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Solvent Effects on the Enthalpy and Entropy of Activation for the Hydrolysis of β-Lactones

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Abstract The hydrolysis of β-propiolactone and β-butyrolactone in binary water + dioxane mixtures was investigated by kinetic studies. The following conclusions were reached: First, β-propiolactone is more reactive than β-butyrolactone across the range of water + dioxane compositions. This observation was rationalized in terms of the electric charge flow caused by the β-butyrolactone's methyl substituent. Second, hydrolysis of these lactones is essentially enthalpy controlled. Third, an increase in the dioxane percentage, which relaxes the intermolecular hydrogen bonds in the ordered structure of water, reduces the enthalpy of activation $\Delta H^{\#}$ and simultaneously increases the entropy of activation $\Delta S^{\#}$(absolute value) for solvent compositions up to 60% dioxane. Fourth, plotting $\Delta H^{\#}/\Delta S^{\#}$ against the solvent composition yields an N-shaped curve. This results is a consequence of the quadratic and cubic terms appearing in the expressions of $\Delta H^{\#}$ and $\Delta S^{\#}$ as functions of the solvent media composition. Fifth, an $\boldsymbol{ABC}$ classification was set up to characterize the behavior of $\Delta H^{\#}/\Delta S^{\#}$ for the solvolysis of these lactones.

Keywords Lactones · Mixed solvents · Hydrolysis

1 Introduction

The reactivity in nitrosation reactions of amino acids having an –NH_2 group, and its relationship with the alkylating potential of their products, has been investigated in previous work [1–3]. Among other conclusions, it was shown that the species formed from the nitrosation of these amino acids are the corresponding lactones.

Because some lactones have alkylating reactions with a number of nucleophilic sites in tissues [4], the reactivity of lactones and its relationship with their carcinogenic activity was subsequently investigated [5, 6].

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Because the behavior of lactones in their hydrolysis reactions is a good indicator of their reactivity as electrophilic molecules, the hydrolysis of 4-6-membered lactones was investigated in neutral water and in slightly acidic media, and in water + dioxane mixtures [5].

Over a small range of water + dioxane concentrations (water/dioxane ratio not lower than 4/6), an isokinetic $\Delta H^{\#}/\Delta S^{\#}$ relationship was observed for the hydrolysis of β-propiolactone (BPL) and β-butyrolactone (BBL).

Since: (i) At low water + dioxane ratios, plotting $\Delta H^{\#}/\Delta S^{\#}$ shows a weak but perceptible deviation from linearity; (ii) BPL and BBL are potent carcinogenic molecules, with their behavior in their hydrolysis reactions being an indicator of their reactivity as alkylating agents [6]; and (iii) previous results [5] have shown that the reactivity of β-lactones diminishes in water + dioxane mixtures when the percentage of dioxane increases, an investigation of possible ways of inhibiting the electrophilic capacity of these lactones by changing the composition of the medium should be of biological interest. The present study addresses this aim.

2 Experimental

2.1 Materials

β-Propiolactone and β-butyrolactone were obtained from Sigma; dioxane was from Panreac (Barcelona, Spain). Water was deionized with a MilliQ-Gradient (Millipore).

2.2 Procedures

Hydroxy acids resulting from the hydrolysis of the lactones were used as control species for monitoring the reaction kinetics. The concentration of hydroxy acid was determined by titration with NaOH, whose concentration had been standardized by titration with potassium hydrogen phthalate. In the titration procedure, 1 mL aliquots of the reacting mixture (lactone and unbuffered CO_2-free water) were removed from time to time, added to 9 mL of ice water, and titrated immediately to a bromothymol blue endpoint (the hydroxy acid pK_a values were in the range 4.5 to 4.7 [7]).

Kinetic runs were performed in triplicate. Temperatures (in the 25 to 35 °C range; see Fig. 1 and Table 1) were kept constant to ±0.05 °C using a Lauda-Ecoline RE 120 thermostat.

