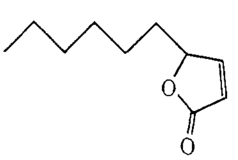
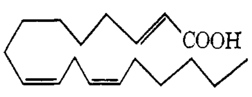
A typical procedure for path A is as follows. The reaction was carried out on 21.4 g (0.1 mol) of methyl dodecanoate as described by Rathke[7] for the conversion of ethyl hexanoate to ethyl 2-iodohexanoate except that the solution of iodine in THF was replaced by a solution of 28.3 g (0.12 mol) of PhSeBr which was prepared by the addition of 9.60 g (0.06 mol) of bromine to 18.7 g (0.06) of diphenyl diselenide in THF. After the PhSeBr had been added to the enolate at −78°, the reaction mixture was stirred for 1 hr then allowed to warm to room temperature and poured into a cold aqueous solution of NH_4Cl and extracted with ethyl acetate, washed with 1 *N* HCl and $NaHCO_3$, dried, and filtered. To the resulting yellow solution was slowly added 30 ml (0.23 mol) of 40% (7.7 *M*) peracetic acid. The turbid white mixture was stirred at 23–25° for 2 hr, poured into cold (0°) water, washed with Na_2CO_3, $NaHSO_3$, and brine, dried, filtered, concentrated, and distilled to yield 17.6 g (83%) of (*E*)-methyl 2-dodecenoate, bp 89–91° (0.63 mm).

Following the above procedure exactly (0.1 mol scale) the unsaturated lactone **10** was obtained in 56% isolated yield [bp 93–95° (0.9 mm)] from the corresponding saturated γ-lactone.



10



11

With several modifications, procedure A has enabled us to effect the first synthesis of the recently isolated[10] pollen attractant (**11**) of foraging honey bees. The enolate of methyl linoleate was prepared as described in procedure A, then 1.2 equiv of diphenyl diselenide was added in place of phenylselenenyl bromide.[11] After the reaction mixture had warmed to room temperature, ∼3 equiv of sodium periodate (dissolved in aqueous methanol) was added as the oxidant instead of the peracid or hydrogen peroxide usually employed. The methyl ester of octadeca-(*E*,2*Z*,*Z*)-9,12-trienoic acid (**11**) was isolated (preparative tlc) in 80% yield. Its ir, nmr, and uv spectra were identical with those published for the methyl ester of the natural substance.

These new procedures for the synthesis of α,β-unsaturated carbonyl compounds should often prove superior to those previously available.

Acknowledgment. We thank Crist Filer for donating a sample of 4-acetoxycyclohexanone. One of us (K. B. S.) is grateful to Professor Hans J. Reich (Wisconsin) for communicating unpublished results similar to ours. Reich and coworkers have observed that ketone enolates as well as ester enolates react with PhSeBr to give after oxidation the unsaturated carbonyl compounds. We thank the National Science Foundation (GP-30485X), Hoffmann-La Roche Inc., the Mobil Foundation, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support.

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(11) The use of PhSeBr in this case gave poor yields presumably because it readily adds to olefins. We shall soon report on the synthetic utility of processes which begin with the addition of ArSeX reagents to olefins.

Hydrogen–Deuterium Exchange Kinetics of the C-2 Protons of Imidazole and Histidine Compounds[1]

Sir:

The kinetics of the deuteration at the 2 position in imidazole and some substituted imidazoles has been studied by various workers.[2–5] The mechanism proposed for the reaction involves the interaction of the protonated form of the imidazole with OD^- or D_2O, with replacement of the proton at the 2 position by a negative charge to produce an ylide (slow step). The second, fast step, involves reaction of the ylide with D_2O, with substitution of deuterium at the 2 position.[5] We have been concerned with the determination of the p*K* values[6–8] and the kinetics of the deuteration of histidine residues in proteins.[9] In this communication we report on the kinetics of the deuteration of various substituted imidazole and histidine compounds, which serve as suitable model compounds for the exchange behavior in proteins.

