Intramolecular Catalysis by the Ionised Carboxy-group of the Hydrolysis of Enol Esters, and of the General Acid Catalysed Ketonisation of the Enols produced

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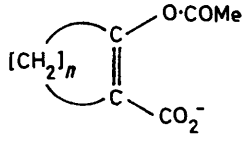
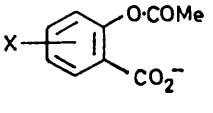
2-Acetoxycyclohexene-1-carboxylate ion is hydrolysed extraordinarily rapidly to the 2-hydroxy-compound. The ketonisation of this enol is slow enough to be measured between pH 7—11. In the case of 2-acetoxycyclopentene-1-carboxylate ion both reactions are too fast to measure by conventional techniques. A mechanism involving intramolecular nucleophilic catalysis leading to a β-keto-keten intermediate is suggested to account for the rapid hydrolysis of the enol esters. The ketonisation of 2-hydroxycyclohexene-1-carboxylate is subject to both general acid and general base catalysis, and attack by general acids is itself general base-catalysed by the neighbouring carboxylate group. Rate constants measured for the general base-catalysed ketonisation of ethyl 2-hydroxycyclohexene-1-carboxylate agree closely with those calculated from the known equilibrium and rate constants for enolisation of ethyl 2-oxocyclohexane-1-carboxylate.

An important part of our work on the mechanisms of simple reactions as models for enzymic processes concerns the way in which efficiency in intramolecular catalysis depends on structure. We [1] and other workers [2] have shown that intramolecular nucleophilic catalysis, like many cyclisations, can be extremely sensitive to relatively minor structural changes. It is of considerable interest to extend this approach to reactions involving intramolecular general species catalysis. General acid and general base catalysis are undoubtedly more common enzymic mechanisms, yet they seem to be relatively inefficient processes in intramolecular catalysis. Intramolecular nucleophilic reactions are commonly faster than their intermolecular counterparts by factors as large as 10^6—10^8M, whereas known rate enhancements attributable to intramolecular general base catalysis do not normally exceed 20M.

We are therefore examining a number of systems known or expected to involve intramolecular general base catalysis. The work described in this paper was planned as an investigation of the effects of changing ring size on the efficiency of intramolecular catalysis by the ionised carboxy-group of the hydrolysis of a series



(1) a; $n = 3$
b; $n = 4$



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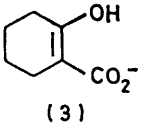

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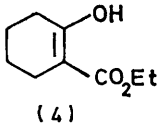


(4)

of enol acetates (1). The general base catalysis mechanism is firmly established [3] for the hydrolysis of the corresponding phenol acetates [substituted aspirins (2)], but no systematic variation of geometry is possible using the aromatic system.

In fact an examination of the two compounds (1) shows that the enol esters behave quite differently from the acetyl salicylates. Hydrolysis of the ester group is an extremely rapid reaction, too fast to measure by conventional techniques, and leads in the case of 2-acetoxycyclohexene-1-carboxylate ion (1b) to the enol (3). The subsequent ketonisation of this enol proved slow enough to be measured between pH 7—11, and we have collected some data for this reaction, and for the ketonisation of the corresponding ester (4), for comparison. The rapid hydrolysis of the esters (1) cannot be studied directly, but the rates are so high that all but one of the likely mechanisms can be ruled out with some confidence.

EXPERIMENTAL

Materials.—Inorganic salts were of analytical grade, and were used without further purification. Distilled water was distilled twice more before use, from all-glass apparatus. Amines were distilled, or their hydrochlorides were recrystallised.

Benzyl 2-Acetoxycyclohexene-1-carboxylate.—Ethyl 2-oxocyclohexane-1-carboxylate was converted into the benzyl ester by the base-catalysed exchange method.[4] Fractional distillation gave a sample, b.p. 135—140° at 0·05 mmHg, with the expected spectroscopic properties: less than 1% of unchanged ethyl ester would have been readily detected in the ^{1}H n.m.r. spectrum. This ester was converted into the enol acetate by acid-catalysed exchange with isopropenyl acetate, clearly the most satisfactory of a number of methods tried. A solution of benzyl 2-oxocyclohexane-1-carboxylate (20 g) in a large excess (500 ml) of isopropenyl acetate was heated to reflux for 6 h in the presence of toluene-*p*-sulphonic acid (4 g). Next day $NaHCO_3$ (25 g) was added, the solution was filtered, and the unchanged isopropenyl acetate was distilled off. The residue was dissolved in ether, washed twice with aqueous $NaHCO_3$, and dried. Removal of solvent and subsequent distillation gave a pale yellow

[1] A. J. Kirby and P. W. Lancaster, in ' Chemical Reactivity and Biological Role of Functional Groups in Enzymes,' ed. R. M. S. Smellie, Academic Press, London and New York, 1970, p. 99.

