VINYL ETHER HYDROLYSIS. 30. EFFECT OF β-CARBOXY AND β-CARBOMETHOXY SUBSTITUTION

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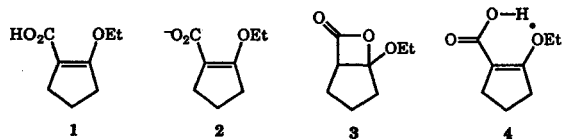*Department of Chemistry, University of Toronto, Toronto, Ontario M5S 1A1, Canada*

Rates of hydrolysis of the vinyl ether functional groups of (Z)- and (E)-β-methoxyacrylic acid and (Z)- and (E)-β-methoxymethacrylic acid and their methyl esters were measured in aqueous perchloric acid solution. Additional rate measurements were also made for one substrate, (Z)-β-methoxymethacrylic acid, in buffer solutions down to pH 7, and a rate profile was constructed. The results show that the β-carboxy and β-carbomethoxy substituents produce strong rate retardations, ranging from 2000- to 25 000-fold, for both Z- and E-isomers in both the acrylic and methacrylic acid series. The rate profile for (Z)-β-methoxymethacrylic acid indicates that ionization of this substrate to the carboxylate ion form raises the rate of hydrolysis by a factor of 240. It is argued that this difference in reactivity of ionized and non-ionized forms of the substrate is due to conjugative and inductive effects of the substituents, rather than β-lactone formation as suggested in an earlier observation of the same phenomenon in a different system.

INTRODUCTION

The acid-catalyzed hydrolysis of vinyl ethers is a mechanistically well defined reaction, known to occur through rate-determining proton transfer from the catalyst to the β-carbon atom of the substrate, followed by rapid hydration of the ensuing alkoxycarbocation and rapid decomposition of a hemiacetal intermediate,[1]

(1)
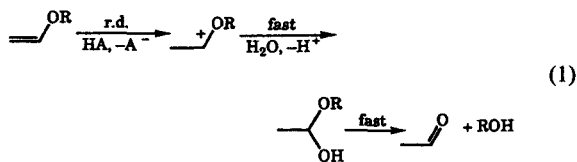
In an early study of this reaction using 2-ethoxycyclopentene-1-carboxylic acid (1) as the substrate,[2] it was found that ionization of this substance to the carboxylate form (2) raised the rate of hydrolysis *ca* 200-fold. The hypothesis was then
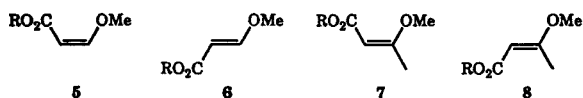
advanced that this increase might be due to catalysis by the carboxylate group through nucleophilic participation forming a β-lactone intermediate (3). β-Lactones, however, because of their four-membered ring structure, are rather strained molecules: their strain energy has been estimated at 23 kcal mol⁻¹ (1 kcal = 4·184 kJ).[3] It is not clear, therefore, that β-lactose formation would have a catalytic effect.

An alternative hypothesis is that this difference in reaction rate is due to diminished reactivity of the non-ionized form of the substrate produced by hydrogen bonding between the carboxylic acid group and the ether oxygen atom, as shown in 4. Such hydrogen bonding would withdraw electron density from the oxygen atom, decreasing its ability to stabilize the adjacent positive charge developing in the transition state of the hydrolysis reaction. Such hydrogen bonding is, of course, not possible in the carboxylate ion.

Such hydrogen bonding is also not possible in systems where the carboxy and alkoxy groups are *trans* rather than *cis* to one another. In order to test this alternative hypothesis, we have therefore examined the hydrolysis of the cis and trans pairs (Z)- and (E)-β-methoxyacrylic (5 and 6, R = H) and (Z)- and (E)-β-methoxymethacrylic acid (7 and 8, R = H). We prepared these acids from the corresponding methyl esters (5–8, R = CH₃), and we consequently also determined rates of hydrolysis of these substances.

