Proton transfer from imidazole, benzimidazole, and their 1-alkyl derivatives. FMO analysis of the effect of methyl and benzo substitution[1]

ERWIN BUNCEL AND HELEN A. JOLY
Department of Chemistry, Queen's University, Kingston, Ont., Canada K7L 3N6
AND
JOHN R. JONES
Department of Chemistry, University of Surrey, Guildford, GU2 5XH, U.K.
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This paper is dedicated to Professor Arthur N. Bourns

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The rate–pH profile for detritiation from the C-2 position of 1-methylimidazole has been determined in aqueous solution at 85°C. The profile is consistent with a mechanism involving attack by hydroxide ion on the conjugate acid of the substrate to give an ylid intermediate in the rate-determining step. At higher pH, hydroxide-catalyzed exchange of the neutral species becomes increasingly important. Comparison of the second-order rate constants derived from the rate–pH profiles of imidazole, 1-methylimidazole, benzimidazole, and 1-methylbenzimidazole showed that methyl substitution caused the rate to increase by 2- to 3-fold while benzo annelation increased the rate by 10- to 20-fold. Frontier molecular orbital (FMO) analysis of the reaction scheme for proton transfer from imidazole, benzimidazole, and their 1-alkyl derivatives has been used to explain the rate-accelerating effect of methyl substitution and benzo annelation in these processes.

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Opérant à 85°C et dans une solution aqueuse, on a déterminé un profil de la vitesse/pH pour la réaction de détritiation de la position C-2 du méthyl-1 imidazole. Le profil est en accord avec un mécanisme impliquant une étape déterminante dans laquelle un ion hydroxyde attaque l'acide conjugué du substrat pour conduire à un ylide intermédiaire. A des pH plus élevés, l'échange catalysé par des bases des espèces neutres devient de plus en plus important. Une comparaison des constantes de vitesse du deuxième ordre, obtenues à partir des profils de vitesse/pH, des imidazole, méthyl-1 imidazole, benzimidazole et méthyl-1 benzimidazole a permis de montrer que la substitution par des groupements méthyles multiplie la vitesse par 2 à 3 alors que l'annelation par un noyau benzénique multiplie les vitesses par 10 à 20. Dans le but d'expliquer l'accélération de la vitesse lors de substitutions par des groupements méthyles et lors de l'annelation par des cycles benzéniques, on a utilisé une analyse, par les orbitales moléculaires frontières, du schéma réactionnel des transferts protoniques de l'imidazole, du benzimidazole et de leurs dérivés substitués par un groupement méthyle en position 1.

[Traduit par la revue]

The rate of hydrogen isotope exchange from the C-2 position of the imidazole ring is of interest, in part because of its presence in biologically important systems such as adenine and guanine, fundamental components of nucleic acids, and in drugs such as puromycin. Imidazole is also the primary component of histidine which is present at the active site of many enzymes. The importance of the imidazole ring can be coupled with the use of deuterium and tritium labels as probes in the investigation of chemical and biochemical processes. For instance, the rate of hydrogen isotope exchange from the C-2 position of the imidazole nucleus present in the histidine residues of the enzymes β-lactamase II and superoxide dismutase has been used to identify the specific histidine residues which act as ligands towards metal ions (1, 2). It is useful therefore to have some knowledge of the factors which can influence the rates of deuterium or tritium loss from the imidazole moiety in different structural environments.

Past studies (3) of proton abstraction from compounds containing the imidazole nucleus suggest that reaction occurs via rate-determining hydroxide attack on either the protonated or the neutral forms of the substrate to form an ylid intermediate. On the basis of such a mechanism one would expect the rate of isotopic hydrogen exchange to be dramatically increased on introduction of a positive charge at sites adjacent to the exchanging hydrogen.

Isotopic exchange involving 1-methylimidazole has previously been studied by two groups of workers but the results obtained are at variance. Harris and Randall (4) reported that the rate–pH profile for deuteration of the C-2 position of 1-methylimidazole at 26°C in the pH region 0–14 was sigmoid. Between pH values 0–4 the rate was undetectable but increased sharply between pH 4–8, beyond which the rate leveled off. This study was qualitative in the sense that the overall rate was not dissected into constituent second order rate constants. Wong and Keck (5) also determined a rate–pH profile for C-2 hydrogen/deuterium exchange between pH 0–14 at 81°C. This study showed some discrepancy with the findings of the previous workers in that the rate increased from pH 2 until pH 8.

