All the cyclopropanes, except that from *trans*-2-octene, were compared by glpc and mass spectrometry to authentic samples prepared by the Simmons–Smith procedure.[9] That from *trans*-2-octene proved to be a single stereoisomer, presumably *trans*-1-methyl-2-*n*-pentyl-cyclopropane, which had similar but nonidentical gas chromatographic and mass spectrometric behavior with the corresponding cis isomer. The latter, contaminated with 7% of the trans isomer, was produced from a sample of *cis*-2-octene which contained 6% trans isomer. Thus, the cyclopropanations appear to be stereospecific with retention as in the corresponding reactions with diazomethane.[10] The yields of diphenyl sulfide (6) varied from 81% to nearly quantitative.
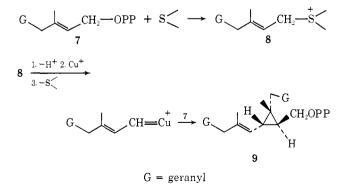
$$(C_6H_5)_2\overset{+}{S}-\overset{-}{C}H_2 + \quad \xrightarrow{Cu(Acac)_2} \quad (C_6H_5)_2S + \quad$$

5   6

Ethylene (6%) was detected as a by-product in the cyclopropanation of cyclohexene.

The best yields were obtained when the ylide was generated (3.47 mmol of methyldiphenylsulfonium tetrafluoroborate[11] and 6.79 mmol of sodium hybride were used) in the presence of the olefin (5 ml) and catalyst (1.52 mmol)[12] in the THF (8 ml) solution, but the olefin and catalyst can also be added to the preformed ylide in THF solution. In the case of cyclohexene, cyclopropanation does not occur with dimethylsulfonium methylide; a likely explanation is that, as expected, diphenyl sulfide is a better leaving group than dimethyl sulfide.

In experiments designed to assess the ease of conversion of sulfonium salts to ylides, without the use of strong bases such as the sodium hydride which we used, the disappearance of the methyl signal in the nmr spectrum of methyldiphenylsulfonium tetrafluoroborate was monitored in D_2O. Exchange was complete after 4 hr in a solution containing Na_2CO_3 (0.2 g/25 ml); during the same time no change occurred in the aromatic region. Thus, it is not unreasonable to expect a basic function of an enzyme to be capable of deprotonating sulfonium salts *in vivo*.

A reasonable biosynthetic route for presqualene pyrophosphate (9), based on the same concept, in-

$$G\diagdown\diagup\diagdown\diagdown_{CH_2-OPP} + S\diagdown \longrightarrow G\diagdown\diagup\diagdown\diagdown_{CH_2-\overset{+}{S}\diagdown}$$

7   8

$$8 \xrightarrow[3.\ -S\diagdown]{1.\ -H^+\ 2.\ Cu^+}$$

$$G\diagdown\diagup\diagdown\diagdown_{CH=\overset{+}{C}u} \xrightarrow{7} G\diagdown\diagup\diagdown\diagdown$$

9

G = geranyl

involves reaction of farnesyl pyrophosphate (7) with a sulfide, deprotonation at the allylic position of the resulting sulfonium salt (8), and metal-induced transfer of the carbene to the 2-double bond of a farnesyl pyrophosphate molecule. Precisely the correct stereochemistry about both the cyclopropane ring and the double bonds is expected from this route; indeed presqualene alcohol has been prepared by zinc iodide induced decomposition of an appropriate diazoalkene in the presence of farnesol,[13] a reaction which presumably involves a metal–carbene complex. Previous suggestions[14] for presqualene biosynthesis involve reactions which are not applicable to cyclopropanation of olefins by *S*-adenosylmethionine (1). The hypothesis presented here has the attractive feature that it is capable of explaining, by a single mechanistic concept, the two major types of cyclopropanation reactions in nature.

