(q), 13.5 (q), 19.7 (q), 19.8 (q), 20.6 (t), 21.4 (t), 22.6 (q), 22.7 (q), 24.5 (t), 24.8 (t), 26.9 (q), 28.0 (d), 32.3 (t), 32.7 (d), 32.8 (d), 37.3 (t), 37.5 (3 t), 39.4 (t), 41.8 (t), 61.6 (s), 62.9 (s), 78.4 (s), 101.9 (s), 130.1 (s), 144.5 (s), 195.5 (s). **2b**: MS *m/e* 478.3647 (calcd for $C_{29}H_{50}O_5$, 478.3661); IR (neat) δ 952, 1090, 1140, 1230, 1263, 1380, 1462, 1668 (sh), 1682, 3390 cm^{-1}; UV (*n*-hexane) λ_{max} 244 nm (ϵ 5400); CD (*n*-hexane) λ 215 ($\Delta\epsilon$ +3.4), 234 (0), 247 (−2.8), 333 nm (−2.6); ^1H NMR ($CDCl_3$) δ 1.47 (s, 3 H), 1.50 (s, 3 H), 1.85 (s, 3 H), 1.93 (s, 3 H), 7.42 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 10.2 (q), 12.5 (q), 14.0 (q), 19.6 (q), 19.8 (q), 20.3 (t), 20.8 (t), 22.6 (q), 22.7 (q), 24.5 (t), 24.8 (t), 25.8 (q), 28.0 (d), 32.6 (d), 32.7 (t), 32.8 (d), 37.3 (t), 37.4 (t), 37.5 (2 t), 39.4 (t), 44.1 (t), 61.5 (s), 63.3 (s), 78.4 (s), 102.0 (s), 129.9 (s), 145.2 (s), 195.7 (s).

The fraction of **3** was further purified by preparative HPLC. Isomers **3a** and **3b** were eluted in that order from a Micropak Si-10 column (8 mm × 50 cm) with a 19:1 mixture of *n*-hexane and isopropyl ether. **3a**: MS *m/e* 534.4267 (calcd for $C_{33}H_{58}O_5$, 534.4287); IR (neat) ν 958, 1089, 1196, 1260, 1363, 1376, 1460, 1682 cm^{-1}; UV (*n*-hexane) λ_{max} 242 nm (ϵ 5600); CD (*n*-hexane) λ 224 ($\Delta\epsilon$ +2.8), 238 (0), 254 (−4.5), 332 nm (−1.3); ^1H NMR ($CDCl_3$) δ 1.03 (s, 9 H), 1.42 (s, 3 H), 1.47 (s, 3 H), 1.78 (s, 3 H), 1.84 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 10.1 (q), 12.1 (q), 13.3 (q), 19.6 (q), 19.7 (q), 20.2 (t), 20.7 (t), 22.6 (q), 22.7 (q), 24.4 (t), 24.7 (t), 26.0 (3 q), 27.9 (d), 32.5 (d), 32.7 (d and t), 33.0 (q), 37.2 (t), 37.3 (t), 37.4 (t), 39.3 (t), 44.4 (t), 62.6 (s) 63.6 (s), 77.2 (s), 79.7 (s), 100.0 (s), 129.2 (s), 144.3 (s), 195.6 (s). **3b**: MS *m/e* 534.4237 (calcd for $C_{33}H_{58}O_5$, 534.4287); IR (neat) ν 955, 1089, 1196, 1257, 1363, 1376, 1460, 1682 cm^{-1}; UV (*n*-hexane) λ_{max} 243 nm (ϵ 5400); CD (*n*-hexane) λ 225 ($\Delta\epsilon$ −1.6), 236 (0), 254 (+3.3), 332 nm (+1.1); ^1H NMR ($CDCl_3$) δ 1.03 (s, 9 H), 1.29 (s, 3 H), 1.45 (s, 3 H), 1.78 (s, 3 H), 1.85 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 10.2 (q), 12.0 (q), 13.0 (q), 19.5 (q), 19.7 (q), 20.3 (t), 21.3 (t), 22.5 (q), 22.6 (q), 24.4 (t), 24.7 (t), 26.1 (3 q), 27.9 (d), 32.7 (d and t), 32.9 (d), 33.3 (q), 37.2 (t), 37.3 (t), 37.5 (t), 37.7 (t), 39.3 (t), 41.3 (t), 62.6 (s), 63.4 (s), 77.6 (s), 79.7 (s), 100.0 (s), 129.4 (s), 144.2 (s), 195.5 (s).

Acknowledgment. We thank Dr. R. K. Tikare for preliminary work on the reaction of α-tocopherol with the *tert*-butylperoxyl radical, S. Nakano for technical assistance, Dr. M. M. Dooley for her help in the preparation of this manuscript, K. Shizukuishi of Hitachi Seisakusho Co., Ltd., and R. Katouno of Nissei Sangyo Co., Ltd., for high-resolution mass spectroscopy, and Dr. K. U. Ingold of National Research Council of Canada for a stimulating discussion. This study was in part supported by Grant-in-Aid for Scientific Research for the Ministry of Education, Science and Culture (Grants 59570930 and 62470078).

Supplementary Material Available: Figure 6 representing the time course of the alteration in the ^1H NMR signal of the reaction mixture from **4**, Table II showing the structural assignment of the spectral data of products **2a**, **2b**, **3a**, **3b**, **5**, and **6** and Tables III–VI listing bond lengths, bond angles, atomic coordinates, and thermal parameters for **5a** and **5b** (8 pages). Ordering information is given on any current masthead page.

