Strain Effects in Acyl Transfer Reactions. Part III.[1] Hydroxide and Buffer-catalysed Hydrolysis of Small and Medium Ring Lactones

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Second-order rate constants for the alkaline hydrolyses of lactones and esters at 319 K decrease in the order methyl formate > δ-valerolactone > β-propiolactone > γ-butyrolactone, ε-caprolactone > methyl acetate. The enhanced reactivity of the δ-lactone is due to a reduction in enthalpy of activation but the β-lactone derives its extra reactivity solely from a favourable increase in the entropy of activation for $B_{AC}2$ hydrolysis. Only the β-lactone exhibits detectable activity towards either pyridine or 1-methylimidazole in aqueous solution. For both amines, nucleophilic substitution with alkyl oxygen fission proceeds faster than attack at the acyl centre and results in the formation of a betaine as the major product. No reactivity could be detected for either amine with methyl formate or δ-valerolactone. It thus appears that conformational orientation factors are capable of accelerating the reaction of the ester group with strong nucleophiles whereas angle-strain effects become more important for weaker ones.

RING-OPENING reactions of lactones offer a unique approach to the investigation of conformational and strain influences on the reactivity of the ester linkage. Of several investigations of lactone hydrolysis,[2-8] that of Huisgen and Ott [6] has provided the broadest survey in progressing from five- to sixteen-membered rings. These authors concluded that the marked enhancement in reactivity of small-ring lactones is a consequence of the compulsory constraint of their ester group in the *cis*-conformation. Bruice has advanced an analogous argument based on the similarity in rates of hydrolysis of γ- and δ-lactones with that of *p*-nitrophenyl acetate.[9] Indeed, he has suggested that part of the catalytic activity of chymotrypsin could result from the adoption of the *cis*-conformation by the ester group in the corresponding acyl–enzyme intermediate.

On the other hand, observations on 2,2,2-trifluoroethyl formate suggest that it, too, exists in the *cis*-conformation in the ground state but that this property does not give it any special reactivity in hydrolysis.[10]

While the alkaline hydrolysis of lactones proceeds by acyl–oxygen fission and involves rate-determining attack of hydroxide, as established for γ-butyrolactone and alkyl esters by oxygen isotope exchange,[11,12] the ring strain in β-propiolactone endows it with an unusual reactivity towards water [13] and several tertiary amines associated with the $B_{AL}2$ mechanism. Thus, pyridine and many other tertiary amines interact with β-propiolactone in water to give betaines.[14] Moreover, this type of reaction is also characteristic of guanosine [15] and there is strong evidence that the *N*-7-alkylation of guanine residues in deoxyribonucleic acid by β-propiolactone is the molecular basis of the chemical carcinogenicity of the latter compound.[16]

It is apparent that proper evaluation of conformational and strain effects in the reactivity of the ester linkage necessitates a detailed investigation of the nucleophilic reactions of lactones under standard conditions. This paper reports studies on the alkaline hydrolysis of lactones having four- to seven-membered rings and on their additional reactions with two tertiary amines in aqueous solution.

EXPERIMENTAL

Materials.—Methyl acetate, methyl formate, ethyl acetate, β-propiolactone, γ-butyrolactone, and ε-caprolactone were commercial products purified by distillation immediately before use, purity being routinely checked by g.l.c. δ-Valerolactone, prepared from pentane-1,5-diol,[17] had b.p. 317 K at 0·1 mmHg. Pyridine and 1-methylimidazole were purified by standard methods and distilled under nitrogen prior to use. Glass-distilled water was used throughout and standard solutions were prepared using AnalaR grade potassium chloride and Convol potassium hydroxide solution (Hopkin and Williams).

Apparatus.—A Radiometer PHM 26 in conjunction with a G2222B glass electrode was used for measurement of pH and coupled to a TTT11 titrator and ABU12 autoburette for pH-stat titrations in a thermostatted vessel (25 ml). This was provided with a mechanical stirrer, K401 calomel electrode, and G202C glass electrode and flushed with water-saturated, carbon dioxide-free nitrogen. Temperature control was maintained by circulation of water from a Haake model Fe thermostat (±0·05 K). N.m.r. spectra were recorded at 100 MHz using a Varian

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HA100 and i.r. spectra were obtained with a Perkin-Elmer 157 G for Nujol mulls.

