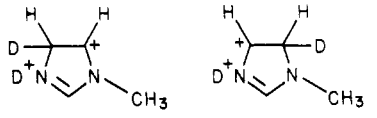
Acid-catalyzed exchange of ring protons in 1-methylimidazole is known to occur (in D_2O) by electrophilic attack on the imidazolium ion (E pathway). Significant reaction rates are observed only at high temperatures and in moderately strong acid media; relative reactivities at 163 °C and 1 N DCl are H-2 (1), H-5 (30), and H-4 (50). An alternative mechanism (E′), involving electrophilic attack at C-4 or C-5 in the neutral molecule, has now been demonstrated for imidazoles which have low pK values and which have one or two substituents capable of stabilizing a carbonium ion. Exchange by the E′ pathway occurs far more readily than E exchange; thus, in 0.1–3 N DCl at 50 °C, $t_{1/2} \simeq 9$ h for 4-fluoro-2-methyl-, 12 h for 4-fluoro-1-methyl, 16 h for 2-fluoro-4-methyl-, and 54 h for 4-fluoroimidazole. Under these conditions, no exchange is observed at C-2. For exchange of H-4 in 1-methylimidazole (50 °C, 1 N DCl) the estimated $t_{1/2} \simeq 84$ years. To date, fluorine has been found the only common substituent capable of providing the necessary combination of electronegativity and resonance overlap to permit facile exchange by the E′ pathway.

As an extension of our studies on solvent deuterium isotope exchange of imidazole ring protons in neutral and alkaline media (at 50–100 °C),[2,3] we examined the behavior of the previously investigated compounds in dilute acid. These experiments were undertaken, primarily, to verify the pD dependence profile for exchange predicted by the mechanisms and rate expressions under consideration. Thus, on the basis of rate data reported for the ylide exchange of these compounds at 50 °C[3] and for the acid-catalyzed exchange of 1-methylimidazole ring protons at 163 °C,[4] no significant exchange was expected for nitro- or fluoroimidazoles at the lower temperature. We were surprised, therefore, to find that several fluoroimidazoles exhibited remarkably facile isotope exchange in 1 N DCl at 50 °C. In this report, we account for the unexpected results on the basis of a special pathway for acid-catalyzed exchange which, under such mild conditions, may be available only to fluoroimidazoles.

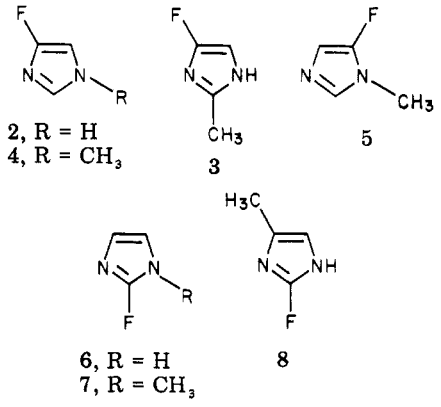
In their study of acid-catalyzed exchange of 1-methylimidazole ring protons at 163 °C, Wong and Keck[4] found log k_{obsd}, at each position, to increase linearly with D_0. These results are compatible with electrophilic attack by D^+ on the imidazolium ion (Scheme I, path E). Although H-2 is the proton most reactive to exchange in neutral or alkaline media, it becomes the least reactive proton in acid media. At 163 °C and in 1 N DCl, relative rates of exchange are as follows: H-2, 1; H-5, 30; H-4, 50.[4,5] The low reactivity at C-2 may be due to the reluctance of the amidinium ion component to surrender its resonance stabilization in the intermediate. The greater reactivity at C-4 over C-5 may result from reduced Coulombic repulsion in the carbonium ion intermediate, as in **1a** vs. **1b** (ref 6b, footnote 12). Even at the lowest acid concentrations necessary to observe electrophilic exchange, no evidence was found for exchange involving the neutral imidazole species 1.