1   2   3   4

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RO$_2$C　OMe　　　　OMe　RO$_2$C　OMe　　　　　OMe

　　　　　　RO$_2$C　　　　　　　　　　　RO$_2$C

5　　　　　　**6**　　　　**7**　　　　**8**

EXPERIMENTAL

Materials. Methyl (Z)- and (E)-β-methoxyacrylates were prepared by the trimethylamine-catalyzed addition of methanol to methyl propiolate (Aldrich).[4] The mixture of isomers obtained (Z:E = 3:7) was separated by chromatography on silica gel with CHCl$_3$–EtOAc mixtures as eluents; the products had ^{1}H NMR spectra consistent with literature values.[5]

(E)-β-Methoxyacrylic acid was obtained by saponification of methyl (E)-β-methoxyacrylate. The ester (0·55 g) was added to 0·30 g of potassium hydroxide dissolved in 20 ml of water and the mixture was stirred until it became homogeneous (*ca* 1 h). The resulting solution was then extracted with diethyl ether and the aqueous layer was acidified to pH 2 and extracted with diethyl ether again. The second ether extract was dried with anhydrous magnesium sulfate and the solvent was removed, giving a white solid residue, which was recrystallized from hexane; ^{1}H NMR (CDCl$_3$), δ (ppm) = 7·71 (d, J = 12·4 Hz, 1H), 5·17 (d, J = 12·4 Hz, 1H), 3·55 (s, 3H); HRMS, m/z = 102·03195 (theoretical, 102·03169).

(Z)-β-Methoxyacrylic acid was prepared by photoisomerization of the E-isomer. A 0·01 M solution of (E)-β-methoxyacrylic acid in acetonitrile was irradiated in a Rayonet photochemical reactor operating at 254 nm. A steady-state mixture of acids with a ratio Z:E = 1:3 was reached in 20 min; longer exposure gave unwanted side-products. The isometric acids were separated by chromatography on silica gel using EtOAc–MeOH mixtures as eluents. The Z-acid solidified on standing overnight; ^{1}H NMR (CDCl$_3$), δ (ppm) = 6·58 (d, J = 7·6 Hz, 1H), 4·94 (d, J = 7·6 Hz, 1H), 3·93 (s, 3H); ^{13}C NMR (CDCl$_3$), δ (ppm) = 168·47 (C≡O), 161·03 (C-3), 97·67 (C-2), 63·19 (MeO).

Methyl (E)-β-methoxymethacrylate was obtained by acid-catalyzed elimination of ethanol from the dimethyl ketal of methyl acetoacetate, itself obtained by treating methyl acetoacetate (Aldrich) with trimethyl orthoformate in methanol solution.[6] The product was purified by distillation followed by chromatography on silica gel with CHCl$_3$–EtOAc as eluent. This ester was converted into its Z-isomer by irradiation at 254 nm in acetonitrile solution for 20 min. The resulting mixture of esters was separated by chromatography; both isomers had ^{1}H NMR spectra consistent with their structures and in agreement with literature values.[7] Methyl (Z)-β-methoxymethacrylate is unstable and must be protected from light to keep it from being converted back to the E-isomer.

(E)-β-Methoxymethacrylic acid was obtained by saponification as described above for (E)-β-methoxyacrylic acid; ^{1}H NMR (CDCl$_3$), δ (ppm) = 10–12 (bs, 1H), 5·02 (s, 1H), 3·65 (s, 1H), 2·52 (s, 3H); ^{13}C NMR (CDCl$_3$), δ (ppm) = 175·66, 174·19, 91·05 (C-2), 56·03 (MeO), 19·64 (Me); HRMS, m/z = 116·04707 (theoretical, 116·04734). This acid was converted into its Z-isomer by irradiation at 2564 nm; ^{1}H NMR (CDCl$_3$), δ (ppm) = 4·98 (s, 1H), 3·88 (s, 3H), 2·06 (s, 3H); ^{13}C NMR (CDCl$_3$), δ (ppm) = 168·11, 167·83, 98·31 (C-2), 56·85 (MeO), 18·78 (Me); HRMS, m/z = 116·04752 (theoretical, 116·04734)).

All other materials were of the best available commercial grades.

Determination of acidity constant. The acid ionization constant of (Z)-β-methoxymethacrylic acid was determined spectroscopically using the difference in absorbance between the acid and its carboxylate anion at 255 nm. Measurements were made with a Cary 118 spectrometer whose cell compartment was thermostated at 25·0 ± 0·05 °C.

