Mechanism of Alkaline Hydrolysis of Lactones: Dipolar Aprotic *versus* Protic Solvent Effects as a Diagnostic Tool

By **M. Balakrishnan, G. Venkoba Rao,** and **N. Venkatasubramanian,*** Department of Chemistry, Vivekananda College, Madras 600004, India

Rate data for alkaline hydrolysis of γ-butyrolactone, γ-valerolactone, phthalide, and 3-phenylphthalide and their open chain analogues, ethyl acetate, isopropyl acetate, methyl benzoate, and benzyl benzoate respectively have been evaluated in the mixed solvents dimethyl sulphoxide (DMSO)–water, ethanol–water, and acetone–water. The lactones are hydrolysed faster than the open chain esters in all the solvent systems, and the rate enhancements are higher in aqueous ethanol than in aqueous DMSO or aqueous acetone. This shows the minor importance of the electrostatic repulsion between the OH^- ion and the ' lone pair dipole ' of oxygen, the absence of which in the case of lactones was considered to cause their higher reactivity over open chain esters in $B_{AC}2$ reactions.

CONSIDERABLE attention has been focused on the mechanism of hydrolysis of lactones under near neutral and acidic conditions.[1] Although a few papers have appeared on the alkaline hydrolysis of lactones,[2-5] the mechanism has not been unequivocally settled. Further, there is very little recorded work on the differential

---

[1] C. K. Ingold, ' Structure and Mechanism in Organic Chemstry,' Cornell University Press, New York, 1969.

[2] R. Huisgen and M. Ott, *Tetrahedron*, 1959, **6**, 253.

[3] H. K. Hall, M. K. Brandt, and R. M. Mason, *J. Amer. Chem. Soc.*, 1958, **80**, 6420.

[4] C. M. Stevens and D. S. Tarbell, *J. Org. Chem.*, 1954, **19**, 1996.

[5] M. L. Bender, H. Matsui, R. J. Thomas, and S. W. Tabey, *J. Amer. Chem. Soc.*, 1961, **83**, 4193.

effects of solvents on the alkaline hydrolysis of lactones. The present work was undertaken with these ends in view, and kinetic data for alkaline hydrolyses of some aliphatic and aromatic lactones and their open chain analogues in aqueous dimethyl sulphoxide (DMSO), aqueous ethanol, and in a few cases in aqueous acetone are now reported.

RESULTS AND DISCUSSION

The rate data for the saponification of the various lactones and esters studied are collected in Tables 1—3.

TABLE 1

Alkaline hydrolysis of lactones and their open chain analogues in aqueous DMSO at 30 °C

	$10k$/l mol^{-1} s^{-1}		
Compound	60% DMSO *	70% DMSO *	80% DMSO *
γ-Butyrolactone	19·6	23·6	45·2
γ-Valerolactone	8·19	10·6	14·5
Phthalide	5·11	6·60	12·2
Ethyl acetate	2·74	3·25	4·11
Isopropyl acetate	0·411	0·480	0·653
Methyl benzoate	1·07	1·37	2·61

* v/v.

TABLE 2

Alkaline hydrolysis of lactones and their open chain analogues in aqueous EtOH at 30 °C

	10^2k/l mol^{-1} s^{-1}		
Compound	60% EtOH *	70% EtOH *	80% EtOH *
γ-Butyrolactone	40·7	31·7	22·3
γ-Valerolactone	20·6	19·7	16·0
Phthalide	10·0	7·10	5·88
3-Phenylphthalide			7·46
3-*p*-Tolylphthalide			6·96
3-(4-Methoxyphenyl)-phthalide			6·72
Ethyl acetate	2·71	2·11	1·51
Isopopryl acetate	0·797	0·608	0·537
Methyl benzoate	0·596	0·383	0·238
Benzyl benzoate			0·275

* v/v.