The rate–pH profiles obtained for detritiation of 9-alkylpurines (6), 1-methylguanosine (7), and 1-methylinosine (7), which are structurally similar to 1-methylimidazole in that they possess the imidazole nucleus and the pyrrole nitrogen adjacent to C-2 is substituted by an alkyl group, show some deviation in highly basic media from the profile reported for 1-methylimidazole (4, 5), since the rates of proton exchange for the former compounds increase with pH in this region. A re-investigation of the 1-methylimidazole system using a more sensitive means of obtaining rate data was desirable and the results of the detritiation study are reported herein. The resulting reactivity relationships involving imidazole (**1**, R = H), 1-methylimidazole (**1**, R = Me) and the corresponding benzimidazole derivatives (**2**, R = H or Me) which have come to light in

[1]Hydrogen exchange studies, Part 15; for Part 14, see ref. 23.

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this work are unusual in terms of qualitative electronic considerations, but can be explained using frontier molecular orbital theory.

R = H or Me

1 2

Experimental

Preparation of [2-^{3}H]-1-methylimidazole

Tritiated water (5 μL, 50 Ci/mL) was added to freshly distilled 1-methylimidazole (100 μL) in a small glass ampoule. After sealing, the ampoule was submerged in an oil bath at 85°C for 72 h. The ampoule was then opened, 1 mL of methanol was added to exchange labile tritium and the solvent was removed by lyophilization. Addition of 1 mL portions of methanol was continued until the activity of the lyophilized methanol was found to be insignificant. The purity of the [2-^{3}H]-1-methylimidazole as well as the specificity of labelling of the tritium in the C2 position was checked by ^{1}H and ^{3}H nmr.

Kinetics

The rates of detritiation of [2-^{3}H]-1-methylimidazole in a series of aqueous buffer solutions of known pH – temperature dependence (8) were determined by measuring the increase in the radioactivity of the reaction medium with time in a fashion similar to that used for imidazole (9) and benzimidazole (10). [2-^{3}H]-1-methylimidazole (10 μL) was dissolved in 20 mL of an aqueous buffer solution previously thermostatted at 85.0 ± 0.2°C. Ten 0.5 mL aliquots of the reaction mixture were withdrawn individually at specific time intervals, placed into small round bottom flasks and cooled in liquid nitrogen. Lyophilization of the quenched samples enabled separation of the water from the substrate. A 0.1 mL aliquot of the water collected was placed in 6 mL of Unisolve E liquid scintillator and assayed for tritium (C_t) on a Beckman 100 liquid scintillation counter. The exchange reaction was generally followed for at least two half-lives. The infinity reading (C_∞), i.e., the activity of the water after complete exchange, was obtained by counting the activity of 0.1 mL of the original reaction mixture. All samples were counted for 2 min to ensure statistical accuracy. The pseudo first order rate constant, k_{obs}, was obtained from the slope ($-2.303k_{obs}$) of the plot of log ($C_\infty - C_t$) as a function of time t. The rate constant data in Table 1 are average values of two or more determinations which generally agreed to within 2–3%. For very slow reactions an initial rate method was employed wherein the tritium content of the water (C_t) was measured for only the first 3–5% of the reaction. A linear plot of C_t vs. t is obtained with slope equal to the zero-order rate constant (k_0). The first order rate constant k_{obs} for the slow reactions was obtained by dividing k_0 by the total radioactivity of the substrate (C_∞) obtained as before.

Potassium hydrogen phthalate and sodium borate buffers were used for kinetic measurements carried out at low and intermediate pH ranges, respectively, while sodium hydroxide solutions were used for measurements at higher pH values.

Results and discussion

Kinetic analysis and reaction mechanism

The results obtained for detritiation of [2-^{3}H]-1-methylimidazole in aqueous buffers at 85°C are listed in Table 1 and shown graphically in Fig. 1 in the form of a rate–pH profile for the pH range 2.5–11.5. Exchange rates in more basic media (pH > 11.5) were too fast to be reliably determined by the kinetic technique used.