Kinetics. Rates of vinyl ether hydrolysis were also determined spectroscopically by monitoring the decrease in absorbance of the strong vinyl ether band at 235–250 nm. Measurements were made with a Cary 2200 spectrometer whose cell compartment was thermostated at 25·0 ± 0·05 °C. The data obtained fit the first-order rate expression well, and observed rate constants were obtained by least-squares fitting to an exponential expression.

RESULTS

Acidity constant

The UV spectrum of (Z)-β-methoxyacrylic acid in aqueous solution containing 0·001 M HClO$_4$ consists of an absorption band with λ$_{max}$ = 250 nm. In 0·01 M aqueous NaOH, this band shifts to λ$_{max}$ = 240 nm and decreases in intensity. This difference in UV spectra of the non-ionized and carboxylate ion forms of this acid was used to determine its acidity constant. Measurements were made at the point of maximum difference, λ = 255 nm, in aqueous HClO$_4$ and NaOH solutions and in aqueous buffers of formic, acetic and cacodylic acids and hydrogenphosphate and hydrogen-*tert*-butylphosphonate anions. The ionic strength of all solutions was maintained at 0·10 M. The data are summarized in Ref. 8 and are displayed in Figure 1.

Hydrogen ion concentrations of the buffer solutions needed for construction of the titration curve shown in Figure 1 were obtained by calculation, using literature pK$_a$ values for the buffer acids and activity coefficients
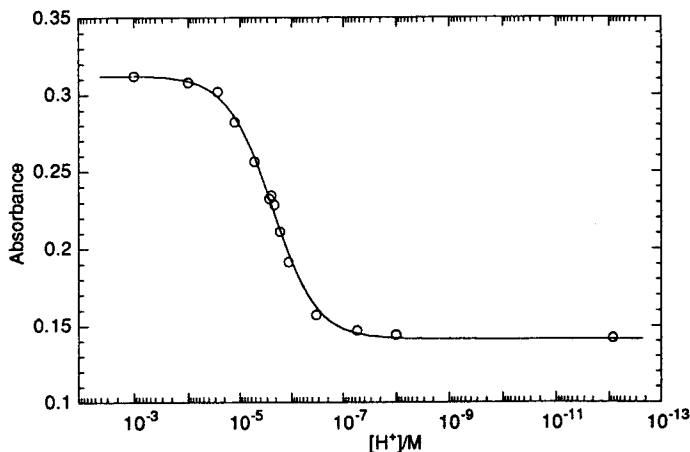
Figure 1. Spectrophotometric titration curve for the ionization of (Z)-β-methoxymethacrylic acid in aqueous solution at 25 °C

recommended by Bates.[9] The data were fitted by non-linear least-squares analysis to the expression

$$A = \frac{\varepsilon_{HA}[H^+] + \varepsilon_A Q_a}{Q_a + [H^+]} [HA]_{st}$$ (2)

where A is absorbance, ε_{HA} and ε_A are the molar absorptivities of the acidic and basic forms of the substrate, Q_a is its acidity constant and $[HA]_{st}$ is the stoichiometric substrate concentration (which was held constant at 1×10^{-4} M). This gave $\varepsilon_{HA} = (3\cdot13 \pm 0\cdot02) \times 10^3$ M^{-1}cm^{-1}, $\varepsilon_A = (1\cdot41 \pm 0\cdot02) \times 10^3$ M^{-1} cm^{-1} and $Q_a = (2\cdot39 \pm 0\cdot14) \times 10^{'6}$ M, $pQ_\alpha = 5\cdot62 \pm 0\cdot03$. The line shown in Figure 1 was drawn using these parameters; it reproduces the data well.

The acidity constant Q_a is a concentration quotient applicable at the ionic strength of the present determination, $\mu = 0\cdot10$ M. It may be converted into a thermodynamic acidity constant by applying appropriate activity coefficients.[9] The result so obtained, $pK_a = 5\cdot81$, is consistent with a prediction, $pK_a = 5\cdot54$, based on a σ–ρ correlation of acidity constants for a series of β-substituted methacrylic acids.[10]

Kinetics

The hydrolysis of all eight of the vinyl ethers used in this study was examined in perchloric acid solutions. Substrates derived from methacrylic acid were sufficiently reactive to give convenient rates in dilute acid and rate measurements were made over the concentration range $[HClO_4] = 0\cdot02$–$0\cdot10$ M for all four substances of this kind, with an extension down to $[HClO_4] = 0\cdot001$ M for (Z)-β-methoxymethacrylic acid. The ionic strength was maintained at 0.10 M and triplicate measurements were made at each acid concentration. The data are summarized in Ref. 8.