1a 1b

Results and Discussion

Most of our exchange studies at pD 9–14 were conducted at 50 °C, and, since we intended to demonstrate the *absence* of acid-catalyzed exchange at this temperature, we did not seek to force exchange to occur at higher temperatures. At 50 °C and in 1 N DCl, neither imidazole nor any of the following alkylimidazoles showed measurable loss of ring proton NMR signals over a 30-day period: 1-methyl-, 2-methyl-, 4-methyl-, 1,2-dimethyl-, 1,4-dimethyl-, and 1,5-dimethylimidazole. An extrapolation from the rate data for 1-methylimidazole at 163 °C to 50 °C (E_a assumed equal to 21 kcal/mol)[3] and 1 N DCl suggests $t_{1/2} \simeq 84$ years for this compound. The following imidazoles also gave no evidence of exchange over 30 days at 50 °C in 1 or 3 N DCl: 2-amino-, 2-amino-4-methyl-, 2-chloro-, 2-nitro-, 4-nitro-, 1-methyl-2-nitro-, 1-methyl-4-nitro-, 1-methyl-5-nitro-, 4-methyl-2-nitro-, 2-methyl-4-nitro-, 4-bromo-2-methyl-, 4-(trifluoromethyl)-, 4-methyl-2-(trifluoromethyl)-, and 4,5-difluoroimidazole. On the other hand, there was relatively rapid exchange of H-5 in 4-fluoro- (**2**), 4-fluoro-2-methyl- (**3**), 4-fluoro-1-methyl- (**4**), and 2-fluoro-4-methylimidazole (**8**); exchange was much slower in 5-fluoro-1-methylimidazole (**5**) (Table I). In the cases of 2-fluoro- (**6**) and 2-fluoro-1-methylimidazole (**7**), loss of fluorine occurred too rapidly[6] to permit observation of exchange.



2, R = H
4, R = CH_3 3 5

6, R = H 8
7, R = CH_3

In contrast with the results for 1-methylimidazole,[4] k_{obsd} for the fluoroimidazoles, remained essentially constant in

(1) Visiting Associate, National Institutes of Health, 1973–1977.
(2) Y. Takeuchi, H. J. C. Yeh, K. L. Kirk, and L. A. Cohen, *J. Org. Chem.*, **43**, 3565 (1978).
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(4) J. L. Wong and J. H. Keck, Jr., *J. Org. Chem.*, **39**, 2398 (1974).
(5) As demonstrated previously,[2] the NMR signal assignments for H-4 and H-5 are actually the reverse of those made by Wong and Keck.[4] The specific rate constants reported by these authors also appear to be in error: on the basis of their values of k_{obsd} for acid-catalyzed exchange, we find k_d(H-2) = 2.0×10^{-8}, k_d(H-5) = 6.03×10^{-7}, and k_d(H-4) = 9.78×10^{-7} M^{-1} s^{-1}.
(6) (a) K. L. Kirk, W. Nagai, and L. A. Cohen, *J. Am. Chem. Soc.*, **95**, 8389 (1973); (b) K. L. Kirk and L. A. Cohen, *ibid.*, **95**, 4619 (1973).

Scheme I

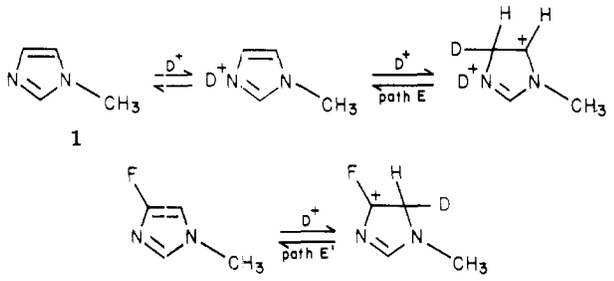


Table I. Rate Constants for Acid-Catalyzed Exchange of Fluoroimidazoles[a]

compd	site	$t_{1/2}$, h	$k_{E'}$, min^{-1} M^{-1}	k_{obsd} (decomp), min^{-1}	pK_1 (H_2O, 25 °C)
2[b]	5	54	0.0552	c	2.44
3	5	9	3.14	c	3.40
4[d]	5	12	0.0707	3.20×10^{-5}	1.90
5[d]	4	6860	0.0119	c	3.85
6[b]	4,5		e	2.22×10^{-4}	2.40
7[d]	4,5		e	1.27×10^{-4}	2.30
8[d]	5	16.4	0.710	c	3.06

[a] In 1 N DCl at 50 °C. [b] Reference 6b. [c] No decomposition observed prior to complete exchange. [d] Reference 3. [e] No exchange observed prior to complete decomposition.

