

in the dark for 4 days. During this period the evolution of gases ceased and a clear solution was obtained. The reaction mixture was diluted with water (50 ml) and neutralized with solid sodium bicarbonate. In addition, 30 ml of water was added and the whole extracted with six portions of 50 ml of chloroform. The combined extracts were dried over anhydrous sodium sulfate and then evaporated to dryness to obtain 0.83 g of a residue.

By thin layer chromatography on silica gel, using commercially available plates (DC-Fertigplatten Kieselgel F 254, Merck) and developing them with ethyl acetate, it could be shown that the obtained product was a mixture of the starting compound (R_f 0.59) and 3-azidopyridazine 1-oxide (R_f 0.45) (detection in uv light).

A solution of 300 mg of the crude product in 3 ml of chloroform was separated on a chromatoplate with the above-mentioned absorbent, and the part containing the azide was separated and the compound eluted with chloroform. Upon evaporation of the solvent 12 mg of the residue which consisted of practically pure 3-azidopyridazine 1-oxide¹⁰ was obtained (yield 2.4%); mp 151–152° and mixture melting point with an authentic specimen obtained from nitrosation of 3-hydrazinopyridazine 1-

oxide¹² was undepressed. Moreover, ir spectra of both products were identical [2179 and 2146 cm^{-1} (N_3) and 1263 cm^{-1} (N-O)].

Registry No.—1, 23439-79-4; 3, 23406-38-4; 4, 23406-39-5; 6, R = H, 23406-40-8; 6, R = Et, 23406-41-9; 7, 23406-42-0; 8, R = H, 23439-80-7; 8, R = Me, 23406-43-1; 8, R = Ph, 23406-44-2; 8, R = PhCOCH₂, 23406-45-3; 8, R = CH₃COCH₂, 23406-46-4; 9, R = Me, 23439-81-8; 9, R = Ph, 23406-47-5; 10a, R = H, 23406-48-6; 10a, R = Me, 23406-49-7; 10a, R = PhCOCH₂, 23439-82-9; 10a, R = CH₃COCH₂, 23439-83-0; 10b, R = H, 23439-84-1; 10b, R = Me, 23406-50-0; 10b, R = PhCOCH₂, 23439-85-2; 10b, R = CH₃COCH₂, 23410-93-7; 11a, R = Me, 23410-94-8; 11a, R = Ph, 23410-95-9; 11b, R = Me, 23410-96-0; 11b, R = Ph, 23439-86-3.

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The Kinetics of Deuteration of Imidazole¹

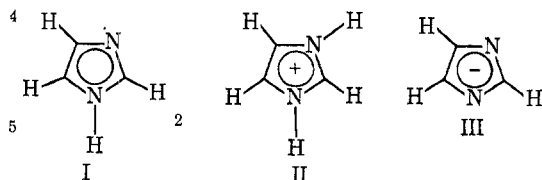
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Rates of deuteration of imidazole in heavy aqueous solution were measured at various pD values at 65 and 70° for the 2 position and at 180 and 190° for the 4(5) position. Parallel rate-determining proton abstractions from the conjugate acid of imidazole by OD⁻ and by D₂O leading to an ylide intermediate accounted for the observed pD-rate profile for 2-position deuteration. These paths, together with proton abstraction from the imidazole molecule by OD⁻, accounted for the 4(5)-position profile. The relative reactivities of hydrogen exchange sites in imidazole and other heterocycles were interpreted in terms of CNDO/2 ylide or anion stabilities.