The rate profile for 1-methylimidazole is similar to that obtained (10) for 1-methylbenzimidazole (Fig. 1) as well as for

TABLE 1. Rates of detritiation of [2-^{3}H]-1-methylimidazole as function of pH at 85.0 ± 0.2°C

pH at 85.0°C	$k_{obs} \times 10^4$ (s^{-1})	pH at 85.0°C	$k_{obs} \times 10^4$ (s^{-1})
2.56	0.0204	9.18	29.6
3.77	0.248	10.52	28.5
4.94	2.80	10.82	28.4
6.25	21.2	11.20	34.7
7.70	30.3	11.51	34.5

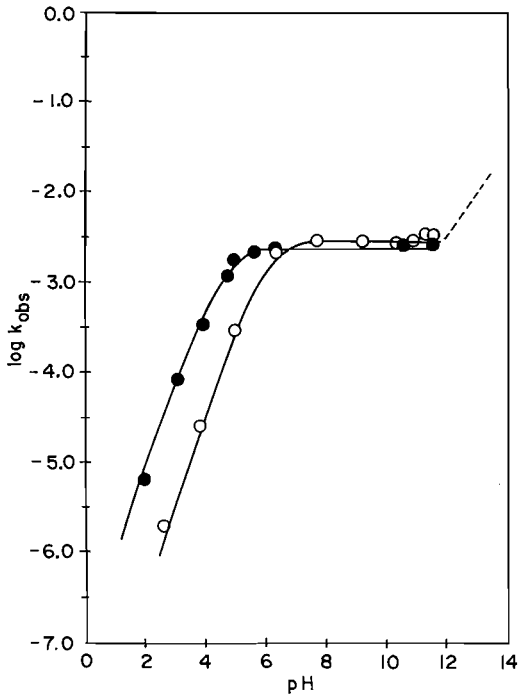


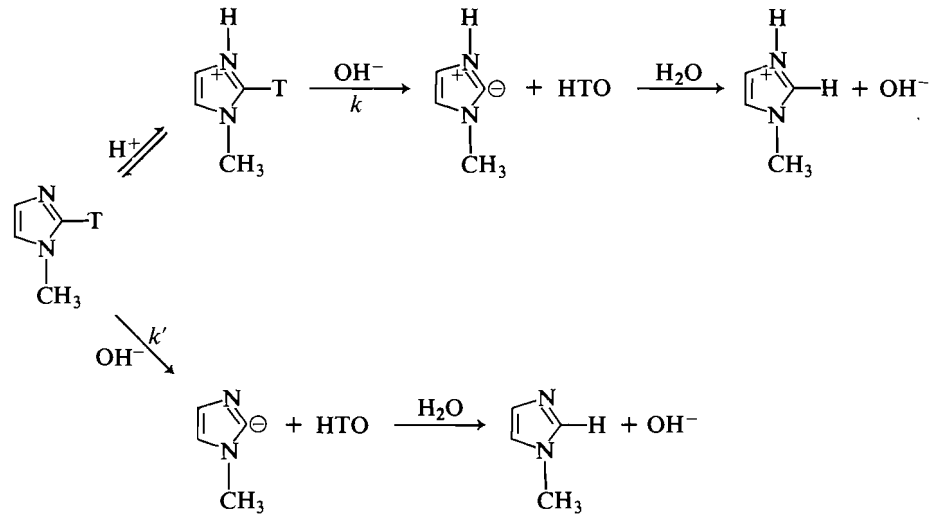
FIG. 1. Rate–pH profiles for the detritiation of [2-^{3}H]-1-methylimidazole ○ and [2-^{3}H]-1-methylbenzimidazole ●. The solid lines represent the theoretical profiles calculated from eq. [9] using the values from the text and the dashed line is the theoretical behaviour expected on the basis of eq. [5].

1-methylguanosine, 1-methylinosine (7), and 9-alkylpurines. Initially the rate increases with increasing pH until a pH-independent region is obtained, extending between pH 7 and 10. Such behaviour is consistent with a mechanism in which the conjugate acid of the substrate is being attacked by hydroxide ion in the rate determining step. At pH > 11 the rate increases again with increasing pH. This has been attributed to rate-determining attack by hydroxide ion on the neutral form of the substrate (Scheme 1). Though the rate of tritium exchange in more highly basic media (pH > 11.5) could not be determined, one would expect 1-methylimidazole to behave in a manner similar to that of the 9-alkylpurines (6), namely that the rate would increase with increasing pH. The expected behaviour is indicated by a dashed line in Fig. 1.