This method of cyclopropanation may have theoretical and synthetic value. It is apparently the only method of generation of copper–carbenes other than the rather severely limited diazoalkane procedure; the safety and ease of preparation of ylides may make the latter most attractive precursors of these reactive intermediates. Moreover, unlike N_2, the diarylsulfide leaving group is subject to modification which should allow changes in the ease of reaction as well as a study of the encumbrance of the carbenoid by the leaving group. Investigation of these factors as well as of extensions of this principle of carbenoid generation to other types of progenitors is in progress.

(13) L. J. Altman, R. C. Kowerski, and H. C. Rilling, *J. Amer. Chem. Soc.*, 93, 1783 (1971).

(14) E. E. van Tamelen and M. A. Schwartz, *J. Amer. Chem. Soc.*, 93, 1780 (1971); H. C. Rilling, C. D. Poulter, W. W. Epstein, and B. Larsen, *ibid.*, 93, 1783 (1971); W. W. Epstein and H. C. Rilling, *J. Biol. Chem.*, 245, 4597 (1970); J. Edmond, G. Popjak, S. Wong, and V. P. Williams, *ibid.*, 246, 6254 (1971); B. M. Trost and W. G. Biddlecom, *J. Org. Chem.*, 38, 3438 (1973).

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Mechanism of Hydrogen Exchange in Amides

Sir:

There has been considerable recent interest in hydrogen exchange in amides.[1] It seems to be generally accepted that the mechanism for the acid-catalyzed ex-

(9) H. E. Simmons, T. L. Cairns, S. A. Vladuchick, and C. M. Hoiness, *Org. React.*, 20, 1 (1973).

(10) W. Kirmse, M. Kapps, and R. B. Hager, *Chem. Ber.*, 99, 2855 (1966).

(11) V. Franzen, H. J. Schmidt, and C. Mertz, *Chem. Ber.*, 94, 2942 (1961). The sulfonium salt was best prepared using Meerwein's reagent: E. J. Corey, M. Jantelat, and W. Oppolzer, *Tetrahedron Lett.*, 2325 (1967).

(12) Increasing the quantity of catalyst does not improve the yield.

(1) (a) W. E. Stewart and T. H. Siddall, III, *Chem. Rev.*, 70, 517 (1970); (b) M. S. Miller and I. M. Klotz, *J. Amer. Chem. Soc.*, 95, 5694 (1973), D. L. Hunston and I. M. Klotz, *J. Phys. Chem.*, 75, 2123 (1971); (c) R. S. Molday, S. W. Englander, and R. G. Kallen, *Biochemistry*, 11, 150 (1972), R. S. Molday and R. G. Kallen, *J. Amer. Chem. Soc.*, 94, 6739 (1972); (d) M. Liler, *J. Chem. Soc., Perkin Trans. 2*, 720, 816 (1972); (e) L. C. Martinelli, C. D. Blanton, and J. F. Whidby, *J. Amer. Chem. Soc.*, 93, 5111 (1971), *J. Phys. Chem.*, 75, 1895 (1971); (f) R. L. Vold, E. S. Daniel, and S. O. Chan, *J. Amer. Chem. Soc.*, 92, 6771 (1970); (g) M. Sheinblatt, *ibid.*, 92, 2505 (1970); (h) C. Y. S. Chen and C. A. Swenson, *ibid.*, 91, 234 (1969); (i) T. Schleich, R. Gentzler, and P. H. von Hippel, *ibid.*, 90, 5954 (1968).