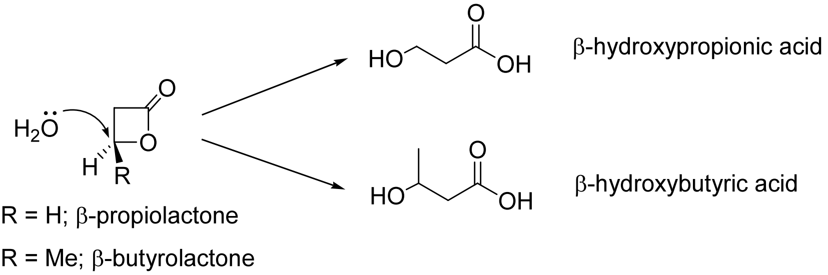
3 Results and Discussion

The hydrolysis of BPL and BBL (Scheme 1) was investigated at different water + dioxane volume ratios (from 2:8 up to 10:0).

Experiments performed to determine the influence of changing the lactone concentration revealed that the reactions are first order with respect to this reagent:

$$\frac{\mathrm{d[HA]}}{\mathrm{d}t} = k[\mathrm{H_2O}][\mathrm{L}] = k_1[\mathrm{L}] \tag{1}$$

where [L] denotes the concentration of lactone, [HA] that of the formed hydroxy acid, and $k_1 = k[\mathrm{H_2O}]$ is the pseudo-first-order rate constant.



Scheme 1 Hydrolysis of BPL and BBL in neutral media

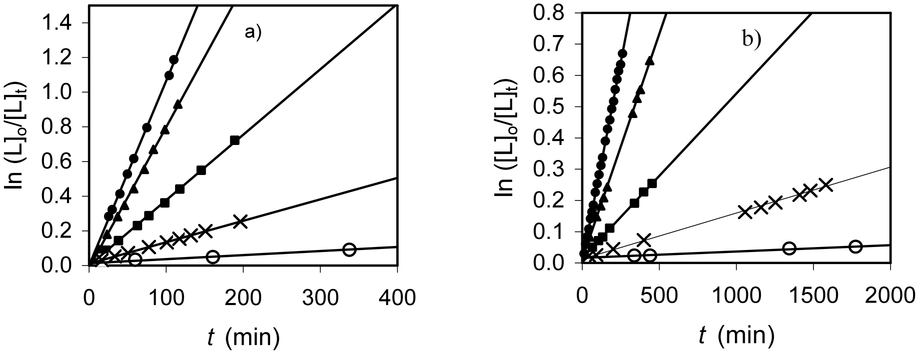


Figure 1 Integrated form of the pseudo-first-order rate equation (Eq. 1) for hydrolysis of BPL (plot **a**) and of BBL (plot **b**) in 10:0 (●), 8:2 (▲), 6:4 (■), 4:6 (×) and 2:8 (○) water + dioxane mixtures (volume/volume) where $[\mathrm{L}]_\mathrm{o} = 0.08\ \mathrm{mol{\cdot}L^{-1}}$ and $t = 35.0\,^\circ\mathrm{C}$

Figure 1 shows the integrated form of Eq. 1 in terms of the concentration of lactone at time t, $[\mathrm{L}]_t$, and its initial concentration, $[\mathrm{L}]_\mathrm{o}$, in several water + dioxane mixtures.

Table 1 reports the values of the hydrolysis rate constants for β-propiolactone and β-butyrolactone in different water + dioxane mixtures. Table 2 shows the values of the activation parameters for both hydrolysis reactions.

The very similar $\Delta S^{\#}$ values found for the hydrolysis of BPL and BBL (Table 2) are consistent with the analogous geometry of these lactones. These values also show that the reactivity of these lactones is mainly enthalpy controlled.

The higher $\Delta H^{\#}$ value obtained for the hydrolysis of β-butyrolactone must be caused by the presence of the methyl group as a charge donor on the β-carbon, which causes a decrease in its electrophilic character. Because, in general terms, substitution of groups on carbon atoms 2 or 3 in lactones results in a decrease or loss of alkylating potential and carcinogenicity [8], the steric hindrance of the BBL methyl group must also contribute to the higher $\Delta H^{\#}$ value.

There is a considerable diversity in the behavior of the thermodynamic quantities of activation related to solvent composition for the different binary solvent systems. Complex behavior for $\Delta H^{\#}$ that is related to variations in solvent composition has been reported by Tommila [9] for the hydrolysis of methyl-, ethyl-, and i-propylbenzenesulfonates in water + acetone and water + dioxane mixtures.

