Efficient Intramolecular General Acid Catalysis of Enol Ether Hydrolysis. Hydrogen-bonding Stabilisation of the Transition State for Proton Transfer to Carbon

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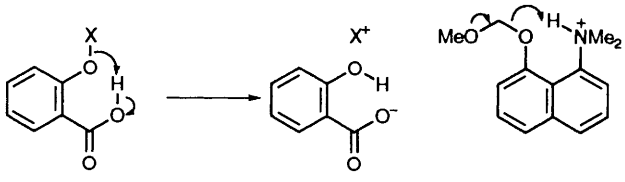
The intrinsically low efficiency of intramolecular general acid–base catalysis is enhanced when the proton transfer generates a strong intramolecular hydrogen bond. This principle is shown to apply to proton transfer to carbon: the carboxy groups of methyl vinyl ethers **3***E* and **3***Z* derived from 2-carboxyphenylacetaldehyde act as general acids to catalyse the hydrolysis of the neighbouring enol ether groups with effective molarities (EM) of about 300 and 2000 M, respectively. The solvent deuterium isotope effects confirm that the usual mechanism for enol ether hydrolysis is operative. In this system the oxocarbocation intermediate is trapped by the neighbouring carboxylate group to give the acylal **6**, rather than the formal product of hydrolysis.

The measurement of effective molarities (EM)[1] for intramolecular reactions allows us to measure the efficiencies of bringing functional groups together for the different classes of reaction involved in enzyme catalysis. These measurements reveal a remarkable difference in efficiency between the two most common mechanisms used by enzymes. Nucleophilic catalysis (involving ring formation in the intramolecular case) can be enormously efficient, with EMs up to 10^{8-9} M observed in simple systems, rising to 10^{13} M where ring-formation is favoured by the relief of ground-state strain.[1] The potential contribution of EMs of this magnitude to the efficiency of enzyme catalysis is obvious. General acid–base catalysis, on the other hand, is characterised by EMs of the order of 1–10 M in simple intramolecular systems. Yet proton transfer is the most common step in enzyme mechanism, and potentially rate determining in reactions involving high-energy intermediates, in reactions where it is concerted with the making or breaking of bonds between heavy atoms, or where the proton transfer is to or from carbon. Such reactions require catalysis by the functional groups of the active site, which must clearly be more efficient than that observed in simple intramolecular models. This work is part of a larger investigation aimed at identifying the structural features associated with efficient proton transfer catalysis, using simple systems where the structure is known in detail and the mechanism can be assigned unambiguously.

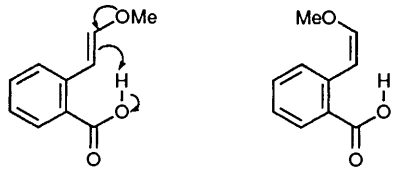
We have suggested[2,3] that the key to efficient proton-transfer catalysis lies in strong hydrogen-bonding of the in-flight proton in the transition state. This conclusion was based on what was historically[1] the single exception to the rule of low EM for intramolecular proton-transfer catalysis, the hydrolysis of derivatives **1** of salicylic acid, and the subsequent development of a second highly efficient system (**2**)[2,3] which retains this and not other potentially relevant properties of the salicylic acid structure. In each case the product is stabilised by a strong intramolecular hydrogen bond, and we suggest that this is reflected in the stabilisation of the transition state leading to it.

There remains the problem of proton transfer to carbon, for which strong hydrogen bonding is not at first sight an obvious solution. We report in this and the following paper results with two quite different systems, based on **1** and **2** respectively, in which enol ethers are hydrolysed with highly efficient catalysis by neighbouring general acid groups; together with good reasons for believing that here too the key to high catalytic efficiency lies in strong hydrogen bonding—in both cases involving C–H protons. In this paper we describe the hydrolysis



1 **2**

of **3***E* and **3***Z*, which are simple models for the enol and enediol intermediates involved in many enzyme-catalysed aldolase, isomerase and other reactions.

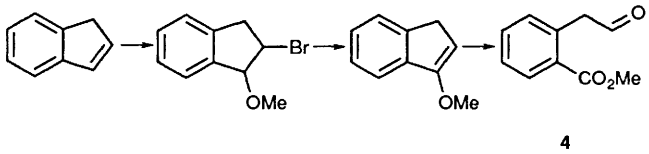


3*E* **3***Z*

The design is based on the salicylic acid system (compare the arrows shown for the expected mechanism of intramolecular general-acid catalysis for **3E** with those for **1**). Our initial results with **3***E* confirmed that intramolecular catalysis of the hydrolysis reaction is indeed more efficient than any previously reported for the reactions of enols or enol ethers.[4]

Methods and Results

Synthesis of Substrates.—2-(2-Methoxycarbonylphenyl)acetaldehyde **4** was prepared according to Scheme 1. It was



