Alkaline Hydrolysis of Propella-δ- and ε-lactones

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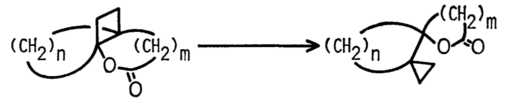
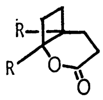
Second-order rate constants for the alkaline hydrolysis of a series of propella-δ- and ε-lactones at 32.3 °C have been determined. The conclusion to be drawn from the kinetic data is as follows. In the case of propella-δ-lactones, the steric effect of the third ring on the hydrolysis plays an important role, whereas the hydrolysis of propella-ε-lactones is mainly governed by the steric effect attributable to the flexibility of the ε-lactone ring, and, on the contrary, the steric effect of the third ring is of no great consequence.

In a continuation of the studies on the transformation of readily available [*n*.3.2]propellanes into other important polycarbocyclic ring systems,1) we previously reported on the novel cyclobutyl-cyclopropylcarbinyl rearrangement of propella-δ-lactones (**1**)—(**4**), composed of a cyclobutane ring, a δ-lactone ring, and one of five to eight membered rings as the third ring, to the corresponding dispiro-γ-lactones (**9**)—(**12**) under acidic conditions as well as thermal conditions.2) In these reactions, the remarkable ring size effect of the third rings on the rearrangement was observed, and it was inferred that the steric effect of the third rings reinforced the puckered geometry of the cyclobutane ring in δ-lactones which was favorable for the rearrangement to the γ-lactones. Of all the propella-δ-lactones, in particular, this was the case for **2** because of the steric requirement of the cyclohexane ring fused to bridgehead positions to adopt the chair conformation. Furthermore, this reasoning could be applicable to the results of the rearrangement of propella-ε-lactones (**5**) and (**6**), being higher homologues of δ-lactones (**1**) and (**2**).3)



	m	n	
1	2	3	9
2	2	4	10
3	2	5	11
4	2	6	12
5	3	3	—
6	3	4	13



	R
7	H
8	CH$_3$

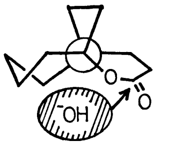
On the other hand, it is well-known that the transition state of alkaline hydrolysis of lactones is the formation of the tetrahedral intermediate and that the hydroxide anion attacks perpendicularly to the plane of the carbonyl group.4) Also, it becomes apparent that the substituent effect which affects the rate of the hydrolysis is primarily due to the steric factor in the transition state.4c,5)

In this connection, it is very interesting to see if the steric effect of the third ring influences the rate of alkaline hydrolysis of propellalactones. Therefore, we have studied the rate constants for the alkaline hydrolysis of a series of propella-δ- and ε-lactones.

Results and Discussion

The kinetic data for the alkaline hydrolysis of various lactones studied are summarized in Tables 1 and 2.

Firstly, the effect of alicyclic rings or two methyl groups substituted at the 4- and 5-positions of δ-valerolactone on the alkaline hydrolysis was taken up. As shown in Table 1, the rate constants of a series of δ-lactones obviously decreased with going on from δ-valerolactone to tricyclic propella-δ-lactones through bicyclic ones. The striking aspect of the present data is that the rate constant of bicyclic δ-lactone (**7**) compared with that of δ-valerolactone decreased by a factor of about one-twentieth by the fusion of such a small cyclobutane ring. Moreover, the further deceleration was naturally observed in the cases of propella-δ-lactones (**1**)—(**4**), or bicyclic δ-lactone (**8**), being substituted by two methyl groups at the both angular bridgehead positions of **7**. For example, the rate constant of **4** is less than that of **7** by a factor of about twenty-eighth by the additional fusion of a eight membered ring to the bicyclo[4.2.0] ring system. The effect of the third ring on the present alkaline hydrolysis may be regarded as the steric hindrance toward the attack of the hydroxide anion to the carbonyl group which is situated in position β to a bridgehead carbon atom, and, accordingly, it would be expected that the degree of the deceleration of the rate might be consistent with that of enlargement of the third ring size. In fact, however, the rate constants was in the order of **2**>**1**>**3**≈**4**, and that of **2**, having a cyclohexane ring, was twice of that of **1**, having a cyclopentane ring, and was even one and half times larger than that of **8**.



These results are of very significance in connection with those of the rearrangement of **1**—**4** to the corresponding dispiro-γ-lactones (**9**)—(**12**) described in the introduction. The two reactions exhibited very similar feature of the ring size effect of the third ring. As borne out by the inspection of molecular model as well as by the reasoning for the previous rearrangement, this unique feature of **2** in reactivity may be attributed to the puckered geometry of the cyclobutane ring reinforced by the chair conformation of