change proceeds simply by protonation on nitrogen (eq A) as proposed originally by Berger, Loewenstein, and Meiboom.[2] However, all the evidence for this mechanism—the observation that the hydroxide-catalyzed reaction is faster than the hydronium-catalyzed one,[2] the observation of general-acid catalysis,[3] and the observation that the rate decreases when R is an electron-withdrawing group[1c]—is also consistent with an alternative but more circuitous mechanism that proceeds by protonation on the more basic[1a] oxygen, followed by deprotonation to the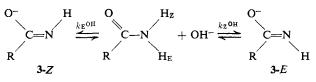 imidic acid tautomer (eq B). Evidence for this mechanism—the suggestion that proton exchange and rotation about the C–N bond in polyacrylamide do not occur via a common intermediate[4] and a discrepancy between rates of acid-catalyzed hydrogen exchange in N-alkyl amides and rates of this exchange estimated by correcting rates of acid-catalyzed isomerization of N,N-dialkyl amides[5]—is indicative but not conclusive. We therefore sought direct evidence to exclude mechanism A.

A distinction between the two mechanisms may be made with primary amides (R' = H). Mechanism A implies that the two hydrogens of $RCONH_2$ should exchange at the same rate in acid, since rapid rotation about the C–N bond in $RCONH_3^+$ should render the hydrogens equivalent. On the other hand, mechanism B predicts that they should exchange at different rates, since they remain diastereotopic[6] in the conjugate acid (1) and since the intermediates (2-Z, 2-E) are expected

to be configurationally stable.[7] Moreover, by analogy with imidic esters,[8] we may expect 2-E to be more stable than 2-Z, owing to mutual repulsion of the lone-pair dipole moments in 2-Z. Then to the extent that product-development control is operative, we may expect k_Z^H to be greater than k_E^H. For purposes of comparison, we may consider the base-catalyzed exchange, for which there is no mechanistic ambiguity. There has been no report that bases remove the diastereotopic hydrogens at different rates, so it is necessary to establish this. However, we may expect 3-Z to be more stable

(as with carboxylic esters[9]), owing to lone-pair repulsions[7] in 3-E, so k_E^{OH} should be greater than k_Z^{OH}.

Proton nmr, with ^{14}N decoupling, provides a method for determining the relative rates of exchange of the hydrogens. At room temperature, rotation about the C–N bond in amides and their O-protonated conjugate acids is quite slow[1a] on an nmr time scale, so that intramolecular hydrogen exchange does not interfere. In solutions buffered near pH 5, intermolecular hydrogen exchange is also slow, and the two N–H protons of $RCONH_2$ (R = CH_3, CH_2=CH, and CH_2=CCH_3 at ca. 1 M in H_2O; R = $(CH_3)_3C$ and C_6H_5 at ca. 1 M in 50% methanol) appear as moderately sharp (6–12 Hz half width) singlets ca. 6 ppm downfield from internal tert-butyl alcohol and well downfield from the strong O–H absorption. These two singlets are separated by ca. 0.7 ppm (see Figures 1b and 2b), and, chiefly by analogy to formamide,[10] the low-field one may be assigned[1a] to H_E, the proton trans to oxygen. As the pH is raised, these two peaks broaden, even at the optimum ^{14}N decoupling frequency. The peak at lower field is broader in all the amides studied (see Figures 1a and 2a). This verifies our expectation that the two hydrogens exchange at different rates in base, and that H_E, the one trans to oxygen, is removed more rapidly.

The rate constants k may be calculated from the line widths $(\Delta\nu)_{1/2}$ by the simple formula,[11] $k = \pi[(\Delta\nu)_{1/2} - (\Delta\nu)_{1/2}^0]$, where $(\Delta\nu)_{1/2}^0$ is the line width in the absence of exchange. Since k varies with pH, and since only the ratio of k_E^{OH} to k_Z^{OH} is relevant, these ratios are listed in Table I as r_{OH}. The values suggest that al-

Table I. Relative Rates of Exchange of E and Z Hydrogens of $RCONH_2$, as Catalyzed by Base and by Acid

R	r_{OH}^a	r_H^a
CH_3	5.1 ± 0.6	1.14 ± 0.06
CH_2=CH	4.2 ± 0.2	1.40 ± 0.04
CH_2=CCH_3	1.9 ± 0.2	1.88 ± 0.06
$(CH_3)_3C$	1.69 ± 0.05	1.25 ± 0.02
C_6H_5	3.1 ± 0.5	2.4 ± 0.2

^{a} $r = k_E/k_Z$, at room temperature. All values are averages of at least two determinations, at different pH.

though H_E is removed more rapidly, its removal can be subject to a slight steric hindrance by the group R.

