Kinetic Studies and Mechanisms of Reactions for Cyclopropane-1,1-dicarboxylic Acid and Cyclobutane-1,1-dicarboxylic Acid in Potassium Bromide[1]

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Kinetic studies of the thermal solid state reactions of cyclopropane-1,1-dicarboxylic acid and of cyclobutane-1,1-dicarboxylic acid separately mixed with potassium bromide in pressed pellets have been made by heating the pellets and observing the changes in absorption of several infrared bands of the reactants or products. Cyclobutane-1,1-dicarboxylic acid decomposed by a first-order reaction to yield carbon dioxide and cyclobutanecarboxylic acid. The apparent rate constant was determined to be $k(s^{-1}) = 3.0 \times 10^{13} \exp[(-31.9 \pm 2.0 \text{ kcal})/RT]$. Cyclopropane-1,1-dicarboxylic acid did not decarboxylate; instead it isomerized to the corresponding 2-carboxybutyrolactone. The apparent first-order rate constant for the isomerization reaction was found to be $k(s^{-1}) = 8.0 \times 10^{13} \exp[(-28.2 \pm 0.7 \text{ kcal})/RT]$.

Kinetic studies[3-5] of the thermal decarboxylation of cyclobutane-1,1-dicarboxylic acid (CBDA) and of cyclopropane-1,1-dicarboxylic acid (CPDA) as molten solids and as solutions in various ionic liquid solvents have shown rather different isokinetic temperatures for the two,[3] which could indicate that more than one interaction mechanism is present.[6] Indeed, the work of Bus, Steinberg, and de Boer[4] appears to substantiate the fact that CPDA does not decarboxylate directly but instead isomerizes to α-carboxy-γ-butyrolactone (2-carboxybutyrolactone) which may then decarboxylate to γ-butyrolactone.

A kinetic study for the pyrolysis of malonic acid in potassium bromide has been presented,[7] and in this medium the results show almost the identical isokinetic temperature as those for the cyclic diacids, including that of cyclobutane-1,1-dicarboxylic acid, obtained in other media.[3] In view of the reported difference in isokinetic temperature for cyclopropane-1,1-dicarboxylic acid and the possible isomerization reaction, we decided to investigate the pyrolysis of the two "substituted malonic acids", cyclobutane-1,1-dicarboxylic acid and cyclopropane-1,1-dicarboxylic acid, in solid potassium bromide solution.

A method similar to that of Bent and Crawford[8] was used for the kinetic study in which the reactants were incorporated in a potassium bromide solid matrix and quantitative kinetic results were obtained by observing the change in infrared absorption of reactants and products as a function of time.

Results and Discussion

Cyclobutane-1,1-dicarboxylic Acid. The infrared spectrum of CBDA in potassium bromide pressed pellets compared favorably with that reported elsewhere[9] and also with a split mull spectrum of the compound obtained in this work. The 1709-cm^{-1} absorption peak attributed to the carbonyl stretching frequency is the most intense peak in the spectrum; it is so intense that only a few other peaks are intense enough to be of use for measurement in a kinetic study at a concentration where the carbonyl peak remains on scale. It was felt that this peak would be a very important peak to follow since the reaction expected in KBr was decarboxylation.

When CBDA (mp 156–158 °C) was heated in potassium bromide for a period of time at temperatures between 150 and 185 °C, an infrared spectrum similar to that of cyclobutane monocarboxylic acid[10] was obtained. Carbon dioxide is evolved as evidenced by a sharp peak which appears near 2355 cm^{-1} due to some of this gas becoming trapped in the potassium bromide matrix of the pellet. Otherwise, the spectrum was matched by a point-by-point comparison with that of a sample of authentic liquid cyclobutanecarboxylic acid (Aldrich Chemical Co.) pressed in a KBr pellet.

Toward the end of each reaction time, some of the liquid cyclobutane carboxylic acid was vaporized from the pellet as evidenced by the pellet surface becoming moist upon repressing and also by the strong odor of the acid clearly detectable in the sample tubes. This volatilization process influenced the rate constant plots where it was noted that with long heating times a fall-off of the curve resulted. Heating times in all experimental runs were extended to at least 3 half-lives.