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Scheme 1

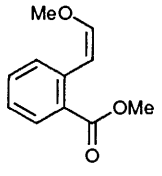
converted into the methyl esters **5***E* and **5***Z* of the target enol ethers by reaction of the enolate (generated by reaction with potassium hydride) with dimethyl sulfate. In tetrahydrofuran (THF) as the solvent the product was exclusively **5***E*; in dimethylformamide (DMF) a mixture of isomers (*ca.* 1:2 *E*:*Z*)

Table 1 Kinetic parameters for the hydrolysis reactions of enol ethers **3***E* and **3***Z*, and their methyl esters **5***E* and **5***Z*, at 39 °C and ionic strength 1.0 mol dm^{-3} (KCl)

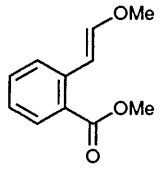
	3*E*	**3***Z*	**5***E*	**5***Z*
k_H/dm^3 mol^{-1} s^{-1}	9.81 ± 0.13 × 10^{-3}	6.91 ± 0.13 × 10^{-2}	3.29 ± 0.03 × 10^{-3}	1.41 ± 0.01 × 10^{-2}
$\Delta H^{\ddagger}$/kJ mol^{-1}			80 ± 1	
$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}			−25 ± 3	
k_0/s^{-1}	1.73 ± 0.02 × 10^{-3}	2.17 ± 0.02 × 10^{-2}		
$\Delta H^{\ddagger}$/kJ mol^{-1} [a]	65.6 ± 1.7, 67.2 ± 0.8			
$\Delta S^{\ddagger}$/J mol^{-1} K^{-1} [a]	−67.4 ± 5.0, −63.2 ± 3.3			
k_H in D_2O [c]	4.03 ± 0.11 × 10^{-3}	2.65 ± 0.05 × 10^{-2}		
k_0/s^{-1} in D_2O	5.80 ± 0.11 × 10^{-4}	7.13 ± 0.07 × 10^{-3}		
pK_a	3.67 ± 0.02	3.80 ± 0.02		
pK_a(D_2O)	4.22 ± 0.03	4.30 ± 0.02		
k_H/k_D	2.43 ± 0.07	2.61 ± 0.07		
$k_0(H_2O)/k_0(D_2O)$	2.99 ± 0.06	3.045 ± 0.041		
k_{HA}:HCO_2H [c]	— [b]	— [b]	7.1 ± 0.3 × 10^{-6}	1.35 ± 0.10 × 10^{-5}
$\Delta H^{\ddagger}$/kJ mol^{-1}			73 ± 1	
$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}			−105 ± 3	
k_{HA}:$MeOCH_2CO_2H$ [c]	— [b]	— [b]		1.53 ± 0.09 × 10^{-5}
k_{HA}:$ClCH_2CO_2H$ [c]	— [b]	— [b]		6.72 ± 0.20 × 10^{-5}
k_{HA}:$NCCH_2CO_2H$ [c]	— [b]	— [b]	6.1 ± 0.4 × 10^{-5}	9.10 ± 0.33 × 10^{-5}
Brønsted α			0.77 ± 0.07	0.70 ± 0.06
k_{HA} for pK_a 3.67 [c,d]			6.1 ± 1.0 × 10^{-6}	
k_{HA} for pK_a 3.80 [c,d]				1.0 ± 0.1 × 10^{-5}

[a] Separate measurements at pH 2.03 and 2.35, respectively. [b] No detectable catalysis. [c] dm^3 mol^{-1} s^{-1}. [d] Estimated from Brønsted α and rate constants given (see the text).

was obtained. These could be separated by flash column chromatography, and were further purified by preparative HPLC. The crude mixture slowly decomposed to 2-methoxycarbonylbenzaldehyde, as did the aldehyde starting material, but purified samples could be stored without noticeable decomposition. The esters were readily converted into **3***E* and **3***Z* by saponification, and isolated as the free acids. The hydrolyses of the methyl esters were also studied for comparison: samples for kinetic investigation were synthesised by the reaction of diazomethane with the free acids, as this allowed more efficient purification.



5*E*

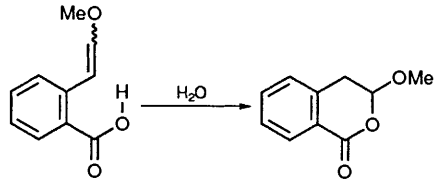


5*Z*

Reaction Products.—All four substrates were hydrolysed on a preparative scale in 0.1 mol dm^{-3} HCl, under conditions similar to those used for the kinetic measurements. As expected for the hydrolysis of simple enol ethers, the methyl esters **5***E* and **5***Z* gave the aldehyde **4**, as shown by comparison of the ^1H NMR spectrum with that of an authentic sample prepared previously. **3***E* and **3***Z* gave the acylal **6**, formed by rapid intramolecular trapping of the intermediate oxocarbonium ion by the carboxy group (see below).* Thus the reaction is formally an isomerisation rather than hydrolysis.

