Studies of the Isomerization of Unsaturated Carboxylic Acids. II.[1] The Thermal Rearrangement of Citraconic Acid to Itaconic Acid in Aqueous Solutions

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(Received March 22, 1975)

The thermal reaction of citraconic acid (**2**) in water gives a mixture of products similar to that obtained from itaconic acid (**1**) in water. After 22 h at 170 °C, the equilibrium composition about 74%, 18%, and 8% **1**, **2**, and mesaconic acid respectively. At the optimum conditions (170 °C for 3 h), the yield of **1** is 65%. The mechanism of the reaction is discussed.

Itaconic acid (**1**) is a relatively innocuous vinyl monomer and has been used extensively in industry.[2] This important acid has been conveniently prepared from citraconic anhydride.[3] It is interesting that, in this preparative method, terminal olefin **1** is obtained from citraconic acid (**2**) by thermal rearrangement in water;[4] this is in contrast to the general concept that internal olefins are thermodynamically more stable than the corresponding terminal ones. In spite of extensive studies of base-catalyzed rearrangements[5] and isomerizations[5] of unsaturated acids[6–8] and other compounds,[9,10] similar reactions[5] under neutral to acidic conditions have not received much attention.

The present report will describe the results of studies of the factors that govern equilibration between **1** and **2** under neutral to acidic conditions, and a plausible mechanism of the reaction will be proposed. Under the present conditions, **1** is the most abundant component of the three acids, whereas, under basic conditions, mesaconic acid (**3**) predominates over the others. Thus, the equilibrium between **1** and **2** is practically more important than that between **2** and **3**.

Experimental

All the melting and boiling points are uncorrected.

Materials. Commercial-grade itaconic acid (methylenesuccinic acid) (**1**) was purified by recrystallization from water. The following compounds were prepared by the methods described in the literature: citraconic acid (methylmaleic acid)[11] (**2**), mp 90 °C; mesaconic acid (methylfumalic acid)[11] (**3**), mp 204 °C; citramalic acid (2-hydroxy-2-methylbutanedioic acid)[12] (**4**), mp 116 °C, and paraconic acid (3-carboxy-4-butanolide)[13] (**5**), mp 54 °C.

The methyl ester of **5** was isolated by distillation from the reaction mixture obtained under the conditions that give **5** in the highest yield (170 °C, 22 h) and was identified by the aid of NMR and elemental analyses.

The water was distilled prior to use, and the deuterium oxide was 99.8% pure. The organic solvents were purified by ordinary methods. The other reagents were of a reagent grade.

Procedure. *Reactions in Aqueous Solutions*: A mixture of 1.0 g (7.7 mmol) of **2** and 2.0 g (0.11 mol) of water was sealed into a glass tube, which was then heated to an appropriate temperature in an autoclave filled with water. For the analysis, all the acids were converted into the corresponding methyl esters by the following treatment. From the reaction mixture, the water was removed as benzene azeotrope, and the acids in the residue, together with the glutaric acid added as an internal standard of gas chromatography, were esterified with methanol by refluxing for 5 h in the presence of sulfuric acid. After the removal of the methanol, the mixture was neutralized with an aqueous sodium carbonate and the esters were extracted with benzene. For runs under basic conditions, the reaction mixture was neutralized with sulfuric acid before the water was removed from the mixture. The organic acids were extracted from the residue with hot methanol and worked up similarly. The reactions of the other acids in water were carried out similarly.

Reactions in Deuterium Oxide: A mixture of 1.0 g of **1** and 2.2 g of deuterium oxide was heated at 170 °C for 3 h. The compositions of the products were determined from glc, as will be described below. The deuterium content in α-methylene of **1** was calculated from the relative intensities at δ 6.3 $(=\mathrm{CH_2})$, 5.8 $(=\mathrm{CH_2})$, and 3.3 $(-\mathrm{CH_2}-)$ in the NMR spectrum (in D_2O).

