Tetrahedron Letters No.35, pp. 3085-3094, 1965. Pergamon Press Ltd.
Printed in Great Britain.

ON THE KINETICS OF DEHYDRATION OF THE DIASTEREOMERIC 2,3-DIPHENYL-3-HYDROXYPROPIONIC ACIDS IN ACETIC ANHYDRIDE

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(Received 12 July 1965)

The mechanism of dehydration of β-hydroxy acids on heating or under the action of dehydration agents, contrary to the mechanism of dehydration of alcohols has been investigated to a rather limited extent.

Noyce et al. (1) showed that 3-aryl-3-hydroxypropionic acids are dehydrated under the action of sulfuric acid via a carbonium ion mechanism. In the case of 3-hydroxybutyric acid and 3-hydroxypropionic acid however the authors assumed as more probable an enolization mechanism.

Zimmerman and Ahramjian (2) investigated in a preparative manner the dehydration of the two diastereomeric 2,3-diphenyl-3-hydroxypropionic acids (I) in an 1:1 acetic anhydride - triethylamine mixture. Under these conditions they found no stereospecificity, but high stereoselectivity - only α-phenyl-trans-cinnamic acid was obtained. These authors assumed a carbanion mechanism.

Later Ivanoff, Marecoff and Amidjine (3) also studied in a preparative manner the dehydration of some aryl-substituted 3-hydroxypropionic acids on heating in acetic anhydride. In the case of I they obtained α-phenyl-trans-cinnamic acid and trans-stilbene (from the method of purification and m.p. it may be concluded that these authors used the threo isomer in their experiments).

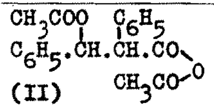
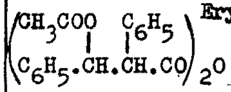
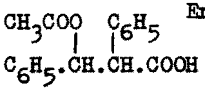
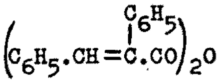
It is the purpose of the present study to examine the dehydration in acetic anhydride of the two diastereomeric acids I in order to establish whether the reaction takes place stereospecifically in the absence of triethylamine and further to study the kinetics and mechanism of the reaction.

Preparative studies

The hydroxy acids were obtained and purified according to (4). The acetic anhydride used, twice rectified, contained ca. 0,5% CH_3COOH, according to gaschromatographic determinations (Silicone-elastomer - E 301 at 120°C).

Heating 0,5 g threo I with 2 ml acetic anhydride in a sealed tube at 70°C for 5 hours lead to the mixed anhydride of threo-3-acetoxy-2,3-diphenylpropionic acid with acetic acid (II), which was obtained in 76% yield after removing the excess of acetic anhydride under reduced pressure at 40°C and subsequent recristallization from benzene-heptane. At 100°C for one hour however only the simple anhydride of threo-3-acetoxy-2,3-diphenylpropionic acid (III) was isolated in 55% yield (a certain amount of solid product was also isolated which according to IR- and UV-spectra consisted of a mixture of the anhydrides of the acetoxy acid and the unsaturated acid). Similar behaviour was observed in the case of erythro-I. Addition of water to the reaction mixture at room temperature hydrolyses the mentioned anhydrides to the 3-acetoxy-2,3-diphenylpropionic acids (IV). Heating α-phenyl-trans-cinnamic

TABLE 1.

Compounds		Analytic Data C % Calc.	Analytic Data C % Found	Analytic Data H % Calc.	Analytic Data H % Found	IR-Frequencies* [cm⁻¹] ν_{CO}	IR-Frequencies* [cm⁻¹] ν_{CH_3}	UV - Absorption Bands λ [mμ]	UV - Absorption Bands E	M. p. [°C]
 $\mathrm{C_6H_5.\overset{CH_3COO}{CH}.\overset{C_6H_5}{CH}.CO{-}O{-}COCH_3}$ (II)	Threo	69,92	70,32	5,56	5,78	1760;1828 (CCl_4)	1375 (CCl_4)	-	-	85 - 87 (from benzene-heptane or ether-hexane)
 $\left(\mathrm{C_6H_5.\overset{CH_3COO}{CH}.\overset{C_6H_5}{CH}.CO}\right)_2\mathrm{O}$	Erythro	74,17	73,66	5,49	5,21	1756;1824 (CCl_4)	1375 (CCl_4)	-	-	131 - 133 (from heptane)
(III)	Threo	74,17	74,27	5,49	5,56	1756;1824 (CCl_4)	1375 (CCl_4)	-	-	141 - 143 (from benzene-heptane)
 $\mathrm{C_6H_5.\overset{CH_3COO}{CH}.\overset{C_6H_5}{CH}.COOH}$	Erythro	71,82	71,93	5,67	5,73	1705;1735 (nujol)	1375 (nujol)	-	-	180 - 185 (from heptane)
(IV)	Threo	71,82	72,20	5,67	5,74	1705;1735 (nujol)	1375 (nujol)	-	-	194,5 - 198,5 (from benzene-hexane)
 $\left(\mathrm{C_6H_5.CH{=}\overset{C_6H_5}{C}.CO}\right)_2\mathrm{O}$	Cis	83,70	83,51	5,15	5,34	1743;1803 (CCl_4)	-	292 (hexane)	28500	142,5 - 143,2 (from ether)
(V)	Trans	83,70	83,65	5,15	5,28	1723;1782 (CCl_4)	-	291 (hexane)	29600	113 - 117 (from benzene-heptane or ether-hexane)