Kinetic Measurements.—The rates of hydrolysis of the four enol ethers were determined at 39 °C and ionic strength 1.0 mol dm^{-3} by following their disappearance directly in the spectrometer, at wavelengths in the range 255–265 nm. pHs greater than 2 were maintained with appropriate buffers, and buffer concentrations varied to identify possible general acid catalysis.

* Lactol formation by internal capture of an oxocarbocation has been observed in several previous cases.[5–7]



3*E*,*Z* **6**

No buffer catalysis was detected for the free acid substrates **3***E* and **3***Z*. In some cases a slight decrease in rate was observed with increasing buffer concentration. This is attributed to a specific salt effect: a brief survey of salts effects showed no correlation with the nucleophilicity of the anion.

Buffer catalysis by carboxylic acids was observable for the esters **5***E* and **5***Z*. This was particularly difficult to measure accurately for **5***E* because of the very slow reaction rates involved, and only two values were obtained. However, **5***Z* reacted fast enough to construct a Brønsted plot, and the two sets of data are consistent. Second-order rate constants for buffer catalysis are given in Table 1.

The pH–rate profiles for the hydrolysis of the methyl esters **5***E* and **5***Z* are straight lines of slope −1 (Fig. 1), as expected for the acid-catalysed hydrolysis of enol ethers.[5] Second-order rate constants, k_H, also appear in Table 1, and are consistent with reported values for similar compounds. pH–rate profiles for the reactions of the acids **3***E* and **3***Z* (Fig. 1) are non-linear, and follow the ionisation of the neighbouring carboxy group. The data were analysed in the usual way,[8] considering the reaction of the substrate in both the neutral and ionised forms. In this case there is good evidence (in particular the absence of general acid catalysis by buffer carboxylic acids) that the reaction involves the neutral, carboxylic acid form rather than the kinetically equivalent specific acid catalysed reaction of the carboxylate anion. So the data given in Table 1 were obtained by fitting the experimental results to eqn. (1).

$$k_{obs} = (k_0 + k_H a_H) \times a_H/(a_H + K_a) \quad (1)$$

Solvent Deuterium Isotope Effect.—The simplest criterion of whether proton transfer to carbon is rate determining is the

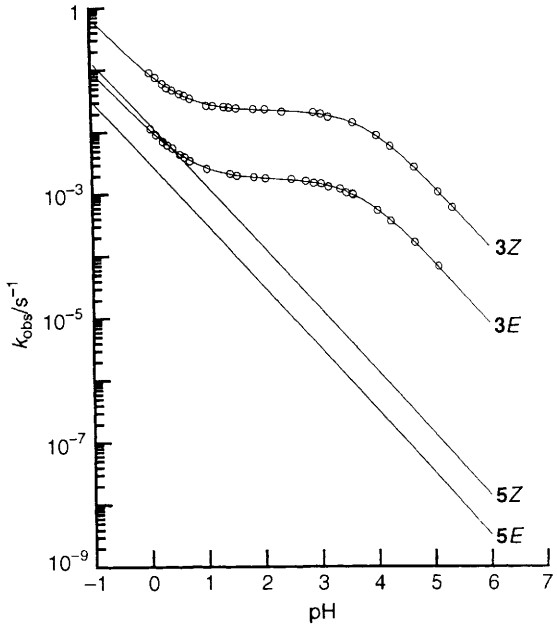


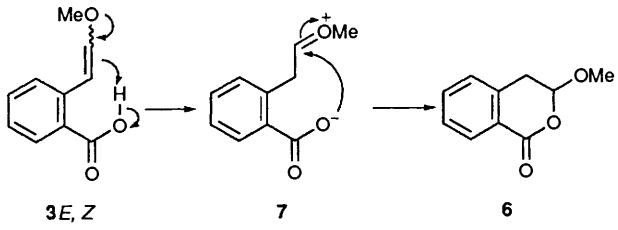
Fig. 1 pH–rate profiles for the hydrolyses of enol ethers **3***E* and (upper curve) **3***Z*, and their methyl esters **5***E* and **5***Z* (lower lines, data points not shown). The points are experimental, the lines calculated using the rate constants given in Table 1.

solvent isotope effect. If the transfer is rapid and reversible, then reaction is expected to be faster in D_2O. The measured rate constants and the derived solvent deuterium isotope effects are given in Table 1. A significant kinetic deuterium isotope effect is seen for both proton-catalysed and intramolecular reactions. These data indicate that the reaction is following the usual course of rate-determining proton transfer to carbon. This is consistent with the observed clean pseudo-first-order kinetics, and significantly different rate constants for both *E* and *Z* isomers in all cases (partial change in the rate-determining step could lead to isomerisation and hence deviation from good first-order kinetics, as discussed in the following paper[9]).