All five peaks of the starting acid chosen for the kinetic study (1709, 1407, 1290, 1215, and 1155 cm^{-1}) appeared to give good reproduction of rate constant data for the kinetics of the decarboxylation reaction.

Abell and Tien[3] studied the thermal decarboxylation of CBDA in the molten state and in various solvents, obtaining a rate constant of 32.9×10^{-4} s^{-1} for the molten acid at 180 °C. The rate constants obtained in this research are presented in Table I, and the average value, $45 \pm 10 \times 10^{-4}$ s^{-1} at 185 °C, compares favorably with the value of Abell and Tien. It appears that the acid decarboxylates in KBr to cyclobutanecarboxylic acid in a manner similar to that of the acid in the pure state and in liquid solutions.

A mechanism that has gained acceptance for the decarboxylation of dicarboxylic acids is that given by Fraenkel et al.[11] In this mechanism, a strong nucleophile attacks one of the electrophilic carboxylic carboxyl groups strengthening the carbon–oxygen bonds while weakening the carbon–carbon bonds of the acid. One of the carboxyl groups is finally split from the diacid as carbon dioxide, leaving its acidic proton with the resultant monoacid. In the cyclobutyl diacid–KBr system, the bromide ion probably serves as the nucleophile.

Cyclopropane-1,1-dicarboxylic Acid. Partial infrared spectral data for the cyclopropyl diacid have been reported in the literature,[5] and these, as well as a split mull spectrum obtained by us, agree with the spectrum which we obtained in the KBr pellets.

The two acidic protons of the cyclopropyl diacid have been shown to have quite different acidic strengths[12] when compared with those of the cyclobutane diacid, and these observations have been the subject of some controversy and speculation. It has been shown by X-ray crystallography[13] that the crystal structure of CPDA involves one acidic proton in intermolecular hydrogen bonding and one in intramolecular hydrogen bonding. This is not the case for CBDA, where both acid protons are involved in intermolecular hydrogen bonding giving rise to a chain-type structure[14,15] similar to that of malonic acid.[16]

Table I. Rate Constants ($\times 10^4$ s^{-1}) for the Thermal Reaction of Cyclobutane-1,1-dicarboxylic Acid in KBr Obtained by Following the Disappearance of the Infrared Absorption Bands Indicated

	absorption bands, cm^{-1}				
temp, °C	1709	1407	1290	1215	1155
184.9	36.6	44.7	62.4	34.5	45.9
174.9	13.0	17.5	25.2	14.2	19.5
169.2	10.7	11.9	16.3	10.1	12.9
163.9	5.48	6.98	9.05	5.25	6.59
153.8	1.45	2.03	2.77	1.78	2.68

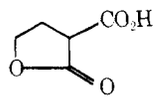
The fact that the two acid protons for the cyclopropyl diacid are in different environments explains what appear to be two different carbonyl stretching frequencies (1713 and 1612 cm^{-1}) for the cyclopropyl diacid. The intermolecular hydrogen-bonded carboxyl group without doubt gives rise to the absorption frequency at 1713 cm^{-1}, whereas the intramolecularly hydrogen-bonded carboxyl group accounts for the carbonyl stretching at 1612 cm^{-1}.[5] When we prepared the monopotassium salt of the cyclopropyl diacid, the 1713-cm^{-1} carbonyl stretching vibration was found to be shifted to the 1600–1650-cm^{-1} region as might be expected for the carbonyl stretching frequency of a salt. The intermolecular hydrogen-bonded proton should be the one most readily exchanged during the salt formation.

When the cyclopropyl diacid (mp 136–139 °C) was heated in potassium bromide, it was discovered that reaction was so rapid at 150 °C and even at 130 °C that no satisfactory kinetic measurements could be made by our method of choice. However, upon lowering the temperature to 100 °C and below, the reaction could be readily followed by infrared spectroscopy. The spectra gradually change with time for the heated pellets, but since no absorption appeared for the heated product which could be attributed to carbon dioxide, we concluded that decarboxylation did not take place. There seems no logical reason why the carbon dioxide absorption which became very evident in the heated pellets for CBDA should not appear also for heated pellets containing CPDA if decarboxylation did, indeed, occur as had been reported[3] for this acid.

