cis-trans Isomerizations. I. The Mechanism of a Catalyzed Isomerization of Maleic Acid to Fumaric Acid*

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While it has been known for many years that the isomerization of maleic acid to fumaric acid may be catalyzed by inorganic acids and salts,[1] the mechanism of the reaction is still a matter of controversy. It has been suggested[2] that in cis–trans isomerizations catalyzed by strong acids, one of the doubly bonded carbons shares a pair of electrons with a proton, leaving the other carbon with six electrons free to rotate about a single bond. Dissociation of the proton after rotation would then produce the more stable isomer. However, studies by Horrex,[3] using deuterium chloride as the catalyst, eliminated such intermediates. He found that in the isomerization of maleic acid there was no deuterium exchange with the protons attached to the carbons of the double bond. Mayo and Walling[4] have recently pointed out that in cases such as this, when a carbonyl group is conjugated with the ethylene linkage, the catalyst may associate with the carbonyl group. The double bond is then assumed to shift during isomerization, leaving an electron deficient carbon and a single bond around which rotation may occur. This mechanism satisfactorily explains Horrex's results.

The mechanisms mentioned attribute the catalysis by inorganic acids to their ability to donate protons. It might thus be expected that in aqueous solution strong acids, due to nearly complete ionization, would exert similar catalytic effects. However, studies reported in this communication have shown that this expectation is not realized. It was found, for example, that hydrochloric acid is more than fifty times as effective a catalyst as perchloric acid. These results, together with the reported[1b] strong catalysis of isomerization by alkali thiocyanates, suggested that the anion also played an important role in the reaction.

As a consequence of a study of bromine addition

to maleic acid (the results to be published later), a plausible mechanism for the isomerization, involving both a proton and an anion, was suggested. In this communication this mechanism is presented. Measurements on the rates of isomerization of maleic acid in water with salts and strong acids as catalysts have been made, and the results have been found to be in agreement with the proposed mechanism.

Experimental

Materials.—The maleic acid, an Eastman Kodak Co. product, was recrystallized three times from hot water, m. p. 139°. The salts and acids were either Merck reagent grade or Baker C. P. chemicals.

Procedure.—The isomerization experiments were carried out as follows: 6 or 8 soft glass test-tubes each containing 10 cc. of an aqueous solution with known concentrations of catalyst and maleic acid were sealed, and the tubes were heated at a fixed temperature (usually 99.9°) in the dark. At selected intervals the tubes were withdrawn, immersed in an ice-bath, and shaken for an hour. They were then opened and the precipitated fumaric acid was filtered off with suction on a small Hirsch funnel. The precipitates were carefully washed with two 1-cc. portions of ice water and were then added to beakers containing an excess of standard alkali. The remaining alkali was titrated with standard acid, using phenolphthalein indicator.

Experimental Results

Rate constants were calculated for a reaction of first order with respect to maleic acid concentration and one of second order with respect to it; i. e., using expressions

$$k_1 c = \frac{2.303}{t_2 - t_1} \log \frac{a - x_1}{a - x_2}$$

and

$$k_2 c = \frac{1}{t_2 - t_1} \left[\frac{1}{a - x_2} - \frac{1}{a - x_1} \right]$$

respectively, where k_1 represents the first order constant, k_2 the second order constant, c the concentration of catalyst, and the other symbols have their usual meanings. The calculations were based on the amount of fumaric acid precipitated at 0° after a given interval. These values, as determined above, had to be corrected for the solubility of fumaric acid at 0° (0.035 M).

In most runs using the halogen acids as catalysts, it was found that the values of $k_2 c$ were more

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(1) (a) Skraup, Monatsh., 12, 118 (1891); (b) Terry and Eichelberger, THIS JOURNAL, 47, 1402 (1925); (c) Anschütz, Ann., 254, 173 (1889); (d) Fittig, ibid., 259, 30 (1890); (e) Michael, J. prakt. Chem., 52, 323 (1895).

(2) Price and Meister, THIS JOURNAL, 61, 1595 (1939).

(3) Horrex, Trans. Faraday Soc., 33, 570 (1937).

