ACTA CHEMICA SCANDINAVICA 16 (1962) 1124–1126

The Mechanism of the Acid-catalyzed Hydrolysis of γ-Lactones with a Tertiary Alkyl-Oxygen Bond

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Submitted in honour of the sixtieth birthday of my teacher, Professor *Arne Fredga*

It is shown that in aqueous acid solution optically active γ-methyl-γ-caprolactone is formed from the corresponding acid with completely retained configuration. This fact verifies the hypothesis that the acid-catalyzed reversible conversion of a γ-lactone to a hydroxy acid proceeds by mechanism $A_{AC}2$ even with two alkyl groups in γ-position.

In a previous paper [1] it was reported that, in aqueous solution, acid hydrolysis of the γ-lactone ring of terpenylic acid is a bimolecular reaction proceeding through an intermediate complex containing a molecule of water in addition to a proton. This result might be considered somewhat surprising when it is remembered that in terpenylic acid the alkyl-oxygen bond of the lactone ring is tertiary. It is a well-known fact that open-chain esters derived from primary and secondary alcohols are normally hydrolyzed by the bimolecular mechanism $A_{AC}2$ (acyl-oxygen cleavage), while esters from tertiary alcohols are subjected to alkyl-oxygen cleavage without water taking part ($A_{AL}1$).

However, on the part of terpenylic acid two mechanisms had to be considered, either of which should be recognizable by the observed kinetic characteristics. One of these is the $A_{AC}2$ mechanism, which has been shown to be utilized by γ-butyrolactone [2,3], the other a bimolecular mechanism involving acid hydrolysis and esterification with alkyl-oxygen cleavage. The latter, however, has hitherto apparently not been observed. From the fact that changing the hydroxyl group from primary to secondary to tertiary causes an appreciable increase in the rates of lactonization of γ-hydroxy acids and a decrease in the rates for the reverse reaction [4–6], it was concluded that mechanism $A_{AC}2$ applies. It was pointed out that these rate changes, accompanying substitution by alkyl groups, merely could be explained as a result of an increase in the power of ring formation.

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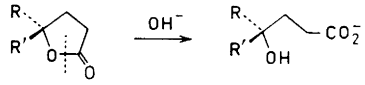
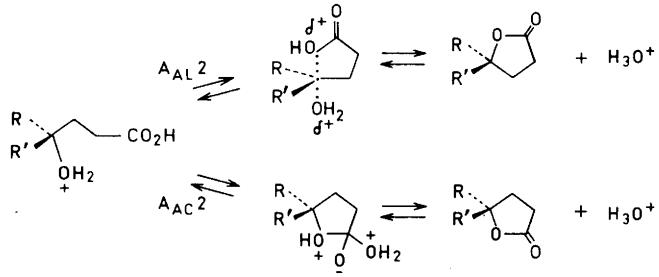
It may be worth noting, that Stevens and Tarbell [7] assumed that the above mentioned increase in rates of lactonization was indicative of a carbonium ion mechanism ($A_{AL}1$), when the alkyl-oxygen bond is tertiary.

It was thought that the simplest way to detect the point of bond split in the acid hydrolysis of a γ-dialkylated γ-lactone, or what is equivalent, the point of union in the reverse reaction, should be to make use of an optically active lactone, asymmetric in the γ-position. As the alkaline hydrolysis of various γ-lactones has been shown to obey a second order rate law [1,4,7], in accord with mechanism $B_{AC}2$, it was assumed that no configurational change should occur in this case:



Upon adding an excess of strong acid, the lactonization rapidly goes to an equilibrium mixture of lactone and γ-hydroxy acid containing 1 or 2 % of acid (Sebelius [4] reported 1.8 % of acid in the equilibrium mixture from γ-isocaprolactone). Lactonization by mechanism $A_{AL}2$, being a special case of the bimolecular mechanism of nucleophilic substitution (S_N2), then should give a lactone with inversed configuration, while ring closure by mechanism $A_{AC}2$ should reform the original lactone. (The intermediate complex has in the latter case been assigned the status of a molecule in analogy with what has been found for esters [8]).



The results from the experiments using optically active γ-methyl-γ-caprolactone are consistent with what is expected for lactonization by acyl-oxygen bonding. When reformed in aqueous alcoholic solution after alkaline hydrolysis, the resulting lactone had the calculated value of rotation in the same direction as the original one.