In all four cases, the observed first-order rate constants were accurately proportional to acid concentration, and hydronium ion catalytic coefficients (k_{H^+}) were therefore evaluated by linear least-squares analysis. The results are given in Table 1.

The four substrates derived from acrylic acid were considerably less reactive, and concentrated acid solutions had to be used to obtain conveniently measureable rates. Determinations were made over the concentration range $[HClO_4] = 3$–7 M; five different concentrations were used for each substrate and triplicate measurements were made at each concentration. These data are summarized in Ref. 8.
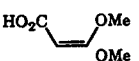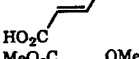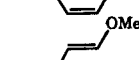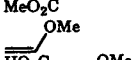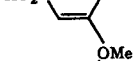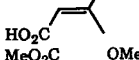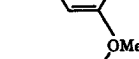
Observed first-order rate constants determined in these concentrated acid solutions increased more strongly than in direct proportion to acid concentration. This is commonly the case for vinyl ether hydrolysis,[11] and the situation is usually handled by u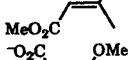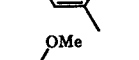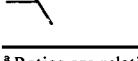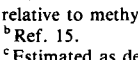sing an acidity function to correlate the data; the Cox–Yates X_0 function[12] appears to be the best scale currently available for this purpose.[13] The correlating function that applies to a rate-determining proton transfer such as the present reaction (A-S_E2 mechanism) is given by the equation[14]

$$\log(k_{obs}/[H^+]) = \log(k_{H^+}) + mX_0$$ (3)

where k_{H^+} is the hydronium ion catalytic coefficient that applies in dilute solution and m is a slope parameter. As Figure 2 illustrates, the present reactions conformed to this relationship well; linear least-squares analysis gave the catalytic coefficients listed in Table 1.

Rates of hydrolysis of (Z)-β-methoxymethacrylic acid were also measured in aqueous buffer solutions of formic acid, acetic acid and hydrogenphosphate ion. Series of solutions of constant buffer ratio and constant ionic strength (0·10 M) but varying buffer concen-

Table 1. Summary of hydronium-ion catalytic coefficients for vinyl ether hydrolysis in aqueous solution at 25 °C

Substrate	$k_{H^+}/\ 10^{-3}\,M^{-1}\,s^{-1}$	Rate ratio[a]
HO2C — OMe, OMe	0·346	2170
HO2C	0·105	7140
MeO2C — OMe, OMe	0·226	3320
MeO2C	0·0760	9·870
HO2C — OMe, OMe	750[b]	1·00
— OMe	103	2700
HO2C	13·6	20 400
MeO2C — OMe, OMe	122	2280
MeO2C	11·1	25 000
-O2C — OMe	24 300	11·4
OMe	278 000[c]	1·00

[a] Ratios are relative to methyl vinyl ether for the acrylic acid series and relative to methyl isopropenyl ether for the methacrylic acid series.
[b] Ref. 15.
[c] Estimated as described in text.

tration were used; this served to hold hydronium ion concentrations constant within given buffer solution series. Five buffer concentrations, spanning a fivefold variation, were used to make up a series, and triplicate rate measurements were made at each concentration. The data are summarized in Ref. 8.

Strong buffer catalysis was observed, as expected for a rate-determining proton transfer reaction. Observed rate constants within a buffer series were accurately proportional to buffer concentration, and the data were therefore fitted by linear least-squares analysis to the expression

$$k_{obs} = k_0 + k_{cat}[\text{buffer}] \qquad (4)$$

The zero buffer concentration intercepts, k_0, obtained in this way, together with rate constants measured for this substrate in dilute perchloric acid solutions, are displayed as the rate profile shown in Figure 3.