In recent years, considerable attention has been focussed upon the relative electrophilic reactivities of various ring sites in aromatic heterocyclic compounds.^{2,3} These electrophilic reactivities depend both upon the nature of the substrate and the nature of the electrophile. The case of imidazole (I) is of particular interest because the 4(5) position is said to be more reactive in iodination than the 2 position,⁴ while the reverse is true for deuteration.⁵ In order that different positions of a given substrate be compared for the same or different electrophilic reagents, it is important that the detailed kinetics of substitution for each site and each reaction be known. For example, imidazole may exist in the conjugate acid II or conjugate base III forms in addition to that of the molecule I. Kinetic



data could indicate which of these forms undergoes attack. The kinetics of iodination of imidazole has been studied in depth,^{4,6,7} whereas that for the deutera-

tion of imidazole has not been presented in comparable detail.^{5,8,9} Thus, Harris and Randall⁵ reported the kinetics of protonation of the 2 position of 1-methylimidazole, Olofson, Thompson, and Michelman¹⁰ the rate of deuteration of the 2 positions of 1,3-dimethylimidazolium and other dialkylazolium cations, and Haake, Bauscher, and Miller¹¹ the rate of deuteration of 1,3,4-trimethylimidazolium cation. However, no kinetic studies of hydrogen exchange in the 4 and 5 positions of imidazole have been reported, and no detailed mechanistic analyses presented for either the 2 or the 4 and 5 positions. Accordingly, the purpose of this investigation was to study the kinetics of deuteration of the 2 and the equivalent 4 and 5 positions in imidazole, to propose mechanisms compatible with these rate laws and interpret the observed deuteration reactivities according to mechanistic and theoretical arguments.

Experimental Section

Materials.—Imidazole was recrystallized three times from benzene, mp 90.0°. Deuterium chloride (38% in D₂O), sodium deuterioxide (40% in D₂O), and heavy water (99.5%), obtained from Merck Sharp and Dohme of Canada Ltd., Volk Radiochemical, and International Chemical and Nuclear Corporation, were used without further purification. Reagent grade sodium chloride was also used without further purification.

Kinetic Runs.—All kinetic runs were made in heavy water solution. DCl or NaOD were added to adjust the pD of the solution from 0 to 14. The ionic strength of the solution was set

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at 1.00 *M* by measured addition of heavy aqueous NaCl. Eight 1.0-ml aliquots were prepared for each run; each aliquot was sealed in a 3.0-ml thick-wall borosilicate glass tube. Seven of the tubes were then plunged into an oil bath set at an appropriate elevated temperature, then removed at intervals and quenched in cold water. Samples taken from the tubes were analyzed with the Varian A-60A nuclear magnetic resonance spectrometer. Proton peak areas were determined by the cut and weigh method; the same proton peak area observed in a sample from the eighth (unheated) aliquot was used as a reference. Pseudo-first-order rate constants were obtained from plots of log (per cent area) vs. time.

Kinetic runs were made at 65.0 and 70.0° for deuteration of the 2 position and at 180 and 190° for the 4(5) position. The uncertainty in the lower temperatures was $\pm 0.1^\circ$ and that at the higher temperatures $\pm 1.0^\circ$. Rate constants were reproducible to within $\pm 10\%$.

pD values outside the buffer region were measured with the Beckman Zeromatic pH meter, corrected by the formula of Glaskoe and Long [pD = pH (meter reading) + 0.40].¹² Within the region of self-buffering ($5 < \text{pD} < 10$) pD values were calculated from the equilibrium relation

$$\text{p}K_a = \text{pD} - \log \frac{[\text{Im}]}{[\text{Im}^+]} = 7.62 \pm 0.02$$

where [Im] and [Im⁺] are the concentrations of imidazole and its conjugate acid, respectively. The p*K*_a value is the average of two measurements at 25° made on heavy water solutions with buffer ratio of unity and ionic strength of 1.0 *M*.