Acid-Catalyzed Hydrolysis of Vinyl Acetals. Reaction through the Acetal Rather Than the Vinyl Ether Functional Group

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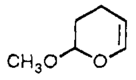
Contributon from the Department of Chemistry, University of Toronto, Toronto, Ontario M5S 1A1, Canada. *Received March 10, 1989*

Abstract: The hydrolysis of three vinyl acetals, 9-methoxy-1-oxacyclonon-2-ene and the *cis*- and *trans*-1-propenyl methyl acetals of acetaldehyde, was monitored by ^1H NMR spectroscopy in dilute mineral acid solution, and rates of the reactions were also measured in dilute mineral acids and semicarbazide, acetic acid, and cacodylic acid buffers. The NMR spectra showed biphasic changes, which could be assigned to the formation and decay of enol intermediates generated by initial acetal group hydrolysis. Biphasic absorbance changes also appeared in the ultraviolet spectra of these substrates reacting in dilute mineral acid solution, and rate constants for two successive reactions could be evaluated. These rate constants were assigned to the individual reaction steps, and further support for the assigned reaction path was obtained, by comparison with rate constants measured in the buffer solutions, where acetal hydrolysis was the only reaction observed, and also by comparison with rates of ketonization of the enols generated independently from the corresponding trimethylsilyl enol ethers. Solvent isotope effects provided yet more evidence for the assigned reaction path. Estimates of rates of hydrolysis of the vinyl ether groups of these substrates show that these vinyl ether functions are too unreactive to compete with acetal hydrolysis. Simultaneous vinyl ether and acetal hydrolysis, however, does occur in the case of 6-membered cyclic vinyl acetals, such as 2-methoxy-2,3-dihydropyran, and this is probably because intramolecular recapture of the alkoxycarbocationic intermediate slows acetal hydrolysis in the case of these smaller ring compounds.

Vinyl acetals contain vinyl ether as well as acetal functional groups, and, since both groups undergo hydrolysis readily, hydrolytic decomposition of vinyl acetals might occur through initial reaction of either group. The acid-catalyzed hydrolysis of the cyclic acetals 2-methoxy-2,3-dihydropyran (**1**) and 2-ethoxy-2,3-dihydropyran (**2**) have in fact been interpreted in terms of simultaneous reaction of both functional groups at similar rates.[1] Hydrolysis of the larger analogue 9-methoxy-1-oxacyclonon-2-ene (**3**), on the other hand, was originally believed to occur solely through reaction of the vinyl ether group.[2]



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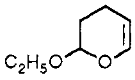

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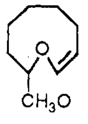
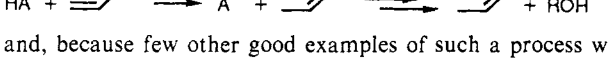


3

This assignment of a vinyl ether reaction pathway to **3** was of more than usual importance because certain aspects of the process were thought to provide an exception to the conventional mechanism for vinyl ether hydrolysis. This conventional mechanism involves rate-determining (rd) proton transfer from catalyst to substrate, eq 1,



(1)

and, because few other good examples of such a process were known, vinyl ether hydrolysis had become a prototype rate-de-

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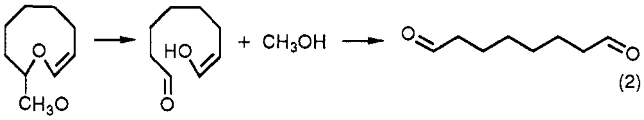
[1] (a) Kankaanpera, A. *Acta Chem. Scand.* **1969**, *23*, 1465–1470. (b) Burt, R. A.; Chiang, Y.; Kresge, A. J. *Can. J. Chem.* **1980**, *58*, 2199–2202.

[2] Cooper, J. D.; Vitullo, V. P.; Whalen, D. L. *J. Am. Chem. Soc.* **1971**, *93*, 6294–6296.

0002-7863/89/1511-7185$01.50/0

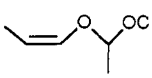
termining proton-transfer reaction that was being used to probe details of the proton-transfer process and acid–base catalysis.[3] This mechanistic exception, however, made the proton-transfer step of vinyl ether hydrolysis rapid and reversible and left some subsequent step to be rate-determining, and that impaired the usefulness of the reaction for this general purpose.

We recently reexamined the hydrolysis of **3** and found that the process originally observed is not a vinyl ether reaction at all.[4] Hydrolysis actually occurs through initial rapid reaction of the acetal group followed by somewhat slower ketonization of the enol so formed, eq 2, and since ketonization and vinyl ether hydrolysis are rather similar processes, the former was quite naturally mistaken for the later.



(2)

We have now extended our study of vinyl acetals to two acyclic analogues of **3**, the *cis*- and *trans*-1-propenyl methyl acetals of acetaldehyde, **4** and **5**. These substances also react by initial hydrolysis of their acetal groups followed by enol ketonization, with no significant reaction through the vinyl ether groups, and, as in the case of **3**, both reaction steps may be observed under certain conditions. Our new results provide additional insight into the chemistry of vinyl acetals and lead to a rationalization of the different reactivity patterns of **1** and **2** versus **3**–**5**.



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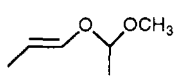

5

We describe this new work here and also give a full account of our investigation of **3**, which we had so far published only in preliminary form.[4]

Experimental Section

Materials. Samples of 9-methoxy-1-oxacyclonon-2-ene were kindly provided by Professor D. L. Whalen. *cis*- and *trans*-1-propenyl methyl acetals of acetaldehyde were prepared by sodium hydride induced dehydrochlorination of the methyl 2-chloropropyl acetal, which had been obtained by transacetalization of acetaldehyde dimethyl acetal with 2-chloropropanol, eq 3. The cis and trans isomers were separated by gas chromatography; their NMR spectra were consistent with their structures and also with spectral details reported for these substances prepared in another way.[5] Trimethylsilyl enol ethers of propionaldehyde and butyraldehyde were synthesized from the aldehydes by treatment with trimethylsilyl chloride,[6] and cis and trans isomers were separated by gas chromatography.

$$\begin{aligned} &CH_3C(Cl)HCH_2OH + CH_3CH(OCH_3)_2 \rightarrow \\ &\quad CH_3C(Cl)HCH_2OCH(CH_3)OCH_3 \rightarrow \\ &\qquad CH_3CH{=}CHOCH(CH_3)OCH_3 \quad (3) \end{aligned}$$

All other materials were best available commercial grades. Solutions were prepared with deionized water purified further by distillation or with deuterium oxide (MSD, 99.8 atm % D) as received.