[2] D. R. Storm and D. E. Koshland, *Proc. Nat. Acad. Sci. U.S.A.*, 1970, **66**, 445; S. Milstien and L. A. Cohen, *ibid.*, 1970, **67**, 1143; T. C. Bruice and W. C. Bradbury, *J. Amer. Chem. Soc.*, 1968, **90**, 3808.

[3] A. R. Fersht and A. J. Kirby, *J. Amer. Chem. Soc.*, 1967, **89**, 4853, 4857.

[4] H. Plieninger and C. E. Castro, *Chem. Ber.*, 1954, **87**, 1760.

liquid (15 g), b.p. 153—154° at 0·35 mmHg. This was dissolved in ether and refluxed for 1 h in the presence of activated charcoal. Two further distillations gave a sample with $\nu_{max.}$ 1760, 1710, and 1650 cm^{-1}, $\lambda_{max.}$ (95% ethanol) 225 nm (shoulder) (ε 10,000), τ 4·90 ($ArCH_2$) and 8·15 (O·COMe) (Found: C, 70·0; H, 6·6. $C_{16}H_{18}O_4$ requires C, 70·05; H, 6·55%). The benzylic protons absorb slightly upfield from their position in the spectrum of the original keto-ester, and less than 2% of starting material could be seen to be present.

Benzyl 2-Acetoxycyclopentene-1-carboxylate.—This was prepared similarly, and had b.p. 147—149° at 0·3 mmHg (Found: C, 68·8; H, 6·5. $C_{15}H_{16}O_4$ requires C, 69·2; H, 6·15%). This sample had the expected spectroscopic properties, and since no accurate kinetic measurements could be made using this compound (it disappeared immediately when dissolved in water), further purification was not considered necessary.

2-Acetoxycyclohexene-1-carboxylic Acid.—The benzyl ester prepared above was readily hydrogenolysed at atmospheric pressure over 5% palladised charcoal catalyst. But the acid produced had very limited stability, and could not be characterised directly. As a general precaution the solution being hydrogenolysed was protected from moisture by means of a tower of KOH pellets. Hydrogenation in ethanol gave ethyl 2-oxocyclohexanone-1-carboxylate as the main product. The benzyl ester is stable in ethanol under these conditions. Hydrogenolysis in carefully dried dioxan gave a solution which when diluted with ethanol again gave ethyl 2-oxocyclohexane-1-carboxylate as the major product (75%) and cyclohexanone (25%, by g.l.c.). Hydrogenolysis in dry ethyl acetate was a faster reaction; the calculated volume of hydrogen was taken up in 2 h, compared with 6 h in dioxan. In this case evaporation and exposure to high vacuum removed the toluene produced (no aromatic protons evident in the n.m.r. spectrum). The residue had strong CO_2H bands in the i.r., and a strong singlet at τ 7·82 in the n.m.r., spectrum assigned to the acetoxy-methyl group. But decomposition, as shown by changes in the n.m.r. spectrum, was rapid. The dioxan solutions used in the kinetic work were more stable, and could be kept, frozen at −30°, without appreciable decomposition.

These results are consistent with the presence in solution after hydrogenation of the free acid form of (Ib). Ethanolysis of this ester, if it involved nucleophilic catalysis by the carboxy-group, would be expected to give ethyl acetate and ethyl 2-oxocyclohexane-1-carboxylate as the ester products. The other products would be 2-oxocyclohexane-1-carboxylic acid and acetic acid, respectively, and the keto-acid would be rapidly decarboxylated to cyclohexanone. As final confirmation that the expected acid is formed in solution on hydrogenolysis of the benzyl ester, when the dioxan solution was added to aqueous buffer at pH *ca.* 8 the reaction observed could be identified as the ketonisation of 2-hydroxycyclohexene-1-carboxylate (see later).