Kinetic Measurements.—All reactions were run in water at unit ionic strength (KCl) under pseudo-first order conditions in the presence of 10^{-5}M-EDTA to avoid effects from trace metal ions. They were initiated by the injection of substrate, dissolved in a small volume of dioxan, into 20 ml of the appropriate reaction solution to give an initial concentration of $2—4 \times 10^{-3}$M. In certain reactions involving larger concentrations of tertiary amine, the substrate concentration was increased up to ten-fold. The rate of reaction was followed to completion by the addition of 0·1N-potassium hydroxide solution at constant pH.

Kinetic data were usually analysed for at least three half-lives and pseudo-first-order rate constants, k_{obs}, obtained in the usual way. All reactions displayed good first-order kinetic behaviour. Hydroxide concentrations were calculated from the observed pH and the dissociation product for water at the appropriate temperature.

Standard solutions of pyridine and of 1-methylimidazole were prepared by dilution of freshly-distilled amine with 4M-potassium chloride solution and distilled water to unit ionic strength and standardised by titration with 1N-hydrochloric acid.

Product Analysis.—The alkaline hydrolyses of β-, γ-, δ-, and ε-lactones to the corresponding hydroxy-carboxylic acids are well documented.[2-6] In kinetic runs, the consumption of alkali was that expected for complete conversion of lactone into hydroxy-acid. The reaction between pyridine and β-propiolactone has been shown to give 1-(2-carboxyethyl)pyridinium hydroxide, inner salt, in some 90% yield in aqueous solution.[14]

1-(2-*Carboxyethyl*)-3-*methylimidazolium Hydroxide, Inner Salt.*—β-Propiolactone (oxetan-2-one) (3·0 g) was added dropwise to a well-stirred solution of 1-methylimidazole (5 g) in distilled water at room temperature. After 30 min the solution was evaporated *in vacuo* and the oily residue repeatedly evaporated with absolute ethanol to remove water. The resulting oil was triturated with ether and with ethyl acetate to give a solid (5·5 g) which was recrystallised from dry acetonitrile to give the *product* (4·5 g, 70%) as deliquescent crystals, m.p. 88—89·5° (Found: C, 53·8; H, 6·4; N, 18·1. $C_7H_{10}N_2O_2$ requires C, 54·5; H, 6·5; N, 18·2%), τ (D_2O) 1·14 (s, $\overset{+}{N}CH$), 2·38 and 2·44 (AB, CH=CH, *J* 1·5 Hz), 5·46 (t, $\overset{+}{N}CH_2$, *J* 6·5 Hz), 5·98 (s, $\overset{+}{N}CH_3$), and 7·14 (t, $CH_2CO_2^-$, *J* 6·5 Hz) $\nu_{max.}$ 1595br,s cm^{-1} (CO_2^-), $\lambda_{max.}$ (H_2O) 212 nm (ε 4 × 10^3).

In kinetic runs involving aqueous pyridine or 1-methylimidazole solutions with β-propiolactone, the yield of hydrolysis product was calculated from the titre of akali required for its neutralisation and the remainder of the product was deemed to be the betaine since t.l.c. examination of the product mixture [18] did not reveal the formation of any acrylic acid.

RESULTS

The four lactones and three esters were hydrolysed at 319 K in potassium hydroxide solutions between pH 7·5 and 12 at unit ionic strength. In all cases the pseudo-first-order rate constants proved to be directly dependent on $[OH^-]$ and thus obey the rate equation (1). No significant value of k_1 could be measured for any substrate

$$\text{Rate} = k_1 + k_2[OH^-]\ s^{-1} \quad (1)$$

other than β-propiolactone. Consequently, the second-order rate constants were usually computed as the average quotients of the apparent first-order rate constant and the hydroxide ion concentration determined at several different pH values. In the case of β-propiolactone k_1 and k_2 were computed by linear regression analysis of data collected over the pH range 7—11 using equation (1). These computed rate constants (Table 1) were used to calculate the theoretical curves for lactone and ester hydrolysis (Figure 1).