* IR-Spectrophotometer UR-10-Carl Zeiss-Jena; KBr-cells 1mm; 1% in CCl_4 or mull in nujol;NaCl-prism

acid, as well as the cis isomer at 135°C with acetic anhydride gave only the corresponding simple anhydride (V).

As the abouve compounds have not been described in the literature, the analytic data and the physical constants are presented in table 1.

The same mixture of α-phenylcinnamic acids (in the form of anhydrides) was obtained from both diastereomers on heating in an excess of acetic anhydride I or III, respectively, for several hours at 140°C. After traitement in a preparative manner (5) this mixture was found to contain mainly the trans-isomer - the amount of the cis-isomer was ca.10%* . Threo I gave also an insignificant amount of stilbene (under 0,5% according to UV-spectra estimation). The amount of stilbene obtained is increased on heating threo I in a 1:1 mixture of $CH_3COOH/(CH_3CO)_2O$. No formation of stilbene is observed when heating preliminarily, at 70°C, the reaction mixture in order to convert I into II.

Kinetic studies

The kinetics of the dehydration reaction were studied at four temperatures in the 125,9 - 140,9 °C interval. Sealed tubes were used (twelve for each run) with 1,5 ml 0,4% solution of the respective hydroxy acid in acetic anhydride, containing ca. 0,5% acetic acid. In order to convert the hydroxy-acid into II** the sealed tubes were initially heated for 5 hours at 70°C, under which conditions no elimination could be

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*A separate experiment showed that under these conditions a detectable, but considerably slower, isomerisation of the α-phenyl-cis-cinnamic acid to the trans isomer takes place.

**In accordance with the above mentioned observations, II will convert into III at the temperature of the kinetic experiments.

detected. The sealed tubes were then placed in an ultrathermostate "Höppler" at the required temperature and the tubes were then taken out at suitable intervals. The reaction was quenched by cooling with cold water. The infinity concentration of the product was determined after eight half-lives. The course of the reaction was followed by determining the concentration of the α-phenylcinnamic anhydrides obtained, by measuring in methanolic solutions the peak at λ=291 mμ (due to the conjugated double bond). The extinction coefficients were the same for both isomers. The absorption maximum in methanolic solution remained practically constant for the first 2-3 hours after the dilution of the samples with methanol. After this period however the extinction slowly decreased and the peak shifted to shorter wave lengths. The measurements were carried out 2 hours after dilution of the samples using an automatic recording UV-spectrophotometer - Lères T2D. It was found that the presence of unchanged III, acetic anhydride, acetic acid and methylacetate did not interfere with the measurements.

The reaction was found to be first order with regard to the hydroxy acid as may be seen from the plot log(c-x)/t (fig.1).

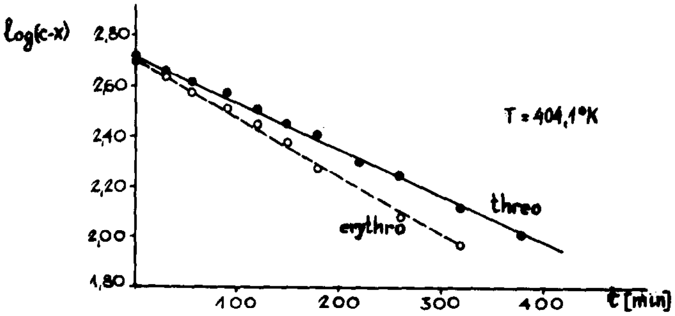


FIG. 1.