(4) Mayo and Walling, Chem. Rev., 27, 433 (1940).

nearly constant than the values of k_1c. This is illustrated by the typical set of data given in Table I. It is observed that the values of k_1c continually drop off as the reaction proceeds while the values of k_2c rise somewhat at first and then drop off. These results may be explained by assuming that the reactions are actually of first order with respect to maleic acid concentration but are complicated by the simul-

TABLE I

THE ACTION OF HYDROCHLORIC ACID ON MALEIC ACID AT 99.9°

Initial concentrations: maleic acid, 0.460 M; hydrochloric acid, 2.79 M

t, sec.	Concn. of maleic acid	$k_1c \times 10^6$, sec.$^{-1}$	$k_2c \times 10^6$, (moles/l.)$^{-1}$ sec.$^{-1}$
0	0.460	..	...
1,200	.412	91.0	212
2,400	.371	87.5	222
3,600	.336	83.0	233
6,300	.275	73.5	244
10,200	.224	56.5	212
15,000	.185	39.7	197

chloric acid as the catalyst, only a very slight falling off in the values of k_1c with time was observed.

It was found that the values of k_2c were fairly constant within a run when salts were used as catalysts. However, the rate constants seemed to show a slight rise during the initial time intervals, followed by a slight falling off later. This falling off was probably due to the removal of the catalyst by side reactions such as addition and polymerization.

In Table II are listed the results of experiments using several different substances as catalysts. In order to avoid the complications mentioned above, the rate constants within a run were extrapolated to zero time and this value was taken as the correct constant. In addition to k_1c and k_2c, values for k_1 and k_2 are listed. The values given for the reactions catalyzed by sodium bromide, perchloric acid, and sulfuric acid may be somewhat in error due to salt effects and complications introduced by the very slow uncatalyzed isomerization of maleic acid in water at 100°.

TABLE II

THE ISOMERIZATION OF MALEIC ACID TO FUMARIC ACID AT 99.9°

Run	Catalyst	c = concn. of catalyst (moles/l.)	Init. concn. of maleic acid, moles/l.	$k_1c \times 10^6$, sec.$^{-1}$	$k_1 \times 10^6$, (moles/l.)$^{-1}$ sec.$^{-1}$	$k_2c \times 10^6$, (moles/l.)$^{-1}$ sec.$^{-1}$	$k_2 \times 10^6$, (moles/l.)$^{-2}$ sec.$^{-1}$
1	HCl	1.63	0.885	29.7	18.2	35.3	21.7
2	HCl	1.78	.885	37.2	20.8	42.5	23.9
3	HCl	2.68	.885	89.3	33.3	111	41.5
4	HCl	2.79	.460	95.0	34.0	225	80.6
5	HCl	2.83	.235	100	35.3	584	207.0
6	HBr	1.63	.885	18.3	11.3	20.0	12.3
7	HBr	2.98	.885	82.2	27.7	102	34.3
8	H$_2$SO$_4$	2.74	.885	4.27	1.56	4.94	1.80
9	HClO$_4$	5.19	.885	3.20	0.617	3.72	0.717
10	KCNS	0.0445	.885	56.6	1270	74.2	1670
11	KCNS	.0890	.885	109	1230	144	1620
12	KCNS	.0926	.460	68.4	736	158	1710
13	KCNS	.0938	.235	36.7	390	173	1850
14	NH$_4$CNS	.0857	.885	105	1230	139	1620
15	NaBr	1.78	.885	2.10	1.18	2.50	1.40
16	NaBr	5.34	.885	6.41	1.20	7.70	1.44

Saturated solutions of LiClO$_4$ and Na$_2$SO$_4$ had no appreciable catalytic effect.

taneously occurring addition reaction of the halogen acids to the unsaturated acids. This addition reaction consumes both the unsaturated acids and the catalyst and is responsible for the falling off in the values of k_1c within a run. Studies in which the initial concentration of maleic acid was varied have supported this view. In addition, analysis of reaction mixtures after isomerization showed that considerable quantities of halosuccinic acid were present. In the runs using sulfuric acid or per-

TABLE III

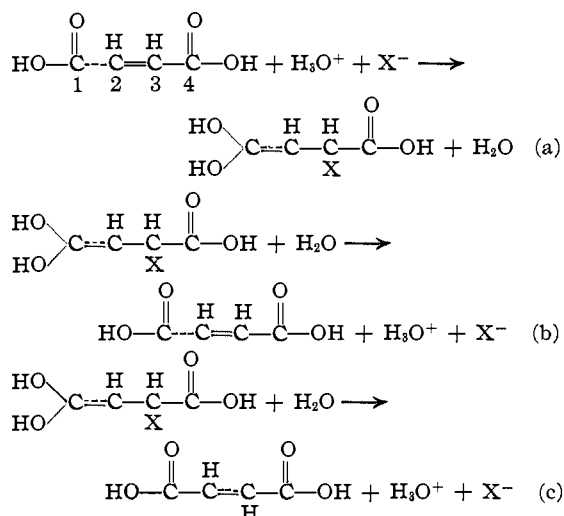THE EFFECT OF TEMPERATURE ON THE RATE OF ISOMERIZATION

Initial concentration of maleic acid, 0.885 (mole/liter).

