during 6 h at room temperature and then filtered under argon and the liquid phase evaporated under reduced pressure (0.05 Torr). The resulting residue was stirred with anydrous *n*-hexane (60 mL) during 1 h and filtered under argon, and the liquid phase concentrated in vacuo (0.05 Torr). The crude reaction product was an essentially pure, yellow liquid which was trap-to-trap condensed in vacuo (0.001 Torr; preheated oil bath temperature, 80–90 °C).

***N*-(1,4-Dimethyl-3-oxahexa-1,5-dienyl)morpholine (4b):** ^{1}H NMR ($CDCl_3$) δ 1.05 (d, 3 H), 1.75 (s, 3 H), 2.6–3.0 (m, 4 H), 3.6–3.8 (m, 4 H), 4.0–4.2 (m, 1 H), 5.1–5.4 (m, 2 H), 5.6 (s, 1 H), 5.65–6.2 (m, 1 H); ^{13}C NMR (neat) δ 13.6 (q), 22.2 (q), 51.8 (t), 68.2 (t), 79.4 (d), 116.4 (t), 130.7 (d), 132.7 (s), 141.8 (d).

General Preparative Procedure for Aromatic β-Oxy Enamines 4i–m. The method is the same as for compounds **4a–h** and **2a–h**, except that dry mercury(II) chloride (0.54 g, 2 mmol), the appropriate allyl prop-2-ynyl ether 1 (20 mmol), dry *N*-methylaniline (10.8 mL, 100 mmol), anhydrous THF (15 mL), and potassium carbonate (0.55 g, 4 mmol) were used. The crude reaction product was an essentially pure, yellow liquid which was trap-to-trap condensed in vacuo (0.001 Torr; preheated oil bath temperature, 100–110 °C).

***N*-Methyl-*N*-(1-methyl-3-oxahexa-1,5-dienyl)aniline (4i):** ^{1}H NMR ($CDCl_3$) δ 1.65 and 1.75 (2 s, 3 H), 3.05 and 3.0 (2 s, 3 H), 4.25 (d, 2 H), 5.05–5.5 (m, 3 H), 5.9 and 6.25 (2 s, 1 H), 6.6–7.35 (m, 5 H); ^{13}C NMR (neat) δ 15.3 and 11.5 (2 q, $CH_3C(N)$=CH), 37.6 and 39.9 (2 q, CH_3N), 73.1 and 73.5 (2 t,CH_2O), 121.4 and 124.8 (2 s, NC=CH), 141.5 and 147.2 (2 d, NC=CH). (First values in duplicate signals refer to the *E* isomer.)

Determination of Rearrangement Half-Lives. The half-lives shown in Tables I and III were measured by using ^{13}C NMR spectroscopy. For compounds **4a–d** and **2a–g** a peak at ca. δ 52 (assigned to C-2 and C-6 of the morpholino moiety of the β-oxy enamines) gradually disappeared and a new peak at ca. δ 49 (assigned to the analogous nuclei of the aminoaldehydes, which are expected to have similar relaxation times) appeared at the same rate. For compounds **4i–l** the change in the methyl signal of the *N*-methylanilino moiety from ca. δ 37 and 40 for the (*E*)- and (*Z*)-enamine, respectively, to ca. δ 38 for the amino aldehyde was observed. The approximate half-lives were deduced from the reasonably time-independent first-order rate constant obtained for each transformation.

Prolonged heating of β-oxy enamines **2** and **4** under argon atmosphere at the appropriate temperature, over a period of ca. $10t_{1/2}$, followed by fractional condensation at 0.001 Torr, results in almost quantitative transformation into the corresponding amino aldehyde **20** or **5**.

2,3-Dimethyl-2-morpholinopent-4-enal (5d): IR (Nujol 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.9–1.3 (m, 6 H), 2.3–3.0 (m, 5 H), 3.6–3.85 (m, 4 H), 4.9–5.3 (m, 3 H), 5.7–6.4 (m, 1 H), 9.5 (s, 1 H); ^{13}C NMR (neat) δ 12.1 (q), 15.2 (q), 41.5 (d), 48.5 (t), 68.9 (t), 70.6 (s), 116.6 (t), 140.4 (d), 193.4 (d).

2-Methyl-2-morpholino-3-(3-pyridyl)propenal (20e): IR (Nujol) 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.0 (s, 3 H), 2.5–2.8 (m, 4 H), 2.9 (dd, 2 H), 3.4–3.85 (m, 4 H), 7.0–7.8 (m, 2 H), 8.3–8.65 (m, 2 H), 9.45 (s, 1 H); ^{13}C NMR (neat) δ 15.7 (q), 36.0 (t), 48.4 (t), 68.7 (t), 69.1 (s), 124.4 (d), 134.0 (s), 139.5 (d), 149.0 (d), 152.8 (d), 195.1 (d).