Similar results were obtained in ethanol and dioxan when benzyl 2-acetoxycyclopentene-1-carboxylate was hydrogenolysed, except that the final ketonisation was too fast to be observed in this case.

* In 0·05M-TRIS buffer, 80% free base, pH 9·11 in water, the observed rate constant at 25° was $7·44 \times 10^{-2}$ min^{-1}. This fell to $1·07 \times 10^{-2}$ min^{-1} in D_2O. Under these conditions in H_2O buffer catalysis accounts for 80% of reaction; the remaining 20% is due almost entirely to catalysis by hydroxide ion.

Kinetic Methods and Results.—When the fresh dioxan solution of 2-acetoxycyclohexene-1-carboxylic acid, prepared above by hydrogenolysis of the benzyl ester, is diluted with aqueous buffers, the u.v. absorption at 250 nm rapidly disappears. The disappearance of this band is slow enough to follow by conventional methods in the pH range 7—11, and the reaction concerned is catalysed by both acid and basic components of the buffer. Rates were measured by adding one drop of the dioxan solution to the buffer solution made up to ionic strength 1·0 (KCl) in the thermostatted cell compartment of a Zeiss PMQ II spectrophotometer, maintained at 25·0 ± 0·1°. Second-order rate constants for both buffer components were obtained by measurements of the total buffer constant at various buffer ratios.

The reaction is characterised by a large solvent deuterium isotope effect, in the region of 7,* suggesting strongly that proton transfer to carbon is involved. One possibility was that the enol acetate had been rapidly hydrolysed to the enol, and that the reaction we observed was the disappearance of the chromophore of the enol as it was converted into the more stable keto-form. We therefore prepared the enol, 2-hydroxycyclohexene-1-carboxylic acid by the following simple method. The benzyl ester of the enol, benzyl 2-hydroxycyclohexene-1-carboxylate, is the predominant form in organic solvents of benzyl 2-oxocyclohexane-1-carboxylate. So hydrogenolysis of the dioxan solution of the benzyl keto-ester, which had been allowed to come to equilibrium (24 h at room temperature), is expected to give predominantly 2-hydroxycyclohexene-1-carboxylic acid. (Some keto-acid will also be produced, but this has no significant absorption at 250 nm, and does not interfere). After hydrogenation the catalyst was filtered off and one drop of the dioxan solution added to the buffer solutions, as before. The absorption at 250 nm present in these solutions also disappeared, at a rate identical with that observed starting with the enol acetate under the same conditions. Second-order rate constants for buffer catalysis were identical also. Identical rates were observed for the compound prepared in the two different ways about ten times under various conditions. Some of the later measurements on the catalysed reaction were made using the enol prepared directly from its benzyl ester.

For comparison, and as an independent check of the validity of the method, we measured the rate of ketonisation of the enol form of ethyl 2-oxocyclohexane-1-carboxylate, for which rate and equilibrium constants for enolisation are known. This keto-ester exists predominantly as the enol form in organic solvents such as dioxan,[5] but almost exclusively in the keto-form in water.[6] When a drop of the equilibrated (24 h) dioxan solution of this ester is added to aqueous buffer the absorption due to the enol ($\lambda_{max.}$ 260 nm) rapidly disappears. In this case the reaction was slow enough to measure only below pH 5, and was subject to general base catalysis only. We measured second-order rate constants for catalysis by the three carboxylate anions used by Bell and Goldsmith [7] in their study of the reverse reaction. In each case the catalytic constants were almost identical to those calculated from the data of Bell and Goldsmith (at ionic strength 0·1) and the known [6] equilibrium constant for enolisation in water. All these results appear in Tables 1 and 2.

[5] S. J. Rhoads and C. Pryde, *J. Org. Chem.*, 1965, **30**, 3212.
[6] R. P. Bell and D. C. Vogelsong, *J. Chem. Soc.*, 1958, 243.
[7] R. P. Bell and H. L. Goldsmith, *Proc. Roy. Soc.*, 1952, *A*, **210**, 322.

