JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 1, 247–257 (1988)

CONCERNING THE WEAKNESS OF INTRAMOLECULAR GENERAL ACID CATALYSIS IN THE HYDROLYSIS OF VINYL ETHERS. *o*-CARBOXY-α-METHOXY-β,β-DIMETHYLSTYRENE

A. J. KRESGE* AND Y. YIN

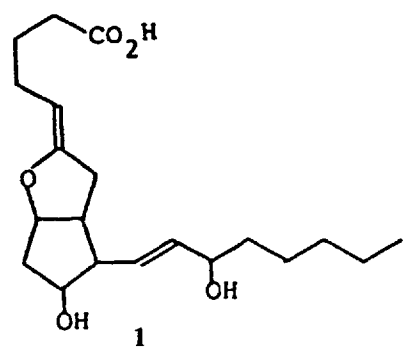
Department of Chemistry, University of Toronto, Toronto, Ontario, Canada M5S 1A1

ABSTRACT

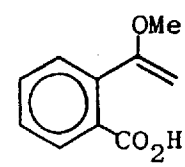
The rate of hydrolysis of the aromatic vinyl ether *o*-carboxy-α-methoxy-β,β-dimethylstyrene was found to be accelerated 25-fold by ionization of its carboxylic acid group, but the effective molarity which may be calculated if all of this rate acceleration is ascribed to intramolecular general acid catalysis is only EM = 1·1 M. This is similar to the small effective molarities found before for intramolecular catalysis by carboxylic acid groups of aliphatic vinyl ethers, which shows that, unlike the situation in other intramolecular reactions, e.g. ketone enolization, the extra rigidity of aromatic over aliphatic systems does not improve the efficiency of intramolecular catalysis in vinyl ether hydrolysis.

It is suggested that this behaviour is the result of reduced conjugation between the vinyl ether group and the aromatic ring in the transition state of the vinyl ether hydrolysis reaction, which retards the rate and offsets any improvement effected by increased rigidity of the aromatic system.

We have recently shown that hydrolysis of the vinyl ether group of prostacyclin, **1** as well as some related substances, is accelerated 100-fold through intramolecular general acid catalysis by the molecule's carboxylic acid group.[1] This rate acceleration is greater, by an order of magnitude, than that produced by the adjacent carboxylic acid group in the hydrolysis of the vinyl ether function of *o*-carboxy-α-methoxystyrene, **2**.[2] Such a difference is unexpected, for



1



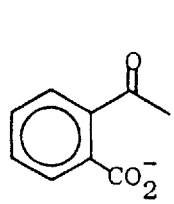
2

0894–3230/88/050247–11$05.50

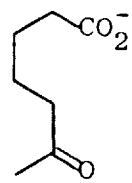
Received 28 December 1987

intramolecular catalysis should be stronger in a relatively rigid system such as **2** than in a more flexible molecule like **1**. This expectation is supported, for example, by the enolization of ketones with structures closely resembling **2** and the relevant part of **1**: intramolecular general base catalysis is at least an order of magnitude more efficient in the enolization of *o*-acetylbenzoate ion, **3**, than in the enolization of 6-oxoheptanoate ion, 4.[3]

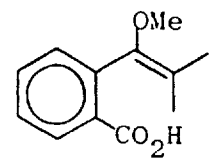
In order to explore this matter further, we have now examined the behavior of *o*-carboxy-α-methoxy-β,β-dimethylstyrene, **5**. Intramolecular general base catalysis of enolization is more efficient in the ketone analog of this substance, *o*-isobutyrylbenzoate ion, **6**, than in the unmethylated material, **3**,[3b,4] and we hoped that the same might be true of vinyl ether hydrolysis. That in fact did prove to be the case, but the improvement amounts to only a factor of two. This still leaves the behavior of vinyl ether hydrolysis markedly different from that of ketone enolization; a rationalization of this difference will be offered.



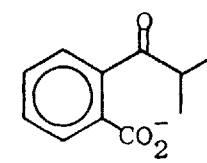
3



4



5

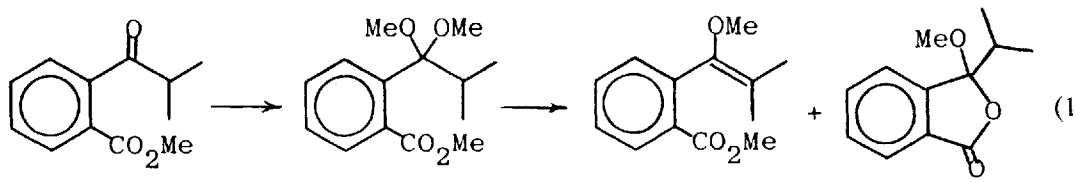


6

EXPERIMENTAL SECTION

Materials

o-Carboxy-α-methoxy-β,β-dimethylstyrene (**5**) was prepared from its methyl ester (**7**) which in turn was generated by converting methyl *o*-isobutyrylbenzoate into its dimethyl ketal and then eliminating a molecule of methanol; equation (1); this reaction also produced the acylal isomer of **7**, 3-methoxy-3-isopropylphthalide, **8**.