Acknowledgment. We thank Prof. J. J. Gajewski for previous criticism of the manuscript and helpful suggestions on secondary deuterium KIE in [1,3]-rearrangements.

Registry No. 1-I, 51580-41-7; 1-II, 109930-19-0; 1-III, 109930-20-3; 1-IV, 79705-05-8; 1-V, 109930-21-4; 1-VI, 109930-22-5; 1-VII, 93740-57-9; 1-VIII, 32904-79-3; 1-IX, 109330-23-6; 1-X, 72421-08-0; 1-XI, 95547-66-3; 1-XII, 4039-82-1; 1-XIII, 109930-24-7; (*E*)-**2a**, 109930-39-4; (*E*)-**2b**, 109930-40-7; (*E*)-**2c**, 109930-41-8; (*E*)-**2d**, 109930-42-9; (*E*)-**2e**, 109930-43-0; (*E*)-**2f**, 109930-44-1; (*E*)-**2g**, 109930-45-2; (*E*)-**2h**, 109930-46-3; (*E*)-**4a**, 109930-26-9; (*E*)-(±)-**4b**, 109930-27-0; (*E*)-**4c**, 109930-28-1; (*E,E*)-**4d**, 109930-29-2; (*E,E*)-**4e**, 109930-30-5; (*E*)-**4f**, 109930-31-6; (*E*)-(±)-**4g**, 109930-32-7; (*E*)-**4h**, 109930-33-8; (*E*)-**4i**, 109930-34-9; (*Z*)-**4i**, 109930-63-4; (*E*)-**4j**, 109930-35-0; (*Z*)-**4j**, 109930-64-5; (*E*)-**4k**, 109930-36-1; (*Z*)-**4k**, 109930-65-6; (*E,E*)-**4l**, 109930-37-2; (*Z,E*)-**4l**, 109930-66-7; (*E*)-**4m**, 109930-38-3; (*Z*)-**4m**, 109930-67-8; (±)-5a, 109930-47-4; (*E*)-(±)-**5b**, 109930-48-5; (±)-**5c**, 109930-49-6; **5d**, 95064-81-6; **5e**, 109930-50-9; (±)-**5f**, 109930-51-0; (±)-**5g**, 109930-52-1; (±)-**5h**, 109930-53-2; (±)-**5i**, 109930-54-3; **5j**, 109930-55-4; (±)-**5k**, 109930-56-5; (*R*,S**)-(±)-**5l**, 109995-88-2; (±)-**5m**, 109930-57-6; **20a**, 95064-87-2; **20b**, 95064-88-3; **20c**, 95064-86-1; **20d**, 109930-58-7; **20e**, 109930-59-8; **20f**, 109930-60-1; **20g**, 109930-61-2; **20h**, 109930-62-3; CH≡CCH(OH)Me, 2028-63-9; CH_2=$CHCH_2Br$, 106-95-6; 2-furoic acid, 88-14-2; dideuterio(2-furyl)methanol, 109930-25-8.

Supplementary Material Available: Spectral and analytical data for compounds **1**, **2**, **4**, **5**, and **20** (7 pages). Ordering information is given on any current masthead page.

Hydrolyses of 2- and 4-Fluoro N-Heterocycles. 2.[1] Nucleophilic Catalysis by Buffer Bases in the Hydrolysis of 2-Fluoro-1-methylpyridinium Iodide

Oliver J. Muscio, Jr.,* and Denise R. Rutherford

Department of Chemistry, Murray State University, Murray, Kentucky 42071-3306

Received May 22, 1987

Pseudo-first-order rate constants are reported for hydrolysis of 2-fluoro-1-methylpyridinium iodide (1) in carboxylate buffers. The reaction is catalyzed by the carboxylase bases, with a Brønsted slope of 0.66. Hydrolyses in 99% ^{18}O-labeled water with 0.04 M unlabeled acetate and complementary hydrolyses in unlabeled water with 90% ^{18}O-labeled acetate indicate that 85–95% of the oxygen in product **2** is derived from the acetate rather than from water. The results are consistent with nucleophilic catalysis by acetate (and presumably by the other carboxylate bases) rather than general base catalysis.

Among mechanisms for nucleophilic substitution, those most frequently observed in reactions of acyl compounds and activated aromatic compounds share in common their addition–elimination pathways, as well as other features. In particular, their reactions with protic nucleophiles are often base catalyzed, and (in addition to specific base catalysis by hydroxide) that catalysis may be by either general base or nucleophilic catalysis routes. General base catalysis results from a rate-limiting proton transfer to the catalytic base or transfer during a rate-limiting step. For the nucleophilic catalysis route to predominate, of necessity an intermediate substitution product must be formed by

(1) For the previous paper, see: Clark, H. R.; Beth, L. D.; Burton, R. M.; Garrett, D. L.; Miller, A. L.; Muscio, Jr., O. J. *J. Org. Chem.* **1981**, *46*, 4363–4369.

