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The Kinetics of the Thermal Isomerization of Cinnamic Acid Catalyzed by Iodine

BY ROSCOE G. DICKINSON AND H. LOTZKAR

It is well known that *cis–trans* isomerizations at ethylenic linkages can be catalyzed by various substances including iodine,[1] but the kinetics of this iodine catalysis have received comparatively little attention. The kinetics of the iodine-sensitized photochemical conversion of *cis*- into *trans*-cinnamic acid have been examined in benzene solution by Berthoud and Urech,[2] whose results are interpretable in terms of an iodine-atom catalysis. The results of the present thermal experiments likewise carried out in benzene solution indicate a close relation between the photochemical and thermal reactions.

Materials.—*cis*-Cinnamic acid was prepared by the reduction of phenylpropiolic acid by hydrogen using colloidal palladium as a catalyst; the method was essentially that of Paal and Hartmann.[3] The phenylpropiolic acid was prepared through the bromination of ethyl cinnamate and subsequent treatment with alcoholic potash; the procedures were those described in "Organic Syntheses,"[4] and the yields reported there were obtained. The colloidal palladium used in the reduction of the phenylpropiolic acid was prepared by the reduction of palladous chloride by hydrogen in aqueous solution in the presence of sodium protalbinate.[5] To effect the reduction of phenylpropiolic acid, the colloidal palladium protected by protalbinate was added to sodium phenylpropionate in somewhat alkaline solution. The solution was placed in a 200-cc. flask connected with a gas buret; the flask was evacuated and one mol of hydrogen added for each mol of phenylpropionate taken. After reduction, the solution was acidified, whereupon the *cis*-cinnamic acid separated as an oil. This was extracted with ether, treated with sodium carbonate and reprecipitated as oil with acid. In one preparation the oil was converted to the aniline salt and crystallized from a ligroin and benzene mixture.[6] The *cis*-cinnamic acid was then liberated with hydrochloric acid and recrystallized from water. In a second preparation, the formation of an aniline salt was omitted. The oil was frozen repeatedly using solid carbon dioxide, whereupon the oil crystallized. It was then twice recrystallized from water. The melting point of the first preparation was from 48 to 53°; that of the second was from 58 to 65°. Both preparations were evidently mixtures of *cis*-cinnamic acids for both gave the same equivalent conductance, 73.3, in 0.003 *M* solution at 25°. Values obtained by other observers are: Bjerrum, 72.5;[7] Vaidya, 74;[8] Olson and Hudson, 72.8.[9]

The *trans*-cinnamic acid was an Eastman product recrystallized from hot water.

The water was commercial distilled water redistilled from alkaline permanganate. The specific conductance of the water at 25° was 1.0×10^{-6} mho cm.$^{-1}$.

Thiophene-free benzene was used.

The iodine was a Merck product.

Analytical Method.—Conductance measurements were employed to determine the fraction of *cis*-cinnamic acid in mixtures of *cis*-cinnamic acid with *trans*-cinnamic acid. For this purpose the specific conductances of a series of known mixtures of the two acids were measured in 0.003 volume molal solution at 25°. The results are given in Table I.

TABLE I

SPECIFIC CONDUCTANCES AT 25° OF MIXTURES OF *cis*- AND *trans*-CINNAMIC ACIDS AT 0.003 *M*

% *cis*-acid	100	90.0	80.0	70.0	60.0	50.0
$\bar{L} \times 10^4$	2.200	2.108	2.025	1.934	1.838	1.743
% *cis*-acid		40.0	30.0	20.0	10.0	0
$\bar{L} \times 10^4$		1.641	1.537	1.421	1.307	1.188

These conductivities were plotted on a large scale and a smooth curve drawn. The cell constant used in these measurements was obtained from measurements on 0.001 *N* potassium chloride solution using Shedlovsky's value, 146.93, for the equivalent conductance at 25°.[10]

Experimental Procedure.—Stock solutions with appropriate known concentrations of *cis*-cinnamic acid and of iodine in benzene were prepared. In carrying out an experiment, 5.00 cc. of cinnamic acid solution and 5.00 cc. of iodine solution were pipetted into a 15-cc. ampoule and sealed off with the exclusion of light. The ampoule was then placed for a measured period of time in a light-tight chamber surrounded by the vapor of a boiling liquid (water was used in some experiments and methylcellosolve in others); in any one experiment the temperature range was less than 0.1°. The ampoule was then removed, cooled with water, opened and the contents transferred to a flask. The benzene and iodine were then pumped off at room temperature. These manipulations were carried out in red light or in the dark. The colorless residue of cinnamic acids (whose weight was presumed to be that of the *cis*-cinnamic acid taken) was dissolved in such a quantity of water as to give a 0.00300 *M* solution. The conductivity of the solution was then measured in a thermostat at 25°.