Results and Discussion

Uncertainties in Concentrations of Reactants.—The largest uncertainty in the kinetic data was that arising from changes in the concentrations of reagents at the higher temperatures. Accurate calculation of these concentrations at 180 and 190° would require consideration of the thermal expansion of the sealed glass ampoules, knowledge of the partial molar volumes of all solutes and the solvent at the temperatures, and the extent of loss of the solute into the vapor phase. A rough calculation that utilized the ideal gas law and the vapor pressure and density of liquid water at 180° indicated a 15% increase in the volume of liquid water attending the increase in temperature from 25 to 180°. The change in volume would introduce corresponding changes in the concentrations of reagents. Accurate calculation of changes in concentration was not feasible. Since the ionic strength was adjusted to a constant value for all reacting solutions, it is reasonable to assume that these changes would be determinate in principle if not in practice. Accordingly, all concentrations used in analyzing reaction orders were room-temperature values. The kinetic runs were pseudo first order in imidazole, where the imidazole concentration was observed in thermally quenched samples at room temperature. Hence, the uncertainty in reagent concentration could affect only the order in the deuterium ion concentration, arising from possible lateral shifts in the concentration coordinate at elevated temperatures.

pD Dependence.—Pseudo-first-order rate constants were determined for the 2 and 4(5) positions at two temperatures each for a range of room temperature pD values. The results are given in Table I. The pD profiles of the pseudo-first-order rate constants for the 2 position at 65° and the 4(5) position at 180° are shown in Figures 1 and 2, respectively. The relative rate constants exhibited in those profiles are based upon pseudo-first-order rate constants at pD = 10.56, that is,

TABLE I
PSEUDO-FIRST-ORDER RATE CONSTANTS FOR THE
DEUTERATION OF IMIDAZOLE

pD ^a	<i>k</i> ₁ × 10 ⁴ (sec ⁻¹)			
	Position 2		Position 4(5)	
	65°	70°	180°	190°
0.26	0.30, 0.20			
2.88	0.17		0.288	
6.92	1.06			
7.32	1.35		0.620	
7.62	1.57		2.11, 0.779, 0.740	1.31, 1.36
7.71			2.15, 0.787	1.35
7.83	1.66		2.35, 0.856	
7.89			0.900	1.50
7.99	1.78		2.47, 0.907	1.52
8.10	1.82		0.945	1.71, 1.61
8.22			2.56	1.85, 1.89
8.40	1.93		2.58, 1.01, 1.05	1.98
8.47	2.06		2.63, 1.11, 1.26, 1.24	2.11
8.90	2.10		2.64, 1.29, 1.37	2.20, 2.16
10.56 ^b	2.47		2.87, 1.44	2.46
12.10			1.68	
13.65	2.43		28.0	
13.80			40.5	

^a Room-temperature values. ^b *k*₁ = 1.75 × 10⁻⁴ sec⁻¹ at 60.0°.

for heavy aqueous imidazole with no added DCl nor NaOD. The 2 position profile is similar in form to that observed by Harris and Randall for the protonation of 1-methylimidazole-2*d*,⁵ except that a nonvanishing rate of deuteration was observed for imidazole even at high acidities, while no protonation of 1-methylimidazole-2*d* was reported at high acidities (pH ~0–1). The 4(5) position profile of imidazole closely resembles that of the 2 position for pD values ranging from 0 to ~10, but does not exhibit the flattening observed for the 2 position of imidazole (and for the 2 position of 1-methylimidazole) for pD > 10; the relative rate constants for pD values of 13.65 and 13.80 are too large to be included in Figure 2.

The Arrhenius activation energy at pD = 10.56 (room-temperature value) is 11.1 ± 3.0 kcal for the 2 position and 22.3 ± 3.0 kcal for the 4(5) position. The corresponding pseudo-unimolecular collision factors are 3.2 × 10³ ± 2.6 × 10³ sec⁻¹ and 1.9 × 10⁷ ± 0.7 × 10⁷ sec⁻¹, respectively. It appears therefore that the far greater exchange reactivity of the 2 position relative to the 4(5) position is attributable to activation energy, not to the preexponential factor.