Kinetics. Rates of reaction were measured spectrophotometrically using a Cary 118 spectrometer whose cell compartment was thermostated at 25.0 ± 0.02°. Vinyl acetal hydrolyses were monitored in mineral acid solutions by following the change in vinyl group absorbance at λ = 210–215 nm and in semicarbazide buffers by following the appearance of aldehyde semicarbazone absorbance at λ = 230 nm; reactions in acetic and cacodylic acid buffers were also followed by the appearance of semicarbazone, which was formed from the small amounts of semicarbazide added to these solutions. Control experiments showed that the trapping reaction was sufficiently fast, and calculations showed that the added semicarbazide had no significant effect on the pH of these solutions. Rates of ketonization of enols generated from trimethylsilyl ethers were followed by monitoring the enol absorbance at λ = 205–210 nm and in semicarbazide buffers by monitoring the semicarbazone absorbance at λ = 230 nm. Rate constants were calculated by least-squares fitting to single- or double-exponential functions, as required.

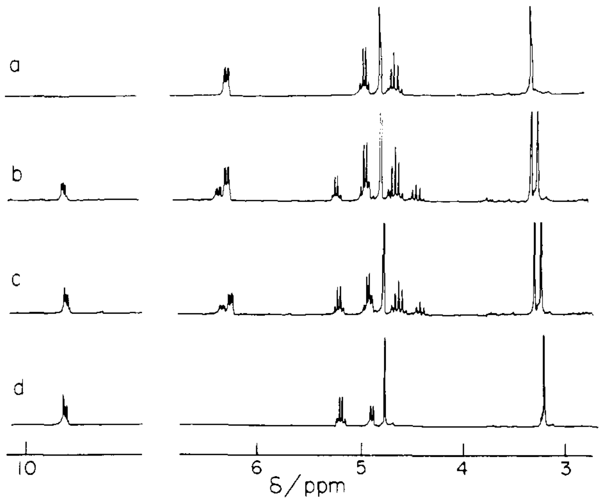

Figure 1. ^1H NMR spectral changes occurring during the hydrolysis of a 0.1 M solution of acetaldehyde *cis*-1-propenyl methyl acetal in 0.001 M DCl/D_2O. Spectra measured at 200 MHz and ambient temperature: (a) substrate in D_2O; (b) after adding DCl; (c) 15 min later; (d) next day.

Results

NMR Spectral Changes. ^1H NMR spectra of an acetonitrile solution of 9-methoxy-1-oxacyclonon-2-ene undergoing hydrolysis after addition of DCl in D_2O, illustrated in Figure 1 of our preliminary publication,[4] show that the vinyl proton signals of the substrate are replaced by a new set, attributable to an enol intermediate;[7] these new signals are then themselves replaced by an NMR spectrum characteristic of the ultimate reaction product, suberaldehyde (cf. eq 2).

Similar biphasic spectral changes occur during the hydrolysis of the *cis*- and *trans*-1-propenyl methyl acetals of acetaldehyde; these are illustrated for the cis isomer in Figure 1. The spectrum of the acetal dissolved in D_2O consists of vinyl proton signals at δ = 6.24 (qd, J = 8.0 Hz, J' = 1.8 Hz) and 4.68 (qd, J = 8.0 Hz, J' = 6.7 Hz), plus a signal from the methine proton bound to the acetal proacyl carbon atom at δ = 4.96 (q, J = 5.5 Hz), a methoxyl proton signal at δ = 3.40 (s), and methyl group signals at δ = 1.55 and 1.37 (not shown). Upon the addition of DCl, these signals diminish and new vinyl proton signals appear at δ = 6.32 (qd, J = 6.4 Hz, J' = 1.8 Hz) and δ = 4.48 (qd, J = 7.0 Hz, J' = 6.3 Hz). These changes are also accompanied by the appearance of signals attributable to acetaldehyde and its hydrate at δ = 9.68 (q, J = 2.8 Hz, $CH_3C\mathit{H}O$) and 5.23 (q, J = 5.2 Hz, $CH_3C\mathit{H}(OH)_2$) and to methanol at δ = 3.34, plus new signals in the methyl region. The new vinyl signals and one of the methyl group resonances then also gradually disappear and are replaced by propionaldehyde signals at δ = 9.66 (m overlapping signals from acetaldehyde, $CH_3CHDC\mathit{H}O$) and δ = 4.94 (d, J = 5.6 Hz, with additional unresolved fine structure, $CH_3CHOC\mathit{H}(OH)_2$) plus other resonances in the methyl region.

These NMR spectral changes rule out any significant amount of reaction occurring through hydrolysis of the vinyl ether group, because such a process, eq 4, would lead to straightforward disappearance of the original vinyl proton signals without production of a new set. A vinyl ether hydrolysis route is also incompatible with the fact that acetaldehyde plus methanol appear before

$$\begin{aligned} &CH_3CH{=}CHOC(CH_3)HOCH_3 \xrightarrow[\text{rd}]{H_2O} \\ &\quad CH_3CH_2C(OH)HC(CH_3)HOCH_3 \rightarrow CH_3CH_2C(O)H + \\ &\qquad HOC(CH_3)HOCH_3 \rightarrow CH_3C(O)H + CH_3OH \quad (4) \end{aligned}$$

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(3) For a brief review and an application to pharmaceutical chemistry, see: Kresge, A. J. *Acc. Chem. Res.* **1987**, *20*, 364–370.