(1)

7 **8**

o-Isobutyrylbenzoic acid[5] (1·6 g) was dissolved in 12 ml of dry acetone, and 1·5 g of potassium carbonate plus 1 ml of dimethyl sulfate were added. This mixture was heated under reflux overnight; solid material was then removed by filtration and the acetone solvent was evaporated from the filtrate. The residual oil, whose proton NMR spectrum was consistent with expectation for methyl *o*-isobutyrylbenzoate ($CDCl_3$: 1·23, d, 6H, J = 7 Hz; 3·08, septet, 1 H, J = 7 Hz; 3·92, s, 3H; 7·23–8·30, m, 4H), was used directly without further purification.

This oily residue was dissolved in 5 ml of dry methanol, 1·2 g of trimethyl orthoformate plus a few mg of *p*-toluenesulfonic acid were added, and the resulting solution was heated under

reflux overnight. The reaction mixture was then subjected to vacuum distillation and a fraction boiling at 70–75°C/0·1 torr was collected. This was separated into three components, the last of which proved to be unreacted methyl *o*-isobutyrylbenzoate, by preparative gas chromatography using a 10-foot OV101 column.

The first substance to be eluted was identified as *o*-carbomethoxy-α-methoxy-β,β-dimethylstyrene, **7**, by its NMR and mass spectra: ^{1}H-NMR, $CDCl_3$: 1·45, s, 3H; 1·78, s, 3H; 3·37, s, 3H; 7·2–7·8, m, 4H; ^{13}C-NMR, $CDCl_3$: 17·19, 19·52, 52·34, 57·04, 114·83, 127·87, 129·63, 131·15, 131·77, 132·40. 136·37, 147·14, 168·59; mass spectrum: 220·1100; calculated for $C_{13}H_{16}O_3$, 220·1095. The second component was likewise identified as the cyclic acylal isomer of this ester, 3-methoxy-3-isopropylphthalide, **8** ^{1}H-NMR, $CDCl_3$: 0·86, d, 3H, J = 7 Hz; 1·03, d, 3H, 7 Hz; 2·36, septet, 1H, J = 7 Hz; 3·01, s, 3H; 7·2–8·0, m, 4H; mass spectrum: 175·0767 calculated for $C_{11}H_{11}O_2^+$, 175·0756; 163·0396, calculated for $C_9H_7O_3^+$, 163·0393; there are two sets of isopropyl methyl group signals in the proton NMR spectrum of this substance because its methyl groups are diastereotopic.

A stock solution of *o*-carboxy-α-methoxy-β,β-dimethylstyrene, **5**, for kinetic measurements was prepared by saponifying 0·008 g of the ester **7** with 0·5 ml of 0·5 M aqueous sodium hydroxide diluted to 1·0 ml with methanol; the reaction was allowed to proceed at room temperature for three days, during which time the initially cloudy mixture became clear.

All other materials were best available commercial grades; solutions were made with deionized water purified further by distillation.

Kinetics

Reactions were monitored spectroscopically and also by HPLC analysis. The latter method was used for very slow runs at pH > 6 where subsequent transformations of the initially formed reaction product complicated spectral monitoring.

The spectral method was based upon changes in absorbance at λ = 240 nm for the vinyl ether, **5**, and λ = 264 nm for its methyl ester, **7**. All measurements were made with a Cary Model 118 spectrometer whose cell compartment was thermostatted at 25·0 ± 0·1°C. Reactions were initiated by adding 2–5 μl of substrate stock solution (methanol or aqueous methanol solvent) to a cuvette containing 3·0 ml of aqueous acid or buffer solution which had been allowed to come to temperature equilibrium with the spectrometer cell compartment. Initial substrate concentrations were *ca.* 10^{-4} M. The kinetic data followed the first-order rate law accurately, and observed rate constants were evaluated by least squares analysis, either by fitting the data to an exponenetial function or by the Guggenheim method.

HPLC analyses were conducted with a VISTA 5500 instrument coupled to a Polychrom 9060 Diode Array detector. Reversed-phase, ion-pair partition chromatography was used with a 15- or 30-cm carbon-18 column and 0·005 or 0·01 M tetrabutylammonium acetate in acetonitrile-water mixtures as the eluent. Either 4-methoxyacetophenone or 3,4-dimethoxyacetophenone was used as an internal standard. Reactions were conducted in flasks immersed in a constant temperature bath operating at 25·0 ± 0·1°C. Substrate concentrations were of the order of 1×10^{-4} M and the amount of internal standard was adjusted to give absorbance readings in the range 0·8–1·4. At appropriate times, aliquots of reaction mixture were injected onto the column through a 100 μl injection loop valve and integrals of the peaks for different components were recorded. First-order rate constants were evaluated by least squares analysis as slopes of plots of $\ln[(I_s/I_{st})_t - (I_s/I_{st})_\infty]$ vs. time, where I_s and I_{st} represent integrals of substrate and standard respectively. A typical example of such a plot is shown in Figure 1.