0022-3263/87/1952-5194$01.50/0

Table I. Pseudo-First-Order Rate Constants for Hydrolysis of 1 in Buffer Solutions at 50 °C

buffer base	pH	[B⁻], M	10^3k, s^{-1}	pH	[B⁻], M	10^3k, s^{-1}
acetate	5.2	0.0940	5.5	4.1		
		0.0625	3.8		0.0625	3.8
		0.0470	2.9			
		0.0310	1.6		0.0310	1.9
		0.0235	1.4		0.0206	1.8
		0.0117	0.85		0.0125	0.94
formate	4.5	0.225	4.3	3.5	0.250	4.7
		0.150	3.0		0.188	3.6
					0.125	2.6
		0.075	1.5		0.082	1.8
		0.038	0.9		0.041	0.90
chloroacetate	3.6	0.50	2.0	2.7	0.50	1.8
		0.35	1.4		0.35	1.4
		0.25	1.0		0.25	0.99
		0.10	0.47		0.10	0.55

the basic catalyst at a rate greater than that of the reaction of the final nucleophile with the substrate. The intermediate product is then transformed to final product by a second substitution at a rate comparable to or greater than that of the first substitution. If the latter criterion is not met, the concentration of the intermediate will build to detectable levels, and the reactions are more properly treated as sequential.[2]

Both routes yield rate expressions that include the catalytic base, and distinguishing between these mechanisms can be very difficult.[3] It is difficult to predict which pathway will be followed in the reactions of a particular substrate, although changes in mechanism within a series of related compounds can be understood in terms of hard/soft acid–base theory, the strength of the base, and the nucleofugacity of the leaving group.[2c,d]

In our previous work we presented evidence for water catalysis of the hydrolysis of 2-fluoropyridine in concentrated acid by a general base mechanism involving proton transfer during the rate-limiting step.[1] We have since found further support for this mechanism in the observation of a substantial solvent deuterium isotope effect for the hydrolysis.[4]

This observation is significant, because the available kinetic evidence suggests that water catalysis is not important in the hydrolysis of 2-fluoropyrimidine.[1,2] An examination of the effect of buffers upon the hydrolyses of these substrates and the possibility of specific acid, general base catalysis would be of interest, but neither is sufficiently basic to be activated by protonation within the pH range of aqueous buffers.

A possible alternative, and one that avoids the mechanistic ambiguity of specific acid, general base catalysis (type n) vs general acid catalysis (type e)[5] is an examination of the hydrolysis of 1-methyl-2-fluoropyridinium iodide (1), which is activated by the *N*-methyl group and is not likely to be subject to acid catalysis. If proton transfer is important during the rate-limiting step, the hydrolysis of 1 should be subject to general base catalysis in buffer solutions. We have found that the hydrolysis is indeed catalyzed by carboxylate buffer bases. However, it is now evident that the mechanism for catalysis is one in which the buffer base is the initial nucleophile, rather than a general base-promoted proton transfer from the attacking water.[6]

Results and Discussion

Kinetics of Buffer-Catalyzed Hydrolysis. The rates of hydrolysis of 1 in carboxylic acid buffer solutions were determined either potentiometrically, by monitoring liberated fluoride with a fluoride-selective electrode (acetate, formate) or spectrophotometrically, by following the increase in absorbance at 288 nm (chloroacetate). The wavelength monitored corresponds to an absorption maximum for the hydrolysis product, 1-methyl-2-pyridone (2). The substrate 1 does not absorb significantly at this wavelength. Trial runs indicated that comparable rate constants were obtained by these two methods.

That the hydrolysis did, in fact, involve displacement of fluoride by attack at the C(2) position, rather than attack at the 1-methyl substituent with 2-fluoropyridine as the leaving group, was demonstrated in several ways. Most obvious was the observation of liberated fluoride. 2-Fluoropyridine is not sufficiently basic to be protonated and thus itself hydrolyze under these buffered conditions.[1] In addition, the UV spectrum of the hydrolysis solution, upon completion of the reaction, was identical with that of 2 in the same buffer. Finally, GC–MS analysis of a methylene chloride extract of the reaction mixture upon completion of the hydrolysis showed that 2 was produced in good yield, as indicated by comparison with an extract of a solution containing a known quantity of authentic 2. This is particularly significant in that it excludes the possibility that the iodide counterion of the pyridinium salt is involved as a nucleophile. The 2-iodopyridinium iodide that would result has been reported to undergo alkaline hydrolysis at a rate that is over a 1000-fold slower than that of 1[7] and would not be expected to hydrolyze appreciably under the conditions reported here.