Mechanism.—A suitable mechanism for the deuteration of imidazole would be one that accounted quantitatively for the pD-rate profiles exhibited in Figures 1 and 2, and also conformed to other available evidence. In addition to the profiles, we know that 1-methylimidazole-2*d* undergoes protonation (2 position) readily at room temperature,⁵ whereas the deuteration of the 2 position of imidazole requires a higher temperature. This result would seem to eliminate the conjugate base of imidazole III as the active nucleophile. Olofson, Thompson, and Michelman¹⁰ reported the facile deuteration of 1,3-dimethylimidazolium iodide at 31°, indicating the conjugate acid form of imidazole II as a likely substrate in the hydrogen exchange; these authors postulated that the cationic substrate undergoes base-catalyzed abstraction of a ring proton to form the ylide

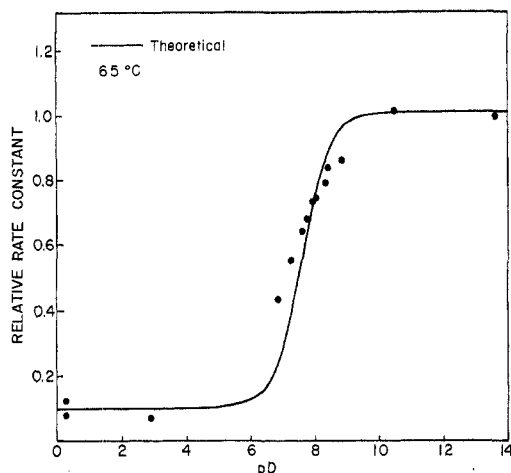
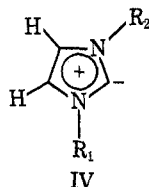
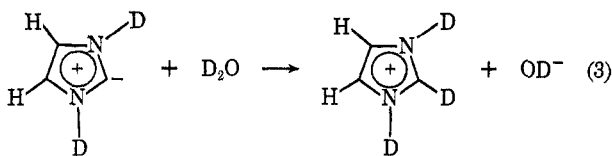
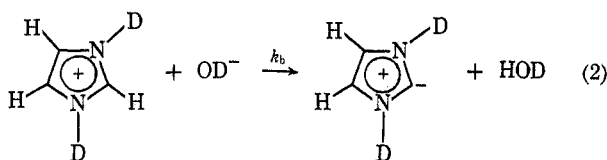
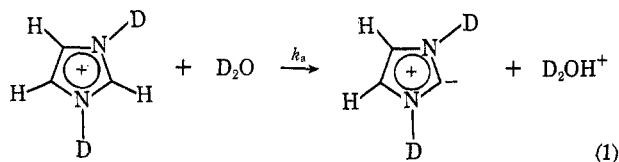


Figure 1.—The pD profile for deuteration of the 2 position in imidazole at 65° and at unit ionic strength.

IV in the rate-determining step. Similarly, Harris and Randall⁵ proposed the same mechanism for the protonation of 1-methylimidazole-2d.



The deuteration of the 2 position of imidazole can be interpreted in terms of two rate-determining steps leading to the ylide intermediate.



The pD profile for the 2 position can be derived for the entire pD range by considering the region of self-buffering. Here the observed pseudo-first-order rate constant k_2^{obsd} is $-(\text{slope})$ of $\ln [\text{Im}^0]$ vs. t , where $[\text{Im}^0] = [\text{Im}] + [\text{Im}^+]$. In this pD region, both the molecule Im and the conjugate acid Im^+ coexist in greater than trace concentrations, but cannot be distinguished in the reacting solution because of the rapid equilibrium between them. Steps 1 and 2 give

$$\text{rate} = \{k_a[\text{D}_2\text{O}] + k_b[\text{OD}^-]\}[\text{Im}^+]$$

Since

$$[\text{Im}^+] = [\text{Im}^0][\text{D}^+]/(K_a + [\text{D}^+])$$

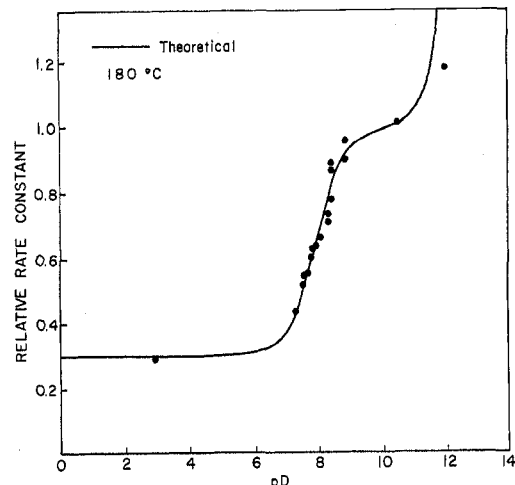


Figure 2.—The pD profile for deuteration of the 4(5) position in imidazole at 180° and at unit ionic strength.