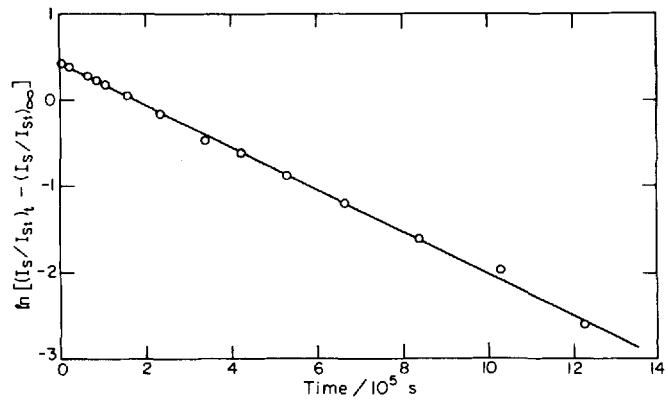
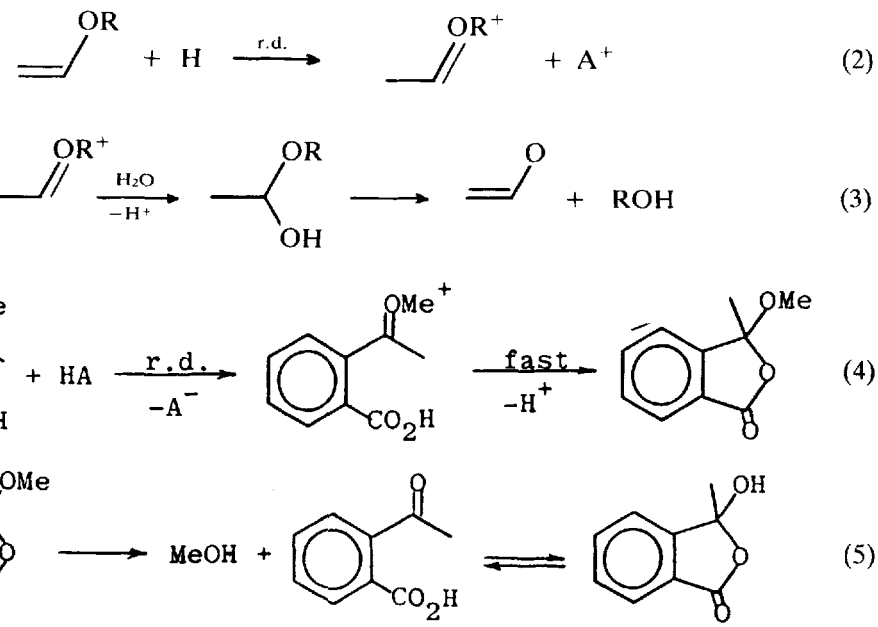


Figure 1. First-order kinetic plot for the hydrolysis of *o*-carboxy-α-methoxy-β,β-dimethylstyrene in aqueous H_2PO_4/HPO_4^{2-} buffer solution at 25°C; the final point represents 95% reaction

RESULTS

A large body of evidence[6] indicates that the acid-catalyzed hydrolysis of simple vinyl ethers occurs through rate-determining proton transfer from the catalyst to the β-carbon atom of the substrate, giving an alkoxycarbocation intermediate, equation (2). This is then followed by rapid steps which convert the alkoxycarbocation into a hemiacetal and then that into the ultimate carbonyl compound and alcohol products, equation (3). In the hydrolysis of *o*-carboxy-α-methoxystyrene (**2**), however, it was found that the carbocation is captured intramolecularily to give an acylal, equation (4). This intermediate is then converted at a slower rate into *o*-acetylbenzoic acid,[2] which exists in equilibrium with its cyclic lactol, equation (5).[3b]



Both UV-spectral examination and HPLC analysis indicate that similar changes take place in the present system, and that the acylol, 3-methoxy-3-isopropylphthalide (**8**), synthesized here as a side-product in the preparation of the vinyl ether substrate **5**, is formed as a relatively stable hydrolysis reaction intermediate. However, reaction rates were measured here by monitoring the disappearance of the vinyl ether substrate, and the rate constants determined therefore refer to the first step of this process only, i.e. to protonation of the vinyl ether carbon–carbon double bond, and are thus equivalent to rates of reaction for a simple, uncomplicated vinyl ether hydrolysis process.