The results of the kinetic runs in carboxylate buffers are summarized in Table I and Figure 1. In each buffer system, the rates were linearly dependent upon buffer concentration and specifically upon the concentration of the buffer base but were not dependent upon the ratio of buffer acid/buffer base or pH at constant buffer base concentration. Thus, there is no evidence for general or

(2) For reviews of mechanisms of base catalysis, and discussions of nucleophilic vs general base catalysis, see: (a) Johnson, S. L. *Adv. Phys. Org. Chem.* **1967**, *5*, 237–330. (b) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969. (c) Bender, M. L.; Bergeron, R. J.; Komiyama, M. *The Bioorganic Chemistry of Enzymatic Catalysis*; Wiley-Interscience: New York, 1984. (d) Jones, R. A. Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed.; Cambridge University: Cambridge, 1984.

(3) Hogg, J. L.; Gopalakrishnan, G. *J. Org. Chem.* **1981**, *46*, 4959–4964.

(4) Muscio, Jr., O. J.; Sherman, W. D.; Theobald, P. G., unpublished work in preparation.

(5) Jencks, W. P. *Acc. Chem. Res.* **1976**, *9*, 425–432.

(6) A preliminary report of this work, in which we suggested general base catalysis, was presented at the 33rd Southwest/37th Southeast Joint Regional Meeting of the American Chemical Society, Memphis, TN, October 1985.

(7) Barlin, G. B.; Benbow, J. A. *J. Chem. Soc., Perkin Trans. 2* **1974**, 790–797.

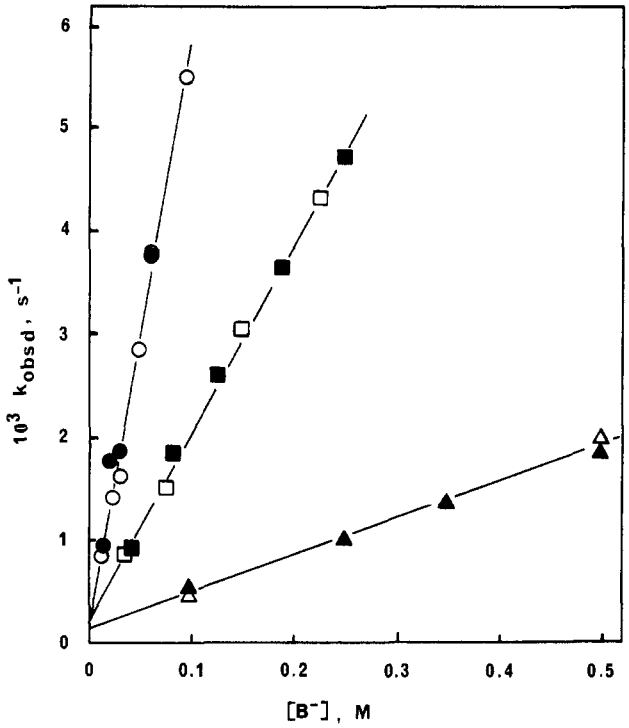


Figure 1. Pseudo-first-order rate constants vs concentration of buffer base for buffer-catalyzed hydrolysis of 1 at 50 °C: (○) acetate, pH 5.2; (●) acetate, pH 4.1; (□) formate, pH 4.5; (■) formate, pH 3.5; (△) chloroacetate, pH 3.6; (▲) chloroacetate, pH 2.7.

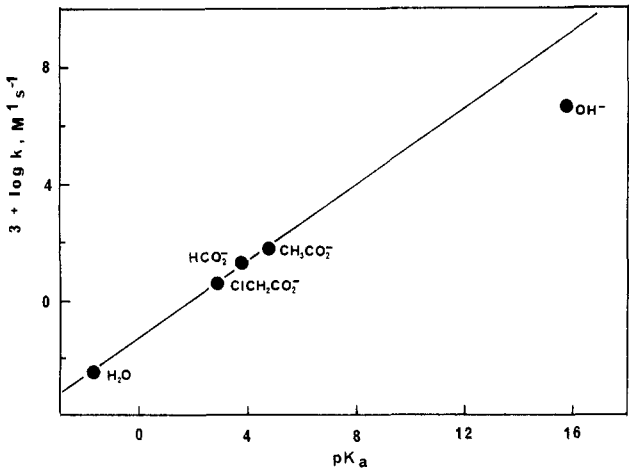
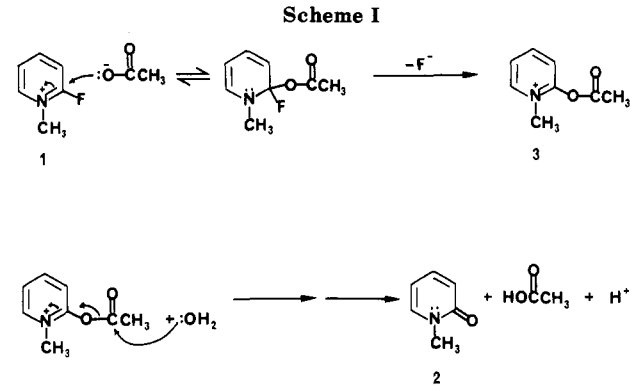