The rate constant values are arithmetic means and the errors were assessed for 99% certainty.

The plot of $\log \frac{K}{T}$ against $\frac{1}{T}$ gave a good straight line (fig.2), which shows that the entropy and enthalpy of activation remain practically constant in the temperature interval investigated. $\Delta S^{\neq}$ and $\Delta H^{\neq}$ were computed by the least squares method from the equation $\log \frac{K}{T} = \log \frac{k}{h} + \frac{\Delta S^{\neq}}{4{,}574} - \frac{\Delta H^{\neq}}{4{,}574\ T}$. The errors are estimated according to the Student-criterion for 99% certainty. The values of the rate constants at different temperatures and those of the activation parameters are given in table 2.

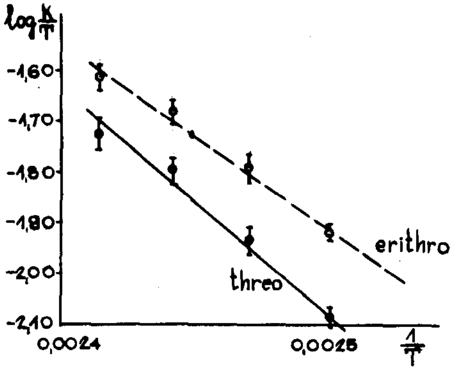


FIG. 2.

In order to determine the effect of the presence of acetic acid on the dehydration process, the kinetics of elimination of threo III were followed in solution of acetic acid free acetic anhydride, as well as in acetic anhydride containing 2, 5 and 10 per cent acetic acid respectively. The acetic anhydride ($n_D^{20} = 1{,}3904$) used in this serie of experiments was purified according to (6) and showed no acetic acid content when subjected to gaschromatographic analysis.

TABLE 2.

	Rate Constants $K.10^5$ [sec^{-1}]				Activation parameters		
	T [°K]				ΔH≠ [kcal]	ΔS≠ [e. u]	ΔF≠ [kcal] at 406,6 °K
	399,1	404,1	409,1	414,1			
Erythro I	4,8± ±0,2	6,6± ±0,4	8,5± ±0,4	10,1± ±0,6	15,4± ±0,13	- 40,1± ±0,13	31,7± ±0,15
Threo I	3,5± ±0,1	4,7± ±0,3	6,5± ±0,4	7,7± ±0,6	16,9± ±0,15	- 37,1± ±0,16	32,0± ±0,17

The kinetic measurements were carried out as described above at 135,9°C. The rate constants are listed in table 3. These data show that the rate of elimination decreases proportionally to the square root of the acetic acid concentration. The same effect is also observed in the case of erythro I, since the ratio $K_{erythro I} / K_{threo I}$ = 1,24, observed at 135,9°C in acetic anhydride containing 9% acetic acid, is similar to the ratio, observed in the case of the dehydration in acetic anhydride with 0,5% acetic acid at 135,9, i.e. 1,30.

TABLE 3.

% Acetic Acid in Acetic Anhydride	Rate Constants of Threo III at 135,9°C $K.10^5$ [sec^{-1}]
0,0	13,7 ± 1,7
2,0	3,6 ± 0,5
5,0	1,5 ± 0,14
10,0	0,71 ± 0,07

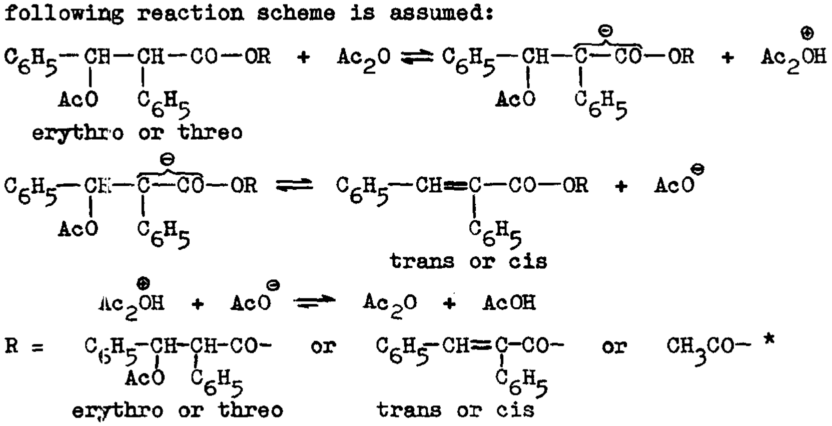
It was further established, in a separate experiment, that prolonged heating (50 hours at 136,5°C) of α-phenyl-trans-cinnamic acid in a mixture of $Ac_2O : AcOH = 2 : 1$ gave no detectable amounts of III, which indicated that the elimination reaction studied proceeds practically as an irreversible reaction.