Analysis. The benzene extracts were analyzed by gas chromatography using a BDS 90m capillary column with Hitachi Perkin-Elmer F6-D at 150 °C. It was confirmed that no rearrangement took place in the course of the esterification and the gas-chromatographic analysis. The NMR spectra were recorded on a Varian T-60A spectrometer.

Results and Discussion

Thermal Reaction of 2 in an Aqueous Solution. Reactions were carried out in the temperature range from 140 °C to 200 °C. No reaction occurred at 100 °C. The gas chromatogram of the reaction mixture revealed that the mixture consisted of five components (**1**—**5**). The main product of the reaction

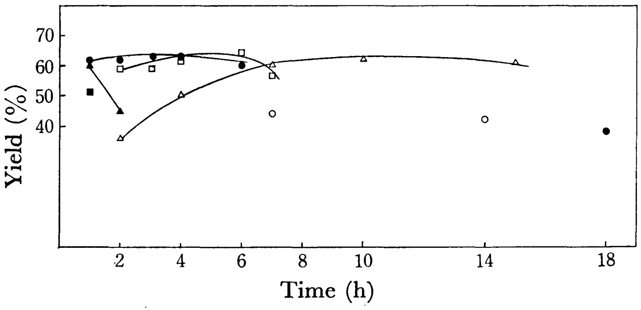


Fig 1. The yield of **1** from the rearrangement of **2** in an aqueous solution.
2, 1.0 g; H_2O, 2.0 g.
○; 140 °C, △; 150 °C, □; 160 °C, ●; 170 °C, ▲; 180 °C, ■; 200 °C.

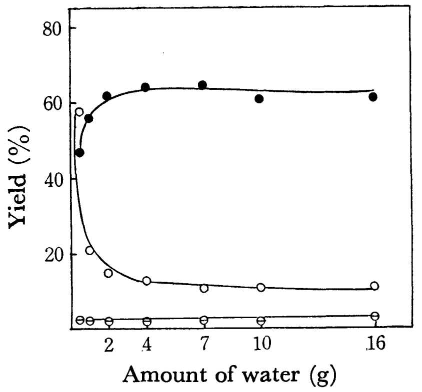
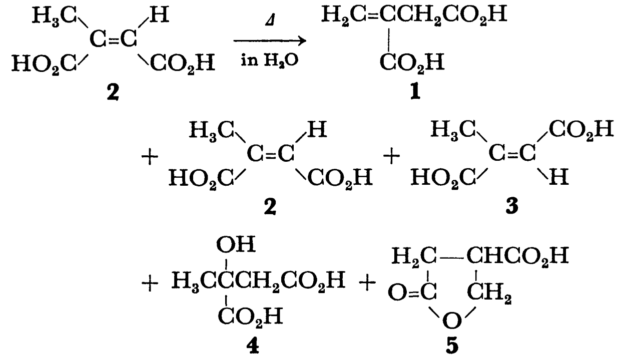


Fig. 2. Effect of the amount of water on the products.
2, 1.0 g; Temp, 170 °C; Time, 3 h.
●; **1**, ○; **2**, ⊖; **3**.

was **1**, and the yield was 65%, as is shown in Figs. 1 and 2. Figure 2 also reveals that the maximum yield of **1** can be achieved when the reaction mixture contains at least twice as much water as **2** in weight. Small amounts of other products (**3**, **4**, and **5**) besides **1** and **2** were formed at higher temperatures or by prolonged heating.



An Equilibrium between the Reaction Products. Reactions starting from **1** and **2** gave mixtures with the same equilibrium composition, whereas those from **3**, **4**, and **5** took place with difficulty and large portions of the starting acids were recovered (Table 1). Table 1 and Fig. 3 show the presence of an equilibrium between **1** and **2**, from which the equilibrium composition at 170 °C was calculated to be 74% **1**, 18% **2**, and 8% **3**. Neither aprotic (acetonitrile, acetone, and diglyme) nor protic (isovaleric acid and methanol) organic solvents were effective for the reaction at 170 °C, which implies that water is acting not only as a solvent but also as a reagent.

