Acknowledgment. We thank the Robert E. Welch Foundation, the National Science Foundation, and the Department of Energy for financial assistance.

(4) Consistent with this analysis is the fact that of the several variables employed the selectivity ratio appears to be sensitive only to temperature. For example, in duplicate runs, with $CO/H_2 = 1$, but with twice the base concentration as given in ref 3, the selectivity ratios were 1.05 and 1.06 for the reduction of *m*-dinitrobenzene with $Rh_6(CO)_{16}$ at 137 °C.

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Intramolecular Proton Exchange in Aqueous Histamine. An NMR Method for Resolving the Ammonium and Imidazole Proton-Exchange Rates

Sir:

We report an NMR method for the separate measurement of the rates of proton exchange in aqueous polyfunctional amines. The method has been appplied to the aqueous histammonium ion which has two functional groups that are both magnetically and chemically distinguishable, namely, the alkyammonium protons of the histamine side chain and the imino protons of the imidazole ring. Histamine is of particular interest because of the possibility of intramolecular proton transfer which could act as a simple model for enzymatic catalysis.[1,2] Extensive occurrence of the imidazole group at the active sites of many enzymes is well established,[3,4] and it has been repeatedly emphasized that general acid–base catalysis is important in enzyme mechanisms,[1,2,5-7] especially when one of the active functional groups is the imidazole ring.[4]

Methods available for the investigation of rapid reactions in solution have been described in detail.[5] In relaxation methods such as temperature or pressure jump, the coupling between the perturbation and the extent of reaction depends on the magnitude of $\Delta H°$ or $\Delta V°$, respectively. When a proton is transferred from one nitrogen atom to another, however, $\Delta H°$ and $\Delta V°$ will be very small (or even zero if the reaction is perfectly symmetrical), and hence the relaxation methods are insensitive to the rate for such a reaction. Also, because these reactions are fast, it is not possible to determine the separate proton-transfer rates directly by observing the two N–H resonances in the NMR spectrum since these resonances are exchange averaged with the water resonance, except at low pH.

The present method is based on measurements of the longitudinal relaxation time in the rotating frame ($T_{1\rho}$)[9,10] of the dominant water resonance wherein the exchange broadening (Δ) is given by eq 1, in which T_1 is the spin–lattice relaxation time. If direct

$$\Delta = (1/T_{1\rho}) - (1/T_1) \qquad (1)$$

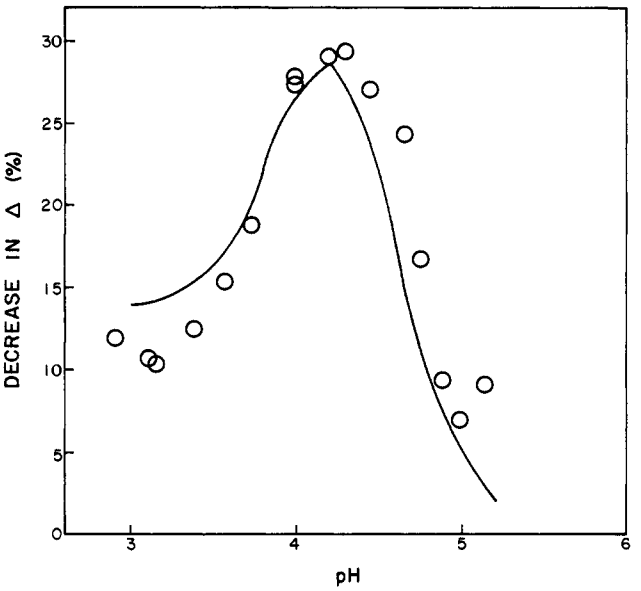

Figure 1. Reduction in exchange broadening vs. pH for 0.0596 M histamine. Δ is measured with $\omega_1 = 200$ and 2513 s^{-1}. The solid curve was computed from the rate law, eq 3.