TABLE 1

Rate data for the hydroxide-catalysed hydrolysis of lactones and esters at 319 K

Substrate	pH Range	No. of runs	k_2/l mol^{-1} s^{-1}
Methyl formate	8·0—9·9	6	149 ± 14
Methyl acetate	10·1—11·9	5	0·93 ± 0·11
Ethyl acetate	10·75—11·9	5	0·39 ± 0·06
β-Propiolactone *	7·1—11·3	12	8·76 ± 0·08
γ-Butyrolactone	8·6—11·5	10	4·03 ± 0·29
δ-Valerolactone	7·5—9·5	7	59·0 ± 3·3
ε-Caprolactone	8·8—10·9	7	3·17 ± 0·19

* $k_1 = 1·39 \pm 0·07 \times 10^{-3}$ s^{-1}.

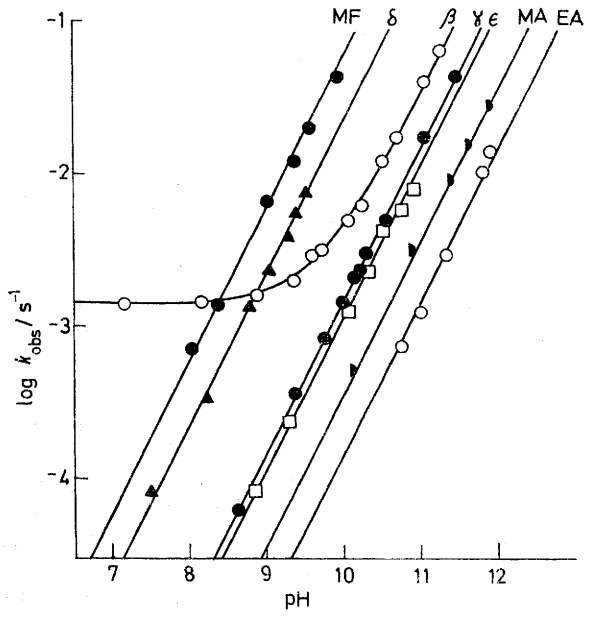

FIGURE 1 Rate of hydrolysis of esters and lactones as a function of pH. Theoretical curves calculated from equation (1) and data of Table 1: MF, methyl formate; MA, methyl acetate; EA, ethyl acetate

In the case of β-propiolactone and δ-valerolactone, independent determinations of the observed rate constants for hydrolysis were made at several pH values using the hydroxamic acid assay.[19] This was achieved by the use of auxiliary buffers to maintain constancy of pH and, in general, corrections were made for minor buffer catalysis observed with t-butylamine and carbonate buffers by extrapolation to zero buffer concentration. More signi-

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ficant levels of catalysis were noted for the hydrolysis of δ-valerolactone in tris(hydroxymethyl)aminomethane solutions. In all cases, the corrected, apparent first-order rate constants showed satisfactory agreement with, but lower accuracy than, those derived by pH-stat titration.

For each of the substrates, alkaline hydrolysis rates were measured at several temperatures in the range 293—319 K at the same hydroxide concentration. These data were used to compute the activation parameters for alkaline hydrolysis at 319 K (Table 2). In addition, the activation parameters for alkaline hydrolysis of β-propiolactone and methyl formate were obtained from the computed values of k_2 obtained at 298 K and 319 K and found to be in satisfactory agreement.