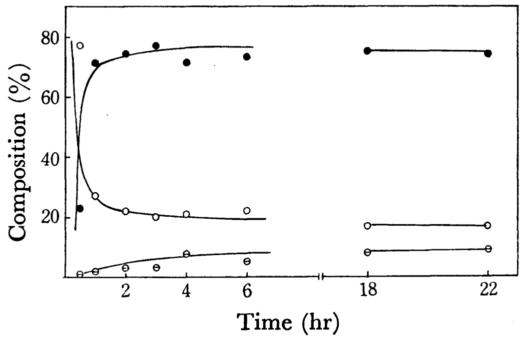
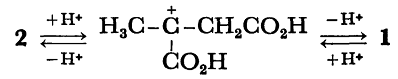


Fig. 3. An equilibrium between **1** and **2**.
2, 1.0 g; H_2O, 2.0 g; Temp, 170 °C.
●; **1**, ○; **2**, ⊖; **3**.

Since both the formation of **3** from **2** and reactions starting from **3**, **4**, or **5** are too slow to account for the rapid rearrangement between **1** and **2**, the possibility of these acids being intermediates of the reaction can be discarded.

It is quite plausible that the reaction proceeds *via* a protonation-deprotonation process, because the reaction mixture is slightly acidic under the present conditions.



$$\mathbf{2} \underset{-H^+}{\overset{+H^+}{\rightleftarrows}} H_3C\text{-}\underset{\displaystyle CO_2H}{\overset{+}{C}}\text{-}CH_2CO_2H \underset{+H^+}{\overset{-H^+}{\rightleftarrows}} \mathbf{1}$$

However, this mechanism cannot explain the rapid hydrogen-deuterium exchange that accompanies the rearrangement. The NMR analyses of the recovered **1** showed that 65% of the α-methylene protons were exchanged by deuterium when **1** was heated in deuterium oxide for 3 h at 170 °C, whereas practically no exchange was observed at the terminal methylene group. The exchange did not take place when the mixture was heated at 110 °C for 3 h. When **2** was heated in deuterium oxide at 170 °C for 3 h, no exchange was observed at the methyl protons of the

TABLE 1. THERMAL REACTION OF FIVE ACIDS IN AQUEOUS SOLUTION[a)]

Starting acid	Reaction time, h	Yield, %						Composition, %		
		1	2	3	4	5	Total	1	2	3
1	3	62.5	13.8	2.2	3.4	1.1	83.0	79.6	17.6	2.8
2	3	63.4	13.4	2.2	9.1	1.0	89.1	80.2	17.0	2.8
3	3	3.9	0.9	94.0	—	—	98.8	3.9	0.9	95.1
4	3	2.2	1.7	0.4	89.8	—	94.1			
5	3	1.7	0.2	—	0.4	84.7	86.9			
1	22	34.0	8.2	3.7	5.8	21.0	72.6	74.2	17.8	8.0
2	22	33.2	7.6	4.1	11.2	18.6	74.6	74.0	17.0	9.0
3	22	7.8	2.1	62.8	2.0	2.5	83.4	10.7	2.9	86.4
4	22	6.6	1.9	1.5	84.3	1.0	94.3	65.7	19.4	14.7
5	22	11.7	2.3	0.6	1.3	53.8	69.8	80.0	16.0	4.0
1[b)]	3							91.5	5.8	2.6
2[b)]	3							66.1	33.0	0.9

a) Acid, 1.0 g; H_2O, 2.0 g; Temp, 170 °C. b) Reaction in D_2O; composition from glc analysis.