Similar broadening is observed in mildly acidic solutions, with the peak at lower field again broader (see Figures 1c and 2c). The differential broadening is quite visible, especially as judged by the relative peak heights. Furthermore, since this is a 10-Hz broadening produced merely by slight changes in pH, we do not believe that it can be attributed to changes in relaxation times or instrument characteristics. Therefore this result demonstrates unequivocally that the two N–H hydrogens of primary amides exchange at different rates, even in acid.

(2) A. Berger, A. Loewenstein, and S. Meiboom, J. Amer. Chem. Soc., 81, 62 (1959).

(3) I. M. Klotz and B. Frank, J. Amer. Chem. Soc., 87, 2721 (1965).

(4) F. A. Bovey and G. V. D. Tiers, J. Polym. Sci., Part A-1, 849 (1963).

(5) R. B. Martin, J. Chem. Soc., Chem. Commun., 793 (1972), R. B. Martin and W. C. Hutton, J. Amer. Chem. Soc., 95, 4752 (1973).

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(8) (a) M. Kandel and E. H. Cordes, J. Org. Chem., 32, 3061 (1967); (b) H. Lumbroso and D. M. Bertin, Bull. Soc. Chim. Fr., 1728 (1970); (c) O. Exner and O. Schindler, Helv. Chim. Acta, 55, 1921 (1972); (d) C. O. Meese, W. Walter, and M. Berger, J. Amer. Chem. Soc., 96, 2259 (1974).

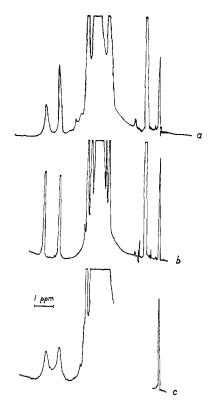(9) R. Huisgen and H. Ott, Tetrahedron, 6, 253 (1959).

(10) L. H. Piette, J. D. Ray, and R. A. Ogg, Jr., J. Mol. Spectrosc., 2, 66 (1958).

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Figure 1.. ^{14}N-Decoupled 100-MHz pmr spectrum of 0.7 M aqueous acetamide: (a) pH 7.94, (b) pH 5.95, (c) pH 1.94. Peaks, from left to right, are N–H$_E$, N–H$_Z$, H$_2$O (with spinning side bands), CH$_3$, and internal $tert$-butyl alcohol.

Table I lists values of r_H, the ratio of $k_E{}^H$ to $k_Z{}^H$. That r_H differs from unity would seem to indicate that mechanism A is not operative, since mechanism A implies that both hydrogens should exchange at the same rate.

Nevertheless, the values of r_H are not consistent with mechanism B. They do not vary monotonically with the steric bulk of R. More importantly, r_H is always greater than unity, which does not accord with our expectation that $k_Z{}^H$ should be greater than $k_E{}^H$. It seems exceedingly unlikely that the less acidic proton of 1 would be the one to be removed more rapidly. We therefore conclude that mechanism B is not operative nor even a mixture of both mechanisms.[5]

We must therefore return to mechanism A, and challenge the assumption that there is rapid rotation about the C–N bond of RCONH$_3{}^+$ during its lifetime, which is very short. In the accompanying publication,[12] it is demonstrated that this assumption is invalid for acid-catalyzed hydrogen exchange in amidinium ions and that even a relatively low barrier to rotation about the C–N bond acts so as to retard exchange of H$_Z$. Since acid-catalyzed exchange of H$_Z$ is in fact slower, we conclude that this same phenomenon is operative in amides and that acid-catalyzed hydrogen exchange in amides proceeds via Mechanism A, but the hydrogens of RCO-NH$_3{}^+$ do not become equivalent because of a restricted rotation about the C–N bond. This conclusion depends on the observation that r_H is not merely different from unity, which would be consistent with mechanism B, but greater than unity.