Rate measurements were made in aqueous perchloric acid solutions, and in cyanoacetic, formic, acetic and cacodylic acid and dihydrogenphosphate anion buffers. The determinations in perchloric acid solutions were performed over the concentration range $[HClO_4] = 0{\cdot}004$ to $0{\cdot}10$ M, with ionic strength held constant at $0{\cdot}10$ M. Those in buffer solutions, were also made at constant ionic strength ($0{\cdot}10$ M), using series of buffer solutions of constant buffer ratio but changing buffer concentration. The buffer concentration was generally varied by a factor of five, and from two to five series were used for each acid. These data are summarized in Tables S1 and S2, which are supplementary material available from the authors.

These rate data were analyzed in terms of a phenomenological scheme, equation (6), which allows for reaction of the substrate in both unionized, carboxylic acid (SH) and ionized, carboxylate (S^-) forms.

$$\begin{array}{ccc} SH & \rightleftharpoons & S^- + H^+ \\ {\scriptstyle H^+ \atop HA}\downarrow\ {\scriptstyle k_{H^+} \atop k_{HA}} & & {\scriptstyle H^+ \atop HA}\downarrow\ {\scriptstyle k'_{H^+} \atop k'_{HA}} \\ \multicolumn{3}{c}{\underbrace{\qquad\qquad\qquad}_{\text{Product}}} \end{array} \tag{6}$$

The rate law for such a scheme is shown in equation (7). It includes terms

$$\begin{aligned} k_{obs} = {} & (k_{H^+}[H^+] + k_{HA}[HA])[H^+]/([H^+] + K_a) \\ & + (k'_{H^+}[H^+] + k'_{HA}(HA])K_a/([H^+] + K_a) \end{aligned} \tag{7}$$

for catalysis by the solvated proton, H^+, and undissociated acids, HA, and it uses unprimed symbols for reactions of SH and primed symbols for reactions of S^-; the fractions $[H^+]/([H^+] + K_a)$ and $K_a/([H^+] + K_a)$, in which K_a is the acid ionization constant of the substrate, denote the proportions of substrate which exist in the unionized and ionized forms respectively. A similar rate law was used to interpret the data for hydrolysis of prostacyclin and related substances.[1]

In conformance with this rate law, observed first-order rate constants were linear functions of buffer acid concentration, and slopes of buffer dilution plots determined at constant $[H^+]$, $(\Delta k_{obs}/\Delta[HA])_{[H^+]}$, depended upon $[H^+]$ in accordance with equation (8).

$$(\Delta k_{obs}/\Delta[HA])_{[H^+]} = (k_{HA}[H^+] + k'_{HA}K_a)/([H^+] + K_a) \tag{8}$$

Values of k_{HA} and $k'_{HA}K_a$ were consequently obtained from slope and intercept parameters evaluated by linear least square analysis of the relationship between $(\Delta k_{obs}/\Delta[HA])_{[H^+]}([H^+] + k_a)$ and $[H^+]$, and k'_{HA} was derived from $k'_{HA}K_a$ using K_a determined as described below. Values of $[H^+]$ needed for this purpose were obtained by calculation, using thermodynamic acid dissociation constants from the literature and activity coefficients recommended by Bates.[7] (in the case of cacodylic acid, an ionization constant appropriate to

Table 1. Rate constants for carbon protonation of *o*-carboxy-α-methoxy-β,β-dimethylstyrene in aqueous solution at 25°[a]

Proton donor	$k/10^{-3}$ M^{-1} s^{-1}	$k'/10^{-3}$ M^{-1} s^{-1}
$CNCH_2CO_2H$	3·10	34·7
HCO_2H	0·489	7·29
CH_3CO_2H	0·183	1·31
$(CH_3)_2AsO_2H$	—	0·499
$H_2PO_4^-$	—	0·0939
H^+	133·	3,320

[a]Ionic strength = 0·10 M (NaCl).

ionic strength = 0·10 M was calculated using a relationship determined in the course of measuring the thermodynamic ionization constant of this acid.[8]) Buffer failure[9] occurred in the cyanoacetic acid buffers used, and H^+ contributions to observed rate constants consequently decreased systematically along buffer dilution solution series, but this was compensated for by adjusting H^+ contributions to a common $[H^+]$ values using known (*vide infra*) values of k_{H^+} and k'_{H^+}. The results obtained in this way are listed in Table 1. Brønsted relations based upon the three carboxylic acid rate constants have the exponents $\alpha = 0{\cdot}54 \pm 0{\cdot}06$ for carbon protonation of SH and $\alpha = 0{\cdot}61 \pm 0{\cdot}06$ for carbon protonation of S^-.