Thermodynamic Reaction Parameters.—Activation parameters were determined (using the Eyring equation) for the proton and formic acid catalysed reactions of **5***E*, and for the reactions of **3***E* at pHs 2.03 and 2.35 (on the plateau, Fig. 1), in HCl and buffered solution, respectively. The values obtained from the latter two measurements were identical to within experimental error, as expected if the same rate constant (k_0) is being measured. These results are shown in Table 1, and indicate the expected entropic advantage for the intramolecular carboxy-catalysed reaction.

Discussion

Mechanism.—The evidence is clear that the mechanism of hydrolysis of the esters **5***E* and **5***Z* is normal for enol ethers, with transfer of a proton to carbon from H_3O^+ or other general acid as the rate-determining step, followed by rapid hydration of the oxocarbocation thus formed. The reactions of the free acids **3***E* and **3***Z* appear to involve the same mechanism: except that no catalysis is apparent from external general acids other than H_3O^+ (simply because catalysis by the neighbouring carboxy group is so efficient that reactions with external general acids are insignificant in comparison), and that the oxocarbocation **7** is captured by the neighbouring carboxylate rather than by water.



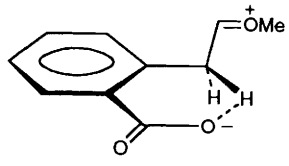
This high efficiency is reflected in half-lives of 6.7 min and 32 s, respectively, for **3***E* and **3***Z* (based on plateau rates, k_0), though the enol ethers derived from phenylacetaldehyde are known to be particularly unreactive.[10] Comparing k_0 for **3***E* and **3***Z* with the typical values of k_H observed for **5***E* and **5***Z* shows that the carboxy group accelerates the rate of enol ether hydrolysis by factors of 830 and 1980, respectively. This is substantially higher than for other examples of intramolecular catalysis of enol ether hydrolysis, though not itself the best measure of intramolecular efficiency.[1]

Effective Molarity.—A very short extrapolation of the buffer catalysis data for the esters **5***E* and **5***Z* to the kinetic pK_a of the acids **3***E* and **3***Z* (the values used are given in Table 1) allows us to estimate second-order rate constants for their intermolecular reactions with a carboxylic acid of the same pK_a as that of the neighbouring CO_2H group. We then calculate EM[1] for the reactions of the two compounds as given in eqn. (2). These

$$EM = \frac{k_{intra}}{k_{inter}} = 284 \pm 47 \text{ M for } \mathbf{3}E; \quad 2170 \pm 220 \text{ M for } \mathbf{3}Z \qquad (2)$$

values are the highest measured for proton transfer to carbon (but see the following paper[9]).

It is not immediately obvious that this high efficiency is consistent with the idea that a strong intramolecular hydrogen bond is required in the product,[2,3] and thus in the transition state leading to it, since this hydrogen bond would involve a C–H proton (**7H**), and the very existence of such hydrogen bonds is a matter of dispute. However, the C–H bond in this case is atypical: it is adjacent to a cation, and as a result is strongly acidic. (The *geometry* is certainly favourable for the formation of a hydrogen bond, as in **7H**, because the compound is

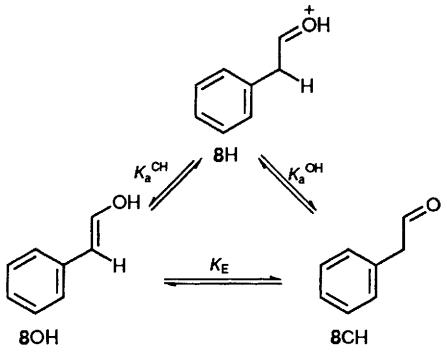


7H

modelled on salicylate.) We can estimate the pK_a of such a system (*i.e.*, the dissociation of the proton identified in **7H**) by applying the thermodynamic cycle of Scheme 2 to a model system with a proton in place of the methyl group (**8H**). Accurate pK_E values of −6 and −3 have been measured[11] for acetaldehyde and for phenylacetaldehyde (**8**OH ⇌ **8**CH), respectively. The corresponding value for **7**OH ⇌ **7**CH will be lowered by any hydrogen-bond stabilisation of the keto-form, and perhaps also by a steric interaction with the *ortho* substituent in the planar conformation of the enol form, so may be expected to lie between these two figures.