This rate profile is similar to that obtained previously for the hydrolysis of 2-ethoxycyclopentene-1-carboxylic acid,[2] and it can be interpreted, as was done in that case, in terms of hydrolysis occurring through both the non-ionized and ionized forms of the substrate [equation (5)]:

$$SH \xrightleftharpoons{Q_a} S^- + H^+ \qquad (5)$$

$$H^+ \downarrow k_{H^+} \qquad H^+ \downarrow k'_{H^+}$$
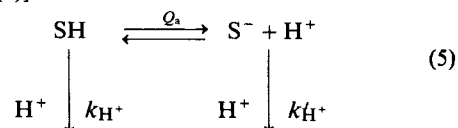
The rate law that applies to this reaction scheme is

$$k_{obs}\ (\text{or}\ k_0) = \frac{k_{H^+}[H^+]^2 + k'_{H^+}Q_a[H^+]}{Q_a + [H^+]} \qquad (6)$$

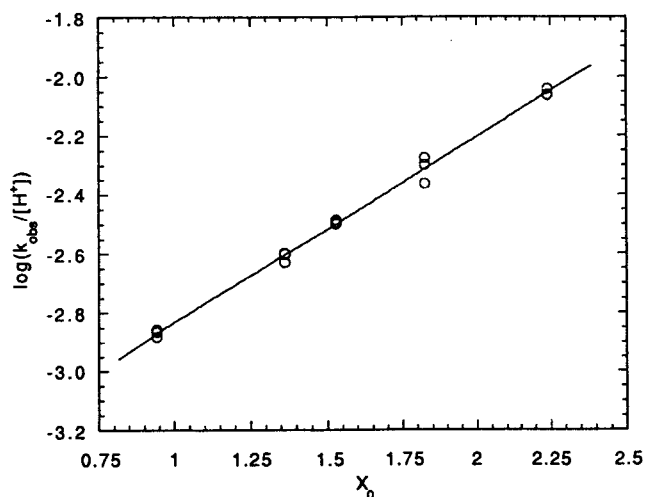Figure 2. Cox–Yates correlation of rates of hydrolysis of (Z)-β-methoxyacrylic acid in aqueous perchloric acid solution at 25 °
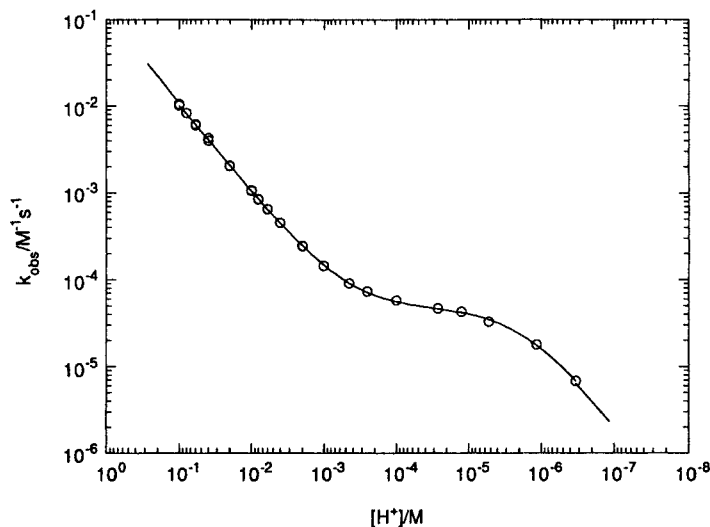
Figure 3. Rate profile for the hydrolysis of (Z)-β-methoxymethacrylic acid in aqueous solution at 25 °C

and least-squares fitting of the data to this expression gave $k_{H^+} = (1\cdot03 \pm 0\cdot01) \times 10^{-1}\,M^{-1}\,s^{-1}$, $k'_{H^+} = (2\cdot43 \pm 0\cdot05) \times 10^1\,M^{-1}\,s^{-1}$ and $Q_a = (1\cdot94 \pm 0\cdot05) \times 10^{-6}\,M$, $pQ_a = 5\cdot71 \pm 0\cdot01$. The last value is consistent with $pQ_a = 5\cdot62 \pm 0\cdot02$ determined for this acid by a spectroscopic method (see above) and it is also similar to $pQ_a = 5\cdot64$ for 2-ethoxycyclopentene-1-carboxylic acid (1) obtained from analysis of the rate profile for hydrolysis of that substance at a higher ionic strength $(0\cdot25\,M)$ than that in the present measurements.[2] The factor by which hydrolysis of the vinyl ether in its carboxylate ion form exceeds that in the non-ionized carboxylic acid form in the present system, $k'_{H^+}/k_{H^+} = 236$, is also similar to that for the 1-ethoxycyclopentene-1-carboxylic acid system, $k'_{H^+}/k_{H^+} = 209$.[2]