The intercepts of these buffer dilution plots represent the buffer-independent part, k_{BI}, of the rate law of equation (7), shown as equation (9).

$$k_{BI} = (k_{H^+}[H^+]^2 + k'_{H^+}K_a[H^+])/([H^+] + K_a) \quad (9)$$

These intercepts, together with observed rate constants measured in perchloric acid solutions, were used to construct the rate profile shown as Figure 2. The combined data were fitted to equation (9) by non-linear least squares analysis; this gave $k_{H^+} = (1{\cdot}33 \pm 0{\cdot}01) \times 10^{-1}$ M^{-1} s^{-1}, $k'_{H^+} + = 3{\cdot}32 \pm 0{\cdot}50$ M^{-1} s^{-1}, and $K_a = (1{\cdot}21 \pm 0{\cdot}24) \times 10^{-4}$ M. The latter is a concentration quotient appropriate to ionic strength = 0·10 M; use of the activity coefficients $\gamma_{H^+} = 0{\cdot}83$[7] and $\gamma_{S^-} = 0{\cdot}80$ (recommended[7] for benzoate ion)

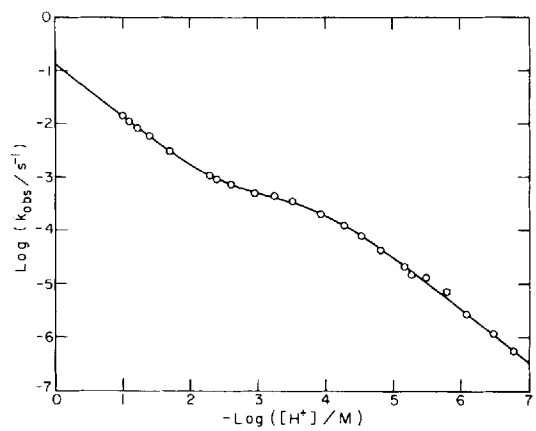


Figure 2. Rate profile for protonation of the double bond of *o*-carboxy-α-methoxy-β,β-dimethylstyrene in aqueous solution at 25°

converts this into a thermodynamic acidity constant which corresponds to $pK_a = 4{\cdot}10$, a result consistent with the known value, $pK_a = 4{\cdot}20$, for benzoic acid.

Rates of hydrolysis of the vinyl ether group of the methyl ester of *o*-carboxy-α-methoxy-β,β-dimethylstyrene were also determined. Measurements were made in perchloric acid solutions over the concentration range $[HClO_4] = 0{\cdot}004$ to $0{\cdot}10$ M at a constant ionic strength of $0{\cdot}10$ M. These data are summarized in Table S3, available from the authors. First-order rate constants were accurately proportional to $[HClO_4]$, and least squares analysis gave the catalytic coefficient $k_{H^+} = (8{\cdot}78 \pm 0{\cdot}09) \times 10^{-2}\ M^{-1}\ s^{-1}$. This is consistent with $k_{H^+} = 13{\cdot}3 = 10^{-2}\ M^{-1}\ s^{-1}$ determined for the carboxylic acid itself, and the rate retardation of $8{\cdot}78/13{\cdot}3 = 0{\cdot}66$ produced in going from the acid to the ester is similar to that, 0·60, observed for the same change in the *o*-carboxy-α-methoxystyrene system.[2] The rate constant determined here for reaction of the ester is also many orders of magnitude greater than the specific rate of acid catalyzed ester hydrolysis of methyl benzoate,[10] which shows that ester hydrolysis did not interfere with the present vinyl ether hydrolysis reaction.

DISCUSSION

The present results give the rate acceleration $k'_{H^+}/k_{H^+} = 25$ for reaction of the vinyl ether group of *o*-carboxy-α-methoxy-β,β-dimethylstyrene. This is twice the acceleration observed for *o*-carboxy-α-methoxystyrene itself,[2] but only one quarter of that found for prostacyclin.[1]

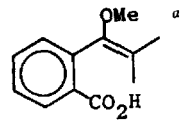
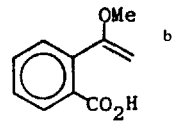
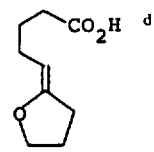
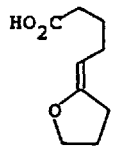
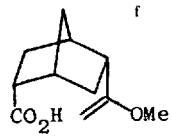
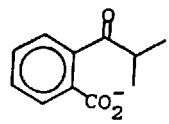
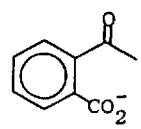
Rate accclerations defined in this way, however, do not necessarily reflect the strength of intramolecular catalysis in an accurate way, because the process to which k'_{H^+} is attributed is not a simple one-step intramolecular reaction. This rate constant is defined in terms of an initial state consisting of the substrate in its ionized carboxylate form, S^-, plus a proton. As shown in equation (10), these substances must first be converted into the carboxylic acid form of the substrate, SH, before intramolecular proton transfer can take place. The rate constant k'_{H^+} is therefore a composite quantity, $k'_{H^+} = k_{HA}^{intra}/K_a$, whose value depends upon the magnitude of K_a as well as the velocity of the intramolecular reaction.