(4) Burt, R. A.; Chiang, Y.; Kresge, A. J.; Okuyama, T.; Tang, Y. S.; Yin, Y. *J. Am. Chem. Soc.* **1987**, *109*, 3787–3788.

(5) Taskinen, E.; Lahteenmaki, H. *Tetrahedron* **1976**, *32*, 2331–2333.

(6) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324–2336.

(7) Capon, B.; Rycroft, D. S.; Watson, T. W.; Zucco, C. *J. Am. Chem. Soc.* **1981**, *103*, 1761–1765. Capon, B.; Siddhanta, A. K. *J. Org. Chem.* **1984**, *49*, 255–257.

Table I. Rate Constants for the Hydrolysis of Vinyl Acetals in Aqueous Solution at 25 °C[a]

	substrate		
constant[b]	9-methoxy-1-oxa-cyclonon-2-ene	*cis*-1-propenyl methyl acetal	*trans*-1-propenyl methyl acetal
	Mineral Acid Solutions		
$(k_{\mathrm{H^+}})_{\mathrm{acetal}}$	14.6 ± 1.3	0.422 ± 0.009	0.865 ± 0.030
$(k_{\mathrm{H^+}})_{\mathrm{enol}}$	6.80 ± 0.46		3.34 ± 0.050
$(k_{\mathrm{D^+}})_{\mathrm{acetal}}$	28.6 ± 1.9	0.740 ± 0.015	2.12 ± 0.47
$(k_{\mathrm{D^+}})_{\mathrm{enol}}$	0.960 ± 0.019	1.62 ± 0.09	0.797 ± 0.049
	Semicarbazide Buffers		
$k_{\mathrm{H^+}}$, BR = 4	11.4 ± 0.2	0.418 ± 0.005	0.911 ± 0.013
$k_{\mathrm{H^+}}$, BR = 2	16.0 ± 0.2	0.394 ± 0.005	0.887 ± 0.015
$k_{\mathrm{H^+}}$, BR = 1			0.954 ± 0.010
$k_{\mathrm{BH^+}}$, BR = 4	$(1.54 \pm 0.26) \times 10^{-2}$	$(-0.41 \pm 0.68) \times 10^{-4}$	$(2.71 \pm 2.02) \times 10^{-4}$
$k_{\mathrm{BH^+}}$, BR = 2	$(1.01 \pm 0.17) \times 10^{-2}$	$(1.12 \pm 0.51) \times 10^{-4}$	$(0.22 \pm 1.61) \times 10^{-4}$
$k_{\mathrm{BH^+}}$, BR = 1			$(0.51 \pm 0.90) \times 10^{-4}$
	Acetic Acid Buffers		
$k_{\mathrm{H^+}}$, BR = 1	14.4 ± 0.5		
k_{HA}, BR = 1	$(6.35 \pm 2.15) \times 10^{-4}$		
	Cacodylic Acid Buffers		
$k_{\mathrm{H^+}}$, BR = 2	15.4 ± 0.4		
k_{HA}, BR = 2	$(4.63 \pm 0.92) \times 10^{-5}$		

[a] Ionic strength = 0.10 M. [b] Units: $M^{-1}\ s^{-1}$; BR = buffer ratio.

propionaldehyde is formed (Figure 1). The vinyl ether route requires these products to appear simultaneously, for, although the hemiacetal of acetaldehyde is produced first in the same step as propionaldehyde (eq 4), it will decompose immediately to acetaldehyde and methanol: the known rate of reaction of this hemiacetal[8] is faster, by more than 2 orders of magnitude, than the process being observed here.

Biphasic spectral changes such as these, produced by two consecutive reactions, can arise only if the second reaction is sufficiently slow relative to the first. This condition is more likely to be fulfilled for the present system in D_2O than in H_2O solution, for rates of the present second reaction, enol ketonization, are slower in D_2O than in H_2O, whereas those of the first reaction, acetal hydrolysis, are faster in D_2O than in H_2O. Solvent isotope effects on both of the reaction steps will therefore act cooperatively, speeding up the first and slowing down the second, to make observation of biphasic changes and detection of the reaction intermediate more favorable in D_2O than in H_2O. This is fortunate, for D_2O is also the better solvent for these ^1H NMR measurements: signals from an H_2O solvent would have obscured some of the resonances that were monitored. It will in fact be seen below that, whereas two reaction steps could be resolved kinetically for all three of the present substrates in D_2O solution, this was possible for only two of the three substrates in H_2O solutions.

Kinetics. Biphasic changes were also observed in the UV spectra of the presently examined vinyl acetals undergoing hydrolysis. This is illustrated in Figure 2, which shows that the absorbance of 9-methoxy-1-oxacyclonon-2-ene dissolved in dilute mineral acid first rises rapidly and then decreases somewhat more slowly. These changes correlate with the appearance and consumption of the enol intermediate observed by ^1H NMR. They obey the rate law for two consecutive first-order reactions, and least-squares fitting to a double-exponential expression produces rate constants for the two reaction steps.

Double-exponential behavior of this kind was observed in D_2O solutions of dilute mineral acids for all three substrates investigated here, but only two of the three gave double-exponential behavior in H_2O solution. The exception was the *cis*-1-propenyl acetal: in this case, independent determination of the second reaction rate showed it to be too fast relative to the first, and only single-exponential behavior was consequently observed. Rate measurements were made for each substrate in each solvent over a range of acid concentrations, which varied by at least a factor of 5; ionic strength was maintained at 0.10 M. These data are summarized in Table S1 of the supplementary material.[9] First-order rate constants within each of the five sets so produced were directly proportional to acid concentration, and linear least-squares analysis gave the second-order hydrogen ion catalytic coefficients listed in Table I.

