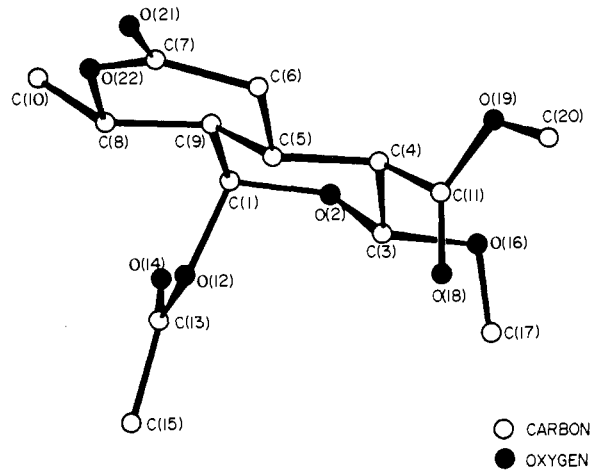

Figure 1. A computer-generated perspective drawing of 1-*O*-acetyl xylomollin. Hydrogens are omitted for clarity.

rived from secologanin.[3c] Both the addition of methanol at C-3,4 and the C-9 epimerization may be artifactual results of isolation. For example, treatment of **5a** (R_2 = H) with methanolic methoxide (25 °C, 16 h) results in the formation of **11** ($^3J_{H_5H_9}$ = 11.50 Hz), which underscores the ease of C-9 epimerization in an iridoid aglucone.

The revised structure proposed for **1** is confirmed by the following crystallographic analysis. Crystals of (−)-xylomollin acetate[15] formed in orthorhombic crystal class with a = 7.344 (1), b = 8.890 (1), and c = 23.565 (4) Å. Systematic extinctions uniquely indicated space group $P2_12_12_1$ and a density measurement suggested one molecule of composition $C_{14}H_{20}O_8$ in the asymmetric unit. Intensity data were collected on a fully automated four-circle diffractometer using graphite monochromated Mo Kα (0.71069 Å) radiation and a variable speed ω scan. Of the 1892 reflections surveyed, 1381 (73%) were judged observed ($F_o \geq 3\sigma(F_o)$) after correction for Lorentz, polarization, and background effects.[16] A phasing model was achieved using a multiple solution weighted tangent formula approach and full-matrix least-squares refinement with anisotropic nonhydrogen atoms and isotopic hydrogens have converged to a standard crystallographic residual of 0.044.[22]

Figure 1 is a computer-generated perspective drawing of the final X-ray model less hydrogens. This X-ray experiment defines only the relative configuration of xylomollin acetate as C-1(S*), -3(R*), -4(R*), -5(S*), -8(S*) and -9(R*). The ether ring has a chair conformation and the lactone ring a slightly flattened chair. The bridgehead hydrogens are trans to each other with an ~180° dihedral angle. All substituents are equatorial save the acetoxy group at C-1. Bond distances and angles generally agree with accepted values; there were no abnormally short intermolecular contacts or unusually high electron density on a final difference synthesis. Additional crystallographic details may be found in the supplementary material described at the end of this paper.

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Supplementary Material Available: Fractional coordinates, bond distances, and bond angles with errors for xylomollin acetate (2 pages). Ordering information is given on any current masthead page.

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(17) Career Development Awardee of the National Institutes of Health, 1976–1981 (CA 00257).

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Evidence for a Preassociation Mechanism for Acid Catalyzed Addition of Semicarbazide to 4-Methoxyphenyl Formate[1]

Sir:

We report kinetic α-deuterium isotope effects for attack of semicarbazide on 4-methoxyphenyl formate which strongly suggest that catalysis of this reaction by the conjugate acid of the nucleophile, and probably by the hydrated proton, occurs by a preassociation mechanism rather than by trapping of the zwitterionic addition compound by proton transfer from these species.