$$S^- + H^+ \overset{K_a}{\rightleftharpoons} SH \xrightarrow{k_{HA}^{intra}} Prod \qquad (10)$$

A more sensible measure of intramolecular catalytic strength would be provided by the ratio $k_{HA}^{intra}/k_{HA}^{inter}$, in which k_{HA}^{inter} is the rate constant for intermolecular proton transfer to the undissociated acid form of the substrate from an external acid of the same type and strength as the catalytic group of the substrate. This means of assessing intramolecular catalytic strength is in fact in common use. Because the rate ratio $k_{HA}^{intra}/k_{HA}^{inter}$ compares first- and second-order rate constants, it has the dimensions of concentration and is generally called the 'effective molarity', EM.[11] Table 2 compares effective molarities and rate accelerations for some vinyl ether hydrolysis reactions.

It may be seen that there is no general correspondence between the two quantities. In order to understand this, it is helpful to derive a relationship between the two. This can be done by using the Brønsted relation to express k_{H^+} in terms of k_{HA}^{inter}, as shown in equation (11), where K_{H^+} is the acidity constant of H^+. Combining that with the definition of rate acceleration (Accelr), equation (12), and then replacing k'_{H^+} with its equivalent, k_{HA}^{intra}/K_a, gives equation (13). This leads to equation (14), which shows that the rate acceleration depends upon EM, and upon K_a and α as well.

Table 2. Rate accelerations and effective molarities for some intramolecular proton transfer reactions

Substrate	Acceleration	Effective Molarity/M
Vinyl ether hydrolysis:		
 [a]	25	1·1
 [b]	12	0·5
Prostacyclin[c]	100	0·6
 [d]	82	0·8
 [e]	73	0·8
 [f]	37	0·4
Homoprostacyclin[g]	8·3	0·08
Enolization:		
 [h]	—	50
 [i]	—	>20
Aliphatic ketocarboxylates[j]	—	0·5–1

[a]This work, with $k_{HA}^{inter} = 3{\cdot}8 \times 10^{-4}$ M^{-1} s^{-1} estimated using the Brønsted relation.
[b]Reference 2, $k_{HA}^{inter} = k_{HCO_2H}$
[c]Reference 12.
[d]Reference 13, with $k_{HA}^{inter} = k_{HOAc}$ for substrate methyl ester.
[e]Reference 14, with $k_{HA}^{inter} = k_{HOAc}$ for substrate methyl ester.
[f]Reference 15, with $k_{HA}^{inter} = 0{\cdot}27$ M^{-1} s^{-1} estimated from k_{HOAc} and $\alpha = 0{\cdot}6$.
[g]Reference 16, with $k_{HA}^{inter} = k_{HOAc}$ for substrate methyl ester.
[h]References 3b and 4.
[i] Reference 3b.
[j] Reference 3a.

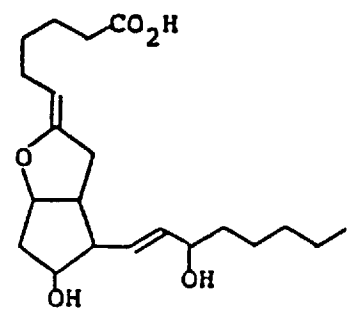
$$k_{H^+} = k_{HA}^{inter}(K_{H^+}\ K_a)^{\alpha} \tag{11}$$

$$\text{Accelr} = k'_{H^+}/k_{H^+} = k'_{H^+}/k_{HA}^{inter}(K_{H^+}/K_a)^{\alpha} \tag{12}$$

$$\text{Accelr} = (k_{HA}^{intra}/K_a)/k/_{HA}^{inter}(K_{H^+}/K_a)^{\alpha} \tag{13}$$

$$\text{Accelr} = \text{EM}/(K_a)^{1-\alpha}(K_{H^+})^{\alpha} \tag{14}$$

In particular, since α is generally less than one, Accelr will be inversely proportional to some fractional power of K_a, and substrates with more strongly acidic catalytic groups (greater K_a) will show smaller rate accelerations than substrates with weaker catalytic groups. This follows also from equation (10), inasmuch as the concentration of SH will be less in the case of a stronger acid and the overall rate of reaction, and therefore k'_{H^+}, will be smaller. The data of Table 2 support this prediction. The effective molarities of all the vinyl ethers there, except the last, are much the same, but the catalytic groups of the first two are aromatic carboxylic acids whereas those of the next four are aliphatic acids; aromatic acids are stronger than aliphatic acids, and the rate accelerations of the first two substrates are consequently less than those of the next four. The effect of EM on Accelr may be seen by comparing the first two entries of Table 2, or the last four. The influence of α is less apparent because this quantity is much the same for all of the substrates listed.