Figure 2. Brønsted plot for the buffer–base-catalyzed hydrolysis of 1 at 50 °C. The least-squares line does not include the point for OH^-, which was extrapolated from the literature.[7] The point for water was obtained from the average of the intercepts of the buffer-catalyzed hydrolyses at zero buffer concentration (Figure 1) divided by the molarity of water (ca. 55 M).

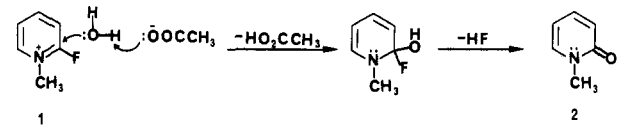
specific acid catalysis. No deviations from linearity were noted at higher buffer concentrations.

The slopes of the plots of the observed pseudo-first-order rate constants vs the concentrations of buffer bases (Figure 1) give the catalytic rate constants for each of the bases, while the intercepts yield the pseudo-first-order rate constant, k_o, for the non-buffer-catalyzed (but possibly water-catalyzed) hydrolysis. All buffers gave the same intercepts within experimental limits. A plot of the logarithmic catalytic constants vs the pK_a values of the carboxylic acids at 25 °C is shown in Figure 2. As will be shown below, acetate is a nucleophilic catalyst in this reaction, as are, presumably, the other carboxylate bases, so that the slope of this Brønsted-type plot, 0.66, is β_{Nu}. The

Scheme I



Scheme II



proposed mechanism for nucleophilic catalysis is illustrated in Scheme I.

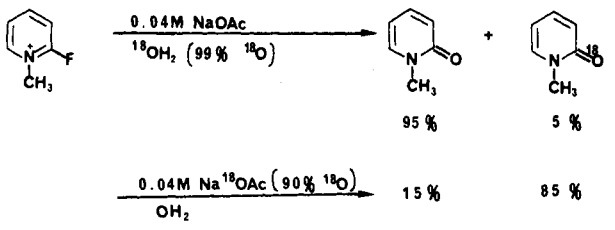
Included in Figure 2 is a point for hydroxide-catalyzed hydrolysis of 1. This point is extrapolated by means of the Arrhenius equation from the literature data[7] obtained at lower temperatures. The fit of this point to the line defined by the carboxylates and water is very poor. Such a negative deviation for hydroxide is not unusual and may be a consequence of the particular difficulty in desolvation of that ion.[8]

Alternatively, one may expect curvature to result in Brønsted plots for multistep nucleophilic substitutions as the pK_a of the attacking nucleophiles increase and exceed that of the leaving group.[9] If the rate of departure of a leaving group depends on its pK, as has been shown for amines and alkoxide ions of similar pK,[10] a change of rate-determining step should take place as the pK of the carboxylate nucleophile exceeds that of fluoride, 3.1,[11] if a similar dependence holds here. In reactions of a series of acetate esters with oxygen anion nucleophiles, it was observed that the Brønsted slope was greatest, approaching 1.0, for those nucleophiles with pK values less than that of the leaving group, while it was smaller, approaching 0.3, for those nucleophiles with pK values greater than that of the leaving group.[12] Although pK values for formate and acetate are greater than 3.1 and those for chloroacetate and water are less than this value, no such curvature is evident within this range. However, when that range is greatly extended to much larger pK values, negative curvature may be the result. This curvature may be attributed to a change in rate-determining step. For strongly basic nucleophiles this may be attack by the nucleophile, while for nucleophiles less basic, departure of the leaving group from an intermediate formed in rapid equilibrium with the reactants will be rate-limiting.[12]

Although large β_{Nu} values have been expected from reactions subject to nucleophilic catalysis, particularly reactions of acyl compounds,[13] the value observed here falls

(8) Kresge, A. J. *Chem. Soc. Rev.* **1973**, *2*, 475–503.
(9) De Rossi, R. H.; Veglia, A. *J. Org. Chem.* **1983**, *48*, 1879–1883.
(10) Bernasconi, C. F.; Muller, M. C.; Schmid, P. *J. Org. Chem.* **1979**, *44*, 3189–3196.
(11) Broene, H. H.; DeVries T. *J. Am. Chem. Soc.* **1947**, *69*, 1644–1652.
(12) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622–2637.
(13) Fife, T. H.; Natrajan, R.; Werner, M. *J. Org. Chem.* **1987**, *52*, 740–746.