The possibility that the cyclopropyl diacid when heated in a KBr pellet underwent ring opening to form an unsaturated diacid was considered. However, certain features in the spectrum of the product obtained by heating CPDA in KBr were not consistent with the spectrum predicted for this unsaturated acid. Furthermore, such an unsaturated-1,1-dicarboxylic acid might be expected to decarboxylate readily under the conditions of these experiments with the resulting carbon dioxide absorption band appearing in the spectrum of the heated pellets.

It was noted that the carboxyl group frequency involved with intramolecular hydrogen bonding (1612 cm^{-1}) disappeared from the infrared spectrum of the heated pellets, and in the carbonyl region there appeared two absorptions, one at 1735 cm^{-1} and one at 1764 cm^{-1}.

Various possible esters and ketones were considered as giving rise to the product spectrum, but there was strong spectral evidence that a ring compound had been formed. The most likely possibility would be 2-carboxybutyrolactone,



Although no IR spectrum[17] for 2-carboxybutyrolactone could be found in the literature, the infrared spectrum for the heated product in the KBr pellet agrees satisfactorally with those having structures similar to 2-carboxybutyrolactone. The NMR spectrum of the heated product (β-CH_2 multiplet at δ 2.1–3.0; α-H plus γ-CH_2 multiplet at δ 3.9–5.1)[18] agrees with the NMR spectra of Dr. R. K. Singh,[19] which was obtained for 2-carboxybutyrolactone mixed with some CPDA.[20]

When CPDA, or some substituted CPDAs, have been heated in the pure state or in various solutions, reactions similar to that which we observed for CPDA in KBr have been reported.[4,5] In our investigation, we conclude that at the temperatures used, 2-carboxybutyrolactone is stable and does not decarboxylate during the heating period used.

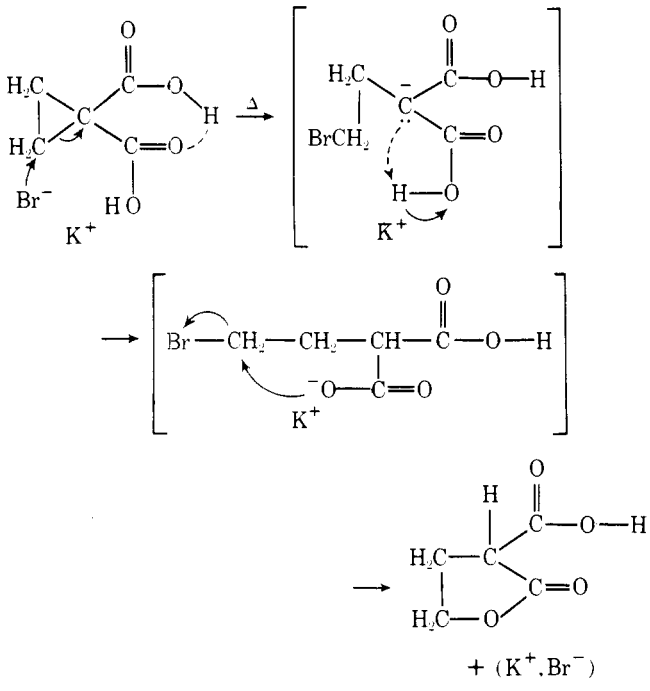
After being heated for short periods of time at much higher temperatures (130 to 170 °C), the cyclopropane-1,1-dicarboxylic acid in KBr pellets did apparently undergo decarboxylation although no carbon dioxide peak was apparent in the spectrum. The spectrum obtained agreed closely with that of γ-butyrolactone. When heated at these higher temperatures, much liquid γ-butyrolactone (IR and NMR analysis) collected on the inside walls of the tube used to contain the sample. No doubt if vaporization of liquid from the pellet occurs during the reaction, carbon dioxide formed in the reaction would completely disappear from the pellet. This would explain the absence of the carbon dioxide peak in the spectrum of the pellets heated at the higher temperatures. It should also be mentioned that the isomerization reaction to produce 2-carboxybutyrolactone in KBr was observed to occur at greatly reduced rates even at room temperature over a period of weeks.