the pseudo-first-order rate constant for 2-position deuteration reduces to

$$k_2^{\text{obsd}} = (k_a[\text{D}_2\text{O}][\text{D}^+] + k_bK_w)/(K_a + [\text{D}^+]) \quad (4)$$

where

$$K_a = [\text{Im}][\text{D}^+]/[\text{Im}^+]$$

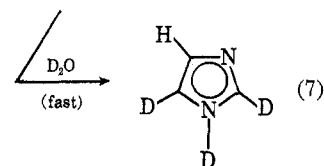
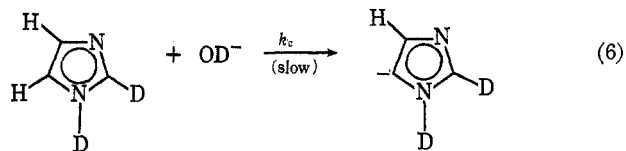
$$K_w = [\text{D}^+][\text{OD}^-]$$

At low pD, $[\text{D}^+] \gg K_a$, and $\lim_{[\text{D}^+] \rightarrow \infty} k_2^{\text{obsd}} = k_a[\text{D}_2\text{O}]$, while at high pD, $[\text{D}^+] \ll K_a$, so that

$$\lim_{[\text{D}^+] \rightarrow 0} k_2^{\text{obsd}} = k_bK_w/K_a \quad (5)$$

Clearly, the limiting relations account for the flattened pD profile in the low and the high pD regions. In Figure 1, the theoretical curve (eq 4) was fitted with $k_a \cdot [\text{D}_2\text{O}]/2.47 \times 10^{-4} = 0.10$, $k_bK_w/K_a (2.47 \times 10^{-4}) = 1.0$, and $K_a = 10^{-7.6}$.

To understand the pD profile of the 4(5) position, steps 1 and 2 [with proton abstraction from the 4(5) position] plus a third path (eq 6) that exhibits direct dependence upon $[\text{D}^+]$ is needed. Therefore, we propose the following additional mechanism operative at high pD values. The acid and self-buffering regions



V

can be adequately described by steps 1 and 2 to pD \sim 8, while the region pD $>$ 8 requires inclusion of 6. At high pD

$$k_{4(5)}^{\text{obsd}} = k_bK_w/K_a + k_c[\text{OD}^-] = k_bK_w/K_a + k_cK_w/[\text{D}^+] \quad (8)$$

The theoretical curve in Figure 2 was fitted with $k_a \cdot [\text{D}_2\text{O}]/1.44 \times 10^{-4} = 0.30$, $k_bK_w/K_a (1.44 \times 10^{-4}) =$

0.98, $k_c/1.44 \times 10^{-4} = 32$, and $K_a = 1.02 \times 10^{-8}$. The theoretical curve and the observed relative rate constants agree satisfactorily.¹³ Theoretical values of the rate constants for pD = 13.65 and pD = 13.80 using the parameters given above are $24.5 \times 10^{-4} \text{ sec}^{-1}$ and $47.5 \times 10^{-4} \text{ sec}^{-1}$, respectively (cf. Table I); in view of the short half-lives of the reactions in strong alkali, the agreement between theory and experiment is acceptable.