The rate of hydrolysis of β-propiolactone was measured in the presence of pyridine or of 1-methylimidazole using the pH-stat technique at 298 K. The reactions all displayed good pseudo-first-order kinetic behaviour and the

TABLE 2

Activation parameters for the alkaline hydrolysis of esters and lactones at 319 K

Substrate	$\Delta G‡$/ kJ mol^{-1}	$\Delta H‡$/ kJ mol^{-1}	$\Delta S‡$/ J K^{-1} mol^{-1}
Methyl formate	65·1 ± 0·3	38·7 ± 2·5	−83 ± 8
Methyl acetate	78·5 ± 0·5	46·4 ± 1·7	−101 ± 7
Ethyl acetate	80·8 ± 0·5	45·1 [a]	−112 [a]
β-Propiolactone	72·56 ± 0·03	50·1 ± 0·9	−70·5 ± 3·0
γ-Butyrolactone	74·6 ± 0·2	44·6 ± 1·3	−94 ± 5
δ-Valerolactone	67·50 ± 0·15	30·1 ± 1·7	−117 ± 6
ε-Caprolactone	75·24 ± 0·17	38·9 ± 2·1	−114 ± 7
Isopropyl acetate [b]	84·9	49·3	−128

[a] Ref. 48 in ref. 11*b*. [b] Ref. 81 in ref. 11*b*.

observed rate constants increased with increasing concentration of tertiary amine as described by equation (2).

$$\text{Rate} = k_1 + k_2[OH^-] + (k_3 + k_4)[\text{Amine}]\ s^{-1} \quad (2)$$

Values of k_{cat}, *i.e.* $(k_3 + k_4)$, were computed by linear regression analysis of the data (Table 3) and used to determine the theoretical slopes for lactone hydrolysis (Figure 2).

For both amines, the amount of alkali required to maintain the pH of the reaction at a constant value throughout hydrolysis of the β-lactone fell with increasing amine concentration. The decrease in the mole fraction of alkali required was used to evaluate two component rate constants, k_3 and k_4, of equation (2) using the assumption that the former corresponded to a reaction producing an acidic, and therefore titratable, product while the latter related to a process giving a neutral, non-titratable product: pyridine, $k_3 = 1{\cdot}035 \pm 0{\cdot}3 \times 10^{-3}$ l mol^{-1} s^{-1}, $k_4 = 1{\cdot}18 \pm 0{\cdot}05 \times 10^{-2}$ l mol^{-1} s^{-1}; 1-methylimidazole, $k_3 = 1{\cdot}2 \pm 0{\cdot}1 \times 10^{-3}$, $k_4 = 3{\cdot}6 \pm 0{\cdot}3 \times 10^{-3}$.

Hydrolyses of methyl formate, δ-valerolactone, and γ-butyrolactone were severally examined in aqueous solutions of pyridine, 1-methylimidazole, and imidazole. In no case was any significant enhancement of reaction rate observed. On the contrary, there was usually a rate retardation which was proportional to the concentration of amine, as illustrated for methyl formate hydrolysis in pyridine solutions (Figure 2).

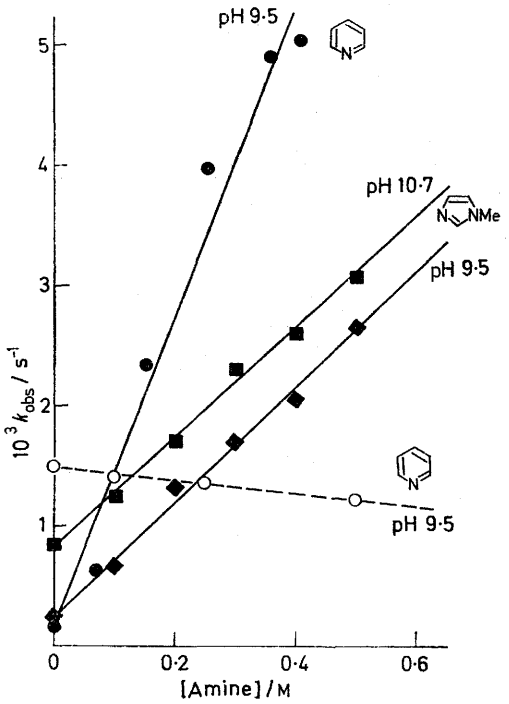


FIGURE 2 Rate constants for the reaction of β-propiolactone (solid symbols) and methyl formate (open symbols) as a function of concentration of 1-methylimidazole or pyridine. Theoretical curves (solid lines) calculated from data of Table 3 and equation (2)