TABLE 2. EFFECT OF ADDITIVES ON THE REACTION[a)]

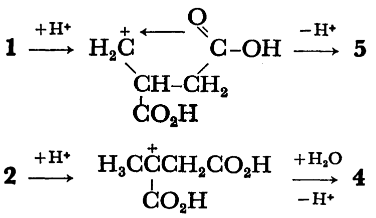
Starting acid	Additive (mg)	Reaction time, h	Yield, %						Composition, %		
			1	**2**	**3**	**4**	**5**	Total	**1**	**2**	**3**
1	None	4	65.3	14.2	1.2	1.0	1.1	82.7	81.8	17.6	1.4
2	None	4	62.5	14.7	2.6	7.6	1.3	88.7	78.4	18.4	3.3
1	H_2SO_4(0.1)	4	57.8	13.4	0.9	1.6	7.2	80.9	80.2	18.5	1.3
1	H_2SO_4(10)	4	61.4	11.2	0.7	0.9	6.1	80.3	83.8	15.3	0.9
2	H_2SO_4(100)	4	44.2	32.6	2.5	15.3	2.0	96.6	55.7	41.1	3.2
1	H_2SO_4(2000)[b)]	5	51.2	1.3	1.4	—	31.7	85.5	95.0	2.4	2.6
2	H_2SO_4(2000)[b)]	5	1.7	57.0	3.2	26.8	—	88.7	2.7	92.1	5.2
3	H_2SO_4(2000)[b)]	5	0.5	1.2	79.0	1.4	—	82.0	0.6	1.5	97.9
2	NaOH(16)	4	14.9	49.4	3.7	—	—	68.0	21.9	72.7	5.4
1	NaOH(50)	4	49.6	21.4	19.8	—	3.9	94.7	54.7	23.6	21.8
1	NaOH(240)	4	14.5	17.9	53.8	0.8	2.2	89.2	16.8	20.8	62.4
1	NaOH(1500)[c)]	10	20.1	23.2	39.6	3.9	2.6	89.4	24.2	28.0	47.8
2	NaOH(1500)[c)]	10	16.0	17.4	43.2	4.7	4.7	86.0	20.9	22.7	56.0
3	NaOH(1500)[c)]	10	16.6	19.2	48.4	5.5	7.4	97.2	19.7	22.8	57.4

a) Acid, 1.0 g; H_2O, 2.0 g; Temp, 170 °C. b) Refluxed. c) Refluxed with 5.0 g of 30% NaOH solution.

recovered **2**, whereas 85% of the α-methylene protons in **1** produced were exchanged by deuterium. If the intermediate carbonium ion is responsible for the reaction, the terminal methylene-protons must be exchanged by deuterium faster than those in the α-methylene group.

The above observation as well as the effect of additives (*vide infra*) establishes that the reaction involves a carbanion as an intermediate, or that water acts as a general base, in spite of acidic reaction conditions.

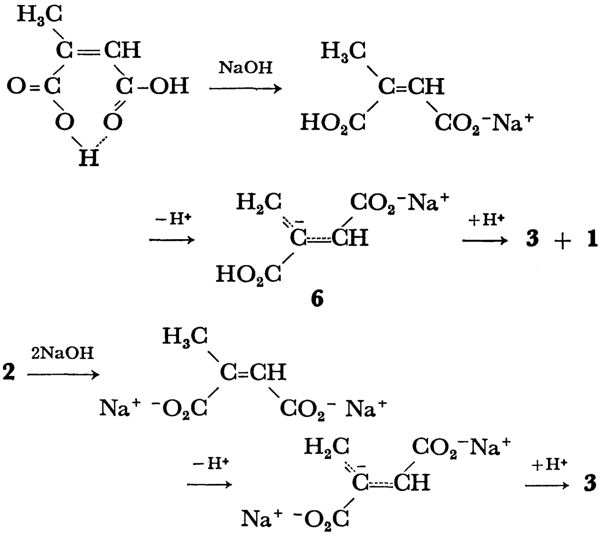
The Effect of Additives on the Reaction. The addition of sulfuric acid not only dramatically retards the rearrangement between **1** and **2**, but also changes the product distribution completely (namely, the distribution of **4** and **5**). This fact again disproves the protonation-deprotonation mechanism for the equilibration. On the other hand, the increase in the yields of **4** and **5** (from **2** and **1** respectively) indicates that these products might be produced *via* carbonium ion intermediates. It should be noted that even *cis-trans* interconversion (**2**⇌**3**) does not proceed in the presence of sulfuric acid.



