

HYDROLYTIC STABILITY OF LACTONES OF 4,6-DIDEOXYHEXONIC ACIDS*

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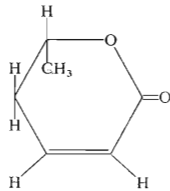
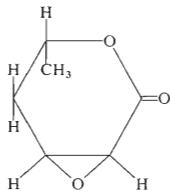
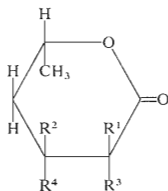
The rate of acid catalyzed hydrolysis of diastereoisomeric lactones of 4,6-dideoxyhexonic acids, studied at 35°C in water, aqueous dioxane and aqueous acetone, decreases in the following order of configurational isomers L-xylo (II), L-lyxo (IV), L-ribo (I) and L-arabino (III). With increasing fraction, up to 50–70% by weight, of the organic component in a mixed solvent the rate of hydrolysis decreases for all lactones investigated, while in the region above 80% of the organic solvent the hydrolysis rate increases to a value higher than in water, under simultaneous decrease of the content of the hydroxy acid in the equilibrium mixture. The content of the organic component in the mixed solvent does not affect the order of reactivities of the lactones investigated.

The esterification of carboxylic acids and the hydrolysis of esters is one of the most systematically investigated reactions because it is a traditional one for the checking of theories concerning the structure-reactivity relationship. In these studies the hydrolysis of lactones was also investigated from the point of view of the effect of substitution of the lactone ring on the reaction rate. These relationships were investigated predominantly on γ -lactones (refs²⁻⁸). δ -Lactones are very labile during hydrolysis^{6,7,9}, but the dependence of the properties of diastereoisomeric δ -lactones on the steric arrangement have been investigated relatively little so far. Nonetheless interest in the problems of stability of sugar δ -lactones is considerable because, for example, the δ -lactone of D-gluconic acid plays an important role in biological systems, and the hydrolysis of this type of compounds is interesting both from the biological^{10,11} and the chemical¹²⁻¹⁴ point of view. For obtaining information on factors affecting the rate of hydrolysis of sugar δ -lactones the group of diastereoisomeric lactones of 4,6-dideoxyhexonic acids and some related substances seems suitable. This is so mainly because the course of the investigated changes is not complicated by the formation of γ -lactones in this case.

The stability of the substance is given both by the properties of the substance itself, and by the medium surrounding it. In this study we investigated external

* Part XX in the series Lactones; Part XIX see ref.¹.

effects, *i.e.* the effects of the reaction medium on the kinetics of acid-catalysed hydrolysis of diastereoisomeric lactones of 4,6-dideoxyhexonic acids of *L-ribo* (*I*), *L-xylo* (*II*), *L-arabino* (*III*), *L-lyxo* (*IV*) configuration and lactones of (*S*)-(-)-5-hydroxycaproic acid (*V*), 2,3-anhydro-4,6-dideoxy-*L-ribo*-hexonic acid (*VI*) and (*S*)-(+)-5-hydroxy-2-hexenoic acid (*VII*) in aqueous 0.005 to 0.02M hydrochloric acid at 35°C. In order to obtain information on the effect of organic solvents we carried out kinetic measurements of the course of acid-catalysed hydrolysis in water-dioxane and water-acetone systems, containing 0.005 to 0.02M-HCl.



I, $R^1 = R^2 = \text{OH}$; $R^3 = R^4 = \text{H}$

II, $R^1 = R^4 = \text{OH}$; $R^2 = R^3 = \text{H}$

III, $R^2 = R^3 = \text{OH}$; $R^1 = R^4 = \text{H}$

IV, $R^3 = R^4 = \text{OH}$; $R^1 = R^2 = \text{H}$

V, $R^1 = R^2 = R^3 = R^4 = \text{H}$

VI

VII

EXPERIMENTAL

Chemicals

Lactone of 4,6-dideoxy-*L-ribo*-hexonic acid¹⁵, lactone of 4,6-dideoxy-*L-arabino*-hexonic acid¹⁶, lactone of 4,6-dideoxy-*L-xylo*-hexonic acid¹⁷, lactone of 4,6-dideoxy-*L-lyxo*-hexonic acid¹⁸, lactone of (*S*)-(-)-5-hydroxycaproic acid¹⁹, lactone of 2,3-anhydro-4,6-dideoxy-*L-ribo*-hexonic acid²⁰, lactone of (*S*)-(+)-5-hydroxy-2-hexenoic acid¹⁵. For the purification of dioxane see²¹, of acetone see²².