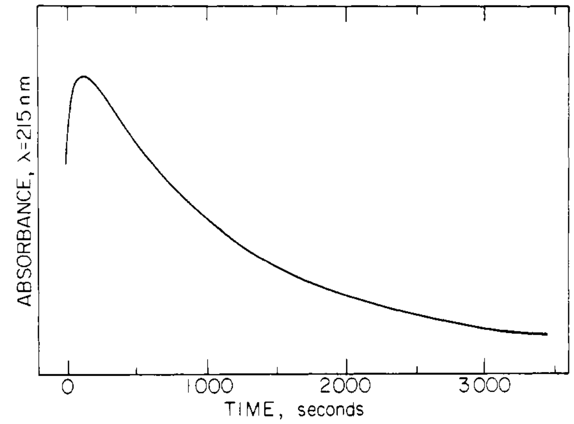

Figure 2. Absorbance changes at λ = 215 nm accompanying the hydrolysis of 9-methoxy-1-oxacyclonen-2-ene in 0.001 M DCl/D_2O at 25 °C.

Rate measurements were also conducted in semicarbazide buffers; only single-exponential behavior was observed in these solutions. Measurements were made in sets of buffers of constant buffer ratio and constant ionic strength (0.10 M) but varying total buffer concentration. These data are summarized in Table S2 of the supplementary material.[9]

Although stoichiometric buffer ratios were constant in these experiments, buffer failure[10] led to small variations in H^+ concentration within any given set. Observed first-order rate constants were therefore fitted to the expression shown in eq 5, treating both

$$k_{\mathrm{obs}} = k_{\mathrm{H^+}}[\mathrm{H^+}] + k_{\mathrm{BH^+}}[\mathrm{BH^+}] \qquad (5)$$

$[H^+]$ and $[BH^+]$ as independent variables. Values of these variables were obtained by calculation using $pK_a = 3.65$ for the conjugate acid of semicarbazide[11] and $\gamma = 0.83$[12] and 0.80[13] as

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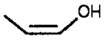
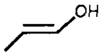
(8) Sorensen, P. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1987**, *109*, 4675–4690.

(9) Supplementary material. See paragraph at the end of this paper regarding availability.

(10) Keeffe, J. R.; Kresge, A. J. *Techniques of Chemistry, Investigations of Rates and Mechanisms of Reactions*; Bernasconi, C. F., Ed.; Wiley: New York, 1986; Vol. 6, Part 1, Chapter XI.

(11) Jencks, W. P.; Regenstein, J. *Handbook of Biochemistry*, 2nd Ed.; Sober, H. A., Ed.; Chemical Rubber Publishing Co.: Cleveland, OH, 1970; p J-203.

Table II. Rate Constants for the Ketonization of Enols Derived from Trimethylsilyl Ethers in Aqueous Solution at 25 °C[a]

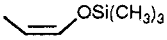
enol	k_{H^+}, M^{-1} s^{-1}	k_{D^+}/M^{-1} s^{-1}
	6.11 ± 0.13	1.06 ± 0.06
	5.01 ± 0.22	
	3.31 ± 0.24	

[a] Ionic strength = 0.10 M.

activity coefficients of H^+ and BH^+, respectively. Least-squares analysis gave the rate constants listed in Table I.

Rate measurements were also made for one of the substrates, 9-methoxy-1-oxacyclonon-2-ene, in acetic and cacodylic acid buffers. Again, only single-exponential behavior was observed. Buffer solutions of constant buffer ratio and constant ionic strength (0.10 M) but varying buffer concentration were used. Buffer failure did not occur in these solutions, and the data were therefore fitted to eq 5, treating the first term, $k_{H^+}[H^+]$, as a constant parameter to be determined. Linear least-squares analysis gave the general acid catalytic coefficients listed in Table I. Hydrogen ion catalytic coefficients were calculated from the parameter $k_{H^+}[H^+]$, plus values of $[H^+]$; the latter were again obtained by calculation using $\gamma = 0.775$ for the acetate ion[12] and $Q_a = 8.20 \times 10^{-7}$ M as the concentration quotient appropriate to ionic strength = 0.10 M for cacodylic acid.[14]

Rates of ketonization of enols generated by rapid hydrolysis of the corresponding trimethylsilyl ethers, **6–8**, were also measured.



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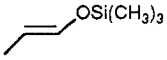

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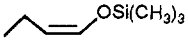

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Determinations were made in mineral acid solutions, in H_2O for all three substrates, and in D_2O as well for **8**, over a range of acid concentrations. These data are summarized in Table S3 of the supplementary material.[9] Observed first-order rate constants were in each case directly proportional to acid concentration, and linear least-squares analysis gave the catalytic coefficients listed in Table II.

Discussion

Reaction Path and Assignment of Rate Constants. H_2O Solutions. The NMR spectral changes that occur during hydrolysis of the three vinyl acetals examined here indicate that this process takes place, as is illustrated in eq 2, through reaction of the acetal functional group followed by ketonization of the enol thus formed. Additional support for this reaction path may be obtained by comparing kinetic results determined in dilute mineral acid solutions, where biphasic UV absorbance changes provide rate constants for two successive reactions, with rate constants measured under conditions where one or the other reaction dominates.

Acetal hydrolysis can be made to dominate in buffer solutions, because this reaction is usually catalyzed only by hydrogen ions,[15] where the ketonization of enols is catalyzed strongly by both general acids and general bases.[16] General catalysis by buffers will therefore accelerate ketonization, and, if this acceleration is strong enough, ketonization will become an invisible fast reaction following a slower rate-determining step; acetal hydrolysis will then be the only process observed. Such a situation would be characterized by single-exponential kinetic behavior and an absence of detectable buffer catalysis.