Table 1 Rate constants as a function of the solvent medium composition and temperature for the neutral solution hydrolysis of β-propiolactone and β-butyrolactone

t (°C)	Water + dioxane mixtures (volume/volume ratio)										
	10/0		9/1[a]	8/2		7/3		6/4		5/5	
	$10^7 k_{\mathrm{BPL}}$	$10^7 k_{\mathrm{BBL}}$	$10^7 k_{\mathrm{BBL}}$	$10^7 k_{\mathrm{BPL}}$	$10^7 k_{\mathrm{BBL}}$	$10^7 k_{\mathrm{BPL}}$	$10^7 k_{\mathrm{BBL}}$	$10^7 k_{\mathrm{BPL}}$	$10^7 k_{\mathrm{BBL}}$	$10^7 k_{\mathrm{BPL}}$	$10^7 k_{\mathrm{BBL}}$
						$(\mathrm{L \cdot mol^{-1} \cdot s^{-1}})$[b]					
25.0	10.6 ± 0.1	2.22 ± 0.03	2.09 ± 0.02	10.3 ± 0.3	1.75 ± 0.01	8.14 ± 0.08	1.34 ± 0.01	6.84 ± 0.07	0.87 ± 0.01	5.1 ± 0.1	0.61 ± 0.01
27.5	14.9 ± 0.3	3.63 ± 0.02	2.81 ± 0.03	13.40 ± 0.06	2.34 ± 0.01	11.06 ± 0.07	1.80 ± 0.02	8.46 ± 0.07	1.20 ± 0.01	7.02 ± 0.03	0.81 ± 0.02
30.0	20.2 ± 0.7	4.38 ± 0.05	3.72 ± 0.03	17.5 ± 0.4	3.10 ± 0.03	14.6 ± 0.2	2.31 ± 0.01	11.8 ± 0.2	1.55 ± 0.02	8.6 ± 0.3	1.09 ± 0.01
32.5	27.4 ± 0.9	5.89 ± 0.08	4.9 ± 0.1	23.2 ± 0.6	4.10 ± 0.04	18.9 ± 0.6	3.11 ± 0.03	14.7 ± 0.4	2.09 ± 0.03	11.0 ± 0.5	1.39 ± 0.01
35.0	31.9 ± 0.9	7.69 ± 0.07	6.64 ± 0.06	30.4 ± 0.9	5.41 ± 0.05	25.3 ± 0.7	4.12 ± 0.03	18.9 ± 0.5	2.63 ± 0.06	14.6 ± 0.3	1.85 ± 0.01

t (°C)	Water + dioxane mixtures (volume/volume ratio)							
	3.5/6.5		3/7		2.5/7.5		2/8	
	$10^7 k_{\mathrm{BPL}}$	$10^7 k_{\mathrm{BBL}}$	$10^7 k_{\mathrm{BPL}}$	$10^7 k_{\mathrm{BBL}}$	$10^7 k_{\mathrm{BPL}}$	$10^7 k_{\mathrm{BBL}}$	$10^7 k_{\mathrm{BPL}}$	$10^7 k_{\mathrm{BBL}}$
				$(\mathrm{L \cdot mol^{-1} \cdot s^{-1}})$[b]				
25.0	2.84 ± 0.04	0.266 ± 0.007	2.21 ± 0.02	0.169 ± 0.002	1.75 ± 0.05	0.143 ± 0.007	1.29 ± 0.01	0.107 ± 0.008
27.5	3.69 ± 0.02	0.365 ± 0.005	2.92 ± 0.01	0.260 ± 0.005	2.27 ± 0.02	0.193 ± 0.005	1.681 ± 0.006	0.136 ± 0.002
30.0	4.9 ± 0.1	0.478 ± 0.008	3.77 ± 0.03	0.355 ± 0.005	2.85 ± 0.04	0.250 ± 0.003	2.14 ± 0.02	0.172 ± 0.003
32.5	6.4 ± 0.2	0.625 ± 0.007	4.95 ± 0.06	0.459 ± 0.007	3.77 ± 0.09	0.339 ± 0.007	2.74 ± 0.02	0.305 ± 0.003
35.0	8.1 ± 0.2	0.814 ± 0.005	6.34 ± 0.09	0.61 ± 0.01	4.8 ± 0.1	0.438 ± 0.005	3.51 ± 0.07	0.224 ± 0.005

[a] Values of the rate constants for BPL are almost the same as those in 10/0 water + dioxane mixtures

[b] Values of the rate constants are given with their 95% confidence interval; $[\mathrm{BPL}]_o = [\mathrm{BBL}]_o = 0.08\ \mathrm{mol \cdot L^{-1}}$