Of the six absorption bands of the starting acid chosen for the kinetic study, only four (1612, 1450, 1420, and 1287 cm^{-1}) gave reproducible rate constant data for the kinetics of the reaction. The rate constant obtained in this research for the isomerization to 2-carboxybutyrolactone of cyclopropane-1,1-dicarboxylic acid in KBr at 100 °C is comparable in value to that obtained[4] for the decarboxylation process in concentrated sulfuric acid at 130 °C. If the temperature were increased by 30 °C, the isomerization rate constant should be even larger, making the isomerization much faster than decarboxylation and thus supporting the claim[4] that decarboxylation after isomerization is the rate-determining step in the decarboxylation of the cyclopropyl diacid to γ-butyrolactone. Rate constants obtained for isomerization in KBr from 80 to 100 °C are a factor of 10 larger than those obtained for decarboxylation[3] of the molten acid, as well as for the acid at 180 °C in 85% phosphoric acid and in 98% sulfuric acid.

Bus et al.[5] obtained a pseudo-first-order rate constant for the thermal isomerization of the cyclopropyl diacid at 131 °C in 45% deuterated sulfuric acid, which is comparable in value to that obtained in this research in KBr at 100 °C. They discovered that the isomerization rate increased with acid concentration. It appears that the protonated acid[5] makes the cyclopropyl ring vulnerable to ring opening by nucleophiles. The positive charge should be considerably delocalized in the highly favored intramolecular hydrogen-bonded structure of the diacid. In dilute acids, the rate-limiting step in the thermal isomerization of the diacid has been suggested to be the nucleophilic attack of water on the β-carbon atom of the protonated acid in aqueous solutions.[4,5] Ring rupture results and is then followed by rapid ring closure to 2-carboxybutyrolactone.

It has also been suggested[4] that in solution there is a competition between isomerization and decarboxylation and that the isomerization rate soon surpasses the decarboxylation rate with increased acidity of the reaction medium. The fact that one proton is much more easily ionized than the other in the cyclopropyl diacid[12] suggests that the oxygen of the intermolecular hydrogen-bonded hydroxyl group is the oxygen atom involved in the ring closure to the lactone once the cyclopropyl ring has been ruptured. It also suggests that rupture

Scheme I



(and subsequent ring closure) occurs more readily in more acidic media, probably since more free carboxyl groups can become protonated thus weakening the cyclopropyl ring.

Since the isomerization rate appears to be greater in the solid ionic medium of a KBr pellet than in acid media at a given temperature, it would seem that the rupture and isomerization depend more on the ionic strength of the medium than on its acidity. For example, Bus et al.[4,5] obtained a rate constant of 3.77×10^{-5} s^{-1} for the thermal isomerization of cyclopropane-1,1-dicarboxylic acid in D_2O at 130 °C, whereas in this research an average rate constant of $16.5 \pm 5.0 \times 10^{-4}$ s^{-1} for the same reaction in KBr at 100 °C was obtained. If it is assumed that the rate constant increases with increased ionic strength rather than acidity of the medium, then these results may be reconciled.

It seems likely that the reaction proceeds by the nucleophilic attack of a bromide ion on the cyclopropyl ring. The ring is thus ruptured and an intermediate carbanion is formed. This carbanion probably rearranges to a strongly nucleophilic carboxyl anion which attacks the hydrocarbon chain in a second nucleophilic attack to form the lactone ring. The first nucleophilic attack of the bromide ion on the cyclopropyl ring is probably the rate-determining step in the reaction sequence. The following mechanism is proposed for the thermal isomerization of cyclopropane-1,1-dicarboxylic acid in KBr to yield 2-carboxybutyrolactone (Scheme I).