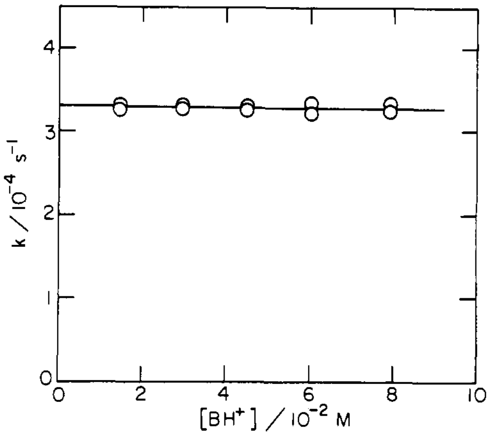

Figure 3. Relationship between buffer acid concentration and first-order rate constants for the hydrolysis of acetaldehyde *cis*-1-propenyl methyl acetal in aqueous semicarbazide buffer solutions at 25 °C; buffer ratio ($[BH^+]/[B]$) = 4.

This situation appears to have been realized in the hydrolysis of the *cis*- and *trans*-propenyl methyl acetals of acetaldehyde in semicarbazide buffers. These reactions showed single-exponential behavior with no induction period, and buffer catalysis could not be detected. The lack of buffer catalysis is illustrated in Figure 3 and is also shown by the general acid catalytic coefficients, k_{BH^+} listed in Table I, whose values are not significantly different from zero. The data for different buffer ratios, moreover, when treated in terms of simple specific hydrogen ion catalysis, give self-consistent sets of hydronium ion catalytic coefficients (Table I). The results agree well with the specific rates $k_{H^+} = 0.422$ and 0.865 M^{-1} s^{-1} measured in dilute mineral acids for the *cis*- and *trans*-acetals, respectively, thus confirming that the hydrolysis of these acetals was indeed being observed in the mineral acid solutions. This agreement also identifies the mineral acid specific rates as acetal hydrolysis rate constants.

Hydrolysis of the third vinyl acetal, 9-methoxy-1-oxacyclonon-2-ene, in buffer solutions also followed single-exponential behavior with no sign of an induction period. Some general catalysis, however, appears to have occurred, for, as the data summarized in Table I show, least-squares analysis produced statistically significant general acid catalytic coefficients. This catalysis, however, was not strong, and it had no general base component. Hydronium ion catalytic coefficients calculated from the intercepts of buffer dilution plots, moreover, showed no systematic variation with buffer ratio or pH. Such behavior is uncharacteristic of enol ketonization,[16] for which strong general acid plus general base catalysis would have been observed and for which rate contributions from catalysis by water and hydroxide ion would have produced systematic differences in quantities calculated as simple hydrogen ion catalytic coefficients. It seems likely, therefore, that enol ketonization makes no significant contribution to these rates of reaction and that the weak general acid catalysis seen is a characteristic of the acetal hydrolysis reaction; general acid catalysis has been found in the hydrolysis of some acetals, especially those whose alcohol portions are good leaving groups such as the enol moiety in the present substrate.[15]

Again, there is good agreement between the hydronium ion catalytic coefficients determined in buffer solutions for this vinyl acetal and one of the specific rates measured in mineral acids, $k_{H^+} = 14.6$ M^{-1} s^{-1}. This reinforces assignment of an acetal hydrolysis reaction path for this substrate, and it also identifies this mineral acid rate constant as belonging to the acetal hydrolysis reaction.

The enol ketonization stage of these vinyl acetal hydrolyses cannot be made the dominant process by manipulating reaction

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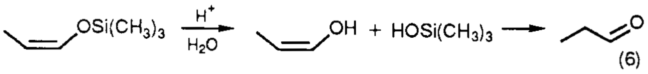
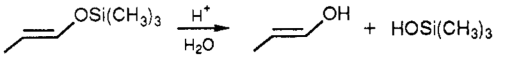
conditions, as was done for the acetal reaction stage, but enol ketonization can be studied in isolation by generating the enols in another way, e.g., from the corresponding trimethylsilyl enol ethers. It is known that the acid-catalyzed cleavage of such ethers gives enols, eq 6,[17] and that ketonization of these enols is often



(6)

much slower than their formation.[17b] We[18] and others[19] have used this method of generating enols extensively before, and we have employed it here to make the *cis*- and *trans*-enols of propionaldehyde, eq 6 and 7, and the *cis*-enol of butyraldehyde, eq 8; the



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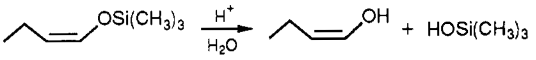

(8)

former two are the enols produced by the hydrolysis of the *cis*- and *trans*-1-propenyl methyl acetals of acetaldehyde, and the latter serves as a surrogate for the enol of suberaldehyde produced in the hydrolysis of the cyclic vinyl acetal, 9-methoxy-1-oxacyclonon-2-ene.

The hydronium ion catalytic coefficient for ketonization of the *trans*-enol of propionaldehyde, $k_{H^+} = 3.31 \pm 0.24$ M^{-1} s^{-1}, agrees well with the remaining rate constant, i.e., the one not assigned to acetal hydrolysis, for the reaction of the *trans*-propenyl acetal in mineral acid solutions, $k_{H^+} = 3.34 \pm 0.50$ M^{-1} s^{-1}. Similarly, the catalytic coefficient for ketonization of the butyraldehyde enol, $k_{H^+} = 6.11 \pm 0.13$ M^{-1} s^{-1}, is consistent with the remaining rate constant for the mineral acid reaction of the cyclic vinyl acetal, $k_{H^+} = 6.80 \pm 0.46$ M^{-1} s^{-1}. Only one rate constant could be determined in mineral acid solutions for the third vinyl acetal, the *cis*-propenyl substrate, and that has already been assigned to the acetal reaction. The fact that it is different from the catalytic coefficient for ketonization of the *cis*-propionaldehyde enol, $k_{H^+} = 0.442 \pm 0.009$ M^{-1} s^{-1} (acetal reaction) vs $k_{H^+} = 5.01 \pm 0.22$ M^{-1} s^{-1} (ketonization), confirms this assignment. The ratio of the two constants, moreover, k(ketonization)/k(acetal reaction) = 12, shows that the second reaction was too fast relative to the first to have been observed; consequently, only one rate constant could be determined. The corresponding rate ratios are much smaller for the other two substrates: k(ketonization)/k(acetal reaction) = 4 for the *trans*-propenyl acetal and 0.5 for the cyclic acetal, and in these cases both rate constants could be evaluated.