Methods

Titration method: About 0.5 mmol of lactone was weighed into a 25 ml flask, the mixture was thermostated at $35^\circ \pm 0.05^\circ\text{C}$ and made up to 25 ml with thermostated solvent of a defined concentration of hydrochloric acid (0.005 to 0.02M-HCl, depending on the rate of hydrolysis of individual lactones). Aliquots were titrated under nitrogen with 0.08M-NaOH using a glass and calomel electrode up to pH 7.5. The rate constants of hydrolysis were calculated from the equation for the equilibrium reaction of pseudo-first order²³. The titration method was used for all lactones except for the investigation of lactones *II*, *III* and *IV* in water.

Polarimetry: The determination was carried out on a JASCO ORD/UV-5 Spectropolarimeter of Japan Spectroscopic Co., Tokio, in an all-glass thermostated cell of 4.5 ml volume, with quartz

windows, at 35°C. The measurement was carried out at 420 nm *i.e.* at optimum relative difference between the rotation value of the lactone and the hydroxy acid. Using this method both the course of hydrolysis of lactones and the lactonization of hydroxy acids were studied. The results were evaluated from graphical records of the dependence of the rotation of the reaction mixture on time, using the relationship in ref.²⁴. The rate constants were determined from acid catalyzed hydrolysis of lactones I, II, III and IV in water.

Graphical records of the lactonization course were not used for the calculation of kinetic constants, because in this case it was difficult to adjust the HCl concentration in the reaction mixture with sufficient accuracy. For the neutralization of excess sodium hydroxide and the sodium salt of the hydroxy acid a much higher amount of acid is necessary than for the adjustment of the pH to the required value, which may cause considerable errors. The results of the measurement of the course of lactonization were therefore used for the determination of the rotation of the equilibrium mixture only.

Hydrolysis of lactones: This was carried out so that about 0.3 mmol of lactone was weighed into the side tube of a Warburg flask of 25 ml volume, 5 ml of hydrochloric acid of corresponding concentration were then pipetted into the flask, and this was then thermostated. The contents of the flask was then shaken and filtered through an S3 filter funnel with sintered disc into a thermostated cell. The beginning of the shaking was taken as the beginning of the reaction.

Lactonization of hydroxy acids: Approximately 1.8 ml of 0.5M-NaOH was added to about 0.6 mmol of lactone and the solution was heated on a boiling water bath for 1 h. Then 0.3M-HCl was added which corresponded to the total amount of NaOH added, followed by such an amount of HCl as brought the molarity of the resulting solution to that necessary for lactonization (0.005M or 0.01M). The contents of the flask was made up with water to 10 ml volume, shaken and filtered through a filter funnel with sintered disc thermostated S3 into a cell. The moment of neutralization with hydrochloric acid was taken as the beginning of the reaction.

RESULTS AND DISCUSSION

The rate constant of generally catalyzed hydrolysis is expressed²³ as $k = k_0 + k_{H^+}[H_3O^+] + K_{OH^-}[OH^-] + k_{HA}[HA] + k_{A^-}[A^-]$, where k is the overall rate constant of hydrolysis, k_0 is the rate constant of spontaneous hydrolysis in water, k_{H^+} and k_{OH^-} are the rate constants for reactions catalyzed with hydronium and hydroxyl ions and k_{HA} and k_{A^-} are the rate constants for the catalysis with the acid and the basic component of the catalyzing acid, while the concentration of these components is $[HA]$ and $[A^-]$. However, as the pH of the reaction medium in this study was about 2, being kept at this value with hydrochloric acid, only the second term of the equation, *i.e.* $k_{H^+}[H_3O^+]$, will be effective because the value of the partial rate constant for spontaneous hydrolysis k_0 is negligible* in comparison with k_{H^+} . This fact may be confirmed by our finding that the dependence of the values of the overall rate constant of hydrolysis k on the concentration of the catalysing mineral acid was linear within the measured range and with the measured lactones, and that it passed through the origin (within the accuracy achieved).

* In this type of substance the rate constant of spontaneous hydrolysis k_0 is usually at least two orders of magnitude smaller than the rate constant of the catalysis with hydronium ion¹³.