Satterthwait and Jencks have established that general acid catalysis of addition of basic amines to phenyl acetates occurs with rate-determining transfer of a proton from the catalyst

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Table I. Experimental Conditions for Determination of Kinetic α-Deuterium Isotope Effects for Addition of Semicarbazide to 4-Methoxyphenyl Formate at 25 °C

pH	$(RNH_2)_{total}$, M	$(RNH_2)_{fb}$, M	(RNH_3^+), M	k_{obsd},[a] min^{-1}	k_{calcd},[b] min^{-1}
2.00	0.25	0.0041	0.25	0.015	0.014
3.65	0.30	0.128	0.172	0.176	0.175
4.55	0.18	0.154	0.036	0.044	0.045
5.23	0.20	0.20	0.0071		0.032

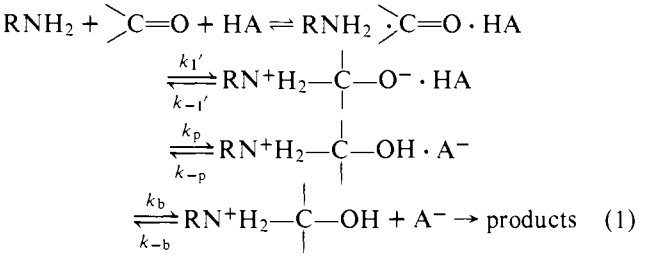
[a] For the protio compound. [b] Calculated first-order rate constants based on the rate law provided in the text.

Table II. Observed Kinetic α-Deuterium Isotope Effects for Addition of Semicarbazide to 4-Methoxyphenyl Formate as a Function of pH at 25 °C

pH	f_H[a]	$f_{RNH_3^+}$	f_0	k_D/k_H[b]
2.00	0.47	0.53		1.21 ± 0.01 (1.21)[c]
3.65	0.03	0.89	0.08	1.16 ± 0.01 (1.156)
4.55		0.63	0.37	1.17 ± 0.01 (1.179)
5.23		0.33	0.67	1.21 ± 0.01 (1.207)

[a] Values of f are the fractions of the aminolysis reaction proceeding through specific acid analysis, f_H, general acid catalysis, $f_{RNH_3^+}$, and the pH-independent route, f_0. Values were calculated from the rate law provided in the text and the concentration data supplied in Table I. [b] Each isotope effect is the mean of not less than five independent determinations. [c] Values in parenthesis are calculated isotope effects based on the data collected in Table III.

to the zwitterionic addition intermediate, $T^{\pm}$, a mechanism enforced by the short lifetime of this intermediate.[2] Subsequently, Jencks predicted that aminolysis of phenyl acetates involving weakly basic amines occurs with rate-determining attack of amine on ester associated with the acid catalyst, a preassociation mechanism.[3] The change in mechanism is predicted on the basis of an impossibly short lifetime for decreasingly stable zwitterionic addition compounds.[3] The preassociation mechanism requires that k_1' be the rate-determining step in the reaction pathway 1.



(1)

We have elected to test this prediction by measuring kinetic α-deuterium isotope effects for each term in the rate law for attack of a weakly basic amine, semicarbazide, on 4-methoxyphenyl formate, a formate ester which reacts with semicarbazide at a rate convenient for the determination of secondary deuterium isotope effects. Bilkadi et al. have previously established the limiting kinetic α-deuterium isotope effect corresponding to complete rehybridization of the acyl carbon atom of methyl formate from sp^2 to sp^3: $k_D/k_H \approx 1.35$.[4] If proton trapping of $T^{\pm}$ is the rate-determining step, one anticipates an isotope effect near this magnitude; in contrast, if the k_1' term of eq 1 is rate determining, one expects a smaller isotope effect which, in principle, could range from near unity to near the upper limit depending on the extent of C–N bond formation in the transition state.[5]

In order to determine isotope effects for attack of semicarbazide on 4-methoxyphenyl formate, it was necessary to determine the rate law for the reaction. To accomplish this end, first-order rate constants for this reaction were measured at 25 °C and an ionic strength of 1.0 at pH 2.0, 3.0, 3.65, 4.0, and 4.5. Four to seven concentrations of semicarbazide were employed at each value of pH; a total of 31 first-order rate constant determinations were made. Each first-order rate constant is based on 50–100 data points and was calculated employing a weighted regression analysis as previously described.[6] Prior to calculation of second-order rate constants, the small contribution of a hydrolysis reaction was subtracted employing a previously determined rate law for this reaction.[7] Second-order rate constants were calculated employing a value of pK_a for the semicarbazide cation of 3.78, determined for the conditions of the kinetic work.