TABLE 1

Buffer catalysis of the ketonisation of 2-hydroxycyclohexene-1-carboxylate, at 25° and ionic strength 1·0

Buffer, B (basic form)	pK_a [a]	Catalytic constant (l mol^{-1} min^{-1}) k_B	k_{BH^+}
HO^-	15·7	300—400	[b]
Me_2NH	10·95	130	[b]
CO_3^{2-}	9·85	1·35	0·74
$Me_2N{\cdot}CH_2{\cdot}CH_2{\cdot}OH$	9·75	12·5	1·6
TRIS	8·50	0·9	2·4
N_2H_4	8·12	1·6	6·4
N-Methylmorpholine	7·82	0·8	22
HPO_4^{2-}	6·50	[b]	185
H_2O	−1·7	[b]	4×10^6

[a] Under the conditions of these experiments. [b] Too slow for accurate measurement.

TABLE 2

General base catalysis of the ketonisation of ethyl 2-hydroxycyclohexene-1-carboxylate, at 25° and ionic strength 1·0

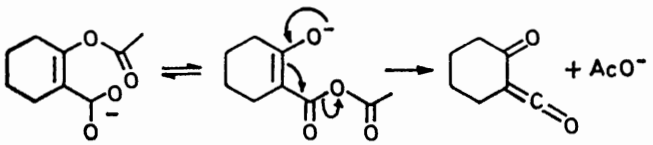
Buffer	k_B/l mol^{-1} min^{-1}	k_B (calc.) [a]/l mol^{-1} min^{-1}
Chloroacetate	1·08	0·92
Glycollate	4·3	3·7
Acetate	15·8	15·5
Phosphate	125	

[a] Using data of Bell and co-workers at lower ionic strength (see text).

DISCUSSION

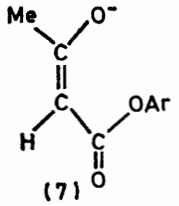
When 2-acetoxycyclohexene-1-carboxylic acid is dissolved in aqueous buffers it is hydrolysed, apparently instantaneously, to the hydroxy-compound, and the only observable reaction is the slow conversion of this enol into the keto-form. Even this reaction is too fast to follow by conventional techniques except between pH 7 and 11. All our data thus concern the ketonisation process, and we can say no more about the hydrolysis of the enol acetate than that it must be extremely fast. This single fact, however, is sufficient to establish the mechanism of the hydrolysis fairly securely.

There is no reason to suppose that intramolecular general base-catalysis of the hydrolysis of the enol acetate (1b) would be very much more efficient than that of the aspirin anion. Yet the half-life of the ester (1b) can be no more than a second or so at 25°, over 10^5 times shorter than that of aspirin.[3] A mechanism involving nucleophilic catalysis and rapid protonation of the anhydride intermediate (5) on carbon is also ruled out because the initial product is not the keto- but the enol form of the acid. An alternative pathway available to the anhydride (5) is the elimination of acetate ion to give the keto-keten (6). This path is clearly much more favourable than it would be in the hydrolysis of aspirin, and there is good reason to suppose that the process in the case of (5) would be very rapid indeed.*



(1b) (5) (6)

Pratt and Bruice [8] have shown that the hydrolysis of acetoacetates by the *E*1cB mechanism is extremely sensitive to the basicity of the leaving group. The slope of their plot of log k_{hyd} against the pK_a of the conjugate acid of the leaving group is −1·29, for the breakdown to keten of the species (7), and we calculate that the rate



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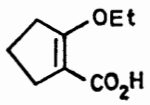


(8)

constant for the elimination of acetate from a corresponding anhydride would be *ca.* $1·5 \times 10^7$ min^{-1} at 30°. The equilibrium constant for the formation of (5) from (1b) will depend on the basicity of the two nucleophilic centres concerned. The pK_a of the conjugate acid of (5) should be no higher than that of the conjugate acid of (7) given by Bruice and Pratt as 8·5.[8] The pK_a of the conjugate acid of (1b) is less certain, but should be little lower than that of the enol ether (8), measured by Fife [9] as 5·65. The logarithm of the equilibrium constant for acetyl transfer between two nucleophilic centres is a linear function of the difference in pK_a, with a slope of 1·7.[10] So the equilibrium constant for the formation of (5) from (1b) could be as high as $1—2 \times 10^{-4}$, giving a calculated rate constant for the disappearance of (1b) by the keten mechanism of *ca.* 10^3 min^{-1}. Our own observations allow us to place a minimum value of 15—20 min^{-1} on this rate constant, so we are satisfied that the keten mechanism can account for the rapid hydrolysis of (1b). This is not true for any of the other likely mechanisms for hydrolysis, which were considered in detail for the hydrolysis of the aspirin anion.[3]