DISCUSSION

The present results show that acid-catalyzed hydrolysis of the vinyl ether functional group of (Z)-β-methoxymethacrylic acid occurs considerably more rapidly when the carboxylic acid group of this substrate is in its ionized carboxylate form than when it is non-ionized. This is similar to the situation found in an earlier study of the hydrolysis of the vinyl ether group of 2-ethoxycyclopentene-1-carboxylic acid.[2] It was speculated in that previous study that the difference might be due to catalysis of the hydrolysis reaction by the carboxylate group through nucleophilic participation to form an intermediate β-lactone. An alternative hypothesis is that hydrolysis of the non-ionized carboxylic acid form is depressed because of hydrogen

bond formation between the carboxylic acid group and the ether oxygen atom of the vinyl ether function.

Such hydrogen bonding can only occur when the carboxylic acid and ether groups are on the same side of the vinyl ether double bond, and this alternative hypothesis therefore requires cis vinyl ethers to be less reactive than their trans isomers. The data in Table 1, however, show that this is not the case. In the acrylic acid series, the cis isomer is more reactive than the trans isomer by a factor of $3\cdot3$, and in the methacrylic acid series the difference is even greater, with the cis acid reacting $7\cdot6$ times faster than the trans acid. This is clearly at variance with this alternative hypothesis, and that explanation must consequently be abandoned.

It is instructive, in seeking to understand this difference in reactivity between the ionized and non-ionized forms of these carboxylic acid-substituted vinyl ethers, to compare rates of reaction of these substances with those of their unsubstituted counterparts. The unsubstituted counterpart of the acrylic acid series is methyl vinyl ether, and the rate constant for hydrolysis of this substance catalyzed by the hydronium ion is available from the literature: $k_{H^+} = 0\cdot75\,M^{-1}\,s^{-1}$.[11] An accurate hydronium ion catalytic coefficient for hydrolysis of the unsubstituted counterpart of the methacrylic acid series, methyl isopropenyl ether, appears not to have determined directly, (the rate of hydrolysis of methyl isopropenyl ether has been measured in hydrogen-phosphate and hydrogen carbonate buffers,[16] but buffer catalysis in these solutions was very strong and too little reaction occurred through the hydronium ion to give a reliable value of the catalytic coefficient for this species) but a reliable value, $k_{H^+} = 278\,M^{-1}\,s^{-1}$,

can be estimated from $k_{H^+} = 579 \text{ M}^{-1}\text{s}^{-1}$ for ethyl isopropenyl ether[17] modified by the factor $1/0\cdot48$ by which ethyl vinyl ethers are more reactive than their methyl analogs.[18]

Comparisons of the substituted and unsubtituted vinyl ethers are made in Table 1. It can be seen that in both the acrylic acid and methacrylic acid series, the carboxylic acid-substituted vinyl ethers are considerably less reactive than their unsubstituted counterparts, by factors ranging from 2000 to 20 000. This diminished reactivity extends even to the carboxylate group, as (Z)-β-methoxymethacrylic acid in its ionized carboxylate form is 11 times less reactive than the unsubstituted vinyl ether. The same is true of the previously studied 2-ethoxycyclopentene-1-carboxylic acid system. The comparison there can provide only lower limits of the rate retardations, inasmuch as measurements on that system were made at $30\,^\circ\text{C}$ and a rate constant is available for the unsubstituted counterpart, ethyl cyclopentenyl ether, only at $25\,^\circ\text{C}$.[17] These limits, however, show the same trend as in the acyclic systems, giving a rate retardation of 2060 for the non-ionized carboxylic acid and a retardation of $9\cdot8$ for the carboxylate ion. It would seem inappropriate, therefore, to regard the greater reactivity of these substrates in their carboxylate forms as a catalysis; the effect is more in the nature of a mitigation of strong retardation by the carboxylic acid group.