For the isomerization of the cyclopropyl diacid in D_2O, Bus et al.[5] obtained an enthalpy for the reaction of 23.5 kcal/mol, whereas for this research a value of 26.8 kcal/mol was obtained for the reaction in KBr. It would be logical to assume that a somewhat larger amount of energy would be required in KBr since energy would be required to move the bromide ions into the required position for the reaction to occur.

Abell and Tien[3] followed the kinetics of decarboxylation of cyclopropane-1,1-dicarboxylic acid and similar four-, five-, and six-membered ring diacids in various solvents in the molten state. In their work a plot of the enthalpies of activation vs. the entropies of activation was made. Two straight lines of different slopes for the isokinetic temperature resulted. One line contained all points for the cycloalkane-1,1-dicarboxylic acids (four-, five-, and six-membered rings). The other line was nearly parallel to the first one, but it contained only points for cyclopropane-1,1-dicarboxylic acid.

From the present research it appears likely that Abell and Tien actually observed the decarboxylation of 2-carboxybutyrolactone to γ-butyrolactone after their starting cyclopropane-1,1-dicarboxylic acid had isomerized to the acid lactone. Their results were based on the rate of carbon dioxide evolution which would lead them to believe that they were observing the direct decarboxylation of the cyclopropyl diacid.

Experimental Section

Chemicals. Potassium bromide was obtained from Merck Chemical Division ("Suprapur" grade) or from Brinkman Instruments, Inc. (spectroscopic grade).

The cyclobutane-1,1-dicarboxylic acid was obtained from Pfaltz and Bauer Co., Inc., and after recrystallization from diethyl ether, a melting point of 156–158 °C (lit.[21] mp 157 °C) was obtained. Cyclopropane-1,1-dicarboxylic acid was prepared from diethyl cyclopropane-1,1-dicarboxylate acquired from the Aldrich Chemical Co. The method of preparation described by Perkin[22] was used except that in the extraction of the acid into diethyl ether the aqueous phase was maintained at a pH of 3.

The solid product obtained by evaporation of the ether solution was purified by dissolving it in anhydrous diethyl ether and allowing the solution to flow through a chromatographic column packed with 20 mesh silicic acid (silica or silica gel) which had been activated by heating with occasional stirring in an oven at 150 °C for 4 h. The material was then recrystallized several times from anhydrous diethyl ether. The final crystals gave a melting range of 136–139 °C as measured with a Meltemp melting point apparatus, while the melting point was 139 °C when measured by differential scanning calorimetry. A melting range of 132–141 °C has been reported[3,21-23] for CPDA. Elemental analyses by Galbraith Laboratories, Inc., gave: C, 46.15 ± 0.07; H, 4.67 ± 0.03; O, 49.23 ± 0.04. Calcd: C, 46.16; H, 4.65; O, 49.19.

Instruments. The constant temperature bath was described previously,[7] except that the fine control of temperature was made by use of a long-stem thermometer immersed in the oil bath and connected to the appropriate heating coil through a Therm-O-Watch electric switching device (L6/1000), manufactured by Instruments for Research and Industry, Cheltenham, Pa. This system made temperature control possible within a ±0.05 °C temperature range.

Two stainless steel dies were used for pressing powdered mixtures of potassium bromide and sample to make pellets. One die had a pressing surface of 6 × 25 mm and the other 7 × 26 mm. Pellets were formed under 20 000 psi gauge pressure in a Carver hydraulic press.

The infrared spectra used for kinetic studies were obtained by means of a Beckman Model IR-12 infrared spectrophotometer. The calibration was checked periodically by scanning the polystyrene spectrum or by scanning the background (atmospheric) spectrum. The reproducibility was usually better than ±2 cm^{-1}. Absorbance values could generally be reproduced to better than ±0.002 absorbance unit.

Nuclear magnetic resonance spectrometers used in this investigation were Varian models, T-60 and EM-360. Tetramethylsilane was used as the internal standard for all organic solvents. Chemical shifts in D_2O were measured from sodium 3-(trimethylsilyl)propionate-*2,2,3,3-d*$_4$ as internal reference standard.