The rate expression for the isotopic exchange reaction over the entire pH region is given by eq. [1] from which eq. [2] follows,

$$[1] \quad \text{Rate} = k[\text{ImH}^+][\text{OH}^-] + k'[\text{Im}][\text{OH}^-] = k_{obs}[\text{Im}]_T$$

$$[2] \quad k_{obs} = (k[\text{ImH}^+] + k'[\text{Im}])[\text{OH}^-]/[\text{Im}]_T$$



SCHEME 1

where $[ImH^+]$ and [Im] represent the concentration of the protonated and neutral forms of 1-methylimidazole, respectively, k and k' are the corresponding second order rate constants, and k_{obs} is the pseudo-first order rate constant for the detritiation of [2-^{3}H]-1-methylimidazole. The $[ImH^+]$ and [Im] terms can be expressed by means of experimentally measurable quantities, i.e.

$$[3] \quad [ImH^+] = [Im]_T/(1 + K_a/[H^+])$$

$$[4] \quad [Im] = [Im]_T/(1 + [H^+]/K_a)$$

Now $[Im]_T = [ImH^+] + [Im]$, where $[Im]_T$ is the total concentration of 1-methylimidazole in solution. Also, the acid association constant of protonated 1-methylimidazole is given by $K_a = [Im][H^+]/[ImH^+]$. Substitution of eqs. [3] and [4] into [1] gives

$$[5] \quad k_{obs} = \frac{k[H^+][OH^-]}{K_a + [H^+]} + \frac{k'K_a[OH^-]}{K_a + [H^+]}$$

At low pH, $[H^+] \gg K_a$ and eq. [5] reduces to

$$[6] \quad k_{obs} = k[OH^-] + \frac{k'K_a[OH^-]}{[H^+]}$$

Since K_a is small, and at low pH, [OH] is small while $[H^+]$ is large, the second term can be neglected and eq. [7] follows.

$$[7] \quad k_{obs} = k[OH^-]$$

In accord with eq. [7], plotting k_{obs} versus $[OH^-]$ for the first three data points in Table 1 (pH 2.56–4.94) gave an excellent linear plot which yielded $k = 1.01 \times 10^4\ L\ mol^{-1}\ s^{-1}$ as the rate constant for deprotonation of the conjugate acid (Scheme 1). The rate constant k' corresponding to deprotonation of the neutral substrate is usually derived by plotting data in the high pH region (see eq. [5]) but this could not be evaluated in the present study as noted above.

At the intermediate pH values, corresponding to the plateau region in Fig. 1, $K_a \gg [H^+]$ and eq. [5] reduces to eq. [8], neglecting the second term.

$$[8] \quad k_{obs} = kK_w/K_a$$

Using the values of k ($1.01 \times 10^4\ L\ mol^{-1}\ s^{-1}$), k_{obs} for the pH-independent region ($2.95 \times 10^{-3}\ s^{-1}$) and K_w at 85°C (3.16×10^{-13}) (11), enables K_a for 1-methylimidazole to be estimated as $1.08 \times 10^{-6}\ mol\ L^{-1}$, i.e. $pK_a = 5.96$ at 85°C. The experimentally (12) determined pK_a value is ca. 7.2 at 25°C. Typical temperature coefficients (13) for nitrogen acids of similar acidities are $-0.022\ pK_a$ units per °C rise, and hence the experimental pK_a at 85°C should be 5.88. Extrapolation of pK_a versus temperature data (12) collected for 1-methylimidazole between 10 and 45°C suggests that the pK_a at 85°C for 1-methylimidazole is 6.09. These values are in good agreement with the calculated value from the rate data as given above.

The solid curve drawn for the 1-methylimidazole rate data in Fig. 1 is the result of calculating, for various $[H^+]$ values, theoretical k_{obs} values by means of eq. [9], using $k = 1.01 \times 10^4\ L\ mol^{-1}\ s^{-1}$, $K_w = 3.16 \times 10^{-13}$, and $K_a = 1.08 \times 10^{-6}\ mol\ L^{-1}$.

$$[9] \quad k_{obs} = kK_w/(K_a + [H^+])$$

Equation [9] is obtained from [5] assuming that the contribution from the hydroxide-catalyzed exchange of the neutral species is small and that the second term can hence be neglected. The agreement with the experimental data is satisfactory.