Sodium hydroxide also retards the rearrangement, but increases the yield of the isomerized product, **3**. The dependency of the product composition (at 170 °C, after 4 h) on the amount of sodium hydroxide added is exemplified by the reaction of **2**, shown in Fig. 4. That these are not equilibrium compositions (except for the values at the zero sodium hydroxide concentration) was confirmed by the fact that the yield of **3** predominated over those of other acids at longer reaction times.

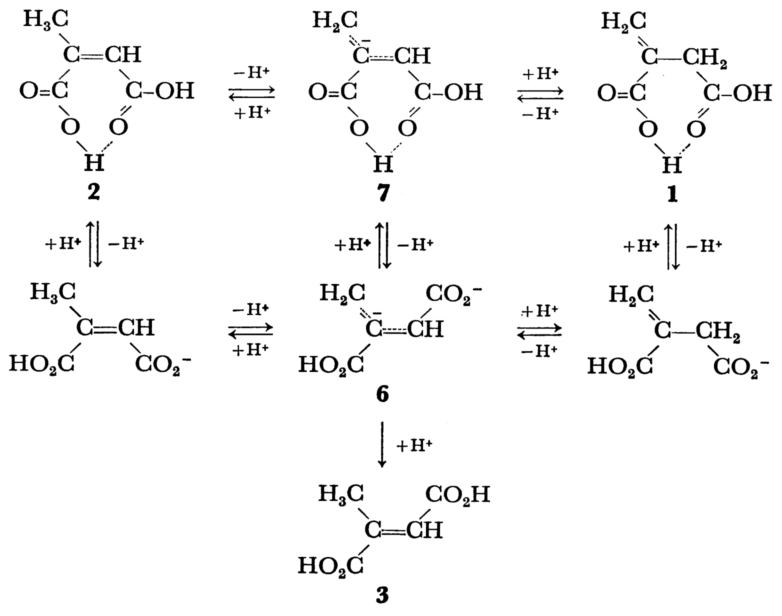
The effect of sodium hydroxide can be interpreted as follows. The added base facilitates the dissociation of carboxylic acids to the corresponding carboxylate anions. Since proton abstraction from a carboxylate anion is a more difficult process than that from an undissociated acid, the rearrangement which proceeds *via* a carbanion intermediate takes place with difficulty from a carboxylate anion. Thus, the species[14)] that undergo the rearrangement are undissociated acids in the range of $0 \leqq [NaOH]/[\mathbf{2}] < 1$, whereas a slower rearrangement takes place only from monocarboxylate anions of dicarboxylic acids in the range of $1 \leqq [NaOH]/[\mathbf{2}] \leqq 2$. As may be seen from Fig. 4, dicarboxylate anions do not undergo the rearrangement without a specific hydroxide ion catalyst, whereas excess sodium hydroxide ($[NaOH]/[\mathbf{2}] > 2$) catalyzes the reaction of dicarboxylate anions.

Undissociated *cis*-acid (**2**) might be stabilized by intramolecular hydrogen bonding,[15)] which is expected to be overcome by ion-pair formation when sodium hydroxide is added to this acid.



Since **6** no more retains the force to hold the *cis*-configuration, it affords a more stable *trans*-acids rather than **2** when reprotonation takes place. The same is true for **1**.

Although the intramolecular hydrogen bonding in **1** and **2** has not been proved directly, its importance in



Scheme 1.