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(1) See, *e. g.*, C. Liebermann, *Ber.*, **23**, 512 (1890).

(2) A. Berthoud and Ch. Urech, *J. chim. phys.*, **27**, 291 (1930).

(3) C. Paal and W. Hartmann, *Ber.*, **42**, 3930 (1909).

(4) "Organic Syntheses," Vol. XII, John Wiley and Sons, Inc., New York, 1932, pp. 36, 60.

(5) C. Paal and C. Amberger, *Ber.*, **37**, 132 (1904).

(6) C. Liebermann, *ibid.*, **23**, 2515 (1890).

(7) N. Bjerrum, *ibid.*, **43**, 571 (1910).

(8) B. K. Vaidya, *Proc. Roy. Soc.* (London), **A129**, 291 (1930).

(9) A. R. Olson and F. L. Hudson, THIS JOURNAL, **55**, 1410 (1933).

(10) T. Shedlovsky, THIS JOURNAL, **54**, 1424 (1932).

TABLE II

SPECIFIC RATE CONSTANTS FOR THE CONVERSION OF *cis*- INTO *trans*-CINNAMIC ACID

No.	Initial concn. of *cis*-cinnamic acid, mole/liter	Concn. of iodine, mole/liter	Temp., °C.	Heating time, hours	Specif. cond. at 0.003 *M*, mho cm.$^{-1}$ $\times 10^4$	*trans*-Cinnamic acid formed, %	k_T moles$^{-1/2}$ $\times$ liters$^{1/2}$ $\times$ hrs.$^{-1}$	$k_{122.5°}$ moles$^{-1/2}$ $\times$ liters$^{1/2}$ $\times$ hrs.$^{-1}$
1	0.03	0.0015	99.4	24	2.088	13.0	0.150	
2	.03	.0015	99.4	50	1.974	25.7	.153	
3	.03	.0015	99.4	100	1.808	43.3	.146	
4	.09	.024	99.4	24	1.836	40.4	.139	
5	.03	.0015	122.2	10	1.913	32.3	1.007	1.033
6	.03	.0015	122.2	35	1.484	74.8	1.017	1.042
7	.03	.0015	122.8	19	1.700	54.1	1.057	1.033
8	.03	.003	122.9	15	1.676	56.5	1.012	0.983
9	.03	.006	122.2	11	1.675	56.6	0.978	1.001
10	.03	.012	122.9	5	1.801	44.0	1.057	1.024
11	.03	.012	122.9	8	1.642	59.8	1.037	1.007
12	.03	.024	122.6	6.5	1.602	63.8	1.011	1.003
13	.09	.0015	122.7	8	1.964	26.7	1.002	0.988
14	.09	.006	122.8	10	1.716	52.5	0.960	.935
15	.09	.024	122.4	6.5	1.639	60.1	.910	.920

When a blank experiment was made by evaporating 20 cc. of benzene alone and any residue dissolved in 100 cc. of water, the specific conductance of the water changed from 1.0×10^{-6} to 1.3×10^{-6} mho cm.$^{-1}$. The analytical conductivity measurements were corrected for this change. Blank experiments in which iodine was heated with benzene in the absence of cinnamic acid, gave no more conductivity change than the benzene above. A blank experiment was made in which a benzene solution 0.03 *M* (volume molal) in cinnamic acid and 0.0015 *M* in iodine was prepared and immediately analyzed without heating; the conductivity of the resulting 0.003 *M* aqueous solution was 0.0002191 (corrected) in satisfactory agreement with the value 0.0002200 expected for pure *cis*-cinnamic acid.