The purities of the various model compounds shown in Table I were checked by pmr spectroscopy. The

Table I

Compound	Apparent dissociation constants[a]			$k_1 \times 10^{-3}$, l. mol^{-1} min^{-1}	$k_2 \times 10^{-3}$, l. mol^{-1} min^{-1}
	pK_1	pK_2	pK_3		
Imidazole		7.6			6.4[b]
Imidazole acetic acid		7.7			2.9[c]
N-Acetyl-L-histidine		7.6			3.1[b]
L-Histidine	6.6	7.6	9.6	14.4[b]	2.8[b]
Histamine	6.4	7.5	10.0	24[c]	4.2[c]
Glycyl-L-histidine	7.2	7.6	10.0	5.0[c]	3.1[c]
β-Alanyl-L-histidine	7.4	7.6	10.0	4.6[b]	3.7[b]

[a] K_1, K_2, and K_3 are defined by the equations $N^+D_3Im^+DCOO^- \rightleftharpoons N^+D_3ImCOO^- + D^+$ (K_1), $ND_2Im^+DCOO^- \rightleftharpoons ND_2ImCOO^- + D^+$ (K_2), and $N^+D_3ImCOO^- \rightleftharpoons ND_2ImCOO^- + D^+$ (K_3) where the structures are defined in the text. A detailed discussion of the origin of these values is given elsewhere.[10] [b] At 37°. [c] At 35°.

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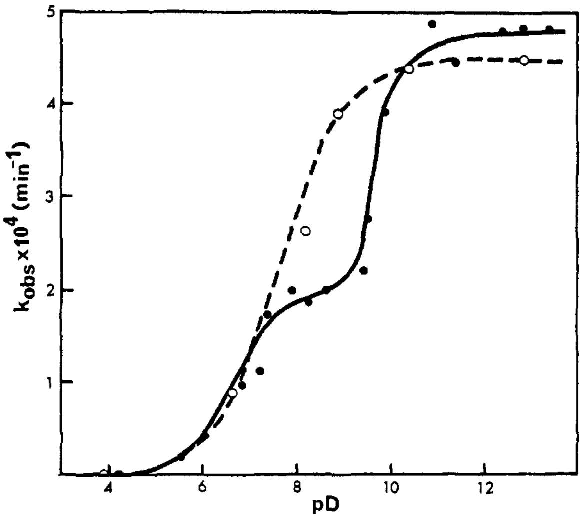

Figure 1. Graph of k_{obsd} (min^{-1}) *vs.* pD for *N*-acetyl-L-histidine (○) and L-histidine (●) at 37°.

rate of H–D exchange of 3–5% solutions of the compounds at various pD values (pD = pH meter reading + 0.4) was determined by following the decrease of the area (or height) of the C-2 proton resonances at 60 MHz as compared with the area (or height) of the C-4 proton resonances which remained constant.[5] A first-order rate constant k_{obsd} was determined from the gradient of a graph of log (corrected area or height of C-2 resonance) *vs.* time.[5,9] At pD <5 and 35° the rate of exchange is negligibly small; hence the reaction involving D_2O, which is appreciable at 65°,[5] can be neglected. Thus, for imidazole

$$\text{rate} = k_{obsd}[\text{Im}_t] = k_2[\text{OD}^-][\text{Im}^+] \quad (1)$$

where $[\text{OD}^-]$ is a constant in any particular run and $[\text{Im}_t]$ and $[\text{Im}^+]$ represent the total concentrations of imidazole and the charged form of imidazole, respectively. Substitution of the apparent dissociation constant of imidazole (K_2) and K_{D_2O}, the ionic product of D_2O, and rearrangement give

$$k_{obsd} = k_2K_{D_2O}/(K_2 + [\text{D}^+]) \quad (2)$$

This allows the determination of k_2 from measurements of k_{obsd} at different values of $[\text{D}^+]$.