Reactivity relationships

One can compare the second order rate constant corresponding to the rate-determining attack of hydroxide ion on the conjugate acid of 1-methylimidazole with the corresponding rate constants previously reported for imidazole (9), benzimidazole (9, 10), and 1-methylbenzimidazole (9), Table 2. Thus inclusion of the results for 1-methylimidazole allows for a more complete discussion of the effect of methyl substitution and benzo annelation on proton transfer from heterocycles containing an imidazole nucleus. Substitution of N-1 of imidazole and benzimidazole with a methyl group causes the rate of proton transfer to increase by a factor of 2 and 3 respectively, while annelation of a benzo group to the imidazole and 1-methylimidazole nucleus results in a 10- or 20-fold rate increase, respectively (Table 2).

It is also noteworthy that substitution by a methyl group at the N-1 position of imidazole and benzimidazole has no effect on the magnitude of the pK_a for N_3-protonation, i.e. a pK_a value of 6.0 was found for both imidazole and 1-methylimidazole, while a pK_a value of 4.6 was found for both benzimidazole and 1-methylbenzimidazole. On the other hand, benzo annelation

TABLE 2. Comparison of pK_a and rate constants derived from rate–pH profiles for imidazole (Im), benzimidazole (ϕIm) and their 1-methyl derivatives

Compound	pK_a	k ($L\ mol^{-1}\ s^{-1}$)	k_{Me}/k_H	$k_{\phi Im-X}/k_{Im-X}$ (X = Me or H)
Imidazole (**1**, H)	5.9	6.0×10^3	2	10 (X = H)
1-Methylimidazole (**1**, Me)	6.0	1.0×10^4		20 (X = Me)
Benzimidazole (**2**, H)	4.6	6.2×10^4	3	
1-Methylbenzimidazole (**2**, Me)	4.6	2.0×10^5		

does have a substantial effect on the pK_a, which decreases by 1.3 pK units for both imidazole and 1-methylimidazole.

An interesting point in these systems is that they lack a saturation effect, that is, the effect of methyl substitution on the rate of C(2)–H exchange, is not diminished by benzo annelation ($k_{MeIm}/k_{Im} = 2$ and $k_{Me\phi Im}/k_{\phi Im} = 3$). Conversely the effect of benzo annelation on the rate of C(2)–H exchange is not reduced by methyl substitution ($k_{\phi Im}/k_{Im} = 10$ and $k_{Me\phi Im}/k_{MeIm} = 20$).

Conventional arguments, such as those based on the inductive effect of the methyl substituent, do not suffice to explain reactivity diferences in these systems. For example, a methyl group acting as an inductively electron-releasing substituent would be expected to destabilize the ylid intermediate and thereby lead to a rate decrease, whereas the opposite is found to be the case. However, Jones and co-workers (3*a*, 11) showed that there is a linear correlation between log k, the second order rate constant for C-2 proton exchange in azoles, and pK_a for N_3-protonation, which is adhered to by imidazole and benzimidazole. We have found that frontier molecular orbital (FMO) theory provides an explanation of reactivity in the series imidazole, benzimidazole and their 1-methylated analogs, as described below.

FMO analysis of reactivities

The effect of benzo annelation and methyl substitution on the rate of proton transfer from these imidazole derivatives can be rationalized by means of the FMO approach (14, 15). We consider the rate-determining step of the reaction and apply FMO theory to obtain the relative energies of the reacting species and of the intermediates involved, as a result of the structural change which is effected.

Thus considering the exchange process as involving abstraction of the C(2)-hydrogen from the reactant species (R), i.e., the protonated substrate, to form the ylid intermediate (I), one can dissect the reactant and intermediate into fragments whose FMOs are known and estimate the relative intramolecular stabilization energies resulting from interaction of the LUMO of one fragment with the HOMO of the other. The magnitude of the stabilization energy (SE) is dependent on the difference in energy between the HOMO and LUMO of the respective fragments; the smaller the energy gap, the greater the orbital overlap and the greater the stabilization energy. In this system, the degree of stabilization increases significantly in going from the reactant to the intermediate, because of the much smaller energy gap and the consequent enhanced LUMO/HOMO interaction present in the latter. If a structural change results in greater stabilization of the intermediates as compared to the reactants, then an increase in rate is expected since the transition state should also be stabilized on effecting the structural change.