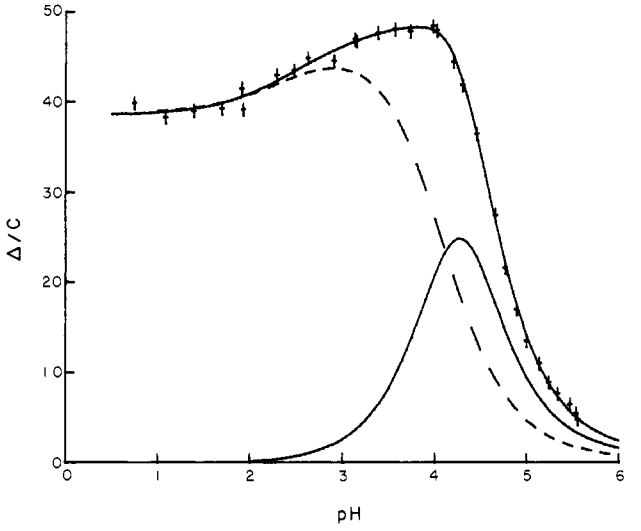

Figure 2. Δ/C vs. pH for 0.0596 M histamine. The upper solid curve is calculated from the rate law and eq 2 with $\omega_1 = 200$ s^{-1}; the dashed line is the calculated imidazole contribution; the lower solid curve is the calculated ammonium contribution.

exchange between the imidazole NH protons (IMH^+) and amino protons (NH_3^+) is slow, then

$$\Delta = \frac{P_{IMH^+}\delta_{IMH^+}{}^2\tau_{IMH^+}}{1 + \tau_{IMH^+}{}^2(\delta_{IMH^+}{}^2 + \omega_1{}^2)} + \frac{P_{NH_3^+}\delta_{NH_3^+}{}^2\tau_{NH_3^+}}{1 + \tau_{NH_3^+}{}^2(\delta_{NH_3^+}{}^2 + \omega_1{}^2)} \qquad (2)$$

where p represents the proton fractions, δ values are the water to NH chemical shifts in rad s^{-1}, τ represents the mean lifetimes, and ω_1 is the RF field strength. The two terms in eq 1 can be examined separately by varying ω_1 and utilizing the fact that δ_{IMH^+} and $\delta_{NH_3^+}$ are quite different. In 6 M HCl, where proton exchange is slow, two NH resonances are observed at 3.1 (1948 rad s^{-1}) and 8.3 ppm (5215 rad s^{-1}) relative to water, and these are assigned to the ammonium and imidazolium protons, respectively.[13,14]

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(14) Δ/C is the exchange broadening divided by the molar histamine concentration; $P_{IMH^+} = C/111$, $P_{NH_3^+} = C/167$.

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Increasing ω_1 to 2513 s^{-1} from 200 s^{-1} causes a large percentage reduction in the ammonium contribution to the exchange broadening, while that from the imidazole protons is affected only slightly (see Figure 1). A maximum diminution occurs at pH 4.2. Such a maximum effect can only occur if the broadenings are additive as in eq 2. The separated broadenings are then used to calculate τ_{IMH^+} and $\tau_{NH_3^+}$ by using eq 2. The rate law for 0.0596 M histamine is described by eq 3 where $[BH^+]$ is the molar

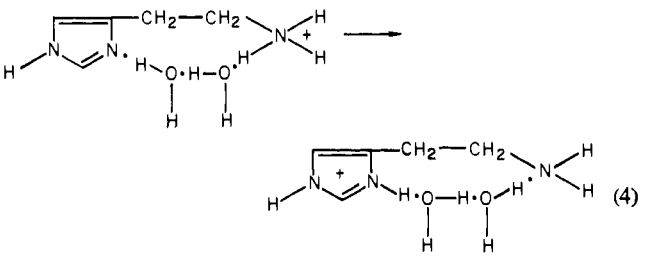
$$1/\tau_{NH_3^+} = 0.151/[H^+] \quad (3a)$$

$$1/\tau_{IMH^+} = 2940 + 2050/(1 + 550[H^+]) + 1.95 \times 10^7[BH^+] \quad (3b)$$

concentration of singly protonated histamine.