Values for pK_a^{OH} of the protonated aldehyde are not so readily available, but calculated values[12] are in the region of −8 for the

conjugate acids of aldehydes. Hence, a pK_a^{CH} in the region of −2 to −5 is predicted.*



Scheme 2

Conclusions

Enolisation thus fulfils Jencks' criterion[14] for a general acid–base catalysed reaction: proton transfer to carboxylate is thermodynamically highly unfavourable in the ground state **8**CH and becomes highly favourable in the fully protonated form **8**H. In a system such as **7**H, with the correct geometry for formation of a strong hydrogen bond the protonated form is stabilised substantially and proton transfer is also kinetically favoured.

Previous authors have commented on the low efficiency of intramolecular general acid catalysis of the hydrolysis of enol ethers,[5] and have pointed out that observed EMs are too small to explain observed enzyme-catalysed rates of enolisation reactions.[15] Gerlt *et al.*[15] suggest specifically that the pK_a^{CH} of the protonated carbonyl compound is the key to understanding the high rates of proton transfer to weak active-site general bases, because the two pK_as (typically 3–7) are of similar magnitude. They suggest that concerted general acid–general base catalysis provides the necessary low-energy route, and this is consistent with our results as a solution to the kinetic problem.† pK_E is particularly favourable for arylacetaldehydes, so pK_a^{CH} is particularly low for derived conjugate acids corresponding to **7**H. Nevertheless, for aldehydes and ketones it is still expected to fall below the pK_a of a typical active-site group, so that the proton transfers involved may become thermoneutral before proton transfer to C=O is complete. Our results in this and the following paper show that high EMs are attainable for proton-transfer reactions when the geometry supports strong hydrogen bonding. The required geometry is not generally present in intramolecular reactions: it may be presumed that it is an essential part of the binding interaction between active site and substrate in the transition state for enzyme-catalysed reactions.

Experimental

^{1}H NMR spectra were recorded at 250 MHz on a Bruker WM 250 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 1310 spectrometer. Mass spectra were recorded on a Kratos AEI MS30 or a Kratos MS390MS machine. Melting points were recorded on a Reichert hot-stage apparatus or with a Gallenkamp apparatus and are uncorrected. Chromatography was performed on Merck Kieselgel 60 (40–63 μm) and refers to flash column chromatography. HPLC was performed using a Dynamax macro HPLC S1 column.

Dimethyl sulfate was distilled from and stored over CaO. Dry THF was distilled from $LiAlH_4$ and stored over sodium wire. Dry DMF was distilled from BaO and stored over 3 Å molecular sieves. Dry dichloromethane was distilled from P_2O_5. Dry *tert*-butyl alcohol was distilled from and stored over CaH_2. All solvents were distilled before use. Extracts were dried over magnesium sulfate unless indicated otherwise.

2-Bromo-1-methoxyindane. Indene (17.5 g, 0.15 mol: Aldrich technical grade, purified by being passed through silica with light petroleum, b.p. 30–40 °C), *N*-bromosuccinimide (26.7 g, 0.15 mol) and dry methanol (100 cm^3) were stirred vigorously in the dark at room temperature for 2 h. The yellow solution was poured into water, extracted with ether (3 × 50 cm^3), dried and evaporated under reduced pressure to give a yellow liquid and a white solid. Redissolution of this mixture in light petroleum (b.p. 30–40 °C), filtration and concentration of the filtrate under reduced pressure gave the bromomethoxyindane pure enough for the next step (31.5 g, 92%); the solid was identified as 2-bromo-1-hydroxyindane. Distillation gave the pure indane[17] (23.2 g, 68%) as a pale yellow liquid, b.p. 82–84 °C/0.3 mmHg (lit.,[17] 106 °C/3 mmHg); ν_{max}(thin film)/cm^{-1} 1600 and 1580 (Ar); δ_H(250 MHz; $CDCl_3$) 7.20–7.50 (4 H, m, ArH), 5.00 (1 H, d, *J* 3.5, CHOMe), 4.50 (1 H, ddd, *J* 3.5, 5 and 6.5, CHBr), 3.69 (1 H, dd, *J* 6.5 and 17, CH_AH_B), 3.60 (3 H, s, OMe) and 3.27 (1 H, dd, *J* 5 and 17, CH_AH_B); *m/z* 226 and 228 (95%, M^+), 195 and 193 (60, *M* − MeO) and 147 (100, *M* − Br) (Found: M^+, 225.9995. $C_{10}H_{11}{}^{79}BrO$ requires *M*, 225.9993).