The values of the rate constants of acid catalyzed hydrolysis of the lactones under study, at 35°C in water, are given in Table I. From the results of the study of acid catalyzed hydrolysis of lactones *I–IV* it follows that the hydrolysis rate of the least stable lactone *II* is almost twenty times higher than that of the most stable lactone *III*. Lactones *I* and *IV* are hydrolyzed approximately at the same rate which is, in comparison with the rate of hydrolysis of lactone *III* more than four times higher. From Table I it follows that the lactone of 2,3-anhydro-4,6-dideoxy-L-ribo-hexonic acid (*VI*) is hydrolyzed more slowly than lactone *III*. In the case of the lactone of 5-hydroxy-2-hexenoic acid catalyzed hydrolysis under the given conditions does not take place. The rate of hydrolysis of δ -caprolactone could not be measured in water, because under the given conditions it was poorly soluble.

The dependence of rate constants of acid-catalyzed hydrolysis of lactones on the solvent composition is shown in Table II for water–dioxane, and in Table III for water–acetone. In both solvent mixtures a mild decrease of the rate is observed with increasing proportion of the organic solvent and at approximately 50% (by weight) of the organic solvent a flat minimum is observed, while in the region above 80% of the organic solvent the reaction rate increases and becomes higher than in water. The rate of hydrolysis in dioxane–water mixture is generally higher than in acetone–water mixture. The minimum of the reaction rate at 50 to 70% probably²⁵ corresponds to the maximum of the acidity function H_0 . The considerable increase of the reaction rate after this minimum may be caused either by the steep decrease of the acidity function H_0 or by the decrease of the activation energy of the reaction, caused by increased solvation with the organic solvent^{25–28}. Even though

TABLE I
Acid Catalyzed Hydrolysis of Lactones at 35°C in Water

Lactone ^a	Rate constant k_H $10^3 \text{ l mol}^{-1} \text{ s}^{-1}$	Hydroxy acid in equilibrium mixture, %
<i>I</i>	2.32	74.9
<i>II</i>	9.28	80.9
<i>III</i>	0.555	75.9
<i>IV</i>	2.48	65.7
<i>VI</i>	0.455	64.2

^a Lactone *V* was poorly soluble; in the case of lactone *VII* hydrolysis does not take place under the given conditions. The majority of substances were available in small amounts only and the data presented are the results of only one or two series of measurements. For lactone *VI* the standard deviation for 5 measurements of the rate constant is 0.023.

TABLE II
Acid Catalyzed Hydrolysis of Lactones in Water-Dioxane Mixtures at 35°C

Lactone	Dioxane, % (by weight)							
	0	10	20	30	45.8	64.1	80	92
Rate constants k_H , $10^3 \text{ l mol}^{-1} \text{ s}^{-1}$								
<i>I</i>	2.32	1.95	1.88	2.00	1.85	1.87	2.67	2.87
<i>II</i>	9.28	—	—	—	8.53	7.85	—	16.2
<i>III</i>	0.555	—	—	—	0.505	0.538	—	1.33
<i>IV</i>	2.48	—	—	—	2.00	2.10	—	3.98
<i>V</i>	^a	^a	^a	^a	^a	4.75	—	8.40
<i>VI</i>	0.455	—	—	—	0.348	0.222	—	1.78
Hydroxy acid in equilibrium mixture, %								
<i>I</i>	74.9	72.5	69.0	71.5	69.9	65.9	58.0	42.4
<i>II</i>	80.9	—	—	—	70.3	66.5	—	53.5
<i>III</i>	75.9	—	—	—	71.7	68.7	—	49.6
<i>IV</i>	65.7	—	—	—	58.0	55.7	—	37.0
<i>V</i>	^a	^a	^a	^a	^a	59.5	—	53.9
<i>VI</i>	64.2	—	—	—	45.7	41.1	—	15.7

^a Poorly soluble.