TABLE 3

Alkaline hydrolysis of lactones and their open chain analogues in aqueous acetone at 30 °C

	10^2k/l mol^{-1} s^{-1}	
Compound	70% Acetone *	80% Acetone *
γ-Butyrolactone	68·1	73·9
Phthalide	10·7	12·3
3-Phenylphthalide		17·1
3-*p*-Tolylphthalide		13·4
3-(4-Methoxyphenyl)phthalide		8·29
Ethyl acetate	5·98	5·68
Methyl benzoate	1·42	1·56
Benzyl benzoate		1·30

* v/v.

Tables 4 and 5 compare the data for these hydrolyses. The following features are apparent.

(i) Lactones are hydrolysed faster than their corresponding open chain analogues. Similar observations have been made earlier.[3-5]

(ii) While these rate enhancements are high in aqueous ethanol (as represented by $k_{\text{lactone}}/k_{\text{open chain ester}}$ values in Table 5), in aqueous DMSO and aqueous acetone they are much smaller.

(iii) The rate of hydrolysis for each ester is larger in aqueous DMSO compared to aqueous ethanol. The lactones, however, are much less sensitive to rate accelerations in DMSO compared to their open chain analogues [as represented by their lower k_s values (Table 4)].

TABLE 4

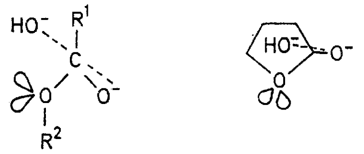
k_s ($=k_{\text{DMSO}}/k_{\text{EtOH}}$) and k_r ($=k_{\text{acetone}}/k_{\text{EtOH}}$) values at 30 °C *

Compound	k_s	k_r
γ-Butyrolactone	7·5	2·1
γ-Valerolactone	5·4	
Phthalide	9·4	1·5
3-Phenylphthalide		2·3
Ethyl acetate	15·4	2·8
Isopropyl acetate	8·0	
Methyl benzoate	36	3·7
Benzyl benzoate		4·7

* In aqueous solvent mixtures containing 70% (v/v) of the organic solvent.

(iv) The trend of reactivities in aqueous acetone parallels that in aqueous DMSO, both being aprotic solvents, but the influence is less pronounced in aqueous acetone.

The enhanced reactivity of lactones over the corresponding acyclic esters was attributed to the absence of repulsion between the attacking OH$^-$ ion and ' lone pair dipole ' on the cyclic oxygen atom because of the rear-side attack of the hydroxide ion on the carbonyl bond [3] which is not possible in the case of the corresponding open chain esters (Scheme). Bender disagreed with the mode of attack of the OH$^-$ ion in the above postulate and favoured a perpendicular attack by the OH$^-$ ion. According to him, the reactivity of lactones could still be explained by invoking a difference in electrostatic repulsion of the lone pair atom dipole of oxygen in the lactone and open chain ester.[6] Further studies on these hydrolyses also could not exclude the possibility of this repulsion.[5,7]



SCHEME

The solvent effects in the present work can be used to test the foregoing rear-side attack hypothesis. It is well established that the OH$^-$ ion is poorly solvated in aqueous DMSO and consequently very active in this solvent.[8] So, notwithstanding the difference in transition state solvation of the two reactions, the repulsion between the ' lone pair dipole ' on the oxygen and this poorly solvated hydroxide ion could be expected to be greater in aqueous DMSO, leading to a considerable

---

[6] M. L. Bender, *Chem. Rev.*, 1960, **60**, 59.

[7] M. L. Bender, personal communication.

[8] A. J. Parker, *Chem. Rev.*, 1969, **69**, 1.

diminution in the reactivity of the open chain esters over that of the corresponding lactones. In other words, the ratio $k_{\text{lactone}}/k_{\text{ester}}$ should have a larger value in aqueous DMSO compared to that in aqueous ethanol. However, exactly the opposite is observed (Table 5). These observations indicate that such a repulsion is of minor consequence as a factor in lactone *versus* open chain ester hydrolysis. Interestingly, these rate ratios are nearly invariant for various compositions within a solvent system. The appreciable lowering of these relative rates for the pairs C and D (Table 5) on transfer from aqueous ethanol to aqueous acetone is also compatible with the above reasoning. No such desolvated hydroxide ions are known to exist in aqueous acetone and if the said electrostatic repulsion were significant, such large differences in these rate ratios in these two solvent systems must be absent.