Calorimetric work was performed by using a Perkin-Elmer Model DSC-2 differential scanning calorimeter. The calorimeter temperature was calibrated by determining the melting temperature of indium sealed in an aluminum pan against an empty gold reference pan. The reproducibility of the melting temperature of indium at 167.0 °C was ±0.1 °C.

Thermal gravimetric analyses were conducted with a Perkin-Elmer Model UU-1 temperature programmer. The temperature accuracy of the thermal balance was calibrated by measuring the weight loss of the alloy, Alumel, at a thermal magnetic transition point of 163 °C. A reproducibility of ±1° could be obtained.

Pellet Preparation. Potassium bromide was ground with an agate mortar and pestle, placed in an oven at 130–140 °C for several weeks to dry, and then stored in a desiccator. The acid under investigation and the potassium bromide were weighed to the nearest 0.00005 g and mixed in a rotating vacuum type evaporator which was simultaneously magnetically stirred.

The concentrations of the acids were adjusted so that a pellet pressed from the mixture gave an infrared spectrum with optimum peak intensities for each compound. The concentration of CBDA in

Table II. Rate Constants ($\times 10^4$ s^{-1}) for the Thermal Reaction of Cyclopropane-1,1-dicarboxylic Acid in KBr Obtained by Following the Disappearance of the Infrared Absorption Bands Indicated

temp, °C	absorption band, cm^{-1} 1612	1450	1420	1287
100.0	26.3	16.0	10.5	13.1
90.0	9.12	6.17	4.25	5.1
80.0	2.15	2.45	2.15	1.15
70.1	1.00	0.59	0.33	0.81

Table III. Activation Parameters for the Thermal Reaction of Cyclobutane-1,1-dicarboxylic Acid in Several Media

medium	ΔH^*, kcal/mol	ΔS^*, cal/(mol deg)	ΔG^* at 180 °C, kcal/mol
H_2SO_4[a]	41.0	21.4	31.3
H_3PO_4[a]	40.0	15.6	32.9
molten CBDA[a]	48.9	37.2	32.0
collidine[a]	23.2	−16.8	30.8
diethylene glycol[a]	30.8	−2.8	32.1
CBDA in KBr[b]	36.8 ± 2	1.05 ± 0.8	36.3 ± 2

[a] Reference 3. [b] This work.

Table IV. Activation Parameters for the Thermal Reaction of Cyclopropane-1,1-dicarboxylic Acid in Several Media

medium	ΔH^*, kcal/mol	ΔS^*, cal/(mol deg)	ΔG^* at 100 °C, kcal/mol
H_2SO_4[a]	13.1	−37.7	27.2
H_3PO_4[a]	25.6	−17.4	32.1
D_2O[b]	23.5	−21.2	31.4
molten CPDA[a]	14.7	−40.1	29.7
collidine[a]	6.7	−58.8	28.6
diethylene glycol[a]	17.1	−36.6	30.8
CPDA in KBr[c]	26.8 ± 2	−9.3 ± 0.8	30.3 ± 2

[a] Reference 3. [b] References 4 and 5. [c] This work.

potassium bromide was 0.0995% (w/w) acid. That of CPDA was 0.210% (w/w) acid.

Kinetics. For each kinetic run, three series of 8–15 pellets each were prepared, and the infrared spectrum was obtained. The absorbances, or transmittances, were measured by the base line technique, and these absorbances were taken as the zero time absorbances.

The pellets were placed individually in Pyrex sample tubes, corked, and separately placed in the bath set at the desired temperature. The tubes were removed from the bath at predetermined timing intervals and cooled to room temperature. Heating times were recorded by means of a stop watch which was allowed to run continuously during the heating process for a particular run.

Each pellet was then repressed in the larger die and reweighed to the nearest 0.00005 g; the infrared spectrum was scanned again. The repressing was necessary due to expansion of the pellets and their becoming opaque during the heating process. The peak absorbances were again measured by the base line technique, and these absorbances were taken as the heating time absorbances. The method employed was similar to that used elsewhere.[7,8] The data were then punched onto computer cards and analyzed by a computer program.[7]

So that many pellets of many different weights could be used for comparison purposes, all absorbances were adjusted by the computer program to the values that each absorbance should have been if each pellet had a uniform weight of 0.20000 g.