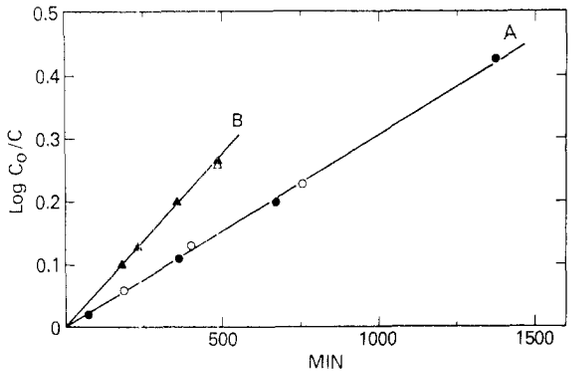


Figure 1. Rates of isotope exchange at 50 °C in 1 N DCl (▲, ●) and 3 N DCl (△, ○): A, 2-fluoro-4-methylimidazole (**3**); B, 4-fluoro-2-methylimidazole (**8**).

media ranging from 0.1 to 3 N DCl (Figure 1). These observations suggest an electrophilic attack on the neutral imidazole species (Scheme I, path E′). In the rate expression (eq 1), the term in parentheses approaches the limit

$$\text{rate} = k_{E'}[\text{Im}][D^+]$$

$$k_{obsd} = k_{E'}K_1[D^+]/(K_1 + [D^+]) \quad (1)$$

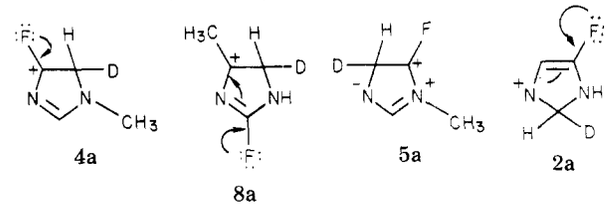
K_1 (the dissociation constant for the imidazolium ion) as $[D^+] \gg K_1$; thus k_{obsd} should remain constant for any pD or D_0 at least 1.5 units lower than the pK_1 for the compound.

Evidently, the first requirement for achievement of measurable exchange (under the stated conditions) is low basicity for the imidazole ring, so that a significant fraction of the neutral species can exist in a medium of moderate acidity; thus, the E′ pathway is not observed with alkylimidazoles, which have pK_1 values above 7. On the other hand, neither is exchange observed with most imidazoles which do have the desired low pK_1 values; e.g., 1-methyl-5-nitroimidazole (pK_1 = 2.13) and 4-trifluoromethylimidazole (pK_1 = 2.28) fall in the same pK range as **2** (pK_1 = 2.44) and **4** (pK_1 = 1.90), compounds which exchange readily. Upon consideration of electrophilic substituent constants (σ_p^+),[7] the results become rational: the fluorine atom (σ_p^+ = −0.07) can assist carbonium ion formation, but the nitro and trifluoromethyl groups have a retarding effect. Fluorine is, in fact, the only common substituent for which σ_p and σ_p^+ have opposite signs, the result of an exaggerated contribution of lone-pair overlap in electrophilic processes.

In **2**, **4**, and **5**, the fluorine substituent alone provides both requirements, i.e., reduction in ring basicity and resonance stabilization of the C-4 carbonium ion (as in **4a**). In **3** and **8**, the stabilizing effects of the fluorine atom and the methyl group are additive (as in **8a**); these compounds show enhanced $k_{E'}$ values. Despite its strong capability for stabilizing a carbonium ion via hyperconjugation (σ_p^+ = −0.31), the methyl group alone is ineffectual because it cannot reduce ring basicity. The difference in $k_{E'}$ values for **3** and **8** suggests that σ_o^+ and σ_p^+ values are different because of distance-dependent inductive components[8] or even that their resonance components may not be equivalent.