1-Methoxyindene. Following the procedure of Doyle,[18] 2-bromo-1-methoxyindane (34 g, 0.15 mol) was dripped rapidly into a mechanically stirred mixture of potassium *tert*-butoxide (26.9 g, 0.22 mol) and dry *tert*-butyl alcohol (100 cm^3). The mixture turned black and was heated to reflux for 30 min, after which the *tert*-butyl alcohol was distilled off, and dichloromethane and silica added to the black residue. After being stirred vigorously for 5 min, the slurry was filtered through a silica plug and the filtrate evaporated under reduced pressure and distilled to give the indene (16.1 g, 74%) as a colourless liquid b.p. 57–58 °C/0.9 mmHg (lit.,[18] 101–104 °C/15 mmHg); R_f [4:1 light petroleum (b.p. 40–60 °C)—CH_2Cl_2] 0.37; ν_{max}(thin film)/cm^{-1} 1620 (C=C), 1600 and 1580 (Ar); δ_H(250 MHz; $CDCl_3$) 7.20–7.60 (4 H, m, ArH), 5.33 (1 H, t, *J* 2.5, HC=COMe), 3.91 (3 H, s, OMe) and 3.35 (2 H, d, *J* 2.5, CH_2).

(2-Methoxycarbonylphenyl)acetaldehyde **4**.—An ozone-enriched stream of dry oxygen was bubbled through a solution of the methoxyindene (1.0 g, 6.8 mmol) in dry dichloromethane at −78 °C until TLC indicated that no more starting material remained (a blue coloration also served to indicate the end of the reaction). The solution was purged with argon, allowed to warm to room temperature, an excess of dimethyl sulfide added and the solution stirred for 12 h before being evaporated under reduced pressure. The residue was passed through a plug of silica with dichloromethane, evaporated under reduced pressure and distilled to give the *aldehyde/ester* **4** (0.57 g, 47%) as a colourless oil, b.p. 125 °C/0.08 mmHg. Final purification by chromatography was frequently necessary to obtain pure samples: purification by HPLC enabled the product to be separated from indan-1-one (from hydrolysis of the starting material); t_R 14 and 15.5 min, respectively, with 3:1 hexane–EtOAc). R_f [1:1 light petroleum (b.p. 40–60 °C)–ether] 0.32; ν_{max}(thin film)/cm^{-1} 2730 (CHO), 1720 and 1710 (C=O), 1600 and 1580 (Ar); δ_H(250 MHz; $CDCl_3$) 9.77 (1 H, t, *J* 1, CHO), 8.04 (1 H, dd, *J* 1.5 and 8, ArH *ortho* to CO_2Me), 7.50 (1 H, td, *J* 1.5 and 8, ArH), 7.37 (1 H, td, *J* 1.5 and 8, ArH), 7.22 (1 H, dd, *J* 1.5 and 8, ArH *ortho* to CH_2), 4.05 (2 H, d, *J* 1, CH_2) and 3.85 (3 H, s, OMe); *m/z* no M^+ observed, 150 (35%, *M* − CO), 119 (90,

* Similar values of pK_a^{CH} were derived by Toullec[13] for the oxocarbenium ions obtained by protonation of α-methoxystyrenes.
† The related thermodynamic problem—how a high-energy enol form might be stabilised in an enzyme active site—is more complicated, as pointed out by Guthrie and Kluger.[16]

150 − MeO), 118 (100, 150 − MeOH) and 90 (100, 118 − CO) (Found: $M^+ - 2$ H, 176.0471. $C_{10}H_8O_3$ requires $M - 2$, 176.0473; found: M^+ − CO, 150.0679. $C_9H_{10}O_2$ requires M − 28 150.0681).

(E)-1-*Methoxy*-2-(2-*methoxycarbonylphenyl*)*ethene* **5E**.—Potassium hydride (washed free of mineral oil, 0.049 g, 1.2 mmol) was stirred in dry THF (5 cm^3) under argon at room temperature, and the aldehyde/ester **4** (0.178 g, 1.0 mmol) in dry THF (5 cm^3) added, to give a deep red solution. This was cooled to −78 °C, dimethyl sulfate (0.11 cm^3, 1.2 mmol) added rapidly and the solution allowed to warm to room temperature before being poured into sodium carbonate solution and extracted with hexane (3 × 10 cm^3). The extract was washed with sodium carbonate and with brine, dried and evaporated under reduced pressure. The residue was chromatographed [SiO_2; 8:1 light petroleum (b.p. 40–60 °C)–ether], distilled, b.p. 67–68 °C/0.02 mmHg, and chromatographed again to give the E *enol ether/ester* **5E** (0.096 g, 50%) as a colourless oil; R_f [4:1 light petroleum (b.p. 40–60 °C)–ether] 0.30; $\nu_{max}(CDCl_3)/cm^{-1}$ 1710 (C=O) and 1635 (C=C); δ_H(250 MHz; $CDCl_3$) 7.88 (1 H, dd, *J* 1.5 and 8, ArH ortho to CO_2Me), 7.37–7.45 (1 H, m, ArH), 7.10–7.25 (2 H, m, ArH), 6.98 (1 H, d, *J* 13, C=CHOMe), 6.74 (1 H, d, *J* 13, HC=COMe), 3.88 (3 H, s, CO_2Me) and 3.72 (3 H, s, MeO); *m*/*z* 192 (55%, M^+), 161 (100, *M* − MeO), 133 (60, 161 − CO) and 91 (55, $PhCH_2^+$) (Found: M^+, 192.0792. $C_{11}H_{12}O_3$ requires *M*, 192.0786).