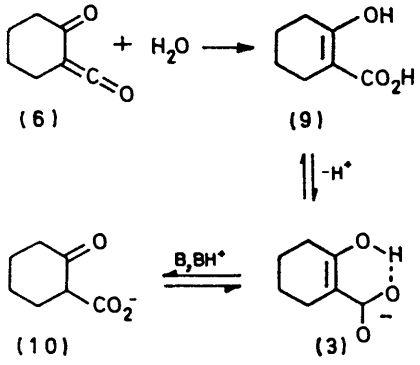
The subsequent hydrolysis of the keto-keten (6) is expected to be another rapid reaction, and to give initially the enol rather than the keto-form of the product because of the relatively slow rate of proton transfer to carbon. Thus it is not unexpected that the first reaction slow enough to measure is the disappearance of the chromophore of the enol (3) as it is converted into

* The rate of formation of (5) is undoubtedly a rapid reaction. D. S. Kemp and T. D. Thibault (*J. Amer. Chem. Soc.*, 1968, **90**, 7154) found a rate constant for formation of the corresponding anhydride from salicyl salicylate of 2·6 min^{-1} at 30°. The acetate ester should be more reactive, and the change from an aromatic to a cyclohexenyl ring probably enhances reactivity also. The *N*-methylmaleamic acid derived from cyclohexene-1,2-dicarboxylic acid is hydrolysed in a reaction involving intramolecular catalysis by the carboxy-group some 400 times faster than *N*-methylphthalamic acid (unpublished work with P. W. Lancaster).

[8] R. F. Pratt and T. C. Bruice, *J. Amer. Chem. Soc.*, 1970, **92**, 5956.
[9] T. H. Fife, *J. Amer. Chem. Soc.*, 1965, **87**, 1084.
[10] W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 1968 **90**, 2622.

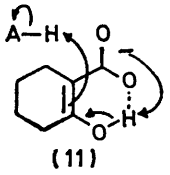
the keto-form (10). This conclusion was confirmed by measuring the rate of ketonisation of authentic enol (3) under the same conditions as were used for the hydrolysis experiments. The enol acid (9) was prepared by hydrogenolysis of its benzyl ester in dioxan, as described in the Experimental section, and a drop of the dioxan solution was dissolved in aqueous buffer. The same u.v. absorption as was observed in the hydrolysis of the enol acetate was observed to disappear at the same rate under given conditions and the reaction was found to be catalysed by buffers with identical second-order rate constants.

The ketonisation of the enol (3) is catalysed by both acidic and basic components of the buffers used. This is expected, since the enolisation of cyclohexanone is subject to both general acid and general base catalysis.[11]



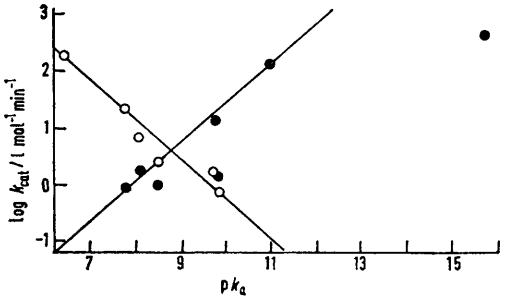
The ketonisation of the enol form of cyclohexanone is a convenient model for the ketonisation of (3), since the electronic effects of the ionised carboxy-group are small. We compare our results (Table 1) with those expected from the data of Lienhard and Wang [11] on the reaction of cyclohexanone. These authors measured rate constants for the general acid and base catalysed enolisation of cyclohexanone. Their data for general acid catalysis are correlated by the Brönsted equation, and so can be extrapolated to give calculated rate constants for other general acids expected to show normal behaviour. Since the equilibrium constant for enol formation from cyclohexanone in water has been accurately measured by Bell and Smith,[12] rate constants for the ketonisation can be calculated.