Studies of substituent effects on solvolysis in imidazole[9] and thiazole[10] systems also provide complexities in their Hammett analyses. In electrophilic exchange of monosubstituted benzenes, *o*- or *p*-CH_3 has been found to be 200–500 times more effective than hydrogen and 100–200 times more effective than *p*-F;[11] surprisingly, however, *o*-F proved to be 7–8 times *less* effective than hydrogen for ring activation. In the present studies, we have not attempted any correlations of rate data with σ values, since the number of compounds and effective substituents are too few to provide a meaningful analysis.

Exchange at C-4 in **5** is almost 600-fold slower than that at C-5 in **4**; this difference is due, primarily, to the fact that **5** is ca. 2 pK units more basic than **4**. With respect to $k_{E'}$ values, however, **5** is only 6-fold less reactive than **4**. Resonance and inductive effects should be of comparable magnitude in either direction along the 4,5 double bond. Possibly, carbonium ion formation at C-5 (in **5**) is repressed by steric hindrance to solvation, because of the adjacent 1-methyl group; alternatively, the loss of electron density at N-1 due to amidine resonance may provide a Coulombic barrier at C-5 (as in **5a**).



All 2-fluoroimidazoles are subject to acid-catalyzed solvolysis,[6] displacement,[6] and condensation[12] reactions. Such transformations of **6** and **7** occurred too rapidly to permit measurement of exchange.[13] On the other hand, an alkyl group at C-4 (or C-5) exerts a powerful stabilizing effect at C-2, and **8** underwent total exchange without detectable decomposition. Although 2-chloroimidazole is a fairly weak base (pK_1 = 3.5) and is completely stable to decomposition under the reaction conditions, the substituent (σ_p^+ = +0.11) is unable to provide the necessary stabilization for

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(11) C. Eaborn and R. Taylor, *J. Chem. Soc.*, 247, 2388 (1961).
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(13) No evidence of exchange in **6**, prior to its total decomposition, was observed by mass spectroscopy; thus, the value of $k_{E'}$ for **6** must be considerably less than that obtained for its isomer, **2**.

the carbonium ion to permit detectable exchange. In 4-bromo-2-methylimidazole (pK_1 = 4.6), the carbonium ion stabilizing ability of the methyl group is inadequate to overcome the deactivating effect of bromine; furthermore, the ring basicity may already be too high to permit detectable exchange under our mild conditions. In principle, the necessary reduction in ring basicity might also be achieved by use of an electron-withdrawing N-substituent, such as an arylsulfonyl group; however, no electronegative group has been found capable of surviving the acidity of the exchange medium.

In no case was exchange observed at C-2, probably because amidine resonance must be sacrificed in the formation of a carbonium ion intermediate. Fluorine at C-5 does not help to overcome this energy barrier by resonance coupling to a positive charge at N-3 (**2a**), nor is C-2 exchange observed for 4,5-difluoroimidazole.

Clearly, the number of possible substituents which meet the requirements for the E′ pathway is extremely limited, and, indeed, fluorine may be unique in its ability to supply the appropriate combination of inductive and resonance effects. An additional, but rather special, case is observed with imidazole trimers.[12]

Little is known regarding the effect of ring substituents in electrophilic attack on imidazoles.[14] The nitration of imidazole is considered to involve attack on the imidazolium ion, while bromination may occur on the neutral molecule. The results of electrophilic isotope exchange studies provide a useful basis for predicting other electrophilic reactions of fluoroimidazoles. For example, 2-fluoroimidazole resists ring nitration at 100 °C, while nitration of 2-fluoro-4-methylimidazole can be observed even at −60 °C![15] This remarkable contrast in behavior is qualitatively consistent with the effect of the 4-methyl group in promoting isotope exchange in 8.

Experimental Section[16]

Materials. Sources or synthetic routes for most compounds used in this study have been described previously.[2,3] Literature methods were used to prepare 2-aminoimidazolium sulfate,[17] 2-amino-4-methylimidazole,[18] 2-methyl-4-nitroimidazole,[19] 4-bromo-2-methylimidazole,[20] and 4-methyl-2-(trifluoromethyl)-imidazole.[21] Synthetic routes to 4,5-difluoroimidazole and 4-methyl-2-nitroimidazole will be described elsewhere. Deuterium chloride (20%) and deuterium oxide (99.8%) were obtained from Aldrich Chemical Co.