Scheme III



within the range (0.5–0.7) reported for nucleophilic substitution of activated aryl halides by oxyanions in hydroxylic solvent.[14]

^{18}O-Labeling Studies. Although the kinetic results are consistent with a mechanism in which the buffer bases function as nucleophilic catalysts (Scheme I), an alternative mechanism in which the buffer bases participate in the rate-limiting step as general base catalysts, as we had originally anticipated, also is consistent (Scheme II).

These two mechanisms can be distinguished through a pair of experiments in which 1 is hydrolyzed in the presence of either ^{18}O-labeled water or ^{18}O-labeled acetate. Since the pyridone oxygen found in the product must originate with either the water or the acetate, it was expected that the results of these two experiments, properly corrected for the degrees of enrichment of the labeled substances, would each be the inverse of the other. The results of these experiments, adjusted for the levels of ^{18}O enrichment of the water and the acetate, are summarized in Scheme III and are discussed below.

Hydrolysis of 1 at 50 °C in 99% ^{18}O-labeled water buffered with 0.040 M unlabeled acetate resulted in formation of 2 that was found by GC-MS analysis to exhibit an enrichment of 5.4% ^{18}O when natural abundances of heavy isotopes were subtracted. Authentic 2 was enriched by 0.3% when subjected to the same reaction conditions. Thus, approximately 5% of the hydrolysis followed pathways leading to incorporation of ^{18}O from water into 2. Possible pathways include direct attack on 1 by water, whether catalyzed or uncatalyzed, as well as attack by water on the acetoxy-substituted position of the pyridinium ring of acetate intermediate 3. These results also indicate that 95% of the oxygen in 2 is derived from acetate.

This conclusion may be compared with an analysis of the kinetics of the hydrolysis in acetate buffer. Extrapolation to 0.040 M acetate gives $k_{obsd} = 2.46 \times 10^{-3}$ s^{-1}. Of this overall pseudo-first-order rate constant, (0.13–0.21) $\times 10^{-3}$ s^{-1} (k_o), or 5–9% of the total reaction, should represent the non-buffer-catalyzed hydrolysis, as determined from the intercepts at zero buffer concentration (k_o), while the remaining 91–95% of the reaction can be attributed to acetate-catalyzed pathways. The above results indicate that only two processes are important under these conditions: attack by water not catalyzed by acetate (k_o) and leading to enrichment in this experiment and an acetate-catalyzed pathway involving nucleophilic attack by acetate and not resulting in enrichment.

Comparable results were obtained when the hydrolysis was carried out in unlabeled water buffered with 0.040 M 90% ^{18}O-labeled acetate. Under these conditions, the resulting 2 was found by GC–MS analysis to be 85.9% enriched in ^{18}O after subtraction of the natural abundances of heavy isotopes and adjustment for the degree of enrichment of the acetate, initially 90% ^{18}O, but estimated to be depleted to 88% when the reaction was half complete. Samples of authentic 2 subjected to the same conditions were enriched by 0.2–1.2%. When the larger value is substracted from the enrichment observed during hydrolysis the results indicate that approximately 85% of the hydrolysis followed a pathway leading to enrichment, which must involve nucleophilic attack by acetate followed by hydrolysis at the acyl carbon.

It is difficult to conceive of a process by which the labeled water and labeled acetate experiments should not give rates of ^{18}O incorporation that are the inverse of each other, since, as noted above, the incorporated oxygen must be derived from one or the other source, but there is an approximately 10% discrepancy between them. Comparisons of both sets of labeling experiments with the corresponding kinetic results show that in each set, the extent of label incorporation is a few percent less than that which would be expected in the proposed nucleophilic catalysis scheme. It may be that some exchange with natural oxygen occurs subsequent to hydrolysis, perhaps during GC–MS analysis. This cannot be demonstrated without access to a sample of 2 of known enrichment, which is not available. In any case, the labeling results clearly show that most of the oxygen in hydrolysis product 2 is derived from acetate rather than from water. The acetate-catalyzed reaction proceeds largely, if not entirely, by nucleophilic catalysis with acetate as the initial nucleophile, rather than by general base catalysis involving proton transfer from nucleophilic water. Presumably, catalysis by the other carboxylate buffers follows the same mode, since their catalytic rate constants all fits the same Brønsted relationship.