Our data for the general acid-catalysed ketonisation of the enol (3) follow the Brönsted equation (Figure) with a coefficient $\alpha = 0{\cdot}66$ (least-squares), a little smaller than the figure of 0·74 found by Lienhard and Wang for the enolisation of cyclohexanone at ionic strength 0·25. Extrapolating to $pK_a = 9{\cdot}75$ a Brönsted plot of their data we find a rate constant for general acid catalysis by protonated *NN*-dimethylethanolamine of the enolisation of cyclohexanone of $3{\cdot}3 \times 10^{-9}$ l mol^{-1} min^{-1}, giving a value for ketonisation (using K_e[12] $= 4{\cdot}1 \times 10^{-6}$) of $8{\cdot}1 \times 10^{-4}$ l mol^{-1} min^{-1}. The second-order rate constant for general acid catalysis by the conjugate acid of *NN*-dimethylethanolamine of the ketonisation of (3) is some 2000 times greater than this (Table 1); and because the Brönsted coefficients are similar for the two reactions similar ratios are found for catalysis by other general acids. We consider that this factor represents a rate enhancement caused by intramolecular catalysis.



The carboxylate group of (3) is expected to form a hydrogen bond to the proton of the enolic hydroxy-group, and in these circumstances it would be surprising if intramolecular general base catalysis of the attack of a general acid HA [as in (11)] did not occur.*

Any form of catalysis which facilitates a particular pathway is expected to involve reaching the transition state earlier. In the case of (11), for example, C–H bond formation and H–A bond breaking will be less far advanced in the transition state than they would be in the absence of assistance from the carboxylate group. This would account for the modest reduction in the Brönsted coefficient (0·66) compared with the value (0·74) found for the enolisation of cyclohexanone. [The Brönsted coefficient is necessarily identical for the enolisation and ketonisation of a given system, because the general acid (or base) is involved in the same transition state in both forward and reverse reactions.]



Brönsted plots for general acid (○) and general base catalysis (●) of the ketonisation of 2-hydroxycyclohexene-1-carboxylate (3) (data from Table 1). The large negative deviations for general base catalysis by carbonate and especially hydroxide are not unusual in plots of this sort. No statistical corrections have been made

A similar comparison with the ketonisation of cyclohexanone can be made for general base catalysis also, although the data of Lienhard and Wang [11] are less extensive in this case. They found a value of k_B for catalysis by imidazole of the enolisation of cyclohexanone of $2{\cdot}3 \times 10^{-3}$ l mol^{-1} min^{-1} at 25° and ionic strength 0·25, giving a rate constant for ketonisation of 560. From our

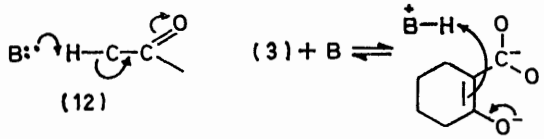
* Fife [9] found a smaller rate enhancement for the hydrolysis of the anion of the ethyl enol ether (8), for which a mechanism of the type shown in (11) is not possible.

[11] G. E. Lienhard and T.-C. Wang, *J. Amer. Chem. Soc.*, 1969, **91**, 1146.

[12] R. P. Bell and P. W. Smith, *J. Chem. Soc.* (*B*), 1966, 241.

Brönsted plot (Figure) a base of this pK_a (7·15) is expected to catalyse the ketonisation of (3) with a rate constant of 0·28, so the reaction of (3) is in this case *slower* than that of cyclohexanone by a factor of 2000. [The Brönsted coefficient β for general base catalysis of the ketonisation of (3) is 0·82, as expected [13] for the enolisation of a ketone of the reactivity [11] of cyclohexanone.]

The mechanism of general base-catalysed ketonisation is defined by being the microscopic reverse of that for the corresponding enolisation, which is generally accepted [14] as (12). The general base-catalysed ketonisation of (3) is therefore expected to involve the reaction of the conjugate base of the enol with the conjugate acid of the general base (13). The rate constant for the reaction



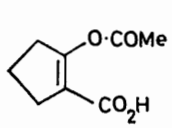
(12)

(3) + B ⇌

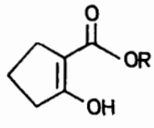
(13)

thus includes the dissociation constant of the enol group. This is expected to be much reduced by the carboxylate group in (3) ⇌ (13), compared with cyclohexanone: the second pK_a of salicylic acid, in which the functional groups have almost the same geometry, is over three pK units higher than that of phenol, because the enol form (monoanion) is stabilised by hydrogen bonding. So the 2000-fold slower ketonisation of (3) by mechanism (13) probably reflects solely the smaller concentration of dianion present. The overall effect of the slower general base-catalysed reaction and the enhanced general acid catalysis rates is to shift the minimum in the pH–rate profile to higher pH (8—9) compared with the cyclohexanone reaction. The observed ketonisation rate in this region, extrapolated to zero buffer concentration, is the sum of the hydroxide- and hydroxonium-catalysed rates: no water-catalysed reaction could be detected.