A series of experiments was made starting with *trans*-cinnamic acid. In one of these a benzene solution 0.03 *M* in *trans*-cinnamic acid and 0.0015 *M* in iodine was heated for ninety-one hours at 99.4°. In no case did the measured conductivity differ significantly from that expected for pure *trans*-cinnamic acid; accordingly, in interpreting measurements of the *cis–trans* conversion, reverse reaction has been regarded as negligible.

Experimental Results.—The kinetic measurements are given in Table II. The initial concentrations given are in moles per 1000 cc. at 22°; the *k*'s given in the table are calculated in terms of these concentrations from the equation:

$$k = \frac{1}{t(I_2)^{1/2}} \ln \frac{(C)_0}{(C)}$$

where (C) is the concentration of *cis*-cinnamic acid. This equation arises from integration of the equation $-d(C)/dt = k(C)\ (I_2)^{1/2}$. Since the temperatures obtained with methylcellosolve varied somewhat from one experiment to another, the rate constants measured using it have been reduced to the temperature 122.5° by means of the Arrhenius equation.

In the tabulated experiments, the initial concentration of *cis*-cinnamic acid has been varied three-fold, and the iodine concentration sixteen-fold; at the upper temperature the ratio of *trans*- to *cis*-acid present at the end of an experiment varied from 0.37 in expt. 13 to 3.0 in expt. 6. In all of these experiments except those (nos. 4, 14, 15) where the concentrations of both acid and iodine were comparatively high, constancy of *k* within probable experimental error was found. The somewhat lower values of *k* found at the highest concentrations are possibly attributable to addition of I_2 to the double bond of cinnamic acid. Dissociation constants of the order of 0.5 mole/liter for the assumed di-iodo compounds would suffice to account for this apparent trend.

The mean values of the constants obtained with the lower cinnamic acid concentration (0.03 *M*) are 0.150 at 99.4° and 1.013 at 122.5° the units being moles, liters at 22° and hours. When the units used are moles, cc. at the temperature of the reaction and seconds, these constants become 1.39×10^{-3} at 99.4°, and 9.59×10^{-3} mole$^{-1/2}$ cc.$^{1/2}$ sec.$^{-1}$ at 122.5°. Between these temperatures, the ten-degree multiplication of the constant is accordingly 2.28.

Discussion.—The fact that the thermal reaction is of one-half order with respect to I_2 suggests that the catalytic agent is atomic iodine just as in the photochemical reaction.[2] A reaction scheme which then leads to the type of rate expression found experimentally is the following

$$\begin{aligned} I_2 &\rightleftharpoons 2I && (1) \text{ and } (1') \\ I + C &\rightleftharpoons AI && (2) \text{ and } (2') \\ AI &\rightleftharpoons BI && (3) \text{ and } (3') \\ BI &\rightleftharpoons T + I && (4) \text{ and } (4') \end{aligned}$$

Here C and T represent *cis*- and *trans*-cinnamic acid; AI and BI represent the molecules resulting from the addition of an iodine atom to these two respective acids. The reversal of all steps has been included in order explicitly to avoid possible conflict with the principle of microscopic reversibility. In order for a conversion of one isomer into the other to occur, in effect a rotation about the ethylenic bond is necessary; this presumably occurs after the addition of the iodine atom. Furthermore, an odd number of inversions of carbon tetrahedra is necessary if a tetrahedral character be attributed to both the ethylenic carbons in the iodine atom addition compound. Whether such inversions occur in the acts of addition and removal of the iodine atom as well as in reactions (3) and (3′), or whether inversion occurs only in reactions (3) and (3′), cannot be decided from the present experiments; nor can these possibilities be distinguished from the case where tetrahedral character is not ascribed to both carbons of the compounds AI and BI so that inversion becomes unnecessary. This latter case is covered in the rate expression given below if k_3 be placed equal to $k_{3'}$ and made very large. The usual treatment of the reaction scheme given above leads, on the assumption that I, AI and BI remain at low concentration, to the following rate expression

$$-\frac{\mathrm{d}(C)}{\mathrm{d}t} = \sqrt{\frac{k_1}{k_{1'}}(\mathrm{I}_2)}\,\frac{k_2k_3k_4\,(C) - k_{2'}k_{3'}k_{4'}\,(T)}{k_{2'}k_{3'} + k_{2'}k_4 + k_3k_4}$$