Experimental Section

2-Fluoro-1-methylpyridinium Iodide (1). The literature methods[7,15] were modified by carrying out the reaction at reflux temperature. 2-Fluoropyridine (4.0 g, 0.041 mol), used as received from Aldrich, was allowed to reflux overnight in 15 mL iodomethane. The resulting precipitate was collected by suction filtration, washed with acetone, and dried under vacuum to give 2.0 g (22%) 1 as white crystals.

Anal. Calcd for C_6H_7FIN: C, 30.15; H, 2.95; N, 5.86. Found: C, 30.07; H, 2.80; N, 5.69.

Kinetics. All buffer solutions were made at 0.5 M ionic strength with sodium chloride. Runs were carried out at 50 ● 0.5 °C for at least two half-lives, and displayed linear, first-order kinetics throughout. In each case, the buffer solution was brought to temperature equilibrium before addition of 1.

Potentiometric runs were conducted in covered, jacketed beakers thermostated with a circulating constant temperature bath. Fluoride concentration was monitored with an Orion Research Model 601A pH meter and an Orion fluoride-selective electrode in combination with an SCE. Potential reading were converted to fluoride concentrations through calibration with solutions of potassium fluoride in the same buffers used in the kinetic runs. Pseudo-first-order rate constants were calculated through plots of ln $([F^-]_\infty - [F^-]_t)$ vs time. ln $[F^-]_\infty$ was calculated from the initial concentration of 1 or through estimation by a method of successive approximations.[16]

Spectrophotometric runs were carried out in a jacketed cell in a thermostated cell holder and were monitored at 288 nm with a Perkin-Elmer Lambda 3. The spectrophotometer was interfaced with an Apple II+ by means of an Adalabs board. First-order rate constants were calculated by the method of Schwartz and Gelb,[17] which estimates A_∞, the absorbance at infinite reaction time. This procedure was routinely followed because we have in the past found that stable infinity points could sometimes not

(14) Bordwell, F. G.; Hughes, D. L. *J. Am. Chem. Soc.* **1986**, *108*, 5991–5997.

(15) Bradlow, H. L.; Vanderwerf, C. A. *J. Org. Chem.* **1951**, *16*, 1143–1152.

(16) Holt, M. J. J.; Norris, A. C. *J. Chem. Educ.* **1977**, *54*, 426–428.

(17) Schwartz, L. M.; Gelb, R. I. *Anal. Chem.* **1978**, *50*, 1592–1594.

be obtained with fluoropyridine substrates in acidic solution. Evidently, a slow reaction of the product may follow the initial hydrolysis.

^{18}O-Label Studies. Buffer containing ^{18}O-labeled water was prepared by dissolving 2.7 mg of sodium acetate (0.033 mmol) and 5.2 μL of acetic acid (0.087 mmol) in 400 μL of labeled water (99% ^{18}O, Stohler Isotopes), giving a solution 0.08 M in acetate. A stock solution of substrate was prepared by dissolving 0.7 mg of 1 in 120 μL of labeled water. Hydrolysis samples were prepared by combining 30 μL of each stock solution in tubes, giving a final acetate concentration of 0.04 M. The tubes were sealed with rubber septa and heated at 50 °C for 50 min, approximately 10 half-lives for hydrolysis. A reference sample was prepared by dissolving 0.6 μL of **2** in 60 μL of the same 0.04 M buffer and also heated for 50 min.

Buffer containing labeled acetate was prepared by dissolving 84.3 mg of acetic acid (1.32 mmol, 90% ^{18}O, Stohler) in distilled water, adding 3.30 mL of 0.100 M KOH, and diluting to 5.0 mL with distilled water, resulting in a solution 0.066 M in labeled acetate. Hydrolysis samples were prepared by dilution of 1.0 mL of the 0.066 M stock solution to 1.65 mL to give a 0.040 M solution into 0.066 mL of which was dissolved 2.8 mg of **1**, and the resulting solution was divided into three portions. Each portion was heated for 1 h (approximately 11 half-lives) in tubes sealed with rubber septa.

Upon completion of the hydrolyses, the reaction tubes were refrigerated until GC–MS analysis with a Hewlett-Packard 5985 system. ^{18}O incorporation was determined from the relative peak intensities of the M and M + 2 parent ions in the mass spectra, as well as from total ionization at M and M + 2 masses. Results from spectral peak intensities and total ionization were in agreement.

Acknowledgment. We thank Dr. M. Selim for mass spectrometric analyses and the Murray State Committee on Institutional Studies and Research for generous support of this research.

Registry No. 1, 367-06-6; acetate, 71-50-1; formate, 71-47-6; chloroacetate, 14526-03-5.