9

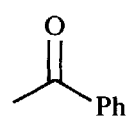
Effective molarities for proton transfer to or from carbon are generally quite small compared to the very large values often found for other intramolecular reactions,[11] and the data presented in Table 2 provide no exception. There are, however, interesting variations within this group. For example, homoprostacyclin, **9**, with one carbon atom more than prostacyclin, **1**, separating the carboxylic acid and vinyl ether groups, shows a much reduced EM; it is well known that intramolecular catalytic efficiency depends critically upon the size of the ring formed in the transition state of the intramolecular process.[11]

A less expected variation apparent in Table 2 is the difference in intramolecular catalytic efficiency between the aromatic vinyl ethers and their aromatic ketone counterparts. The aromatic ketones are considerably better intramolecular catalysts than aliphatic analogs, as expected for more rigid systems, but the aromatic vinyl ethers do not show a corresponding improvement over their aliphatic analogs. This difference in behavior between the two kinds of aromatic systems persists even if some of the rate enhancement observed in each case is attributed to another cause, such an electrostatic acceleration. For example, with an

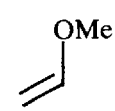
electrostatic effect of the negatively charged carboxylate group speeding up the hydrolysis of *o*-carboxy-α-methoxy-β,β-dimethylstyrene (**5**) 10-fold (electrostatic rate effects are generally small in aqueous solution,[17] and a 10-fold acceleration represents a generous effect), EM for this substance drops from 1·1 to 0·6, and a corresponding electrostatic effect on the enolization of *o*-isobutyrylbenzoate ion (**6**) changes its EM from 50 to 40. This still leaves aromatic ketone enolization as the substantially more efficient intramolecular reaction.

An explanation for this difference may be advanced on the basis of the conformations which the substrataes may be expected to adopt in the transition states of these reactions, and the consequent effect of phenyl substituents on the stability of these transition states. In an intramolecular enolization reaction of an aromatic ketone, such as *o*-acetylbenzoate ion (**3**), the C—H bond being broken, in order to be accessible to the carboxylate group, must lie approximately in the plane of the benzene ring. This bond, however, must also be perpendicular to the carbonyl group, in order to effect conjugation of the developing carbon-carbon double bond with that group and thus allow delocalization of the developing negative charge onto the carbonyl oxygen atom. This requires the carbonyl group to be perpendicular to the benzene ring, and that will take it out of conjugation with the ring. This will occur at little energy cost to the system, for phenyl substitution has little effect on the rate of base catalyzed enolization. For example, specific rates of enolization catalyzed by the hydroxide ion for acetaldehyde, **10**, and acetophenone, **11**, are $k = 1{\cdot}17\ \text{M}^{-1}\ \text{s}^{-1}$[18] and $k = 0{\cdot}25\ \text{M}^{-1}$[19] respectively, which gives a small phenyl group retardation of 0·2, and a similar rate reduction for enolization of these substrates catalyzed by acetate ion can be estimated from the rates of ketonization of the corresponding enolates (by reaction with acetic acid)[18,20] and the carbon-acid pK_a's of the carbonyl compounds.[18,19,21]

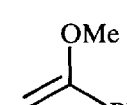
10



11



12



13

The transition state for an intramolecular reaction of an aromatic vinyl ether, such as *o*-carboxy-α-methylstyrene (**2**) will have a conformation similar to that described above for enolization: in order to be accessible to proton transfer from the adjacent acid, the vinyl ether group must turn toward the acid into a position where the vinyl plane is approximately perpendicular to the benzene ring. This will reduce conjugation between the vinyl group and the benzene ring, but now loss of conjugation will involve a considerable energy cost because phenyl substitution at this position raises the rate of vinyl ether hydrolysis substantially. For example, specific rates of hydrogen-ion catalyzed hydrolysis of methyl vinyl ether **12** and methyl α-phenylvinyl ether, **13**, are $k = 0{\cdot}76\ \text{M}^{-1}\ \text{s}^{-1}$[22] and $k = 53\ \text{M}^{-1}\ \text{s}^{-1}$[6b,22] respectively, which gives a significant 70-fold phenyl group rate increase.

These arguments suggest that in vinyl ether hydrolysis any improvement in the efficiency of intramolecular catalysis produced by the rigidity of aromatic over aliphatic systems is offset by a deleterious aromatic group substituent effect, and the net result is little difference in the values of EM for the two kinds of system in this reaction. In enolization, on the other hand, there is no deleterious aromatic substituent effect, and the extra rigidity of aromatic systems and consequent improved intramolecular catalytic efficiency is unopposed and therefore becomes apparent in greater EM values.

ACKNOWLEDGEMENT

We wish to thank Dr. P. A. Walsh for calling our attention to the improved intramolecular catalysis of ketone enolization shown by *o*-isobutyrylbenzoate ion and suggesting that this might also be the case in hydrolysis of the analogous vinyl ether. We are grateful as well to the Natural Sciences and Engineering Research Council of Canada and to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this work.