TABLE III
Acid Catalyzed Hydrolysis of Lactones in Water-Acetone Mixtures at 35°C

Lactone	Acetone, % (by weight)						
	0	10	30	50	70	90	
Rate constants k_H , $10^3 \text{ l mol}^{-1} \text{ s}^{-1}$							
<i>I</i>	2.32	1.80	1.40	1.32	1.37	2.57	
<i>II</i>	9.28	—	—	5.60	5.08	9.58	
<i>III</i>	0.555	—	—	0.408	0.522	1.56	
<i>IV</i>	2.48	—	—	1.60	1.67	3.05	
Hydroxy acid in equilibrium mixture, %							
<i>I</i>	74.9	69.4	66.3	66.0	57.0	38.3	
<i>II</i>	80.9	—	—	67.1	63.1	47.7	
<i>III</i>	75.9	—	—	61.7	54.6	41.2	
<i>IV</i>	65.7	—	—	53.1	45.7	25.7	

a rather considerable increase of the reaction rate is observed in the region of high concentrations of the organic solvent, a remarkable decrease of the equilibrium concentration of the hydroxy acid formed is observed simultaneously in all lactones investigated.

The lactone of 4,6-dideoxy-L-ribo-hexonic acid was investigated in a wider range of concentrations of the organic solvent. We endeavoured to determine the dependence of the rate constant values within the whole concentration range of the organic component of the mixed solvent and to check whether an increase in the reaction rate can be observed in the range near to 10% of the organic solvent. This increase in the reaction rate of the acid-catalysed hydrolysis of esters in mixed solvents has been observed by a number of authors, *cf.*^{27,29-32}. This phenomenon has been explained³³ by the expulsion of water from the structures cross-linked by hydrogen bonds, so that an increase in the number of molecules of "free" water, available for the reaction, takes place. However, this is evidently not a general phenomenon because cases have been published where this increase in rate in the region of low concentration of organic solvent did not take place^{28,31,34,39}. From the data in Table II and III it follows that an increase in the reaction rate does not take place in the case of lactone I either.

On comparing the rates of hydrolysis in acetone and dioxane medium it becomes evident that hydrolysis is faster in dioxane than in acetone within the whole range of concentrations, *i.e.* from 0 to 92% of the organic solvent. This fact may be explained by the predominant role of the permittivity constant of the solvent mixtures^{35,36}. At identical content (by weight) of the organic component in both media the permittivity constant in dioxane-water solution will be substantially lower than in the acetone-water mixture; this is due to the substantially lower permittivity constant of dioxane in comparison with acetone.

According to the data of Tommila and coworkers³⁷ it could be expected that in the concentration range above 80% of the organic component the rate of hydrolysis of lactones in acetone-water mixture would be higher than in dioxane-water mixture, because dioxane which contains two oxygen atoms in the molecule can bind two water molecules by hydrogen bonds, while acetone binds only one water molecule so that the number of "free" water molecules is higher in acetone-water mixtures than in dioxane-water mixtures if the total water content in both solvent mixtures is equal. Similar results are also given for the isopropyl ester of formic acid (Texier and coworkers³⁸). However, our results did not confirm this theory. Of all lactones it is that of 4,6-dideoxy-L-arabino-hexonic acid which is an exception, because at about a 70% concentration of the organic solvent in the reaction medium the reaction rate is equal in dioxane and in acetone, while in the range above 70% of the organic solvent the hydrolysis in acetone is faster. But the difference of the rate constants for the lactone of 4,6-dideoxy-L-arabino-hexonic acid in 90% acetone and

in 92% dioxane is not very large ($0.2 \cdot 10^{-3} \text{ l mol}^{-1} \text{ s}^{-1}$) so that it is not impossible that it is the consequence of an experimental error.

In mixed solvents the change in composition leads to changes in solvation of the dissolved particles, which leads to changes in solvation of the reactants and of the transition complex in the reaction system, and which also might lead to a change in the reaction course. From the results of the measurement of the course of the acid catalyzed hydrolysis of lactones of 4,6-dideoxyhexonic acids in the mixed solvents mentioned it follows that the order of reactivity of the lactones investigated does not change either in dioxane or acetone in the 0 to 90% (by weight) organic solvent concentration range. Therefore it may be concluded that with increasing proportion of the organic component in the reaction medium, changes in the molecules of lactones which would cause a greater change in the reaction course do not occur. To summarize it can be said that the composition of the mixed solvent has a certain effect on the rate of hydrolysis, but that this effect acts approximately equally on all the lactones investigated, so that it cannot be the cause of differing reactivity. Therefore it can be expected that the differing reactivity of the lactones of the series investigated in aqueous medium is caused rather by factors following from the internal arrangement of their molecules. The evaluation of the stability against hydrolysis of lactones of 4,6-dideoxyhexonic acids from this point of view will be the subject of the next study.

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