TABLE 3

Rate data for reactions involving imidazole, 1-methylimidazole, and pyridine at 298 K

Substrate	Amine	pH	No. of runs	[Amine]/M	$(k_3 + k_4)$/l mol^{-1} s^{-1}
β-Propiolactone	1-MeIm	9·51	6	0—0·5	$5{\cdot}0 \pm 0{\cdot}1 \times 10^{-3}$
β-Propiolactone	1-MeIm	10·70	6	0—0·5	$4{\cdot}6 \pm 0{\cdot}2 \times 10^{-3}$
β-Propiolactone	Pyridine	9·50	7	0—0·5	$1{\cdot}29 \pm 0{\cdot}07 \times 10^{-2}$
Methyl formate	Pyridine	9·50	4	0—0·5	
δ-Valerolactone	Imidazole	8·70	4	0—0·5	

DISCUSSION

Alkaline Hydrolysis.—All the alkaline hydrolyses investigated are clearly unimolecular in hydroxide except in the case of β-propiolactone which exhibits the well known [13] water-catalysed reaction below pH 9 (Figure 1). The volatility of methyl formate impeded an investigation of its hydrolysis by the pH-stat method under neutral conditions though data obtained at 298 K below pH 8 suggested that the rate of the water-catalysed reaction was not much below the detectable limit.

The lactones show decreasing reactivity towards

hydroxide in the order δ-valerolactone, β-propiolactone, γ-butyrolactone, and ε-caprolactone (Table 1). All are more reactive than ethyl and methyl acetates, less reactive than methyl formate. The activation parameters for these hydrolyses (Table 2) show that six- and seven-membered lactones owe their enhanced reactivity to a decrease in the enthalpy of activation relative to that for the three acetates but the five- and, more markedly, four-membered lactones derive their additional reactivity from a positive increase in their entropy of activation. Surprisingly, β-propiolactone exhibits the largest enthalpy of activation of any of the carboxylate compounds investigated. Without further consideration of the possible molecular basis for the variations in these parameters, they support the conclusion that the enhancements of reactivity of β-propiolactone and δ-valerolactone are separate manifestations of strain upon the electrophilic reactivity of the ester linkage.

The strain energy released in the transition state must be associated with rate-determining addition of hydroxide to the carbonyl group [11,12] and is thus unlikely to include much contribution from the relief of bond tension as a result of ring-opening processes. In this context it is to be noted that the relative rate of hydrolysis of the strained four-membered ring compound relative to the acyclic case is an order of magnitude less for lactone ester than for lactam amide.[20] It must therefore be assumed that strain relaxation largely results from the combination of three effects, each associated with addition of the nucleophile to the carbonyl group and the attendant change from trigonal to tetrahedral carbon. These are the change in strain resulting from bending at the intracyclic C-1 angle, the change in torsional strain effects, and the change in energy resulting from the loss of the delocalised π-bond system.

The first two of these effects feature in addition reactions of cyclic ketones and may thus be illuminated by the comparison of lactone hydrolysis with borohydride reduction of cyclanones [21] (Figure 3). The juxtaposition of the free energies of activation for these two processes reveals three significant facts. First, as gauged by the comparison of the five-, six-, and seven-membered ring compounds, there is a close similarity not only in the relative but also in the absolute influence of ring strain on the rates of these two nucleophilic processes. Secondly, the acyclic compounds share a comparable stability relative to the above ring compounds which indicates that the energy difference between the *cis*- and *trans*-conformations for esters, variously estimated [6,22,23] between 10 and 16 kJ mol^{-1}, has but a much reduced influence in stabilising acyclic esters relative to 'strainless' lactones. Thirdly, the β-lactone is seen to be less reactive than cyclobutanone relative to the other small-ring compounds by an order of magnitude and the associated energy difference, some 6 kJ mol^{-1}, arises entirely from the relative entropies of activation.[21]