Rate Constant Assignment. D_2O Solutions. Rate constants measured in D_2O solutions of mineral acids were assigned to the various reactions in a different way, using as criteria the relative concentrations of enol and acetal existing during the course of the reactions. The latter were determined from the relative magnitudes of enol and acetal NMR signals. These signals showed that the concentration of enol quickly grew to a level greater than that of the acetal in the hydrolysis of the *trans*-propenyl and cyclic acetals, but that enol never exceeded acetal during hydrolysis of the *cis*-propenyl acetal. These different relationships imply corresponding differences between the rate constants for the two reaction steps.

Consider two successive reactions converting A into B and then B into C, with rate constants k_1 and k_2, eq 9. If k_2 is sufficiently

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C \tag{9}$$

less than k_1, B will build up as the reactions proceed, and eventually its concentration will exceed that of A. If, on the other hand, k_2 is sufficiently greater than k_1, B will always react faster than it is formed, and the concentration of B will never exceed that of A. The value of the rate constant ratio k_2/k_1 at which the transition from the first situation into the second will occur may be determined by considering the expression shown in eq 10,

$$[B]/[A] = \frac{k_1}{k_2 - k_1}(1 - e^{(k_1-k_2)t}) \tag{10}$$

which is easily derived from the integrated form of the rate constant for two consecutive first-order reactions.[20] When $k_2 = 2k_1$, the concentration ratio [B]/[A] approaches a limit of unity at large t (time); when $k_2 < 2k_1$, the limit is greater than unity; and when $k_2 > 2k_1$, it is less than unity. The rate constant ratio at which the transition from [B]/[A] > unity to [B]/[A] < unity occurs is therefore $k_2/k_1 = 2$.

Table III. Summary of Rate Constants and Isotope Effects for the Reaction of Vinyl Acetals in Aqueous Solution at 25 °C[a]

	substrate		
	9-methoxy-1-oxa-cyclonone-2-ene	*cis*-1-propenyl methyl acetal	*trans*-1-propenyl methyl acetal
	Acetal Hydrolysis		
k_{H^+} (M^{-1} s^{-1})	13.9 ± 0.4	0.408 ± 0.003	0.924 ± 0.007
k_{H^+}/k_{D^+}	0.487 ± 0.035	0.552 ± 0.012	0.436 ± 0.097
	Enol Ketonization		
k_{H^+} (M^{-1} s^{-1})	6.16 ± 0.13	5.01 ± 0.22	3.32 ± 0.22
k_{H^+}/k_{D^+}	6.42 ± 0.18	3.09 ± 0.22	4.16 ± 0.36

[a] Ionic strength = 0.10 M; k_{H^+} values are weighted averages computed from all determinations of a given constant.

It follows from this analysis, then, that in the *trans*-propenyl and cyclic acetal systems, where enol concentrations exceeded acetal concentrations and [B]/[A] > 1, $k_2 < 2k_1$ and k(ketonization) < 2k(acetal reaction). This identifies $k_{D^+} = 0.797$ M^{-1} s^{-1} as the rate constant for ketonization and $k_{D^+} = 2.12$ M^{-1} s^{-1} as the rate constant for the acetal reaction in the former case and $k_{D^+} = 0.960$ M^{-1} s^{-1} for ketonization and $k_{D^+} = 28.6$ M^{-1} s^{-1} for the acetal reaction in the latter. In the *cis*-propenyl acetal system, on the other hand, where enol concentrations never exceeded acetal concentrations, these relationships are reversed, and k(ketonization) > 2k(acetal reaction). This leads to the assignment $k_{D^+} = 1.62$ M^{-1} s^{-1} for ketonization and $k_{D^+} = 0.740$ M^{-1} s^{-1} for the acetal reaction.

Solvent Isotope Effects. These rate constant assignments produce solvent isotope effects on the acetal hydrolysis and enol ketonization reaction steps which are characteristic of these processes and thus provide additional support for the proposed reaction paths. Acetal hydrolysis generally occurs by a preequilibrium proton-transfer mechanism, for which the hydrogen ion isotope effect is expected to be inverse, $k_{H^+}/k_{D^+} < 1$.[10,21] A large number of acetal hydrolysis reactions do give inverse effects,[15b] e.g., $k_{H^+}/k_{D^+} = 0.37$ for acetaldehyde ethyl acetal[22] and $k_{H^+}/k_{D^+} = 0.49$ for acetaldehyde ethyl 2,2,2-trichloroethyl acetal.[23] Inverse effects are also observed here for the first of the two successive reactions observed in mineral acid solutions for all three substrates examined (Table III); this is the expected result for acetal hydrolysis, and that reinforces the assignment of this process to that step.

The ketonization of enols, on the other hand, is a rate-determining proton-transfer reaction, for which an isotope effect in the normal direction, $k_{H^+}/k_{D^+} > 1$, is to be expected.[10,21] This is consistent with experience, e.g., $k_{H^+}/k_{D^+} = 4.6$ for the enol of acetaldehyde[16c] and $K_{H^+}/k_{D^+} = 2.8$ for the enol of isobutyraldehyde;[16a] another example, $k_{H^+}/k_{D^+} = 5.8$ for the enol of

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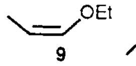
n-butyraldehyde, is provided by the rate measurements made here on this enol generated from the corresponding trimethylsilyl ether (Table II). Normal isotope effects of this magnitude are observed here for the second of the two successive reactions for all three substrates examined (Table III), which again reinforces the identification of the second reaction as enol ketonization.