2-Acetoxycyclopentenecarboxylic Acid.—The hydrolysis of the cyclopentene analogue of (3), (14), presumably involves the same mechanism. In which case both steps of the reaction are too fast to be measured by conventional techniques. This is predictable. The hydrolysis step could be slower than that of (3) and still be too fast to be measured. The ketonisation of the enol acid (15; R = H), which is the initial product of hydrolysis, is expected to be substantially faster than that of the six-membered ring compound. The equilibrium constant for the formation of the enol (15; R = Et) from ethyl 2-oxocyclopentane-1-carboxylate in water is about one fifth that for the cyclohexane derivative (0·4 [15] and 2·04% [6] of enol at equilibrium, respectively); and the rate constants for the general base catalysed enolisation are a few hundred times greater [16] for the five-membered cyclic β-keto-ester. So the ketonisation of (15; R = Et) must be faster by some three orders of magnitude than



(14)

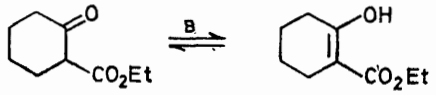


(15)

that of (16) (see later). The experimental observation is that the ketonisation of the anion of (15; R = H) is at least 20 times faster than that of the cyclohexene derivative (3) at pH *ca.* 8.

Ketonisation of Ethyl 2-Hydroxycyclohexenecarboxylate.—The usual approach to the study of a keto–enol tautomerism is to measure rates of enolisation, and the equilibrium constant if possible. The reaction we have measured is unusual in that the ketonisation process is readily measured but study of the enolisation [(10) ⟶ (3), above] is likely to be difficult because of the ease of decarboxylation of the β-keto-acid. To place this work in the context of previous studies on keto–enol tautomerism we have measured the ketonisation for a system which has been studied in detail in the reverse direction.

The enolisation of ethyl 2-oxocyclohexane-1-carboxylate (16) has been the subject of many investigations, the most accurate and recent of which are those of Bell and his co-workers. Bell and Goldsmith [7] measured rate constants for general base catalysis of enolisation by carboxylate ions, and found a Brönsted coefficient β of



(16) (4)

0·67. Bell and Vogelsong [6] later measured the equilibrium constant for the reaction (16) ⇌ (4), and found a value of 2·08 × 10^{-2} in water at 25° and ionic strength 0·08. From these data rate constants for general base catalysis of ketonisation (4) ⟶ (16) can be calculated for the carboxylate anions used.

The ketonisation is very simply measured. Although the concentration of enol is very low in water, it is the predominant form in organic solvents.[5,17] So we prepared a solution of the ester in dioxan, allowed the system to come to equilibrium, and then added a drop of this dioxan solution to a large volume of aqueous buffer. The disappearance of the chromophore associated with the enol form [$\lambda_{max.}$ 258 nm, $\varepsilon_{max.}$ 10,850 (in ethanol [5])] is readily followed spectrophotometrically.

The ketonisation, like the reverse reaction measured by

[13] R. P. Bell, 'The Proton in Chemistry,' Methuen, London, 1959, pp. 171—172.
[14] W. P. Jencks, 'Catalysis in Chemistry and Enzymology,' McGraw-Hill, New York, 1969, p. 229.
[15] A. S. N. Murthy, A. Balasubramanian, C. N. R. Rao, and T. R. Kasturi, *Canad. J. Chem.*, 1962, **40**, 2267.
[16] R. P. Bell, R. D. Smith, and L. A. Woodward, *Proc. Roy. Soc.*, 1947, *A*, **192**, 479.
[17] P B. Russell, *Chem. and Ind.*, 1956, 326.

Bell and Goldsmith,[7] is subject to general base catalysis only. The data are correlated by the Brönsted equation, with a coefficient $\beta = 0{\cdot}63 \pm 0{\cdot}03$ within experimental error of Bell's value for enolisation (0·67). And the rate constants for ketonisation are close to those calculated from the data of Bell and his co-workers at lower ionic strength (Table 2).

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