Since the repressed pellets had rectangular dimensions somewhat larger than their original, the effective path length of each pellet was changed. Therefore, an additional correction was necessary of the zero time absorbances of pellets pressed with the first (smaller) die. The correction factor for each absorption peak was established by taking the ratio of the measured absorbance of the peak after repressing with the larger die to the previously measured absorbance of the same peak after originally pressing with the smaller die. This correction was also included in the computer program used.

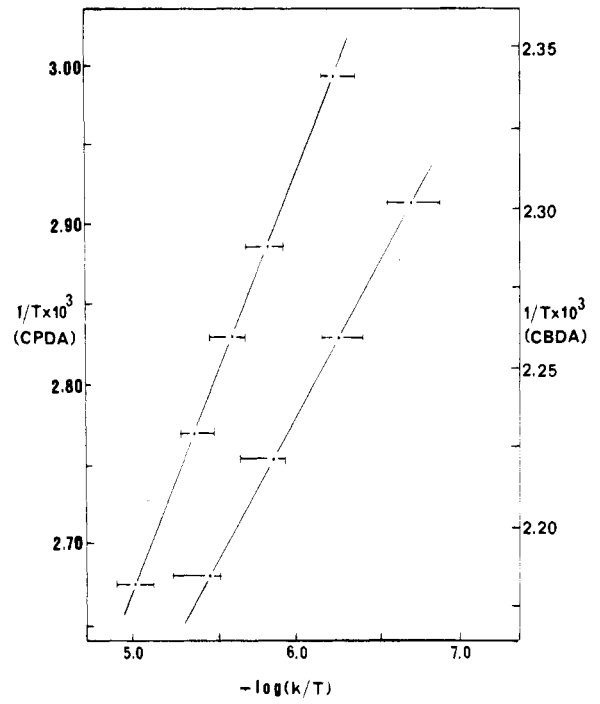


Figure 1. Combined enthalpy of activation plots for thermal reactions of cyclobutane-1,1-dicarboxylic acid and cyclopropane-1,1-dicarboxylic acid in KBr: (●) CPDA at temperatures between 100.0 and 70.1 °C; (■) CBDA at temperatures between 184.9 and 153.8 °C. For CBDA, the spread indicated for each experimental point encompasses the data for the 1155–1709-cm^{-1} absorption bands. For CPDA, the spread encompasses data for the 1287–1612-cm^{-1} bands. (Slopes of lines determined by least-squares fit of data.)

In many cases, the pellets were of sufficient quality to give an interference pattern from reflection between the surfaces. Calculation of the pellet thickness from the interference pattern agreed to ±0.02 mm with that calculated from a ratio of pellet weights and/or that calculated from measured absorbance ratios.

By preparing pellets from mixtures of each acid and potassium bromide in varying concentrations and obtaining their spectra, it was found that the absorption peaks chosen for the kinetic study in the CBDA spectrum (1709, 1407, 1290, 1215, and 1155 cm^{-1}) and in the CPDA spectrum (1612, 1450, 1420, 1287, 1224, and 1166 cm^{-1}) obeyed Beer's law for the concentrations used in the kinetic runs.

Since absorbances of the bands under study were found to be proportional to concentrations of the initial acids present, the order of reaction was determined from plots of the logarithm of the change in absorbance per unit time for a particular band vs. the logarithm of the absorbance for that band. The slope of the line obtained from such plots is equal to the order of the reaction. The slopes were obtained by use of a least-squares computer program which was a modification of the CHEMICAL KINETICS computer program (No. 37) by Isenhour and Jurs.[24] Values for the slopes were 1.05 ± 0.05, and hence it appears that the thermal reactions of CBDA and of CPDA in KBr are first-order, or pseudo-first-order, reactions.