Additional evidence in favor of the additive broadening scheme is obtained from the maximum value of Δ/C[14] (Figure 2). If the two NH sites were exchange averaged by a rapid, direct N-H-N process, the observed chemical shift would be the weighted mean of δ_{IMH^+} and $\delta_{NH_3^+}$. The Δ/C maximum calculated for this case would be 73 for ω_1 = 200 s^{-1} rather than the observed value of 48.

The final fit of a large body of experimental data showed excellent agreement with the separate rate expressions for $\tau_{NH_3^+}$ and τ_{IMH^+}. Although the rate laws found are too complex to fully justify here, we will outline an important conclusion and present the detailed kinetic analysis elsewhere. A very rapid intramolecular proton transfer was detected in singly protonated histamine. Specifically, a proton initially bonded to an amino nitrogen is transferred to an imidazole nitrogen via one or two water molecules with a rate constant of $(1.9 \pm 0.1) \times 10^5$ s^{-1} (eq 4). The reaction



(4)

is illustrated with two water molecules. This is the upper limit as determined at high pH with ^{17}O-labeled water.[15,16] Since it has been reported that imidazole itself catalyzes ^{17}O-H exchange in a reaction which is kinetically indistinguishable from reaction 4[17] in the accessible pH range for such measurements, we can only infer the range of 1-2 water molecules.

Since the distance between the ammonium and imidazolium nitrogens in this reaction is comparable to that between acid-base centers in enzymes, it is probable that such intramolecular proton transfers are important at the active sites of enzymes. That hydrogen-bonded water molecules can fit molecular contours suggests that such intramolecular processes provide a route for proton transfers between "sterically inaccessible" functional groups.

It is noteworthy that the intramolecular reaction can compete favorably with bimolecular reactions at physiological pH. For example, the bimolecular reaction of an enzyme (E), $E + H^+ \rightarrow EH^+$, has a rate constant typically between 10^9 and 10^{10} L mol^{-1} s^{-1}. At pH 7.4, the lifetime of the enzyme will be ca. 10^{-2} s from the bimolecular reaction. For the intramolecular proton transfer from an ammonium ion to imidazole, the lifetime of the imidazole is only 5×10^{-6} s, suggesting that such a process could be dominant near neutrality.

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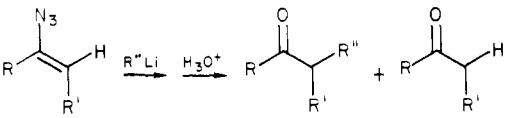
Umpolung of Alkyl Anions by Reactions with Vinyl Azides. In Situ Generation of Primary Enamines[1]

Sir:

The concept of umpolung[2] (dipole reversal in organic reagents) has been shown to be of considerable utility in organic synthesis. Among the better known examples are the use of a dithiane[3] or an oxazoline[4] anion as a masked electrophile (carbonyl). We report an example in which simple alkyl anions, in reactions with vinyl azides, are transformed into alkyl cation reagents.

Vinyl azides have been shown to be versatile compounds in organic synthesis,[5] and though they are attacked by electrophiles,[6] their reaction with carbanions has not been documented. We have found that vinyl azides (**1**) react with readily available alkyllithium

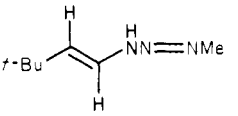


1 **2** **3**

reagents to yield, after acidic treatment, mainly ketones or aldehydes (**2**) that result from regiospecific alkylation at the β-vinylic carbon in **1** (see Table I). Ketones (**3**) are minor byproducts of these transformations.

Since vinyl azides are ambident partners in reactions with electrophiles, one can envisage nucleophilic attack by alkyllithium either at the olefinic carbon (Scheme I, in analogy with organocopper 1,4-additions to conjugated ketones) or at the azide function (Scheme II, in analogy with reactions of simple azides with nucleophiles, including Grignard reagents).[7]

We were able to show that triazenes are intermediates in these reactions by omitting the acidic workup. For instance, triazene **7** is obtained in 91% yield from reaction of **1c** with CH_3Li followed



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by workup with water.[8] This provides evidence for carbanionic attack at the terminal nitrogen of the vinyl azides. The possibility

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