It should be emphasized that the above discussion has been limited to alkyl substituted γ-lactones. A phenyl group, however, in the γ-position may be expected to create a different situation. In fact some observations by Grace and Symons [9] indicate that the acid hydrolysis of γ-phenyl-γ-valerolactone proceeds by alkyl-oxygen cleavage.

Acknowledgement. The author is grateful to fil.mag. Hans-Gustav Jonsson for the supply of γ-methyl-γ-caprolactone.

EXPERIMENTAL

γ-Methyl-γ-caprolactone, prepared according to Cason *et al.*[10], was purified from accompanying ethyl levulinate by alkaline hydrolysis and subsequent lactonization of the hydroxy acid. The pure lactone had b.p. 106—107°/15 mm, n_D^{25} 1.4400.

The optically active lactone has earlier been prepared from the corresponding hydroxy acid by Kenyon and Symons [11]. The acid was resolved by means of brucine and (−)-1-phenylethylamine. The present author used (+)-1-(2-naphthyl)-ethylamine and (−)-1-phenylethylthiuronium chloride with moderate success.

Preparation of optically active γ-methyl-γ-caprolactone. 25.6 g (0.20 mole) of γ-methyl-γ-caprolactone was dissolved by warming in 30 ml of 6.7 N sodium hydroxide. The solution was neutralized to phenolphthalein with dilute hydrochloric acid and added to a boiling solution of 23.8 g (0.05 mole) of the neutral sulphate of (+)-1-(2-naphthyl)-ethylamine in 200 ml of water. The resulting clear solution was cooled down with swirling in ice-water for a few minutes and then left at room temperature for some hours and finally in the refrigerator over-night. Yield 24.2 g (76 %) of air-dried salt, m.p. 129—132°. Three recrystallizations from acetone gave 10.4 g of salt, m.p. 139—141°. The salt was treated with dilute sodium hydroxide, and the liberated amine extracted with ether. The aqueous phase was acidified with dilute hydrochloric acid, and the hydroxy acid extracted repeatedly with ether. The acid was lactonized by repeated distillation with benzene. Yield 2.65 g of lactone, b.p. 99°/10 mm, n_D^{25} 1.4402, α_D^{25} + 17.99° (2 dm). Kenyon and Symons [11] reported α_D^{25} + 7.15° (0.5 dm).

To the mother liquor from the first crystallization, previously warmed to 50°, was added a hot solution of 21.7 g (0.10 mole) of (−)-1-phenylethylthiuronium chloride in 25 ml of water. The salt began to separate almost immediately. After cooling to room temperature the mixture was left over night in the refrigerator. Yield 22.8 g (70 %) of air-dried salt. Unfortunately the salt tended to decompose when recrystallized from water, and two recrystallizations from acetone plus a little methanol did not seem to improve the quality of the product. The remaining salt (10.4 g, m.p. 128—132°) was shaken between dilute hydrochloric acid and ether and the aqueous phase extracted a few times more with ether, giving 2.4 g of lactone, b.p. 98°/9 mm, n_D^{25} 1.4402, α_D^{25} −11.78° (2 dm).

Lactonization in acid solution. As the lactone is not appreciably soluble in water the experiments were carried out in aqueous alcoholic solutions.

a) *Rotations in the appropriate solvent mixtures.* 0.2275 g of (+)-lactone dissolved up to 15 ml in water containing 22 % alcohol by volume. α_D^{25} + 0.17°, $[\alpha]_D^{25}$ + 5.6°.

0.2301 g of (+)-lactone dissolved up to 15 ml in 0.2 N hydrochloric acid containing 22 % alcohol by volume. α_D^{25} + 0.18°, $[\alpha]_D^{25}$ + 5.9°. The rotation was unchanged after 48 h.

b) *Procedure for lactonization.* 0.5788 g of (+)-lactone was shaken with 5 ml of 2 N sodium hydroxide until solution was complete and then diluted to 15 ml with aqueous alcohol (50 % by volume). The rotation, α_D^{25} + 0.29°, was unchanged after 15 h. To 10 ml of this solution was added 5 ml of 2 N hydrochloric acid. The resulting solution, containing 22 % alcohol by volume had α_D^{25} + 0.29° (calculated α_D^{25} + 0.30°). By potentiometric titration the final solution was found to be 0.219 N in hydrochloric acid.

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Received December 19, 1961.