Evidently k_1/k_1' is the dissociation constant of iodine into atoms, and $k_2k_3k_4/k_{2'}k_{3'}k_{4'}$ is the equilibrium constant for the transformation of *cis*- into *trans*-cinnamic acid. Since, in experiments starting with *trans*-cinnamic acid, any isomerization was small, the term in (T) may, for purposes of the experiments of Table II, be dropped. This leaves a rate expression of the form of that found empirically, *viz.*, $-\mathrm{d}(C)/\mathrm{d}t = k(C)(\mathrm{I}_2)^{1/2}$ with $k = \sqrt{\frac{k_1}{k_{1'}}}\,\frac{k_2k_3k_4}{k_{2'}k_{3'} + k_{2'}k_4 + k_3k_4}$.

The local rate (thin layer) of the photochemical conversion is reported to be given by the[2] expression $-\mathrm{d}(C)/\mathrm{d}t = k_{\mathrm{Ph}}I_0^{1/2}(\mathrm{I}_2)^{1/2}(C)$ where I_0 is the radiation incident per unit area per unit time. Assuming the photochemical reaction to proceed by the same mechanism as the thermal except for replacement of step (1) by $\mathrm{I}_2 + h\nu \longrightarrow 2\mathrm{I}$, it is readily seen that $k/k_{\mathrm{Ph}} = \sqrt{k_1/\alpha}$, where α is the molal absorption coefficient of iodine for the wave length used. On the assumption that α varies relatively little with temperature it follows that at a given temperature $\mathrm{d}\ln k/\mathrm{d}T - \mathrm{d}\ln k_{\mathrm{Ph}}/\mathrm{d}T = {}^1/_2\mathrm{d}\ln k_1/\mathrm{d}T$. The multiplication of the photochemical rate between 25 and 35° at constant concentrations and intensity is given as 1.3. From this the over-all activation energy of the photochemical reaction may be calculated from the Arrhenius equation $\mathrm{d}\ln k_{\mathrm{Ph}}/\mathrm{d}T = Q_{\mathrm{Ph}}/RT^2$ treating Q_{Ph} as constant with temperature; the value obtained is 4800 cal. Similarly, for the thermal reaction the Q obtained is 24,200 cal. Hence, for reaction (1), $Q_1 = 2(24{,}200 - 4800) = 38{,}800$ cal. There is evidence[11] that reaction (1′) goes at every kinetic theory collision and accordingly requires no activation energy. If this be the case, Q_1 should equal ΔH for the dissociation of molecular iodine in benzene solution. The value of ΔH for the dissociation of gaseous iodine at 18° obtained with the aid of spectroscopic data[12] is 36,270 cal./mole. Since heats of solution of gases in non-polar solvents often amount to several thousand calories[13] extremely close agreement between the dissociation energies in solution and gas is not to be expected. The reasonably close agreement found in the present case lends independent support to the supposition that the iodine catalysis is brought about by iodine atoms.

Summary

Rates of isomerization of *cis*- into *trans*-cinnamic acid as catalyzed by iodine have been measured in benzene solution at 99.4 and 122.5°. The rates have been found to be substantially of first order with respect to *cis*-cinnamic acid and half-order with respect to iodine. This result has been interpreted as indicating an iodine atom catalysis such as has been supposed to occur in the

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[11] E. Rabinowitch and W. C. Wood, *Trans. Faraday Soc.*, **32**, 547 (1936).

[12] F. R. Bichowsky and F. D. Rossini, "The Thermochemistry of Chemical Substances," Reinhold Publishing Corp., New York, 1936, p. 189.