Other mechanistic paths for 4(5) deuteration operative at high pD values could be proposed, in particular those involving σ intermediate formation. For example, the conjugate base of imidazole could react with D₂O to form a σ intermediate followed by proton removal to yield products. Alternatively, the imidazole molecule I could react rapidly with D₂O to form the intermediate, which could then undergo slow deuterioxide-catalyzed proton removal. Although the present kinetic data do not rule out these possibilities, they seem less likely than path 6 by analogy with the observed kinetics of deuteration of the 4 position in pyrazole,¹⁵ the 1,2 isomer of imidazole. The derived rate equation for 4-position deuteration in pyrazole corresponded to *acid*-catalyzed σ intermediate formation, with pD dependence opposite that observed in 4(5) deuteration of imidazole.

Relative Hydrogen Exchange Reactivities.—To obtain quantitative exchange reactivities of different substrates, the exchange kinetics must be run under comparable reaction conditions. For example, it is not feasible to compare the 2-position reactivity of imidazole determined in D₂O with a position in another substrate determined in CH₃OD. In other cases, too little kinetic information may be supplied (*e.g.*, such as reactant concentrations and ionic strength) to warrant reactivity comparisons. The number of meaningful reactivity comparisons is therefore small, despite the large body of literature on hydrogen exchange kinetics. Accordingly, we propose to limit the discussion of relative exchange to imidazole and related substrates^{11,14,16} studied under comparable conditions.

Haake, *et al.*,¹¹ reported second-order rate constants for deuterioxide-catalyzed deprotonation of the 2 position in five-member cationic systems at 33°, corresponding to our k_b rate constant (path 2). At 65°, eq 5 may be rearranged to give $k_b = k_2^{\text{obsd}} K_a / K_w$. Correcting the pseudo-first-order rate constant k_2^{obsd} to 33° using the Arrhenius activation energy of 11.1 ± 3.0 kcal, then using $pK_a = 7.62$ ¹⁷ and $pK_w = 14.54$,¹⁸ we obtain $k_b = 360 \pm 120 \text{ sec}^{-1} M^{-1}$ (33°). Similarly, Olofson, *et al.*,¹⁴ calculated¹⁹ the second-order rate constant for deuteration of the 2 position in thiazolium cation to be $1 \times 10^6 \text{ sec}^{-1} M^{-1}$ at 31°. These second-order rate constants can be inserted into the Haake, *et al.*,¹¹ cation reactivity order: 3,4-dimethyloxazolium(2)¹¹: thiazolium(2)¹⁴:3,4 - dimethylthiazolium(2)¹¹:imidazo-

lium(2):1,3,4-trimethylimidazolium(2)¹¹ = 2.9×10^5 : 7.7×10^3 : 2.8×10^3 : 2.8 :1. The agreement between imidazolium(2) and 1,3,4-trimethylimidazolium(2) and between thiazolium(2) and 3,4-dimethylimidazolium(2) is good,²⁰ which supports the proposed mechanism (path 2).

Zoltewicz, *et al.*,¹⁶ studied the deuteration of 1-methylpyridinium chloride at 165° in phosphate buffered heavy water. At pD = 6.46 (30°), the pseudo-first-order constant for the 2(6) position was reported to be $7.83 \times 10^{-4} \text{ sec}^{-1}$. Using this pD value and $pK_w = 14.54$,¹⁸ we estimate the second-order constant to be $10^5 \text{ sec}^{-1} M^{-1}$ at 165°. The 3(5) and 4 positions were indicated by the authors to be less reactive than 2(6) by factors of 10^3 and 3.4×10^3 , respectively. Equation 5, the activation energy 22.3 ± 3.0 kcal, and the pseudo-first-order constant for 4(5) deuteration of imidazole (180°) may be used to estimate the second-order constant k_b for imidazolium(4,5) at 165°; here $k_b \sim 2.5 \text{ sec}^{-1} M^{-1}$. The uncertainties in the estimated second-order constants are quite large. However, since room-temperature values in pK_a , pK_w , and pD were used for *all* estimates, their relative magnitudes are likely to be correctly ordered. Accordingly, we propose the following additional reactivity order: imidazolium(2) \gg 1-methylpyridinium(2,6)¹⁶ \gg 1-methylpyridinium-(3,5)¹⁶ $>$ 1-methylpyridinium(4)¹⁶ $>$ imidazolium(4,5).