Run	Temp., °C.	Catalyst	c = concn. of catalyst (moles/l.)	$k_1 \times 10^6$ (moles/l.)$^{-1}$ sec.$^{-1}$	$k_2 \times 10^6$ (moles/l.)$^{-2}$ sec.$^{-1}$
1	99.9	HCl	2.68	33.3	41.5
2	79.8	HCl	2.72	4.98	5.67
3	99.9	KCNS	0.0890	1230	1620
4	79.8	KCNS	.0906	277	387

In Table III are listed the results of similar runs at 79.8 and 99.9°, using hydrochloric acid and potassium thiocyanate as catalysts. From these results the activation energies were calculated. The value for the hydrochloric acid reaction is 24,900 calories, and the thiocyanate reaction has a value of 18,800 calories.

Discussion

The suggested mechanism for the isomerization catalyzed by acids may be formulated as

$$
\underset{1\ \ 2\ \ 3\ \ 4}{HO-\overset{O}{\overset{\|}{C}}---\overset{H}{\underset{}{C}}=\overset{H}{\underset{}{C}}-\overset{O}{\overset{\|}{C}}-OH} + H_3O^+ + X^- \longrightarrow
$$

$$
\overset{HO}{\underset{HO}{>}}C{\cdot}{\cdot}{=}\overset{H}{\underset{}{C}}-\overset{H}{\underset{X}{C}}-\overset{O}{\overset{\|}{C}}-OH + H_2O \quad (a)
$$

$$
\overset{HO}{\underset{HO}{>}}C{\cdot}{\cdot}{=}\overset{H}{\underset{}{C}}-\overset{H}{\underset{X}{C}}-\overset{O}{\overset{\|}{C}}-OH + H_2O \longrightarrow
$$

$$
HO-\overset{O}{\overset{\|}{C}}---\overset{H}{\underset{}{C}}=\overset{H}{\underset{}{C}}-\overset{O}{\overset{\|}{C}}-OH + H_3O^+ + X^- \quad (b)
$$

$$
\overset{HO}{\underset{HO}{>}}C{\cdot}{\cdot}{=}\overset{H}{\underset{}{C}}-\overset{H}{\underset{X}{C}}-\overset{O}{\overset{\|}{C}}-OH + H_2O \longrightarrow
$$

$$
HO-\overset{O}{\overset{\|}{C}}-\overset{H}{\underset{}{C}}{\cdot}{\cdot}{=}\overset{}{\underset{H}{C}}-\overset{O}{\overset{\|}{C}}-OH + H_3O^+ + X^- \quad (c)
$$

where X represents an anion and the dotted line represents the original bond between carbons 1 and 2.[5]

Step (a) involves the addition of a proton to the carbonyl oxygen of carbon 1, the addition of an anion to carbon 3, and the shift of the double bond from between carbons 2 and 3 to carbons 1 and 2. It is assumed that in this process carbon 3 undergoes a Walden inversion. This step is considered to be a rate-determining one for the isomerization. Steps (b) and (c) must be very rapid for, if such were not the case, the intermediate would probably all be converted by a proton shift into a mono substituted succinic acid. In this work some succinic acid derivatives were produced but the isomerization reaction predominated. Although step (a) is formulated as a termolecular reaction, it is probable that association of the proton with the carbonyl oxygen slightly precedes the reaction with the anion. The fairly high energy of activation for the isomerizations suggests that a termolecular reaction is improbable.

(5) Although the mechanism does not require differentiation of the original bond between carbons 1 and 2 from the new one, the differentiation is made to simplify the formulation and explanation.

Step (b) is simply the reverse of step (a): *i. e.*, maleic acid and the catalyst are regenerated. It may be looked upon as a reaction in which the newly formed bond between carbons 1 and 2 is broken, leaving the original single bond in place. Carbon 3 is reinverted in this step and, since an even number of inversions of the ethylenic carbons occurs in the entire process, no isomerization takes place.

Step (c) brings about isomerization to fumaric acid. It is formulated as a reaction in which the original bond between carbons 1 and 2 is broken, leaving a new bond between them. This is equivalent to a Walden inversion of carbon 2, and this inversion, together with the reinversion of carbon 3, gives an odd number of inversions of the ethylenic carbons for steps (a) and (c).