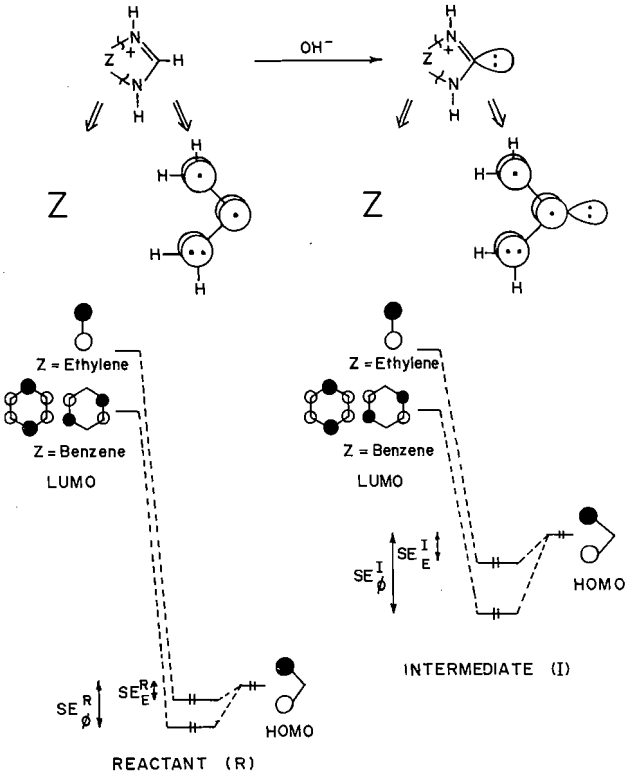
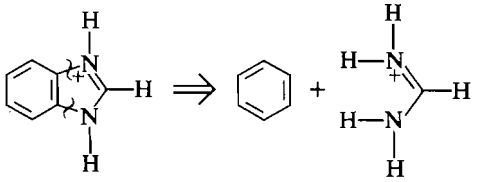


FIG. 2. FMO analysis of the effect of benzo annelation on proton transfer from imidazole showing the interaction between the HOMO of the allyl fragment and the LUMO of ethylene or benzene fragments for the reactant (R) and intermediate (I).

1. Effect of benzo annelation

The FMO analysis of the reaction scheme for benzimidazole and imidazole is shown in Fig. 2. The relative energies of the FMOs of the two reactant species and their corresponding intermediate structures can be estimated by fragmenting the molecules into two moieties whose FMOs are known. Thus benzimidazole is dissected into a benzene and a pseudo allyl fragment;



while imidazole is fragmented into an ethylene and the pseudo allyl fragment:

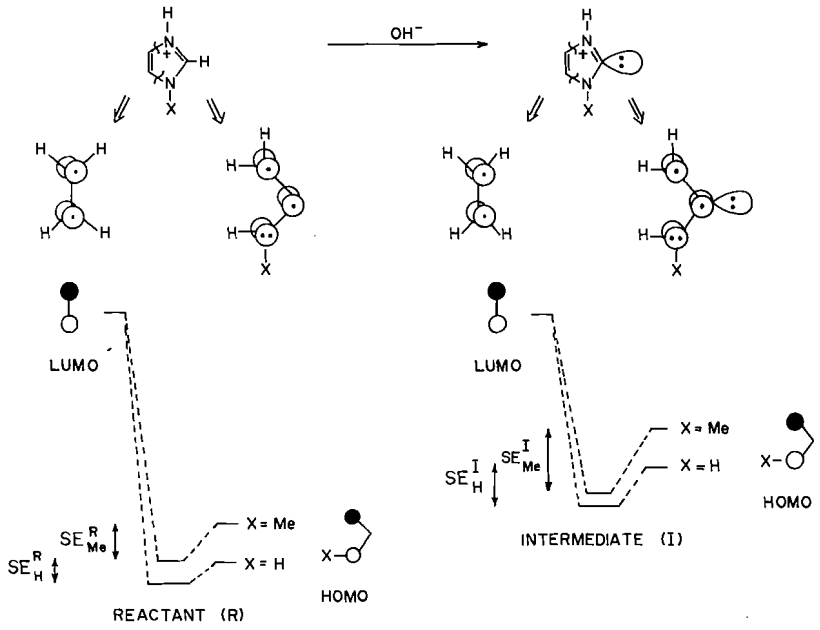
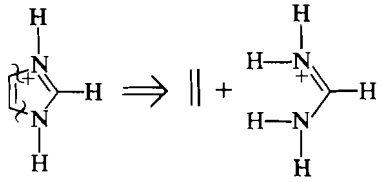


FIG. 3. FMO analysis of the effect of 1-methylation on proton transfer from imidazole.