Discussion of the mechanism of elimination

Comparison of our data with those of (2, 5) shows that the rate of dehydration of the diastereomers I decreases with the change of medium in the order:

$Ac_2O + Et_3N$ (1:1) > $Ac_2O + AcONa$ > Ac_2O > $Ac_2O + AcOH$ (10:1)

This order suggests that the mechanism of the reaction does not change significantly with the change of the basicity of the medium. The carbanion mechanism advanced by Zimmerman and Ahramjian (2) explains well our experimental data if the following reaction scheme is assumed:



$$\underset{AcO}{C_6H_5-\underset{|}{C}H}-\underset{C_6H_5}{\underset{|}{C}H}-CO-OR + Ac_2O \rightleftharpoons \underset{AcO}{C_6H_5-\underset{|}{C}H}-\underset{C_6H_5}{\underset{|}{\overset{\ominus}{C}}}-CO-OR + Ac_2\overset{\oplus}{O}H$$

erythro or threo

$$\underset{AcO}{C_6H_5-\underset{|}{C}H}-\underset{C_6H_5}{\underset{|}{\overset{\ominus}{C}}}-CO-OR \rightleftharpoons C_6H_5-CH{=}\underset{C_6H_5}{\underset{|}{C}}-CO-OR + Ac\overset{\ominus}{O}$$

trans or cis

$$Ac_2\overset{\oplus}{O}H + Ac\overset{\ominus}{O} \rightleftharpoons Ac_2O + AcOH$$

$$R = \underset{AcO}{C_6H_5-\underset{|}{C}H}-\underset{C_6H_5}{\underset{|}{C}H}-CO- \quad \text{or} \quad C_6H_5-CH{=}\underset{C_6H_5}{\underset{|}{C}}-CO- \quad \text{or} \quad CH_3CO-\ ^*$$

erythro or threo trans or cis

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*Zimmerman and Ahramjian assumed that under their conditions the diastereomers I are dehydrated under the form of the mixed anhydrides II; our experiments do not completely exclude the participation of certain although insignificant amounts of II.

The above mechanism is supported by the very large negative entropies of activation. A similar value (-50 e.u.) was found by Bordwell et al. (7) for the elimination of 1-acetoxy-2-nitro-1-phenylcyclohexane in chloroform-ethanol mixture with piperidine as catalyst. The authors also assumed a carbanion mechanism. These values are comparable to certain other reactions in nonpolar media where ions are formed from neutral molecules (8).

An alternative path for the dehydration in acetic anhydride, particularly in the presence of acetic acid, as opposed to that passing via a true carbanion is the reaction proceeding via enol similarly to the mechanism adopted by Noyce and Reed (9) for the dehydration of 4-hydroxy-4-phenyl-2-butanone and its p-nitro derivative under the action of 1,0M sulfuric acid. It can be easily shown however that in such a case the rate of elimination should increase with the increase of acetic acid concentration. Another possibility to be considered is a carbonium ion mechanism similar to that assumed by Noyce et al. for the dehydration of 3-aryl-3-hydroxypropionic acids in sulfuric acid medium (1). Our present kinetic data are insufficient for making a definite choice between this carbonium ion and the above carbanion mechanism since both are consistent with the observed effect of acetic acid on the rate of elimination. The substrates and particularly the experimental conditions of Noyce et al. (1) differ however quite significantly from ours. In sulfuric acid the β-hydroxy group will be protonated to a much higher degree and consequently its cleavage will be much enhanced in comparison with that in acetic anhydride/acetic acid medium. On the other hand in the case of the 2,3-diphenyl-3-hydroxypropionic acids studied the α-hydrogen atom will be considerably more labile than that in the 3-aryl-3-hydroxypropionic acids. These considerations and the above mentioned decrease of the rate of elimination with the decrease of basicity of the medium leads us to consider as more probable in our case the carbanion mechanism.

As in the case discussed it is not a single but several substances which undergo elimination, no straight forward explanation may be given to the fact that the erythro isomer reacts about 1,3 times faster then the threo one.

The investigations are continuing.

Acknowledgement - The authors wish to thank Dr. I.G.Pojarlieff for helpful discussion during the writing of the manuscript.

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