[13] For example, from the tabulations of Bichowsky and Rossini,[12] the following values for the heat content increase, ΔH, per mole on vaporization from various solutions at 18° may be obtained: $\mathrm{I_2}$ from $\mathrm{C_6H_6}$, 8910 cal.; $\mathrm{Br_2}$ from $\mathrm{CCl_4}$, 7150; $\mathrm{Cl_2}$ from $\mathrm{CCl_4}$, 4500; HCl from $\mathrm{CCl_4}$, 3620; $\mathrm{O_2}$ from $\mathrm{H_2O}$, 3850; $\mathrm{H_2}$ from $\mathrm{H_2O}$, 1420. The value of ΔH for the vaporization of atomic iodine from benzene solution calculated from that for molecular iodine together with Q_1 and ΔH for the gaseous dissociation, is 3200 calories per atomic weight.

photochemical iodine-sensitized reaction. Comparison of the temperature coefficients of the thermal and photochemical reactions leads to a calculation of the energy of dissociation of iodine into atoms in benzene solution and gives further evidence in favor of the supposition of an iodine atom catalysis.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

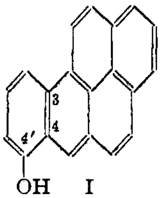
Hydroxy Derivatives of 3,4-Benzpyrene[1] and 1,2-Benzanthracene

BY L. F. FIESER, E. B. HERSHBERG,[2] L. LONG, JR., AND M. S. NEWMAN[3]

The study of hydroxy derivatives of carcinogenically active hydrocarbons was undertaken partly because it is of interest to determine the influence of hydroxyl and modified hydroxyl substituents on the cancer-producing properties of the hydrocarbons, and partly in the hope of broadening the field of biological experimentation. If suitable functional groups can be introduced without complete loss of carcinogenic activity, it should be possible to attach to the carcinogens side chains of such a character as to vary the solubility relations in different directions. Hydroxy compounds would be of further interest, as Cook and his associates[4] have observed, because polynuclear aromatic compounds arising in the body as products of the metabolism of steroids might be expected to appear in an hydroxylated form comparable with oestrone and equilenin.

From the information now available, the most potent of the known carcinogenic hydrocarbons can be classified as either 10-alkyl-1,2-benzanthracenes or as compounds containing the 1,2-benzanthracene ring system with a carbon substituent in the alternate meso position 9.[5] Methylcholanthrene, cholanthrene, 9,10-dimethyl-1,2-benzanthracene and 10-methyl-1,2-benzanthracene are the most powerful agents of the first type, while 3,4-benzpyrene is the most active representative of the second type of hydrocarbon. On the basis of this provisional classification, a systematic investigation has been undertaken to determine the influence of hydroxyl, amino and other groups at various positions on the carcinogenic properties of these hydrocarbons. The results presented in this paper are incidental observations which constitute a start in the direction indicated.

The synthesis of 4′-hydroxy-3,4-benzpyrene (I) was reported in a preliminary communication,[6]



I

and further details of the preparation of the compound and of various derivatives are given in this paper. The hydroxyl group of this compound occupies position 5 in the 1,2-benzanthracene ring system present in the molecule. Dr. M. J. Shear injected the crystalline hydroxy compound into mice and obtained no tumors at the site of injection after sixteen months. Negative results were obtained also with 4′-ketotetrahydro-3,4-benzpyrene, from which I is prepared by dehydrogenation. The action of 4′-methoxy-3,4-benzpyrene suggested that it may prove to be weakly carcinogenic, although it is too early to make a definite decision. Experiments with the acetate, benzoate, *p*-aminobenzoate, and carboxymethyl derivative are in progress.

Although 1,2-benzanthracene itself is almost completely devoid of cancer-producing properties,[7] the fact that some of the simple alkyl derivatives of the hydrocarbon are potent carcinogenic agents suggested the idea of testing samples of the 3-hydroxy and 3-methoxy compounds which were available from an earlier research

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(1) Revised numbering system, see Note 7, THIS JOURNAL, **58**, 2377 (1936).

(2) Lilly Research Fellow.

(3) Now at The Ohio State University.

(4) Cook, Haslewood, Hewett, Hieger, Kennaway and Mayneord, "Reports of the II International Congress of Scientific and Social Campaign against Cancer," **1**, 1 (1936); *Am. J. Cancer*, **29**, 219 (1937).

(5) Fieser and Hershberg, THIS JOURNAL, **59**, 394 (1937); L. F. Fieser, M. Fieser, Hershberg, Newman, Seligman and Shear, *Am. J. Cancer*, **29**, 260 (1937).

(6) Fieser, Hershberg and Newman, THIS JOURNAL, **57**, 1509 (1935).

(7) Barry, Cook, Haslewood, Hewett, Hieger and Kennaway, *Proc. Roy. Soc.* (London), **B117**, 318 (1935).