The same procedure is followed for the intermediate structures. This is shown in Fig. 2 with *Z* corresponding to benzene or ethylene.

The LUMOs of benzene and of ethylene are allowed to interact with the HOMO of the allyl fragment, resulting in molecular orbitals for the benzimidazole and imidazole reacting species, and similarly for the intermediate structures. The relative energies of the LUMOs of ethylene and of benzene can be estimated from the respective electron affinities ($E_{LUMO} = -EA$), which have the values -1.78 and -1.15 eV as determined from electron transmission spectroscopy (16, 17). It follows that greater orbital interaction results between the LUMO of benzene and the HOMO of the allyl fragment, as compared with the corresponding interaction between the ethylene (LUMO) and allyl (HOMO) fragments. The differential stabilization energy for the two reactant species is $\delta SE^R = SE^R_\phi - SE^R_E$, where SE^R_ϕ and SE^R_E are the stabilization energies for the benzene and ethylene cases.

Considering the intermediate structures, the energies of the HOMOs can be taken as corresponding to the ionization potentials (15), i.e. $E_{HOMO} = -IP$. One would expect the energy required to remove an electron from a molecule RH to be much greater than that from the deprotonated species R^-. For example, the first ionization potentials of CH_4 and $CH_3{:}^-$ are 12.99 and 1.08 eV, respectively (18, 19). This would imply that the HOMO of the deprotonated fragment must be significantly higher in energy than that of the parent allyl fragment. The consequent smaller energy gap between the HOMO of the deprotonated allyl fragment and the LUMO of ethylene, or the LUMO of benzene, leads to greater orbital interaction and thus enhanced stabilization in the intermediate structures relative to the reactants. The differential stabilization energy for the two intermediate structures, $\delta SE^I = SE^I_\phi - SE^I_E$, is thus greater than for the reactant species, i.e. $\delta SE^I > \delta SE^R$.

It follows from the above that the transition state for reaction of the benzo annelated reactant will be of lower energy compared to the parent imidazole, thus accounting for the increased reaction rate. A similar analysis can be performed for 1-methylimidazole vs. 1-methylbenzimidazole, which would account for the reactivity difference between these two substrates in an analogous fashion.

2. Effect of methyl substitution

To account for the effect of methylation at N-1 of imidazole and benzimidazole on the rate of C(2)–H exchange, we examine the effect of methyl substitution on the energy of the HOMO of the allyl and the deprotonated allyl fragment. The relative energies of the HOMOs of the allyl and 1-methylallyl fragments is afforded through comparison of the ionization potentials (20) of methylamine (8.97 eV) and dimethylamine (8.24 eV), as well as of methyl (9.95 eV) and ethyl (8.78 eV) radicals (21, 22). Thus the introduction of a methyl group is associated with a decrease in ionization potential, which indicates that the energy of the HOMO for the 1-methylallyl fragment in our system is higher than that for the unsubstituted allyl fragment, in both the reactant and the intermediate.

The FMO analysis for methyl substitution in imidazole is shown in Fig. 3. For the reactants, the orbital interaction is between the ethylene (LUMO) and the allyl (HOMO) fragment for imidazole, as compared with the corresponding interaction between the ethylene (LUMO) and the 1-methylallyl (HOMO) fragments for 1-methylimidazole. The energy of the HOMO for X = Me is greater than for X = H, which results in a greater stabilization energy for the methyl case. The differential stabilization energy for the two reactants is given by $\delta SE^R = SE^R_{Me} - SE^R_H$.

In the intermediate structures, the orbital interactions are now between an ethylene (LUMO) fragment and the deprotonated allyl (HOMO) fragment for imidazole, and between ethylene and deprotonated 1-methylallyl for 1-methylimidazole. The HOMO energies in the intermediates will be significantly higher

than in the reactants, following the argument as applied in Fig. 2. The differential stabilization energy for the intermediates, $\delta SE^I = SE^I_{Me} - SE^I_H$, is hence greater than in the reactants, i.e. $\delta SE^I > \delta SE^R$. The change in structure from X = H to X = Me will hence lead to an intermediate of lower energy. The transition state for the process should thus be stabilized, accounting for the increase in rate on methyl substitution. A similar argument would apply to the case of benzimidazole versus 1-methylbenzimidazole.

Thus FMO analysis provides a satisfactory explanation of relative reactivities in these series of substrates. To our knowledge, this is the first application of FMO theory to reactivity differences in such processes.

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