TABLE 5

$k_{\text{lactone}}/k_{\text{open chain ester}}$ Values for the various pairs * at 30 °C

Solvent (v/v)	A	B	C	D
60% DMSO	7	20	7	
70% DMSO	7	22	5	
80% DMSO	11	22	6	
60% EtOH	15	26	17	
70% EtOH	15	32	19	
80% EtOH	15	30	26	27
70% Acetone	11		7·5	
80% Acetone	13		8·0	5

* A = γ-butyrolactone and ethyl acetate; B = γ-valerolactone and isopropyl acetate; C = Phthalide and methyl benzoate; D = 3-Phenyl phthalide and benzyl benzoate.

To lend further support to the above mechanistic conclusions, it is pertinent to compare with the present systems, the alkaline hydrolysis of dicarboxylic esters in these solvent systems [9,10] where in the second hydrolytic step suffers an electrostatic repulsion between the half ester anion and the hydroxide ion.[9] In agreement with this situation, the $k_{\text{I}}/k_{\text{II}}$ values (k_{I} and k_{II} being the rate constants for the first and second step respectively of the saponification of the dicarboxylic ester) are larger in aqueous DMSO compared to aqueous ethanol, are not invariant for varying compositions within a solvent system, and do not show such large disparities in magnitude between aqueous ethanol and aqueous acetone.*

The faster hydrolyses of lactones can be traced to the *cisoid* arrangement of the carbonyl group and the lone pair on the ethereal oxygen [2] and to the resultant greater polarity of the carbonyl group [11,12] since in the $B_{\text{AC}}2$ hydrolysis, the rate-determining step is the attack of the OH^- ion on the ester carbonyl group.[1,6]

The rate data in Tables 1 and 2 show that the hydrolysis rates in the case of lactones are less sensitive to changes in structure than are the open chain analogues (*cf.* ethyl and isopropyl acetates and γ-butyro- and γ-valero-lactones). The ring holds the carbonyl group in a relatively fixed position and tends to diminish the steric effects of increasing substitution around the alkyl oxygen. The situation is somewhat different with the open chain esters, as increasing substitution on the alkyl carbon reduces markedly the accessibility of the carbonyl carbon.[13] Owing to the operation of resonance effects of the phenyl group, phthalide is hydrolysed much more slowly than the aliphatic lactones. It is not surprising that a phenyl group in the alkyl portion (*cf.* 3-phenylphthalide) and substituents in that phenyl ring (4-methyl and 4-methoxy) exert only very little influence on the rates of hydrolysis. The Hammett correlation for this system, with ρ 0·5, parallels that for the ionisation of (4-substituted-2-benzoyl)benzoic acids [14] and for the hydrolysis of 4′-substituted pseudoesters of *o*-benzoylbenzoic acids.[15]

The higher saponification rates in aqueous DMSO over aqueous ethanol can be ascribed to the cumulative influences of two factors: [8] (i) the presence of a poorly solvated and consequently very active hydroxide ion in aqueous DMSO, and (ii) the superior ability of DMSO to solvate effectively the transition states of these reactions.

The reduced $k_{\text{lactone}}/k_{\text{ester}}$ values in DMSO as well as the smaller k_{s} values for lactones can be interpreted in terms of the 'looseness' and 'tightness' of the transition states of $S_{\text{N}}2$ reactions and the favourable disposition of the two solvent systems towards these transition states. These proposals of Parker and Ko [16] have been successfully applied by us in the alkaline hydrolysis of glycol monobenzoates.[17] The greater polarity of the carbonyl group and the rigid structure tend to 'loosen' the transition state for the hydrolysis of lactones. This type of transition state would be less favoured by an aprotic solvent, *e.g.* DMSO, but preferred by a protic solvent like ethanol. The reverse is true of the comparatively 'tighter' transition states of the open chain esters. As a consequence, rate enhancements ordinarily observed for ester saponifications on transfer from protic to an aprotic solvent are not present in the case of lactones.