REFERENCES

1. For a recent review of this work, see A. J. Kresge, *Accts. Chem. Res.* **20**, 364–370 (1987).
2. G. M. Louden, C. K. Smith, and S. E. Zimmerman, *J. Am. Chem. Soc.* **96**, 465–479 (1974).
3. (a) R. P. Bell and A. D. Covington, *J. Chem. Soc. Perkin Trans. II* 1343–1348 (1975). (b) R. P. Bell, D. W. Earls and J. B. Henshall, *J. Chem. Soc. Perkin Trans. II* 39–44 (1976).
4. E. T. Harper and M. L. Bender, *J. Am. Chem. Soc.* **87**, 5625–5632 (1965).
5. P. L. de Benneville, *J. Org. Chem.* **6**, 462–466 (1941). R. L. Letsinger and W. J. Vullo, *J. Org. Chem.* **25**, 1844–1848 (1960).
6. (a) P. Salomaa, A. Kankaanpera, and M. Lajunen, *Acta Chem. Scand.* **20**, 1790–1801 (1966); A. J. Kresge and Y. Chiang, *J. Chem. Soc. B.*, 53–57, 58–61 (1967); (b) A. J. Kresge, H. L. Chen, Y. Chiang, E. Murrill, M. A. Payne and D. S. Sagatys, *J. Am. Chem. Soc.* **93**, 413–423 (1971); (c) A. J. Kresge, D. S. Sagatys, and H. L. Chen, *J. Am. Chem. Soc.* **99**, 7228–7233 (1977); R. A. Burt, Y. Chiang, E. Murrill, M. A. Payne and D. S. Sagatys, *J. Am. Chem. Soc.* **109**, 3787–3788 (1987); T Okuyama, T. Fueno, H. Nakatsuji and J. Furakawa, *J. Am. Chem. Soc.* **89**, 5826–5831 (1967); M. M. Kreevoy and R. E. Eliason, *J. Phys. Chem.* **72**, 1313–1316 (1968).
7. R. G. Bates, *Determination of pH Theory and Practise*, Wiley, New York, (1973) p. 49.
8. M. L. Kilpatrick, *J. Am. Chem. Soc.* **71**, 2607–2610 (1949).
9. J. R. Keeffe and A. J. Kresge, *Techniques of Chemistry*, Vol. 6, *Investigations of Rates and Mechanisms of Reactions*, C. F. Bernasconi, Editor, Wiley, New York, Part 1, Chapt. XI (1986).
10. C. A. Lane, M. F. Cheung, and G. F. Dorsey, *J. Am. Chem. Soc.* **90**, 6492–6494 (1968); R. A. Cox, M. F. Goldman, and K. Yates, *Can. J. Chem.* **57**, 2960–2966 (1979).
11. For an excellent discussion of effective molarities and an extensive compilation of values, see A. J. Kirby, *Adv. Phys. Org. Chem.* **17**, 183–278 (1980).
12. Y. Chiang, M. J. Cho, B. A. Euser and A. J. Kresge, *J. Am. Chem. Soc.* **108**, 4192–4196 (1986).
13. N. A. Bergman, M. Jansson, Y. Chiang, A. J. Kresge and Y. Yin, *J. Org. Chem.* **52**, 4449–4453 (1987).
14. N. A. Bergman, M. Jansson, Y. Chiang and A. J. Kresge, submitted to *J. Org. Chem.*
15. G. M. Loudon and D. E. Ryono, *J. Am. Chem. Soc.* **98**, 1900–1907 (1976).
16. Y. Chiang and A. J. Kresge, *J. Chem. Soc. Perkin Trans. II*, in press.
17. A. J. Kresge and Y. Chiang, *J. Am. Chem. Soc.* **95**, 803–806 (1973); W. K. Chwang, R. Eliason and A. J. Kresge, *J. Am. Chem. Soc.* **99**, 805–808 (1977). D. B. Dahlberg, M. A. Kuzamko, Y. Chiang, A. J. Kresge and M. F. Powell, *J. Am. Chem. Soc.* **105**, 5387–5890 (1983).
18. Y. Chiang, M. Hojatti, J. R. Keeffe, A. J. Kresge, N. P. Schepp and J. Wirz, *J. Am. Chem. Soc.* **109**, 4000–4009 (1987).
19. Y. Chiang, A. J. Kresge and J. Wirz, *J. Am. Chem. Soc.* **106**, 6392–6395 (1984).
20. Y. Chiang, A. J. Kresge, J. A. Santaballa Lopez, and J. Wirz, submitted to *J. Am. Chem. Soc.*
21. J. R. Keeffe, A. J. Kresge and J. Toullec, *Can. J. Chem.* **64**, 1224–1227 (1986).
22. Y. Chiang, W. K. Chwang, A. J. Kresge, L. H. Robinson, D. S. Sagatys and C. I. Young, *Can. J. Chem.* **56**, 456–460 (1978).