Rate constants were determined by plotting the logarithm of the ratio of the initial absorbance values to the absorbance values at time t (each corrected to the standard pellet weight) vs. time t. All five absorption bands studied for CBDA and four of the six absorption bands studied for CPDA gave good straight line plots from which rate constants could be determined. The results are presented in Tables I and II. The uncertainty in the rate constant values is about 7% based on the average variances of absorbances for the bands used in the kinetic runs (0.003 absorbance unit for five runs using CBDA and 0.005 absorbance unit for three runs using CPDA, made from the same bulk pellet mixture for each acid).

From the experimentally determined rate constants and their corresponding temperatures, the thermodynamic parameters shown in Tables III and IV were calculated on the basis of the absolute reaction rate theory equation, k = (constant)(T) $\exp(\Delta S^*/R)\cdot\exp(-\Delta H^*/RT)$ and $\Delta G_T^* = \Delta H^* - T\Delta S^*$. Values obtained in other media by Abell and Tien[3] are also presented in the tables. Plots of the

negative logarithm of k/T vs. $1/T$ based on the absolute reaction rate theory equation, from which ΔS^*(intercept) and ΔH^*(slope) were determined for the five absorption bands of CBDA and the four absorption bands of CPDA used in this work, are presented in Figure 1.

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Registry No.—Cyclobutane-1,1-dicarboxylic acid, 5445-51-2; cyclopropane-1,1-dicarboxylic acid, 598-10-7; diethyl cyclopropane-1,1-dicarboxylate, 1559-02-0; α-carboxy-γ-butyrolactone, 4360-91-2.

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Synthesis of the 1-, 2-, 3-, and 4-Hydroxy Isomers of Benz[*a*]anthracene-7,12-dione, Benz[*a*]anthracene, and 7,12-Dimethylbenz[*a*]anthracene[1]

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Studies on the mechanisms of chemical carcinogenesis require the use of potential metabolites of known carcinogens. The 1-, 2-, 3-, and 4-hydroxy isomers of benz[*a*]anthracene-7,12-dione (**4a–d**), of benz[*a*]anthracene (**6a–d**), and of 7,12-dimethylbenz[*a*]anthracene (**8b–d**) have been synthesized. A Diels–Alder reaction between the appropriate methoxystyrene (**2a–c**) and 1,4-naphthoquinone (**1**) produced the respective methoxybenz[*a*]anthracene-7,12-diones (**3a–d**). These methoxy diones were demethylated to yield the hydroxydiones **4a–d**, reduced and demethylated to yield the hydroxybenz[*a*]anthracenes (**6a–d**), and converted via the classical Grignard procedure followed by demethylation to the hydroxy-7,12-dimethylbenz[*a*]anthracenes (**8b–d**).

Current interest in the metabolism of carcinogenic polycyclic aromatic hydrocarbons (PAH), such as the potent carcinogen 7,12-dimethylbenz[*a*]anthracene (DMBA) and the weaker carcinogen benz[*a*]anthracene[2] (BA), has led to renewed efforts to synthesize potential metabolites of these compounds. Since recent studies have suggested that the angular ring is the site of metabolic activation for these compounds, our initial efforts were directed toward the synthesis of the A ring (1, 2, 3, 4 positions) phenols of BA and DMBA. Some of these compounds have been previously synthesized by tedious multistep routes.[3–10] We describe here a new, relatively simple, and direct approach to the preparation of these compounds by a general synthetic procedure from readily available starting materials.

Results and Discussion

The key intermediates in the synthesis of the phenolic isomers of BA and DMBA were the 1-, 2-, 3-, and 4-methoxybenz[*a*]anthracene-7,12-diones (**3a–d**) shown in Scheme I. Our recent report that a Diels–Alder reaction between 1,4-naphthoquinone and substituted styrenes produced 1-, 2-, 3-, 4-, and 5-substituted BADs[11,12] indicated that **3a–d** could be prepared easily, in one step. From these diones, the BA derivatives could be obtained in one additional step,[13] and the DMBA derivatives could be obtained in two steps using the classical Grignard procedure.[8,14,15]

The 1- and 3-MeOBADs (**3a** and **3c**) were obtained as a

Scheme I