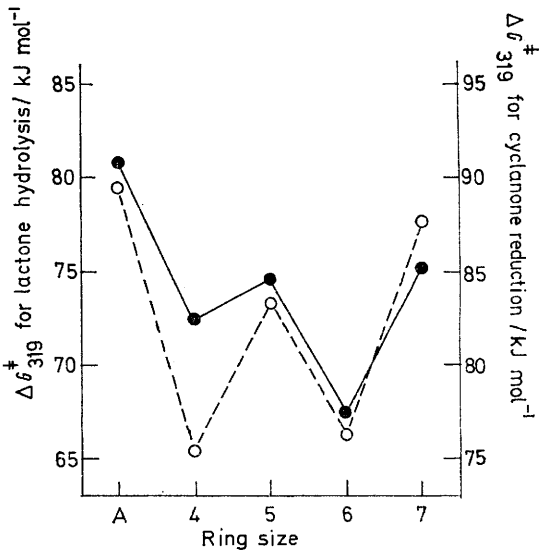
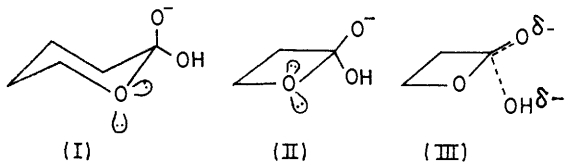


FIGURE 3 Comparison of the free energies of activation for lactone hydrolysis (closed symbols) and cyclanone reduction [21] (open symbols) as a function of ring size. (The respective acyclic compounds are ethyl acetate and di-n-hexyl ketone)

Allinger has elucidated the nature of ring strain in cyclobutanone and cyclohexanone by means of force field calculations.[24] These suggest that serious bending at the trigonal carbon in the former raises its strain energy relative to cyclobutane in spite of a fall in torsional energy resulting from the substitution of a methylene for a carbonyl group. In contrast, the strain in cyclohexanone essentially relates to the unfavourable conformation imposed by the ring on the carbonyl group. Application of these factors to the two most reactive lactones suggests that the tetrahedral addition intermediate (I) in hydrolysis of δ-valerolactone will benefit from favourable *gauche*-interactions



and thus relieve conformational strain. However, the intermediate (II) for the β-lactone will suffer from synperiplanar interactions of electron pairs and polar bonds [25] and show an increase in conformational strain which must be more than offset by relief of angle strain at the carbonyl ring position.

These considerations lead to the expectation of a late transition state for hydroxide attack on δ-valero-

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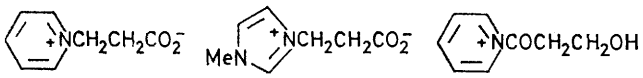
lactone with geometry approaching that of (I) but an earlier transition state for β-propiolactone (III) in which relief of angle strain is limited by avoidance of energetically unfavourable non-bonded interactions which must increase in progression from (III) to (II). It seems reasonable that these latter will be larger for nucleophilic addition of hydroxide and smaller for hydride attack in accord with the observed pattern of reactivity.

Methylimidazole and Pyridine Reactions.—Pyridine and 1-methylimidazole interact strongly with β-propiolactone but show no reactivity towards methyl formate or the five- and six-membered lactones, though detection of such processes is limited by the retardation of the hydrolysis of these three substrates caused by increasing concentration of either amine (Figure 2) which presumably parallels the influence of dioxan on the alkaline hydrolysis of lactams.[1] With β-propiolactone, the reactions of these heterocyclic amines are unimolecular in amine * and independent of hydroxide concentration in the pH region investigated (Figure 2). They must therefore correspond to uncatalysed nucleophilic processes or represent general base catalysis of neutral lactone hydrolysis.



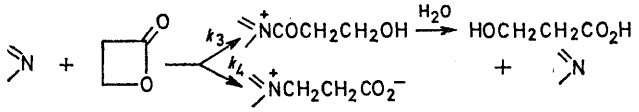
(IV) (V) (VI)

The mole fraction of alkali needed to titrate the acidic product of hydrolysis falls rapidly as the concentration of amine is increased at constant pH. This provides kinetic evidence for the formation of neutral, non-titratable products which is substantiated by isolation and characterisation of the betaines (IV) and (V). While these comprise the major part of the products resulting from the reactions of β-propiolactone with pyridine and 1-methylimidazole respectively, the difference between the rate calculated for their formation, k_4[amine], and the observed rate of disappearance of β-lactone exceeds the rate measured for lactone hydrolysis at the same pH in the absence of the amine. This rate difference is proportional to the concentration of amine and thus establishes a second, minor reaction pathway (designated k_3), unimolecular in amine but leading to an acidic, titratable product.