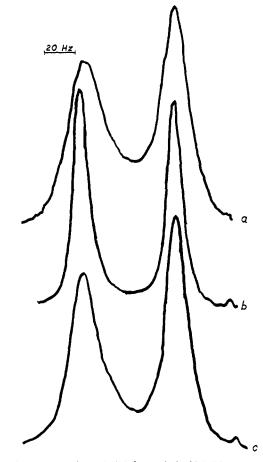The particular values of r_H correspond to barriers ranging from 1 to 3 kcal/mol. We may then rationalize

(12) C. L. Perrin, $J. Amer. Chem. Soc.$, $\mathbf{96}$, 5631 (1974).

Figure 2. N–H region of ^{14}N-decoupled 100-MHz pmr spectrum of 1.05 M aqueous methacrylamide: (a) pH 7.82, (b) pH 5.78, (c) pH 2.51.

the observed values of r_H in terms of the effect of R on the barrier. The barrier should be lower[13] when R = CH$_3$ or (CH$_3$)$_3$C, since these groups have their steric bulk above and below the O–C–N plane, and thus raise the energy of the preferred conformation[14] (4) of RCO-

$$R-\overset{\displaystyle H}{\underset{\displaystyle H}{\diagdown}}\overset{O}{\underset{H}{}}$$

4

NH$_3{}^+$. On the other hand, the other groups have their steric bulk in the O–C–N plane and may be expected to raise the barrier.[16] For those groups that lower the barrier, r_H is close to unity, but, for CH$_2$=CH, CH$_2$=CCH$_3$, and C$_6$H$_5$, there is a greater barrier to exchange of H$_Z$, so r_H is appreciably greater than unity.

In summary, we have observed that the diastereotopic hydrogens of RCONH$_2$ exchange at different rates not only in base but also in acid. Nevertheless, the acid-catalyzed exchange proceeds via RCONH$_3{}^+$, in which restricted rotation about the C–N bond preserves the

(13) The barrier[14] in CH$_3$COCH$_3$, which is isoelectronic to CH$_3$-CONH$_3{}^+$, is lower than that in HCOCH$_3$. This argument has also been applied[15] to rationalize the lowered barrier in cis-butene, as compared to propene or $trans$-butene.

(14) J. P. Lowe, $Progr. Phys. Org. Chem.$, $\mathbf{6}$, 1 (1968).

(15) W. G. Dauben and K. S. Pitzer in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N.Y., 1956, p 58.

(16) The barrier[14] in CH$_2$=CHCOCH$_3$, which is isoelectronic to CH$_2$=CHCONH$_3{}^+$, is higher than that in HCOCH$_3$.

inequivalence of these hydrogens. This conclusion is quite consistent with the observation of Bovey and Tiers,[4] and it also rationalizes, at least in part, the discrepancy noted by Martin[5] since hydrogen exchange in N-alkyl amides, which are s-trans, does not require rotation, but isomerization of N,N-dialkyl amides does.
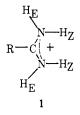
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Hydrogen Exchange in Amidinium Ions. Chemically Significant Consequences of Slow Rotation about a Carbon–Nitrogen Single Bond
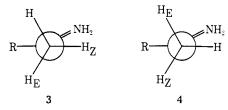
Sir:

A study of acid-catalyzed hydrogen exchange in amides[1] suggested that there may not be free rotation about the C–N bond of $RCONH_3^+$ during its lifetime. A mechanistic ambiguity precludes a definitive test of this possibility in amides but not in amidinium ions (1). These show[2a] diastereotopic "inside" and "out-
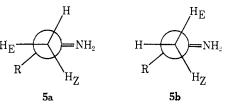