5*E* was also synthesised from the enol ether/acid **3***E* (see below) as the purification above was so difficult: a solution of diazomethane in ether was added dropwise to a solution of the *E* enol ether/acid in ether until the yellow colour persisted. The excess of reagent was allowed to evaporate, and the solution concentrated under reduced pressure to give pure *E* enol ether/ester **5***E*.

(Z)-1-*Methoxy*-2-(2-*methoxycarbonylphenyl*)*ethene* **5Z**.—Potassium hydride (washed free of mineral oil, 0.135 g, 3.4 mmol) was stirred in dry DMF (10 cm^3) under argon at room temperature, and the aldehyde/ester **4** (0.50 g, 2.8 mmol) in dry DMF (10 cm^3) added. Dimethyl sulfate (0.318 cm^3, 3.4 mmol) was added to the deep red solution which was stirred for 3 h before being poured into sodium hydrogen carbonate solution and extracted with hexane. The extract was washed with water and with brine, dried, and evaporated under reduced pressure. The residue was chromatographed [SiO_2; 4:1 light petroleum (b.p. 40–60)–ether] to isolate the *E* and *Z* isomers of the enol ether/ester (ratio *ca.* 1:2) from the crude mixture, and the isomers separated by HPLC [9:1 hexane–EtOAc, 14(*E*) and 16.5 (*Z*) min retention times) to give the pure *Z enol ether/ester* **5***E* (0.27 g, 50%) as a colourless oil; R_f [4:1 light petroleum (b.p. 40–60 °C)–ether] 0.18; $\nu_{max}(CDCl_3)/cm^{-1}$ 1710 (C=O) and 1640 (C=C); δ_H(250 MHz; $CDCl_3$) 8.03 (1 H, dd, *J* 1 and 8, ArH *ortho* to C=C), 7.81 (1 H, dd, *J* 1.5 and 8, ArH *ortho* to CO_2Me), 7.42 (1 H, dt, *J* 1.5 and 8, ArH *para* to CO_2Me), 7.17 (1 H, dt, *J* 1 and 8, ArH *para* to C=C), 6.22 (1 H, d, *J* 7.5, C=CHOMe), 6.06 (1 H, d, *J* 7.5, HC=COMe), 3.87 (3 H, s, CO_2Me) and 3.76 (3 H, s, MeO); *m*/*z* 192 (85%, M^+), 161 (100, *M* − MeO) and 91 (55, $PhCH_2^+$) (Found: M^+, 192.0798. $C_{11}H_{12}O_3$ requires *M*, 192.0786).

(E)-1-*Methoxy*-2-(2-*carboxyphenyl*)*ethene* **3E**.—The *E* enol-ether ester **5***E* (30 mg, 0.016 mmol) was stirred with 1 mol dm^{-3} sodium hydroxide solution for 2 days, by which time a homogeneous solution had formed. The solution was washed with ether, cooled to 0 °C, acidified with 3 mol dm^{-3} HCl and rapidly extracted with ether. The extract was dried and concentrated to give the E *enol ether/acid* **3***E* (23 mg, 83%) as prisms, m.p. 88–90 °C [from light petroleum (b.p. 40–60 °C)]; R_f[1:1 light petroleum (b.p. 40–60 °C)–ether] 0.12; $\nu_{max}(CDCl_3)/cm^{-1}$ 1690 (C=O) and 1625 (C=C); δ_H(250 MHz; $CDCl_3$) 8.02 (1 H, d, *J* 8, ArH *ortho* to CO_2H), 7.40–7.48 (2 H, m, ArH), 7.19–7.25 (1 H, m, ArH), 6.99 (1 H, d, *J* 13, C=CHOMe), 6.81 (1 H, d, *J* 13, HC=COMe) and 3.74 (3 H, s, MeO); *m*/*z* 178 (35%, M^+), 146 (40, *M* − MeOH) and 118 (100, 146 − CO) (Found: M^+, 178.0619. $C_{11}H_{12}O_3$ requires *M*, 178.0630).