Table III. Kinetic α-Deuterium Isotope Effects for Each Term in the Rate Law for Addition of Semicarbazide to 4-Methoxyphenyl Formate

$(k_D/k_H)_0$	$(k_D/k_H)_H$	$(k_D/k_H)_{RNH_3^+}$
1.236 ± 0.019	1.285 ± 0.028	1.144 ± 0.015

Preliminary data analysis clearly indicated the presence of both specific acid and general acid catalyzed terms in the rate law and suggested the presence of a general base term as well. All second-order rate constants were fitted to rate laws including and excluding the general base term utilizing a multiple-regression analysis computer program.[8] The fit of calculated values to observed values was not appreciably improved by the inclusion of the general base term; consequently we elected to employ a rate law in which this term does not appear. The final rate law determined is k_2 (M^{-1} min^{-1}) = 156 ± 10 (H^+) + 7.1 ± 0.30 (RNH_3^+) + 0.11 ± 0.06. This rate law accounts for all observed rate constants with an average deviation of 6.5% and a maximum deviation of 15%.

Kinetic α-deuterium isotope effects for attack of semicarbazide on 4-methoxyphenyl formate were measured at single concentrations of semicarbazide at four values of pH. Conditions of the measurements are collected in Table I; note that the rate law indicated above quite accurately accounts for the observed rate constants for the protio substrate. At each pH and concentration of semicarbazide employed, the fractional contribution of each term in the rate law to the total rate was calculated employing the rate law; these are collected in Table II together with the measured secondary deuterium isotope effects. The four observed values of isotope effects are more than sufficient to permit calculation of isotope effects for the three terms which occur in the rate law; this calculation was done employing a computer-based multiple-regression analysis. Results are collected in Table III. Note that the derived values account well for the observed isotope effects (Table II).

The most reliable isotope effect determined is that for the general acid catalyzed reaction: the corresponding term in the rate law contributed in a significant way at each value of pH employed (Table II) and the associated rate constant is known accurately. The value observed, $k_D/k_H = 1.14$, is clearly much less than the limiting value expected for a trapping mechanism. The observed isotope effect thus strongly suggests a preassociation mechanism, eq 1. The isotope effect also suggests that C–N bond formation is far from complete in the transition state.

The isotope effect for the specific acid catalyzed reaction is not so reliable as that for the general acid catalyzed process and is significantly larger. It depends on the single measurement at pH 2.0. Given some uncertainty in the upper limit for reactions of 4-methoxyphenyl formate, one cannot be certain that the observed effect is less than the maximal one, although it appears to be. At any event, the observed value is entirely consistent with the preassociation mechanism deduced above.

The pH-independent addition of semicarbazide to 4-methoxyphenyl formate presumably reflects rate-determining decomposition of $T^{\pm}$;[2] the isotope effect, which is reliable, is

too small to be consistent with rate-determining proton switch but is consistent with the suggested mechanism.

Our conclusions pertinent to the preassociation mechanism for the acid-catalyzed reactions are entirely in accord with the recent observations of Cox and Jencks.[9] On the basis of a nonlinear Brønsted plot and a sharp maximum in solvent deuterium isotope effects for general acid catalyzed methoxyaminolysis of phenyl acetate, these workers have concluded that the general acid catalyzed pathway for monofunctional acids more acidic than $pK_a = 4$ occurs by the preassociation mechanism.