For compounds which contain a separate nearby ionizable group with a p*K* of 6–12, the kinetics are complicated (see Figure 1) because of the different rate constants for the reaction of OD^- with the two forms of the compound. For example with histidine the two reactive forms are designated $\text{N}^+\text{D}_3\text{Im}^+\text{DCOO}^-$ (His^{2+}) and $\text{ND}_2\text{Im}^+\text{DCOO}^-$ (His^+), where the former structure represents the positively charged forms of the amino group and imidazole ring of histidine and the charged form of the carboxyl group. Thus

$$\text{rate} = k_{obsd}[\text{His}_t] = [\text{OD}^-](k_1[\text{His}^{2+}] + k_2[\text{His}^+]) \quad (3)$$

where $[\text{His}_t]$, $[\text{His}^{2+}]$, and $[\text{His}^+]$ represent the total concentrations of histidine and of the two reactive forms and k_1 and k_2 are second-order rate constants for the reactions of OD^- with His^{2+} and His^+, respectively. Substitution for $[\text{His}^{2+}]$ and $[\text{His}^+]$ in eq 3 in terms of K_1, K_2, and K_3 (defined in Table I) gives[10]

$$k_{obsd} = \frac{k_1K_{D_2O}}{K_1 + [\text{D}^+] + \dfrac{K_1K_3}{[\text{D}^+]} + \dfrac{K_1K_3}{K_2}} + \frac{k_2K_{D_2O}}{K_2 + [\text{D}^+] + \dfrac{K_2[\text{D}^+]}{K_3} + \dfrac{K_2[\text{D}^+]^2}{K_1K_3}} \quad (4)$$

By substitution of values for K_{D_2O}, K_1, K_2, K_3, and k_{obsd} at various values of $[\text{D}^+]$ a series of equations is obtained each with two unknowns, k_1 and k_2. Pairs of these equations are solved for k_1 and k_2 and the results (accuracy 5–10%) are given in Table I.

The S-shaped curve for *N*-acetyl-L-histidine shown in Figure 1 has been obtained hitherto[5] and the apparent p*K* of the imidazole can be determined from the center of the curve.[11,12] However, where there is a charged group nearby to the imidazole ring which titrates at pD >8, it is possible to obtain the p*K* of this group too, from the center of the second S-shaped curve, as shown for histidine in Figure 1.[13] This is useful for proteins such as ribonuclease A, in which there are charged amino groups nearby to histidines 12 and 119. Of greater importance for protein studies are conclusions obtained from examination of second-order rate constants. Firstly, the rate constant decreases greatly from the value of 14.4 in L-histidine, by moving the charged amino group progressively further away to a value of 5.0 in glycyl-L-histidine, 4.6 in β-alanyl-L-histidine, and finally 2.8 by removing the charge altogether as in L-histidine at high pD. Secondly, the rate constant increases greatly by eliminating a nearby charged carboxyl group as shown by comparing imidazole acetic acid with imidazole or L-histidine with histamine. Both effects are explained by a simple electrostatic mechanism in which the rate of attack of OD^- is increased by nearby positively charged groups and decreased by nearby negatively charged groups.

This study allows the determination of the p*K* of titratable groups (with pD >8) adjacent to imidazole rings and provides information on the proximity of nearby charged amino and carboxyl groups. The mapping of the environment of the histidine residues in ribonuclease A is in progress.

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(13) There is a further increase of k_{obsd} above pD 9, in spite of the much lower value of k_2 than k_1, because K_2 is much smaller than K_1; see Table I and eq 4.

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Chemical and Physical Evidence for Anthracene-1,3-Diene Exciplexes. A Quencher-Sensitized Photodimerization

Sir:

The quenching of the fluorescence of aromatic hydrocarbons by 1,3-dienes has been interpreted in