1

side"[3] N–H resonances in the nmr spectrum. In aqueous sulfuric acid these ions undergo[2b] an acid-catalyzed hydrogen exchange, *via* the dication $RC(NH_3^+)=NH_2^+$ (2). It would appear that the hydrogens of the $-NH_3^+$ group have become equivalent, since rotation about the C–N single bond should be very fast. But since 2 is a very strong acid, proton transfer to H_2O or HSO_4^- would be diffusion controlled,[4] so that its lifetime is only ~10^{-11} sec. This is uncomfortably close to the estimated time required to convert one conformer of 2 into another. Judging from the isoelectronic species $RC(CH_3)=O$, R = CH_3, for which the rate of conformational interconversion[5] is 2 × 10^{12} sec^{-1}, we might conclude that the rotation is sufficiently rapid. However, hydrogen bonding to solvent or to counterions may increase the barrier to C–N rotation, which then may not be free.

A barrier of only a few kilocalories per mole could lead to a novel conformational effect. Protonation of the lone pair of one of the nitrogens must produce a Boltzmann distribution of the conformers of 2, so that the dominant conformation is close to the most stable

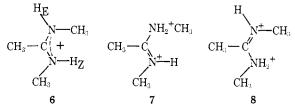one[6] (3). The labeling must be as indicated, since for-

mation of 4 would require rotation about the C–N partial double bond of 1, for which the barrier is *ca.* 20 kcal/mol. If the $-NH_3^+$ group does not rotate before it loses a proton, then the only proton that can be exchanged from 3 is H_E. In order for H_Z to exchange, there must be rotation about the C–N single bond. The transition states for this rotation are the maximum energy conformations 5a and 5b. If rotation

is slow compared to deprotonation, then 5a and 5b are also the transition states for exchange of H_Z, and rotation about the C–N single bond is rate limiting. Even if the rate of rotation is comparable to that of deprotonation, exchange of H_Z is retarded. Only if rotation is rapid would the two hydrogens exchange at the same rate. Thus this conformational effect can be demonstrated by showing that the diastereotopic hydrogens of amidinium ions undergo acid-catalyzed exchange at different rates, despite the equivalence implied by the $-NH_3^+$ group.

Data exist that suggest this result. Neuman and Hammond[2b] observed that for N,N'-dimethylacetamidinium ion, whose dominant configuration is 6, acid-

catalyzed exchange of H_E is 6.4 times as fast as that of H_Z. This rate difference was attributed[2b] to a difference in the rates of protonation of the two nitrogens, which are, of course, nonequivalent. However, we would not expect one nitrogen to be 6.4 times as basic as the other, inasmuch as the two conjugate acids, 7 and 8, are isoelectronic to (E)- and (Z)-3-methyl-2-pentene, respectively, for which the E/Z equilibrium constant[7] is only 1.5. We prefer an interpretation based on the above conformational effect. The two nitrogens are protonated at nearly the same rate, such that 7 is formed ~1.5 times as often as 8, but 8 is formed in a conformation unsuitable for hydrogen exchange. Exchange of H_Z is thus slower because it requires rotation about the C–N bond in 8, but exchange of H_E requires no such rotation. Yet these data are not conclusive proof for this effect, since it can be argued that solvation

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(2) (a) G. S. Hammond and R. C. Neuman, Jr., *J. Phys. Chem.*, 67, 1655 (1963); (b) R. C. Neuman, Jr., and G. S. Hammond, *ibid.*, 67, 1659 (1963).

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(4) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, 3, 1 (1964).

(5) J. R. Lyerla, Jr., and D. M. Grant, *J. Phys. Chem.*, 76, 3213 (1972).

(6) J. P. Lowe, *Progr. Phys. Org. Chem.*, 6, 1 (1968).

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