Strong rate retardations, similar in magnitude to those given by the non-ionized carboxylic acid groups, are also shown by the methyl esters (see Table 1). Both carboxylic acids and carboxylic acid esters are known to stabilize carbon–carbon double bonds, such as those in vinyl ethers, by conjugative interaction, and the stabilizations provided by the two groups are similar in magnitude.[19] Double bond stabilizations should in fact be especially strong in the case of vinyl ethers because of additional conjugation between the acceptor acid or ester groups and the donor alkoxy group, as shown in **9**. Such stabilizations would lower the energy of the initial states of vinyl ether hydrolysis reactions more than the energy of the transition states, for the double bond is being destroyed in the transition state, and that would produce a rate retardation. This retardation, moreover, would be mitigated when the carboxylic acid substituents became ionized, for the additional conjugation shown in **9** would now put negative charge on to an already negatively charged group, and it would consequently be unfavorable. This, of course, would make the carboxylate ion more reactive than the carboxylic acid.
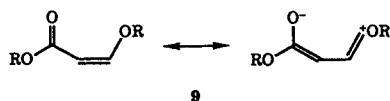
In addition to this initial state stablization, carboxylic acid and ester groups can be expected to provide transition state destabilization, through inductive interaction of these electron-withdrawing substitents $(\sigma_I = 0\cdot30, 0\cdot32)$[20] with the positive charge being generated on the substrate as it accepts a proton. This effect would be reversed by conversion of a carboxylic acid group into a carboxylate ion $(\sigma_I = -0\cdot19)$,[20] again making the ionized carboxylate form of the substrate the more reactive.

In conclusion, it appears possible to explain the difference in hydrolytic reactivity of vinyl ethers with carboyxlic acid and carboxylate ion substituents in the β-position solely in terms of conjugative and inductive effects on initial state and transition state stability, without recourse to nucleophilic participation by the carboxylate group leading to strained β-lactone intermediates.

REFERENCES

1. For a brief review of the evidence, see A. J. Kresge, *Acc. Chem. Res.* **20**, 364–370 (1987).
2. T. H. Fife, *J. Am. Chem. Soc.* **87**, 1084–1089 (1965).
3. A. Greenberg and J. F. Liebman, *Strained Organic Molecules*, p. 321. Academic Press, New York (1978).
4. A. W. McCulloch and A. J. McInnes, *Can. J. Chem.* **52**, 3569–3576 (1974).
5. E. Winterfeldt and H. Preuss, *Chem. Ber.* **99**, 450–458 (1966).
6. E. Taskinen and V.-M. Mukkala, *Tetrahedron* **38**, 613–616 (1982).
7. M. Akano, I. Hori and H. Midorikawa, *Sci. Pap. Inst. Phys. Chem. Res.* **62**, 127–129 (1968).
8. D. Ubusz, MSc, Thesis, University of Toronto (1993).
9. R. G. Bates, *Determination of pH Theory and Practise*, p. 49. Wiley, New York (1973).
10. M. Charton. *J. Org. Chem.* **30**, 974–977 (1965).
11. Y. Chiang, A. J. Kresge and C. I. Young, *Can. J. Chem.* **56**, 461–464 (1978); W. K. Chwang, A. J. Kresge and J. R. Wiseman, *J. Am. Chem. Soc.* **101**, 6972–6975 (1979); A. J. Kresge and Y. Yin, *Can. J. Chem.* **65**, 1753–1756 (1987); A. J. Kresge and Y. Yin, *J. Phys. Org. Chem.* **2**, 43–50 (1989); A. J. Kresge and M. Leibovitch, *J. Org. Chem.* **55**, 5234–5236 (1990).
12. R. A. Cox and K. Yates, *Can. J. Chem.* **59**, 2116–2124 (1981).
13. A. J. Kresge, H. J. Chen, G. L. Capen and M. F. Powell, *Can. J. Chem.* **61**, 249–256 (1983).
14. R. A. Cox and K. Yates, *Can. J. Chem.* **67**, 2944–2951 (1979).

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15. A. J. Kresge, D. S. Sagatys and H. L. Chen, *J. Am. Chem. Soc.* **99**, 7228–7233 (1977).
16. P. Salomaa, A. Kankaanpera and M. Lajunen, *Acta Chem. Scand.* **20**, 1790–1801 (1966).
17. 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).
18. Y. Chiang, W. K. Chwang, A. J. Kresge and S. Szilagyi, *Can. J. Chem.* **58**, 124–129 (1980).
19. J. Hine and M. J. Skoglund, *J. Org. Chem.* **47**, 4766–4770 (1982).
20. M. Charton, *Prog. Phys. Org. Chem.* **13**, 119–251 (1981).