Four possible courses for the pathway must be considered: a bimolecular β-elimination, general base catalysis involving either $B_{AL}2$ or $B_{AC}2$ mechanisms, and nucleophilic catalysis of hydrolysis. The first of these would generate acrylic acid while the remainder would produce 3-hydroxypropionic acid. Only the last of them would result in the formation of a transient acylpyridinium or acylimidazolium species.

Three facts attest to the operation of nucleophilic catalysis. First, no acrylic acid was detectable in reaction products by means of t.l.c.[18] Secondly, many amines are known to interact with β-propiolactone giving the corresponding 3-hydroxypropionamides.[14] Lastly, the reaction of β-propiolactone with imidazole buffers, deemed by Bruice to be nucleophilic in character,[18] reveals the transient formation of an acylimidazole intermediate shown by the appearance and decay of a characteristic absorption at 245 nm.[26] This phenomenon could not be observed in the reaction between β-propiolactone and pyridine, which is only to be expected since the acetylpyridinium cation is hydrolysed at a rate [27] several orders of magnitude greater than that calculated here for the formation of the 1-(3-hydroxypropionyl)pyridinium ion (VI). Thus it can be seen that both tertiary amines react with β-propiolactone in concerted processes which are formulated in the Scheme. It must, however, be noted that the possibility is not excluded of the additional operation of a general base-catalysed process though the appropriate rate constants would be of the order of 10^{-4} l mol^{-1} s^{-1}.

The existence of these alternative reactions and the magnitudes of the rate constants k_3 and k_4 focus attention upon two important aspects of the influence of strain on reactions of the ester group. The fact that nucleophilic catalysis is seen for hydrolysis only of the β-lactone shows that the reactivity of the ester linkage can be enhanced by manipulation of conformational factors, as in the case of δ-valerolactone, and that this is effective for strong nucleophiles such as hydroxide but does not promote either nucleophilic or general catalysis of hydrolysis by weaker bases. On the other



SCHEME

hand, the angle strain present in β-propiolactone is seen to be significantly more effective in assisting the reactions of weaker nucleophiles at the acyl centre as well as promoting substitution at the methylene carbon. It seems reasonable to infer that this type of strain is likely to be of better use in enzymic catalysis of acyl transfer reactions, which characteristically rely on covalent catalysis from groups of only moderate nucleophilicity,[28] than is the control of conformational strain, at least with respect to reaction steps associated with the ester group.

One final problem is raised by consideration of the Brønsted relationship for the reaction of β-propiolactone with water, pyridine, 1-methylimidazole, and hydroxide. Alkyl–oxygen fission involving the first three of these nucleophiles is characterised by a Brønsted

* The adoption of pH-stat monitoring of reaction rates precludes a search for possible general acid catalysis by pyridinium or 1-methylimidazolium cations because of their buffering effects.

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coefficient β of *ca.* 0·9. The well known negative deviation of data for hydroxide attack on the ester carbonyl group from normal relationships [28,29] makes difficult the evaluation of the corresponding coefficient for β-propiolactone on the present data alone, though it appears likely to lie in the range $0{\cdot}8 < \beta < 1{\cdot}1$. Since the outcome of reaction between a given amine and β-propiolactone, at present unpredictable,[11b,14] is linked to the precise relation of the two Brønsted curves for the $B_{AL}2$ and $B_{AC}2$ processes their accurate determination is a matter of some value.

The present data can be coupled with a knowledge of the reactions of strong amines with β-lactones [14] to suggest that the relationship is not simple but may involve a non-linear correlation in the response of the strained substrate to changing demand of the nucleophile as appears likely in the case of certain β-lactams.[1] Further investigation of this problem is in progress.

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