The k_{s} values, which provide a measure of the substituent effects in terms of solvent influences, also demonstrate the less pronounced structural effects in the case of lactones compared to their open chain analogues.

---

* It is seen that the second step of the hydrolysis of dicarboxylic esters has a lower k_{s} value compared to the first step [9] where such anion–anion repulsions are absent. If the said electrostatic repulsions were significant in the present systems, by analogy, it would not be unreasonable to expect lower k_{s} values for open chain esters relative to those of the lactones. In practice, however, the reverse is observed.

[9] N. Venkatasubramanian and G. Venkoba Rao, *Tetrahedron Letters*, 1967, 5275.

[10] P. S. Radhakrishnamurthy and S. V. Anantakrishnan, *Proc. Indian Acad. Sci.*, 1961, **54**, 36; 1962, **56**, 249.

[11] R. J. B. Marsden and L. I. Sutton, *J. Chem. Soc.*, 1936, 1383.

[12] D. Cook, *J. Amer. Chem. Soc.*, 1958, **80**, 49.

[13] E. S. Gould, 'Mechanism and Structure in Organic Chemistry,' Holt Reinhold, New York, 1959.

[14] K. Bowden and G. R. Taylor, *J. Chem. Soc.* (*B*), 1971, 145.

[15] M. V. Bhatt, G. Venkoba Rao, and K. Sunder Raja Rao, paper presented at All India Chemists Convention, Bombay, November 1971.

[16] A. J. Parker and E. C. F. Ko, *J. Amer. Chem. Soc.*, 1968, **90**, 6447.

[17] M. Balakrishnan, G. Venkoba Rao, and N. Venkatasubramanian, *Tetrahedron Letters*, 1972, 4617.

Identical structural variations bring about more distinct changes in k_s values in the open chain esters than in the case of the corresponding lactones. Thus, for example, an extra methyl group in the open chain ester, as between ethyl and isopropyl acetates ' loosens ' the transition state to a greater extent, leading to a greater drop in reactivity in DMSO and subsequently to a greater drop in the k_s value. Such varying sensitivities to DMSO ' catalysis ' observed in the present systems incidentally underscore the greater importance of the transition state solvation factor in enhancements in the rate of saponification in aqueous DMSO.[18]

EXPERIMENTAL

Commercially available samples of the esters (B.D.H.; Fluka AG) were used after purification by fractional distillation or crystallisation from suitable solvents. The 3-Phenylphthalides were prepared by the method of Bhatt and Kamath.[19] DMSO (Crown Zellerbach–Riedel) was used after distillation under reduced pressure. Pure acetone and ethanol were prepared from commercial samples (B.D.H.) by standard procedures. Volume percentages of the solvent were used to obtain the required mixed solvents. The kinetics were followed by titrimetric methods and the experimental conditions and procedures were the same as in our earlier report.[18] All the reactions obeyed second order kinetics and the velocity constants were evaluated from the integrated rate equation:

$$k = \frac{2{\cdot}303}{t(\mathrm{a} - \mathrm{b})} \log_{10} \left[\frac{\mathrm{b}(\mathrm{a} - \mathrm{x})}{\mathrm{a}(\mathrm{b} - \mathrm{x})}\right]$$

where a and b represent the initial concentrations of the substrate and alkali respectively (*ca.* 0·02M). The rate constants represent the average of at least three kinetic runs and are accurate to within ±3%.

We are grateful to Professor M. L. Bender for useful discussions, and acknowledge the generous gift of DMSO by the Crown Zellerbach Corporation, and the award of a research fellowship (to M. B.) by the University Grants Commission of India.

[3/2323 *Received, 12th November*, 1973]

---

[18] M. Balakrishnan, G. Venkoba Rao, and N. Venkatasubramanian, *J.C.S. Perkin II*, 1974, 6.

[19] M. V. Bhatt and K. M. Kamath, *J. Chem. Soc.* (*B*), 1968, 1036.