Kinetics and Stereochemistry of the Thermal Interconversion of 4,5-Dimethyl-2,6-octadienes

Joseph J. Gajewski,* Charles W. Benner, and Christopher M. Hawkins

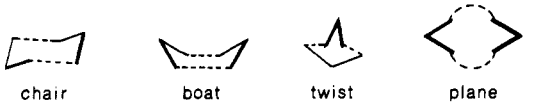
Department of Chemistry, Indiana University, Bloomington, Indiana 47405

Received March 17, 1987

Gas-phase pyrolysis of *threo*-4,5-dimethyl-*cis*,*cis*-1,1,1,8,8,8-hexadeuterio-2,6-octadiene over the temperature range 220.0–260.0 °C resulted in formation of the threo,trans,trans isomer with $\log k = 11.36 - 36000/2.303RT$. NMR analysis with Simplex minimization of the residuals from a Gear numerical integration provided a nearly identical rate constant for the degenerate interconversion of the deuterium isomers of the threo,trans,trans diastereomer at 240 °C. All six 4,5-dimethyl-2,6-octadienes are interconverted at temperatures above 290 °C. Mass spectral analysis of the reaction products from a 1:1 mixture of protio and D_6 diene provided evidence for cleavage–recombination as the pathway for conversion to erythro,trans,trans, erythro,cis,cis, and threo,trans,cis isomers. Competing with the cleavage–recombination is the boatlike shift to the erythro,trans,cis isomer. NMR analysis of the (−)-α-phenylethylamine bis salt of the *threo*-2,3-dimethylsuccinic acid derived from a 33.5-h 240 °C pyrolysis of optically pure hexadeuterio starting material provided evidence for little incursion of antarafacial–antarafacial 3,3-shifts via a twist transition state competing with the chair transition state. An analysis of the energy surface for all the interconversions reveals that at 300 °C, the boat transition state is ~6 kcal/mol higher in energy than the sterically most favorable chair transition state, and the cleavage reaction transition state is only 0.6 kcal/mol higher in energy than the boat transition state.

Doering and Roth's classic work on the stereochemistry of the thermally induced all-carbon 3,3-sigmatropic shift (Cope rearrangement) suggested that the low-energy pathway has a chair transition-state geometry and the boat geometry is ~6 kcal/mol higher in energy.[1] Both of these processes involve suprafacial use of each allylic moiety.[2] Unfortunately, the chair and boat products from the *meso*- and *threo*-3,4-dimethyl-1,5-hexadienes studied could also result from two other orbital symmetry "allowed" pathways involving antarafacial uses of the two three-carbon units, processes which Goldstein described as twist and plane, respectively[3] (Scheme I). To distinguish between all suprafacial and antarafacial possibilities, stereochemical labels at the double bond termini are necessary. In such an

Scheme I



experiment, Hill found that, indeed, the chair was the low-energy path, but the stereochemical labels would not allow a distinction between boat or twist for the higher energy path.[4]

The 3,3-shift in bicyclo[3.2.0]hepta-2,6-diene systems first reported by Mukai,[5] which formally involves the twist pathway, has been interpreted by Baldwin[6] to be a conrotatory cyclobutene ring opening to a *cis*,*trans*,*cis*-triene followed by conrotatory closure to the twist product. The basis for this hypothesis rests on the fact that bicyclo[3.3.0]octa-2,6-dienes do not undergo the 3,3-shift—a reaction which must formally be a twist process. Given the central position of the Cope rearrangement in organic

(1) Doering, W. v. E., Roth, W. R. *Tetrahedron* **1962**, *18*, 67. For reviews, see: Rhodes, S. J.; Raulins, N. R. *Org. React. (N. Y.)* **1970**, 22. Gajewski, J. J. *Hydrocarbon Thermal Isomerizations*; Academic: New York, 1981.

(2) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781.

(3) (a) Goldstein, M. J.; Benzon, M. S. *J. Am. Chem. Soc.* **1972**, *94*, 7149. (b) Goldstein, M. J.; Benzon, M. S. *J. Am. Chem. Soc.* **1972**, *94*, 7147. There is an error in the interconversions in the top scheme of Figure 2 of ref 3b: specifically, ZSSZ and ZRRZ should be interchanged and then ZSSZ interconverts with ESRZ not ERSZ by a boat; ZRRZ interconverts with ERSZ not ESRZ by a boat.

(4) Hill, R. K.; Gilman, N. W. *Chem. Commun.* **1967**, 619.

(5) Miyashi, T.; Nitta, M.; Mukai, T. *J. Am. Chem. Soc.* **1971**, *93*, 3441 and references therein.

(6) Baldwin, J. E.; Kaplan, M. S. *J. Am. Chem. Soc.* **1971**, *93*, 3969; **1972**, *94*, 668; *J. Chem. Soc., Chem. Commun.* **1970**, 1560.

0022-3263/87/1952-5198$01.50/0