2-Chloroimidazole. This compound has been prepared in 25% yield by the action of phosphorus oxychloride on 2-imidazolone.[22] The following method is based on the technique used for the synthesis of 2-fluoroimidazoles.[6] To a solution of 2.64 g (20 mmol) of 2-aminoimidazolium sulfate[17] in 75 mL of concentrated hydrochloric acid, which was maintained at 0 °C (ice–salt), was added a solution of 1.6 g of sodium nitrite in 5 mL of water. After 15 min, an additional 200 mL of concentrated hydrochloric acid was added, and the solution was irradiated at 0 °C for 15 min.[6] The solution was chilled (dry ice–acetone), was neutralized with concentrated sodium hydroxide, and was extracted with three 50-mL portions of ethyl acetate. The combined extracts were dried (Na_2SO_4) and evaporated to give 0.82 g of a colorless solid (40% yield); the material was triturated with ether, and the residue was crystallized from ethyl acetate; mp 164–165 °C (lit.[22] mp 165–166 °C).

4-Fluoro-2-methylimidazole (3). A solution of 1.91 g (14.5 mmol) of 2-methyl-4-nitroimidazole[19] in 150 mL of 50% fluoroboric acid was stirred at −10 °C under argon, while 2.9 g (45 mmol) of zinc dust was added in four portions at 5-min intervals. The mixture was stirred an additional 15 min and was then filtered through a loose glass-wool plug. To the stirred filtrate, at 0 °C, was added 1.03 g (15 mmol) of sodium nitrite dissolved in the minimum amount of water. The solution was kept at 0 °C for 30 min and was then irradiated for 1 h, according to the standard procedure.[23] The solution was neutralized with cold, concentrated sodium hydroxide and was then saturated with hydrogen sulfide. After separation of zinc sulfide by filtration through a Celite mat, the filtrate was extracted with four 50-mL portions of ethyl acetate. The combined extracts were dried (Na_2SO_4) and evaporated. The residual material was chromatographed on silica gel (elution with ethyl acetate) to give 310 mg (21%) of **3**, which was purified further by sublimation; mp 142–143 °C. Identity and homogeneity were confirmed by NMR and mass spectra.

Anal. Calcd for $C_4H_5N_2F$: C, 47.99; H, 5.03; N, 27.99; F, 18.98. Found: C, 47.72; H, 5.18; N, 27.41; F, 19.09.

Kinetic Measurements. The techniques used to follow rates of exchange by NMR spectroscopy are described in previous reports.[2,3] For compounds **3**, **4**, and **5**, identification of the ring proton signals was based on the large differences in coupling constant between protons adjacent to, and distal from, the fluorine atom. Loss of proton signal, in the case of **6**, did not differentiate exchange from decomposition. After partial and total loss of the signal, the reaction mixtures were neutralized and subjected to mass spectral analysis; no evidence for deuterated analogues of **6** was found. Decomposition of **7** was readily observed by the appearance of a multiplicity of new *N*-methyl signals. The specific rate constants in Table I were calculated by use of eq 1. Values of pK_1 (H_2O, 25 °C) were adjusted to pK_1 (D_2O, 50 °C) by the methods previously described.[3] The activity of deuterium ion was assumed equal to its concentration, and temperature effects on activity were neglected.

Registry No. **2**, 30086-17-0; **3**, 71516-19-3; **4**, 66787-67-5; **5**, 66787-68-6; **6**, 57212-34-7; **7**, 66787-69-7; **8**, 57212-35-8; 4-fluoro-5-deuterioimidazole, 71516-20-6; 2-methyl-4-fluoro-5-deuterioimidazole, 71516-21-7; 1-methyl-4-fluoro-5-deuterioimidazole, 71516-22-8; 1-methyl-4-deuterio-5-fluoroimidazole, 71516-23-9; 2-fluoro-4-methyl-5-deuterioimidazole, 71516-24-0; 2-chloroimidazole, 16265-04-6; 2-imidazolone, 5918-93-4; 2-aminoimidazolium sulfate, 1450-93-7; 2-methyl-4-nitroimidazole, 696-23-1.

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