Table 1. Kinetic data for alkaline hydrolysis of δ-lactone series

Compd	T/°C a)	k/l mol^{-1} s^{-1}	$\Delta H^{\ddagger}$/kcal mol^{-1}	$\Delta S^{\ddagger}$/eu	$k_{\rm rel}$ b)
δ-Valerolactone	41.5	24.4±0.3	7.38	−28.9	100
	32.3	17.3±0.0			
	25.0	11.4±0.1			
7	41.5	1.36±0.03	8.79	−30.1	4.8
	32.3	0.854±0.013			
	25.0	0.561±0.006			
8	41.5	0.203±0.002	9.35	−32.1	0.72
	32.3	0.124±0.002			
	25.0	0.0794±0.0005			
1	41.5	0.145±0.002	9.78	−31.4	0.54
	32.3	0.0934±0.0026			
	25.0	0.0544±0.0014			
2	41.5	0.280±0.003	9.33	−31.5	1.0
	32.3	0.179±0.001			
	25.0	0.110±0.002			
3	41.5	0.0309±0.0008	7.69	−40.8	0.14
	32.3	0.0241±0.0008			
4	32.3	0.0290±0.0006			0.17

a) Temperatures are ±0.1 °C. b) Relative rates at 32.3 °C to that of δ-valerolactone = 100.

Table 2. Kinetic data for alkaline hydrolysis of ε-lactone series

Compd	T/°C a)	k/l mol^{-1} s^{-1}	$\Delta H^{\ddagger}$/kcal mol^{-1}	$\Delta S^{\ddagger}$/eu	$k_{\rm rel}$ b)
ε-Caprolactone	41.5	1.58±0.03	8.33	−31.3	
	32.3	1.04±0.02			
	25.0	0.678±0.009			100
5	41.5	0.458±0.006	8.41	−33.5	
	32.3	0.279±0.010			
	25.0	0.194±0.002			29
6	25.0	0.193±0.002			29

a) Temperatures are ±0.1 °C. b) Relative rates at 25.0 °C to that of ε-caprolactone = 100.

the cyclohexane ring. Namely, **2** is packed closely like a compact hemisphere, in other words, **2** has a widespreading room to the direction of endo in comparison with the others, such as **1** and **8**. Therefore, the attack of the hydroxide anion upon the carbonyl carbon atom of **2** may take place more smoothly.

In the case of ε-lactone series, on the other hand, the steric effect of two alicyclic rings fused to ε-caprolactone on the alkaline hydrolysis was much less than in the case of δ-lactone series. Namely, the rate constants of two propella-ε-lactones (**5**) and (**6**), which were the same, were only one-fourth as small as that of ε-caprolactone as shown in Table 2. This marked difference in reactivity between two propellalactone series can be attributed to the difference in flexibility or rigidity between δ- and ε-lactone rings. Inspection of molecular models of two lactone rings clearly indicates that the ε-lactone ring is more flexibile than the δ-lactone one. It may be reasonable that the rate of more flexible ε-lactone for the hydrolysis is much slower than that of more rigid δ-lactone.6) This consideration implies that the flexibility of the ε-lactone makes it possible to depress the hydrolytic rate by the steric effect of adjacent methylene groups to the carbonyl one in the lactone ring itself. In addition, it is deduced from the kinetic data that the steric effect based on the flexibility of the ε-lactone ring plays more important role than that of the third ring.

In conclusion, from the kinetic study of the alkaline hydrolysis of a series of propella-δ- and ε-lactones, the steric effect of the third ring toward the attack of the hydroxide anion has been elucidated. In particular, in the case of propella-δ-lactones, this effect played as important role as in the case of cyclobutylcyclopropylcarbinyl rearrangement of them. In the case of propella-ε-lactones, on the other hand, the alkaline hydrolysis was dominantly governed by the steric effect attributable to the flexibility of the ε-lactone ring, and, that of the third ring was of no great consequence.

Experimental

δ-Valero- and ε-caprolactones are commercial samples (Wako Pure Chemical Ind. or Tokyo Kasei) and were purified by distillation before use. Bicyclic δ-lactones (**7**) and (**8**) and propellalactones (**1**)—(**6**) were prepared as our previous reports2b,3) and were purified by silica-gel column chromatography or distillation. Water was prepared by distillation of deionized water under nitrogen atmosphere and was used throughout. Commercially available ethanol (Wako, super special grade) was used without further purification. Hitachi-Horiba pH meter H-7 SD and Horiba combination electrode #6326 were used for pH measurement.

Kinetic Measurement. The rates of the hydrolysis of the lactones were determined by the pH method of Hall *et al.*[4b,d] Water containing 25% ethanol was used as the solvent to form a homogeneous solution.[8] The second-order rate constants were calculated from the pseudo first-order rate constants and were the avarage of at the least three runs of the same lactone concentration. The rate measurements were made at three different temperatures in the range of 25.0—41.5 °C[9] and the activation parameters were evaluated from the slope of the least-square Arrhenius plots.

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6) This fact may be also explained on the basis of the differences of I-strain between seven and six membered rings as mentioned by Blackburn and Dodds.[7]

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8) In the case of **4**, the satisfactory data were not obtained at 25.0 and 41.5 °C because the solubility was limited at 25.0 °C and ethanol evaporated at 41.5 °C during the long reaction time. Also, the rate constant of **3** at 25 °C did not give reliable data.

9) Since **6** was more reactive and rearranged easily to **13** at 32.3 and 41.5 °C, we could not measure the rate under the above conditions.