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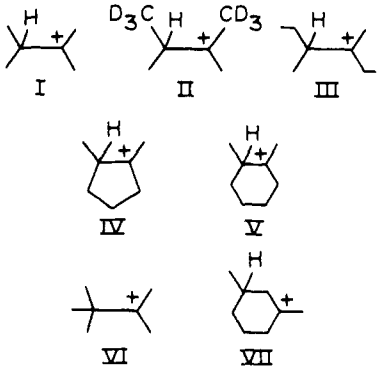
Rates of Degenerate 1,2-Hydride and 1,2-Methide Shifts from the Carbon-13 Nuclear Magnetic Resonance Spectra of Tertiary Alkyl Cations

Sir:

The 1,2 shift of hydride or methide is the most common and important rearrangement of carbonium ions. Until now, all simple ions for which this shift is degenerate have given sharp, averaged NMR spectra at temperatures as low as −160 °C.[1,2] Kinetic line-shape effects have been observed only for cations with special stabilization, such as the norbornyl cation,[3] the benzenonium ion,[4] and their derivatives.[3,4] Because line broadening in the fast exchange limit is proportional to frequency squared, we have been able to observe line broadening in, and measure rates for degenerate 1,2 shifts from, the high-field (67.9 MHz) ^{13}C NMR spectra of I–VI.

Solutions of I–IV,[1,2] VI,[1,2] and a 50:50 mixture of V[2h] and VII[2h] were prepared[5] from the corresponding alcohols in 50:50 SO_2ClF/SO_2F_2; external CD_3OCD_3/CCl_2F_2 or



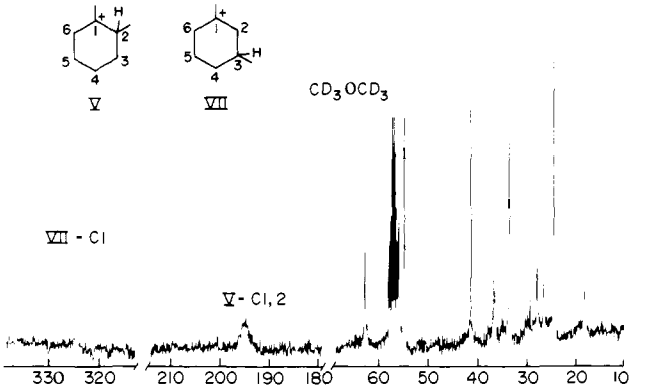


Figure 1. 67.9-MHz ^{13}C NMR spectrum of a 50:50 mixture of V and VII at −135 °C.

Table I. Experimental Line Widths and Rates

compd	temp, °C	W, Hz[a]	$k/10^7$, s^{-1}
I	−119	4	14
	−128	12	4.6
	−138	18	3.1
II	−119	2	28
	−125	2	28
	−130	5	11
	−135	10	5.6
	−138	13	4.3
III	−116	225	0.25
IV	−126	2	28
	−135	6	9.2
	−135	5	11
	−139	18	3.1
V	−119	11	5.0
	−122	12	4.6
	−126	34	1.6
	−128	41	1.4
	−135	125	0.46
	−137	148	0.40
VI	−110	2	28
	−114	5	11
	−125	16	3.5
	−129	34	1.6
	−136	65	0.85

[a] See text for definition of W.

CD_3OCD_3/SO_2F_2 were used as lock substance and reference; temperatures were measured to ±2 °C using the temperature dependence of the chemical shifts of a separate sample of 2-chlorobutane.[6,7] Rates were computed according to the fast exchange limit approximation,[8] $k = (\pi/2) \times (\Delta^2/W)$, where Δ is the chemical-shift separation, in hertz, between the nuclei that are averaged, and W is the width of the broadened peak minus the natural line width. Estimates of Δ range from 261 to 278 ppm.[1,2,9] The value 277 ppm[2a] (18803 Hz) was used throughout, since obtained thermodynamic values are insensitive to Δ. The width of the averaged methyl peak was used as the natural line width.

The mixture of V and VII was prepared to determine whether we might be observing only relaxation broadening of the averaged cation-methine (C-1–C-2) peak, as a result of T_1 shortening induced by chemical-shift anisotropy.[10] This process would broaden the C-1 peak of VII (δ 325 ppm) more than any other. However, in the ^{13}C NMR spectrum[11] of V and VII at −135 °C (Figure 1), only the peak at δ 195 ppm (C-1–C-2 of V) is broadened. Therefore, chemical-shift anisotropy is not the cause of broadening.

The line widths and rates for I–VI are presented in Table I. We have not fit the data to the Arrhenius equation, because, over the narrow range of accessible temperatures, systematic deviations could lead to large errors in E_a and log A. The free

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