Table 2 Activation parameters as a function of the composition of the medium for the neutral solution hydrolysis of β-propiolactone and β-butyrolactone

Water + dioxane	$\Delta H^{\#a}$ (kJ·mol^{-1})		$-\Delta S^{\#a}$ (J·K^{-1}·mol^{-1})	
(volume/volume ratio)	BPL	BBL	BPL	BBL
10/0	83 ± 2	88 ± 3	80 ± 8	78 ± 10
9/1	–	85 ± 1	–	89 ± 2
8/2	80 ± 1	84 ± 1	90 ± 3	94 ± 1
7/3	79 ± 1	83± 1	95 ± 3	98 ± 3
6/4	76 ± 3	82 ± 2	107 ± 10	104 ± 7
5/5	75 ± 3	81 ± 1	112 ± 9	110 ± 3
4/6	73 ± 1	79 ± 2	123 ± 3	122 ± 6
3.5/6.5	78 ± 1	82 ± 1	109 ± 3	114 ± 4
3/7	78 ± 1	84 ± 1	111 ± 3	111 ± 4
2.5/7.5	74 ± 1	83 ± 1	125 ± 5	117 ± 4
2/8	73 ± 1	77 ± 3	130 ± 2	140 ± 10

[a] Values are given with their standard deviations

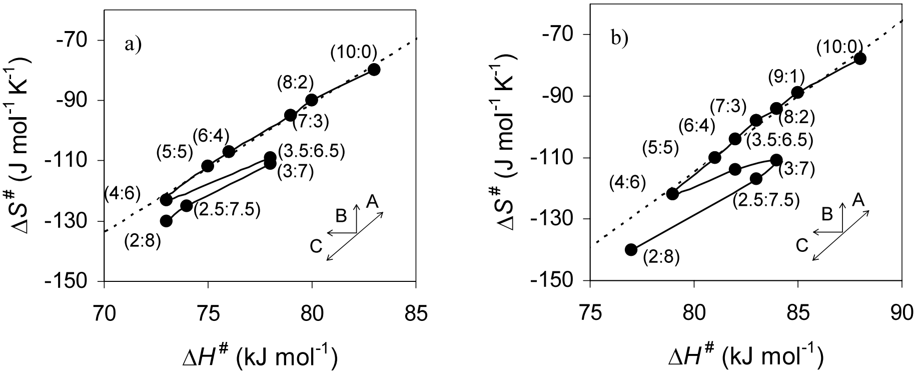


Figure 2 Plot of $\Delta S^{\#}$ against $\Delta H^{\#}$ for the hydrolysis of: (**a**) β-propiolactone and (**b**) β-butyrolactone in water + dioxane mixtures. Dashed lines show results obtained previously over a narrower range of compositions

The behavior of $\Delta H^{\#}$ and $\Delta S^{\#}$ as a function of the solvent composition tends to be complex. It can be observed (see Fig. 2) that the increase in concentration of dioxane, which relaxes the intermolecular hydrogen bonds in the ordered structure of water, reduces the $\Delta H^{\#}$ value and simultaneously increases the $-\Delta S^{\#}$ value up to 60% dioxane. At higher percentages of dioxane, an N-shaped type correlation was observed [10].

As depicted in Fig. 2, previous results [5] obtained over a narrower range of compositions showed a $\Delta S^{\#}/\Delta H^{\#}$ isokinetic effect. Because the strong effect of dioxane on the kinetic parameters is a consequence of a strong lactone + water interaction, when the water/dioxane ratio is not lower than $\approx 4/6$ both the enthalpy and entropy tend to be linear functions of the volume fraction of that solvent mixture, and an isokinetic relationship should result. Figure 2 (dashed lines) shows that this effect indeed occurs [5].