Estimates of Vinyl Ether Hydrolysis Rates. The evidence presented above shows that hydrolysis of the presently examined vinyl acetals occurs through initial reaction of their acetal groups and not of the vinyl ether functions. It is of interest to estimate what the rates of reaction of the vinyl ether groups would be. This may be done using the known rates of reaction of *cis*- and *trans*-1-propenyl ethyl ethers, **9** and **10**, and the rate factor expected to apply in going from an ethyl vinyl ether to a 1-methoxyethyl vinyl ether, i.e., in changing **11** to **12**. This rate factor can be estimated from the known hydrogen ion catalytic coefficients for hydrolysis of ethyl vinyl ether (**11**), $k_{H^+} = 1.75$ M^{-1} s^{-1},[24] and of 2-chloroethyl vinyl ether (**13**), $k_{H^+} = 0.168$ M^{-1} s^{-1},[25] plus polar substituent constants for ethyl ($\sigma_I = -0.01$), 2-chloroethyl ($\sigma_I = 0.07$), and methoxymethyl ($\sigma_I = 0.11$) groups[26] and the knowledge that methyl vinyl ethers are 0.48 times as reactive as ethyl vinyl ethers.[27] This information gives 0.062 as the required factor, and application of that to $k_{H^+} = 0.48$ M^{-1} s^{-1} for **9**[28] and $k_{H^+} = 0.160$ M^{-1} s^{-1} for **10**[28] gives $k_{H^+} = 0.030$ and 0.0099 M^{-1} s^{-1} for hydrolysis of the vinyl ether groups of acetaldehyde *cis*- and *trans*-1-propenyl methyl acetals, **4** and **5**, respectively.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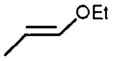
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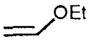
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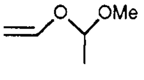
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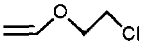
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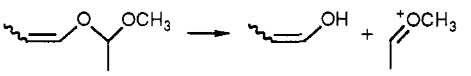
These estimates are consistent with $k_{H^+} = 0.015$ M^{-1} s^{-1} determined experimentally for hydrolysis of the vinyl ether group of the cyclic vinyl acetal, 2-methoxy-2,3-dihydropyran (**1**).[1b] They are also more than 1 order of magnitude less than the rate constants determined here for reaction of the acetal groups of the same substrates, which shows that these vinyl ether groups were simply too unreactive to complete successfully with the acetal hydrolysis reactions.

Reactivities. It is known that the hydrolysis of unsymmetrical acetals proceeds mainly by protonation of the less basic oxygen atom and initial loss of the corresponding alcohol.[29] Hydrolysis of the present substrates is therefore expected to occur through initial loss of the vinyloxy groups, according to eq 11, rather than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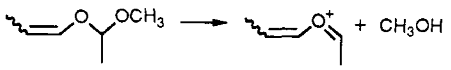
through initial loss of the methoxy group, eq 12. Such a process would be favored on the basis of both the superior leaving group ability of the less basic alcohol and the greater stability of the alkoxycarbocationic intermediate.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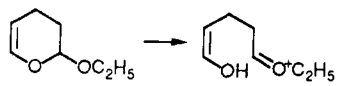
This reaction path would correspond to ring opening in the case of cyclic vinyl acetals, such as 2-ethoxy-2,3-dihydropyran, eq 13,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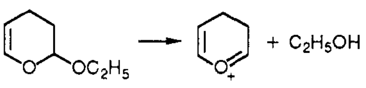
and yet it has been shown that hydrolysis in this case occurs by exocyclic group loss, eq 14,[1a] despite the extra difficulty of forming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a strained cyclic cation. It is likely that this situation is imposed upon the system by reversibility of the ring-opening reaction; recapture of the carbocationic center by the *cis*-enolic hydroxyl group should be especially facile; similar reversibility has recently been found in the hydrolysis of the cyclic acetal of 1,2-cyclohexanediol.[30] Thus, although the reaction of eq 13 is faster, it is nonproductive, and transformation of the starting material into products takes place by the slower process of eq 14. Intramolecular recapture of the carbocation is of course not possible for the acyclic propenyl acetals studied here, and they react by a route (eq 11) corresponding to eq 13. Rates of reaction of the presently examined acetals, $k_{H^+} = 0.41$ and 0.92 M^{-1} s^{-1}, are consequently considerably faster than those of the alkoxydihydropyrans, $k_{H^+} = 0.0013$ M^{-1} s^{-1} for the methoxy derivative[1b] and $k_{H^+} = 0.0082$ for the ethoxy analogue.[1a]

These depressed rate constants for acetal hydrolysis of the alkoxydihydropyrans make the rates of these reactions comparable to those for hydrolysis of the vinyl ether groups of these substances, and these vinyl acetals therefore hydrolyze through concurrent reactions of both functional groups.[1] In the case of the acyclic vinyl acetals, on the other hand, there is no significant reaction through the vinyl ether groups, for, whereas the rates of vinyl ether hydrolysis have remained much the same as they were in the alkoxydihydropyrans, rates of acetal hydrolysis have become much faster.

Intermolecular recapture of the carbocationic center is much less likely in the case of the larger 9-membered ring of 9-methoxy-1-oxacyclononene than for the 6-membered rings of the alkoxydihydropyrans. This follows, for example, from the classic difficulty of forming 9-membered rings relative to 6-membered rings.[31] The larger cyclic vinyl acetal will therefore react through the route used by the acyclic substrates, and its hydrolysis will thus be dominated by initial reaction of its acetal groups with little contribution from the vinyl ether function.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this work.

Supplementary Material Available: Tables S1–S3 of rate data (9 pages). Ordering information is given on any current masthead page.

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