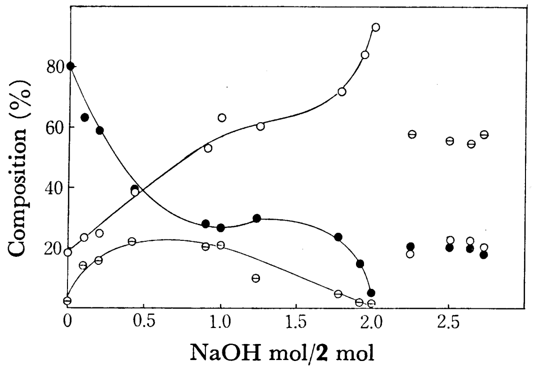


Fig. 4. The effect of sodium hydroxide on the composition.

2, 1.0 g; H_2O, 2.0 g; Temp, 170 °C; Time, 4 h. ●; **1**, ○; **2**, ⊖; **3**.

keeping **3** a minor component under acidic conditions and a major one under basic conditions is supported by the following evidence: the dimethyl ester of **2** isomerized to the *trans*-isomer under neutral conditions,[16] and crotonic acid is the main product in the thermal rearrangement of butenoic acids in an aqueous solution.[17] Thus, the *cis*-configuration is more stable than the *trans*-configuration only for dicarboxylic acids.

All of the present results support the idea that the most plausible mechanism for interconversion between **1**, **2**, and **3** in an aqueous solution is that shown in Scheme 1.

Isotope Effect. When the reaction is carried out in deuterium oxide, the rearrangement from **2** to **1** proceeds as quickly as that in water (protium oxide), whereas that from **1** to **2** is dramatically retarded (Table 1). This result is not accounted for by the solvent-isotope effect, because proton abstractions from **1** and **2** should result in inverse isotope effects and protonation to the intermediate carbanion (**7**) is a process which the two reactions have in common. It should be remembered that **1** undergoes hydrogen-deuterium exchange at the α-methylene group faster than it does the rearrangement under the present conditions, and that the reaction of **1** in deuterium oxide is that of the α-deuterated compound. On the other hand, rather small portions of **2** are deuterated under the same conditions; the intermediate carbanion (**7**) formed from **2** prefers to give the rearranged product, **1**, and only small portions of it return to **2** by deuteration. Thus, the present author believes that the isotope effect observed presently indicates that the rate-determining step of the rearrangement is the process of proton abstraction to form **7**; this is in accord with the discussion in the previous section. The energy diagram may be visualized as is illustrated in Fig. 5.

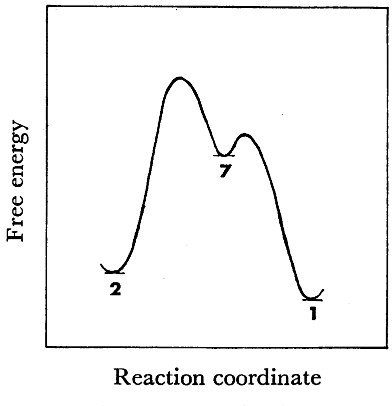


Fig. 5. Schematic energy profile for the rearrangement between **1** and **2**.

Since the reaction is run in a sealed tube at an elevated temperature, the author unfortunately has no device to obtain precise kinetic data to support the mechanism proposed here.

The author wishes to thank Professor Emeritus Sango Kunichika of Kyoto University for his encouragement throughtout this work. He is also grateful to Professors Shinzaburo Oka, Yasumasa Sakakibara, and Atsuyoshi

Ohno for their continuous guidance and helpful discussions.

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14) There are several examples in which the species that exist in smaller amount contribute to the rearrangement. See, for example, J. March, "Advanced Organic Chemistry," McGraw-Hill Book, Co., New York, N. Y. (1968), p. 517.

15) This is true even in aqueous solution because intramolecular hydrogen bonding is stronger than intermolecular one; (a) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Reinhart and Winston, Inc., New York, N. Y. (1959), p. 211. The acidity of **2** is larger than that of water; (b) $pK_a=2.3$, 6.1 for **2**, H. W. Ashton and J. R. Partington, *Trans. Faraday Soc.*, **30**, 598 (1934); (c) $pK_a=16$ for water, R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y. (1959).

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