In the intermediate, either bond between carbons 1 and 2 would be expected to have the same probability of being broken. Thus the rate constants for steps (b) and (c) should be equal, and equal quantities of maleic acid and fumaric acid should be obtained from the decomposition of the intermediate. Practically all of the maleic acid is rearranged because the regenerated acid is again converted into the intermediate and isomerized. On the other hand, nearly all of the fumaric acid is unaffected because of the high activation energy of step (a) for the formation of the intermediate from fumaric acid.

The fact that the activation energy of step (a) should be much greater for fumaric acid than for maleic acid is apparent from a consideration of the free energies of the reactants and products. The free energy of solid fumaric acid is about 7000 calories less than that of solid maleic acid. Although this difference may be reduced somewhat in solution due to corrections for heats of solution, the change is not very great. The maleic acid–HX and fumaric acid–HX intermediates are the same and accordingly have the same free energy. Thus the activation energy for step (a) with fumaric acid should be in the neighborhood of 7000 calories greater than with maleic acid.

It should be noticed that, according to the proposed mechanism, the protons in the carboxyl groups may be replaced during isomerization but those attached to the carbons of the ethylene linkage are not affected. This is in agreement with the observations of Horrex.

Since the anion of the catalyst enters into the rate-determining step of the mechanism, its nature

should affect the rate of the reaction. It is observed from Table II that large differences in catalytic ability were found for the different acids. Insufficient work has been done to correlate catalytic activity with solvation, size, atomic structure, etc., of the anion.

Assuming that step (a) is rate determining, the rate expression from the mechanism is

$$d[F. A.]/dt = (k_a/2)[M. A.][H_3O^+][X^-]$$

where F. A. and M. A. represent fumaric and maleic acids, respectively. Since the rate of isomerization is proportional to the concentration of both anions and proton donors, the reaction should be of higher order than the first with respect to total catalyst concentration. The increase in the values of k_1 with increasing catalyst concentration, as is observed in runs 1 to 5 with hydrochloric acid and runs 5 and 6 with hydrobromic acid, indicates that such is the case. At constant catalyst concentration the reaction should be of first order with respect to maleic acid concentration. The results of runs 3, 4 and 5 are in agreement with this expectation. It is observed that k_1 remained essentially constant when the maleic acid concentration was varied over a considerable range. The slight variation in k_1 is attributable to differences in catalyst concentration in the three runs.

For the isomerizations catalyzed by salts, the same mechanism is applicable except that in this case the protons are supplied by the ionization of other molecules of maleic acid. This appears probable from the fact that in every case the acids are much better catalysts than the salts derived from them. Also, cations which are not protons seem to have no influence on catalytic activity (runs 11 and 14). According to the mechanism, the salt catalyzed isomerization at constant maleic acid concentration should be of first order with respect to salt concentration. From runs 10 and 11, and 15 and 16, such appears to be the case. Although quantitative calculations are impossible because of the complexity of the concentrated solutions and because the value for the dissociation constant of maleic acid at 100° is not known, calculations using values of activities and the dissociation constant at 25°

indicate that the observed catalytic effect of sodium bromide, compared to that of hydrobromic acid, is of the correct order of magnitude.

The rate expression for isomerizations catalyzed by salts is rather complex since the proton concentration in the solutions obeys no simple relationship. However, the proton concentration should be proportional to between $[M. A.]^{1/2}$ and $[M.A.]$ and thus the rate of isomerization should be proportional to between $[M. A.]^{3/2}$ and $[M. A.]^2$. From runs 11, 12, and 13 with potassium thiocyanate as the catalyst, it is observed that this is found to be true. When the concentration of maleic acid was decreased, the values of k_1 fell, and the values of k_2 rose slightly, indicating that the reaction is of slightly lower order than the second with respect to maleic acid concentration.

The mechanism which has been presented for the isomerization of maleic acid is applicable to the cis–trans isomerization of all α–β unsaturated carboxylic acids catalyzed by acids and salts. None of these isomerizations has been studied as extensively as that of maleic acid. However, there are numerous references in the literature concerning such cis-trans interconversions; for example, inorganic acids have been reported to be catalysts for the isomerization of isocrotonic acid,[6] isocinnamic acid,[7] citraconic acid,[8] and cis-methylglutaconic acid.[9]

The mechanism is also applicable to the acid-catalyzed isomerization of esters derived from α–β unsaturated acids. The best known cases of such reactions are those between the esters of maleic acid and the halogen acids.[10]

Summary

A mechanism has been proposed for the isomerization of maleic acid to fumaric acid catalyzed by inorganic acids and salts. Experimental observations are shown to be in agreement with the mechanism. The applicability of the mechanism to other cis-trans isomerizations is discussed.

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