Recently, relative deuteration reactivity was discussed in terms of both the ground state properties of the substrate and ylide intermediate stability.¹¹ ¹³C-H coupling constants were considered indices of the potential acidities of corresponding C-H bonds in the substrate ground state; thus the ¹³C-H coupling constant would suggest the relative ease of proton removal in the transition state, other factors being equal. The ylide intermediate represents an exaggerated model of the transition state.^{10,11,15} It has been shown that large differences in hydrogen exchange reactivity may be found in cases where the ¹³C-H coupling constants are essentially identical in magnitude¹¹; in such cases, the difference in reactivity was attributed to factors specifically affecting ylide (and hence transition state) stability. Therefore, it is of interest to ascertain to what extent calculated ylide and anion stabilities can be used to interpret observed relative exchange reactivities directly. One might expect potential acidity differences to be implicit in the stabilities of the intermediates, if the stabilization energy is proportional to the free energy of activation. The success of a correlation between intermediate stability and reactivity depends upon the following factors: (1) the degree of the similarity between intermediate and transition state, (2) the relative importance of the preexponential factor and energy of activation in the reaction being considered, and (3) the accuracy of the method of calculation. We have used the CNDO/2 method²¹ for estimating cation to ylide deprotonation²² and molecule to anion V deprotonation energies. We neglected the entropy change attending intermediate formation; this neglect is consistent with the apparently dominant

(13) Recently, the pD profile for 2-position deuteration of thiazole was reported to be qualitatively similar to 4(5) deuteration in imidazole. Rate laws 4 and 8 were derived independently by the authors.¹⁴

(14) R. A. Coburn, J. M. Landesberg, D. S. Kemp, and R. A. Olofson, *Tetrahedron*, in press.

(15) E. C. Wu and J. D. Vaughan, *J. Org. Chem.*, **35**, 1146 (1970).

(16) J. A. Zoltewicz, G. M. Kauffman, and C. L. Smith, *J. Amer. Chem. Soc.*, **90**, 5939 (1968).

(17) pK_a was not corrected from 25 to 33° in this estimate.

(18) A. K. Covington, R. A. Robinson, and R. G. Bates, *J. Phys. Chem.*, **70**, 3820 (1966).

(19) Using eq 5 independently conceived by the authors.¹⁴

(20) See reference 14, where thiazolium(2) is compared with 3-ethylthiazolium(2) with similarly good agreement.

(21) J. A. Pople and G. A. Segal, *J. Chem. Phys.*, **44**, 3289 (1966).

(22) Schroeder and Tolles showed that CNDO/2 cation to ylide deprotonation energies correlate well with observed hydrogen exchange reactivities of diazolium and tetrazolium salts, private communication, 1968.

effect of the activation energy noted above for the deuteration of the 2 and 4(5) positions in imidazole. Since geometries are not known for the cations, ylides, anions, and most of the molecules, we assumed the five-member heterocycles to be pentagons 1.38 Å on a side,²³ six-member heterocycles to be hexagons 1.397 Å per side, and C-H and N-H distances to be 1.08 and 1.00 Å,²⁴ respectively. In the CNDO/2 approximation, the deprotonation energy is defined

$$\Delta E_T = E_T(\text{intermediate}) - E_T(\text{substrate})$$

where E_T is the valence electronic energy plus the core repulsion energy. The results of the calculation are given in Table II. Here, calculations were not made for sulfur containing compounds, because the program used did not provide for d orbitals, an essential requirement for substrates and intermediates that contain third period elements.²⁵ A number of conclusions may be drawn from the results of Table II. First, the effect of methyl substituents is of interest. A methyl group in the 4 position leads to a small destabilization in the ylide (2) intermediate, whereas one in the 1 position causes a slightly larger destabilization. Clearly, the 1,3,4-trimethylimidazolium ylide (2) would be further destabilized. This destabilization is probably a consequence of methyl-group electron release, which would render the ring atoms less electronegative and therefore decrease the inductive stabilization of the ylide intermediate. Since the ¹³C-2H coupling constant for the 2 position is not sensitive to methyl substituents on the imidazolium nucleus,¹¹ the observed smaller exchange reactivity of the 1,3,4-trimethylimidazole relative to imidazole is consistent with methyl-group destabilization of the ylide. Further, the apparently smaller reactivity of 3,4-dimethylthiazolium relative to thiazolium supports this conclusion. Second, ΔE_T values correctly indicate that the 2 position in imidazole is more reactive than the 4(5) position, and that the 2(6) position in 1-methylpyridinium²⁶ is more reactive