Table 3 $\boldsymbol{ABC}$ Classification for the solvolysis of some compounds

Compound	*t* (°C)	Solvent range	Class
t-Butyl chloride [11]	25.0	0–90 vol.-% dioxane + H_2O	${}_{35}\boldsymbol{A}_{60}\boldsymbol{B}_{85}\boldsymbol{A}_{100}$
Ethyl benzenesulfonate [12, 13]	50.0	0–95 wt.-% dioxane + H_2O	${}_{20}\boldsymbol{A}_{55}\boldsymbol{B}_{90}\boldsymbol{C}_{95}\boldsymbol{A}_{100}$
i-Propyl benzenesulfonate [9]	50.0	0–98 wt.-% dioxane + H_2O	${}_{10}\boldsymbol{A}_{65}\boldsymbol{B}_{95}\boldsymbol{A}_{100}$
n-Propyl benzenesulfonate [9, 12]	25.0	0–85 wt.-% $Me_2CO + H_2O$	${}_{25}\boldsymbol{A}_{70}\boldsymbol{C}_{90}\boldsymbol{A}_{100}$
Ethyl bromide [14]	60.0	0–90 wt.-% $Me_2CO + H_2O$	${}_{35}\boldsymbol{A}_{72}\boldsymbol{C}_{94}\boldsymbol{A}_{100}$

When the concentration of the more rapidly moving solvent (water) diminishes, quadratic and cubic terms appear in the expressions of $\Delta H^{\#}$ and $\Delta S^{\#}$. The values of these quantities are a consequence of the dependence of the Gibbs energy of a solute species on the immediate environment. By including the cubic terms, N-shaped relationships are generated such as those depicted in Fig. 2 [10].

3.1 $\boldsymbol{ABC}$ classification

When the $\Delta S^{\#}$ values are plotted against those of $\Delta H^{\#}$ for the hydrolysis of β-propiolactone and β-butyrolactone in several binary solvent systems (Fig. 2), somewhat complex curves are obtained. For comparison, it is convenient to use a symbolic terminology to classify the behavior of the thermodynamic quantities of activation related to the variation of the solvent [11].

This classification system may be defined with the aid of a plot of $\Delta S^{\#}/\Delta H^{\#}$ as shown in Fig. 2. In such plots, arrowheads were placed on the curves to indicate the direction of increasing mole fraction of the most rapidly moving component of a binary solvent mixture. In general, this may occur in one of three ways: $\boldsymbol{A}$, both $\Delta H^{\#}$ and $\Delta S^{\#}$ increase; $\boldsymbol{B}$, $\Delta H^{\#}$ decreases while $\Delta S^{\#}$ increases; and $\boldsymbol{C}$, both $\Delta H^{\#}$ and $\Delta S^{\#}$ decrease.

Figure 2 clearly shows that the plots start in the $\boldsymbol{A}$ class, shift to $\boldsymbol{C}$, and then back to $\boldsymbol{A}$. This leads to a convenient shorthand description of the data: $\boldsymbol{ACA}$. It is useful to append subscripts to the letters designating the solvent composition range (as percentages) covered by each class, in terms of the volume/volume ratio of the most rapidly moving component. Thus, for the binary water + dioxane solvent system, a complete description of the relative contributions of $\Delta H^{\#}$ and $\Delta S^{\#}$ to the hydrolysis rate of β-lactones is given by ${}_{20}\boldsymbol{A}_{35}\boldsymbol{C}_{40}\boldsymbol{A}_{100}$ (N-shaped).

For comparison, Table 3 shows a correlation of the solvolysis rates for different compounds in different binary solvent systems and their $\boldsymbol{ABC}$ classification. A similar type of behavior is seen between the hydrolysis of β-lactones and the solvolysis of other compounds.

4 Conclusions

Comparison of the results arising from this study of hydrolysis of β-propiolactone and β-butyrolactone in binary water + dioxane mixtures results in the following conclusions:

(i) β-Propiolactone is more reactive than β-butyrolactone across the full range of water + dioxane compositions. This is due to the flow of electric charge caused by the methyl substituent in β-butyrolactone.

(ii) Hydrolysis of these lactones is essentially enthalpy controlled.
(iii) An increase in the dioxane percentage, which relaxes the intermolecular hydrogen bonds found in the ordered structure of water, reduces $\Delta H^{\#}$ and simultaneously increases $\Delta S^{\#}$ (absolute value) up to 60% dioxane.
(iv) The plot of $\Delta H^{\#}/\Delta S^{\#}$ against the solvent composition is seen to be N-shaped. The results are a consequence of the quadratic and cubic terms appearing in the expressions of $\Delta H^{\#}$ and $\Delta S^{\#}$ as functions of the composition of the medium.
(v) An ***ABC*** classification was set up to characterize the behavior of $\Delta H^{\#}/\Delta S^{\#}$ for the solvolysis of these lactones.

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