(Z)-1-*Methoxy*-2-(2-*carboxyphenyl*)*ethene* **3Z**.—Was prepared from the *Z* enol ether/ester **5***E* according to the method used for the *E* isomer, described above. The Z *enol ether/acid* **3***Z* was isolated as prisms, m.p. 79–81 °C [from light petroleum (b.p. 40–60 °C)]; R_f [1:1 light petroleum (b.p. 40–60 °C)–ether] 0.12; $\nu_{max}(CDCl_3)cm^{-1}$ 1690 (C=O) and 1640 (C=C); δ_H(250 MHz; $CDCl_3$) 8.06 (1 H, dd, *J* 1 and 8, ArH *ortho* to C=C), 7.96 (1 H, dd, *J* 1.5 and 8, ArH *ortho* to CO_2H), 7.46 (1 H, dt, *J* 1.5 and 8, ArH *para* to CO_2H), 7.20 (1 H, dt, *J* 1 and 8, ArH *para* to C=C), 6.23 (1 H, d, *J* 7.5, C=CHOMe), 6.18 (1 H, d, *J* 7.5, HC=COMe) and 3.76 (3 H, s, MeO); *m*/*z* 178 (20%, M^+), 146 (30, M −MeOH) and 118 (100, 146 − CO) (Found: M^+, 178.0632. $C_{11}H_{12}O_3$ requires *M*, 178.0630).

3-*Methoxy*-3,4-*dihydro*-2-*benzopyran*-1-*one* **6**.—30 mg of **3***Z* or **3***E* were incubated with 0.01 mol dm^{-3} HCl solution (as used in the kinetic runs) at 39 °C for 1 and 10 half-lives. The solutions were extracted with ether, dried and evaporated under reduced pressure. **3***Z* and **3***E* produced exclusively the lactol **6**, which was fully characterised spectroscopically: R_f [1:1 light petroleum (b.p. 40–60 °C)–ether] 0.19; $\nu_{max}(CDCl_3)/cm^{-1}$ 1720 (C=O); δ_H(250 MHz; $CDCl_3$) 8.09 (1 H, dd, *J* 1 and 8, ArH *ortho* to C=O), 7.54 (1 H, dt, *J* 1 and 8, ArH *para* to C=O), 7.38 (1 H, t, *J* 8, ArH *para* to CH_2), 7.25 (1 H, d, *J* 8, ArH *ortho* to CH_2), 5.45 (1 H, t, *J* 4, CHOMe), 3.55 (3 H, s, OMe), 3.28 (1 H, dd, *J* 4 and 16.5, CH_AH_B) and 3.10 (1 H, dd, *J* 4 and 16.5, CH_AH_B); *m*/*z* 178 (20%, M^+), 146 (30, *M* − MeOH), and 118 (100, 146 − CO) (Found: M^+, 178.0640. $C_{11}H_{12}O_3$ requires *M*, 178.0630). Under the same conditions **5***Z* and **5***E* gave only the aldehyde ester **4**.

Kinetic Methods.—Reagents were AR grade. Water was distilled, distilled twice more through all-glass apparatus, then degassed with argon. Formic and acetic acids were fractionally recrystallised twice before use; cyanoacetic and chloroacetic acids were recrystallised; methoxyacetic acid was distilled. Buffers were made by adding the appropriate volume of a standard KOH solution to a known volume of a stock solution of the acid in grade A volumetric flasks; KCl solution was added to bring the ionic strength to 1.0 mol dm^{-3}, and the solution finally made up to the mark with water (KBr and KNO_3 were used to maintain ionic strength in the salt-effect experiments). Buffer concentration was varied by dilution in a similar way. KOH and HCl solutions were made by diluting Convol® concentrates. Solutions for the solvent isotope effect experiments were made by dilution of 10 g of 20 wt% DCl (Aldrich 99+ %) to 50 cm^3 with 99.9% D_2O (Fluorochem). This solution was titrated and used as the source for further dilutions for the DCl solutions required; KCl was weighed into the flask before adding the acid and making up to the mark with D_2O. Acetate buffers were made by adding the DCl stock to a stock solution of AcOK in D_2O. The dilutions were performed as above.

Rate constants were obtained by monitoring the change in absorption caused by the disappearance of the chromophore in the UV spectrum at fixed wavelengths. Changes were at least 0.5 A units. Wavelengths used were 263, 265, 258 and 268 nm for **3***E*, **3***Z*, **5***E* and **5***Z*, respectively. A Gilford 2600 spectrophotometer equipped with a thermoset temperature control was used.

Quartz 300 μl cuvettes were equilibrated for 5 min with 290 μl of buffer in the cell compartment before each run; the run was initiated by adding to the buffer 10 μl of a stock solution of the substrate in dioxane, mixing rapidly and waiting for a short time for the temperature to stabilise again. The buffer concentration was always ≥ 100 times the substrate concentration so that pseudo-first-order conditions applied. Rate constants were obtained by using a BBC microcomputer and a program developed in this laboratory by Dr. A. Sutkowski. This program optimised the end points; the values so obtained were regularly checked against the reading after 10 half-lives and did not significantly differ.

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