(23) See reference 18 for a discussion of the problem of unknown molecular geometries.

(24) "Tables of Interatomic Distances and Configurations in Molecules and Ions," The Chemical Society, London, 1968.

(25) D. P. Santry and G. A. Segal, *J. Chem. Phys.*, **47**, 158 (1967).

(26) Recent extended Hückel theory (EHT) calculations²⁷ of ylide and anion stabilities indicated the 3(5) position to be more reactive than the 2(6) position, contrary to experiment. However, the EHT calculations correctly predicted the 4(5) position of pyridazine to be the most reactive in that molecule and the 5 position the most reactive in pyrimidine. The CNDO/2 calculations gave the correct reactivity orders in pyridinium and pyridazine,²⁸ but incorrectly indicated the 2 position to be the most reactive in pyrimidine.²⁸

(27) W. Adam, A. Grimison, and R. Hoffmann, *J. Amer. Chem. Soc.*, **91**, 2590 (1969).

(28) J. D. Vaughan, unpublished results, 1969.

TABLE II
CNDO/2 YLIDE AND ANION STABILITIES^{a, b}

Substrate	Intermediate ^c	ΔE_T (au)
Imidazolium	Ylide (2)	0.631
	Ylide (4, 5)	0.693
Imidazole	Anion (2)	0.951
	Anion (4)	0.989
	Anion (5)	0.969
4-Methylimidazolium	Ylide (2)	0.639
1-Methylimidazolium	Ylide (2)	0.642
4-Methyloxazolium	Ylide (2)	0.604
Oxazole	Anion (2)	0.929
Pyridinium	Ylide (2, 6)	0.667
	Ylide (3, 5)	0.706
	Ylide (4)	0.703

^a Calculations carried out on the CDC 6400 computer, using a program obtained from the Quantum Chemistry Program Exchange (QCPE 91). ^b A small value for ΔE_T implies relatively high stability for the intermediate. ^c For example, ylide (*n*) refers to an ylide intermediate formed from the cation designated in the left column; *n* refers to the position of proton abstraction.

than the 3(5) and (4) positions. Note that 1-methylpyridinium is approximated by pyridinium, since methyl substituents have comparatively small effect upon ylide stabilities. Third, ΔE_T values correctly indicate the conjugate acid form of imidazole to be much more reactive than the molecule in all positions. The same result is indicated for the 2 position in oxazole. Fourth, the relative exchange reactivities for different cationic substrates is roughly predicted to be oxazolium(2) > imidazolium(2) > pyridinium(2,6) > imidazolium(4,5) > pyridinium(4) > pyridinium(3,5). The general trend is correctly indicated except for imidazolium(4,5), which is the least reactive of the substrate positions listed. Replacement of N-H by O evidently leads to enhanced inductive stabilization of the ylide. Though calculations were not made on sulfur-containing substrates, it is readily surmised from CNDO/2 input electronegativities $[(I + A)/2]$ ²¹ that thiazolium(2) would appear less reactive than imidazolium(2) if d orbitals are excluded; it is clear therefore that d orbitals must be included to account for the unusually stable ylide intermediates of thiazolium substrates, in agreement with prior discussions elsewhere.^{10, 11} In summary, it appears that CNDO/2 ylide and anion stabilities can be useful indices of exchange reactivities in heterocycles, especially in those cases where reactivity differences are large.

Registry No.—Imidazole, 288-32-4.