[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, No. 215]

The Reactivity of Atoms and Groups in Organic Compounds. XX. The Effect of Substituents on the Relative Reactivities of the Hydroxyl Group in Derivatives of Benzoic Acid

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Some time ago a report was given of the study of the influence of substituents on the relative reactivities of the hydrogen atom of the carboxyl group in a number of derivatives of benzoic acid.[2] It appeared of interest to determine the relative reactivities of the hydroxyl group in the acids previously studied to discover the influence of the substituents on the carbon–oxygen bond. Comparisons between the effects on the two bonds linked to oxygen gave information in regard to the influence of substituents on reactivity through a chain of atoms; it also furnished evidence in regard to the theory of alternating strong and weak bonds put forward by Flürscheim.[3]

Among the acids studied were several which contained one or two substituents in the *ortho* position. These were studied with the expectation that the results would be helpful in a fuller understanding of the so-called "diortho effect."

The velocity constants of the reactions between the acids and thionyl chloride were determined: $RCOOH + SOCl_2 = RCOCl + HCl + SO_2$. The course of the reaction was followed by determining, from time to time, the pressure produced by the two gases as they were formed in a closed system of constant volume. Since thionyl chloride and the gases formed are corrosive, a new type of all-glass apparatus was designed; it is described in the experimental part of this paper. A large excess of thionyl chloride served as the solvent.

The results of the experiments are given in Table I.

TABLE I

Column I, substituents present in benzoic acid; Column II, average first order velocity constants at 25° of the reaction $RCOOH + SOCl_2 = RCOCl + HCl + SO_2$, time in minutes; Column III, relative values of the constants compared with benzoic acid taken as 1; Column IV, relative reactivities of the acidic hydrogen atoms, when known, benzoic acid taken as 1.

I	II	III	IV[a]
2,6-Dimethoxy	Too fast to measure	...	...
4-Methoxy	0.065 (0.0629–.0677)	9.8	...
2,4,6-Trimethyl	.055 (0.560–.0541)	8.2	...
2,4,6-Triethyl	.051 (.0509–.0501)	7.6	...
2-Methoxy	.026 (.0265–.0260)	3.9	0.04
4-Methyl	.026 (.0257–.0254)	3.8	...
3-Methyl	.011 (.0112–.0111)	1.7	.6
2-Methyl	.0074 (.00735–.00746)	1.1	.4
Benzoic	.0067 (.00661–.00656) (.00672–.00682)	1	1
2-Chloro	.0011 (.00106–.00104)	0.16	16.5
3-Chloro	.00062 (.00062–.00062)	.09	9.6
2,6-Dichloro	.00056 (.00053–.00059)	.08	...
2-Chloro-6-nitro	.00047 (.00047–.00046)	.07	...
2-Nitro	.00021 (.00017–.00024)	.03	83
3-Nitro	Too slow to measure		

[a] Norris and Strain, ref. 2.

A comparison of the figures in Column III shows that the relative reactivities of the hydroxyl group in all the acids which contain CH_3, C_2H_5 or CH_3O groups are greater than the reactivity of the hydroxyl group in benzoic acid. The presence of two of these groups in the ortho positions greatly increases reactivity. It has been shown[4] that the acyl chlorides prepared from these diortho substituted acids react so rapidly with ethyl alcohol at 0° that the rates of the reaction could not be measured. The hydroxyl groups in the acids which contained Cl and NO_2 were less reactive than the hydroxyl group in benzoic acid. The presence of two of these substituents in the ortho positions greatly reduced reactivity. The acyl chlorides of these acids reacted so slowly at 0° with ethyl alcohol that the rates of the reactions could not be measured. These facts will be helpful in arriving at a satisfactory interpretation of steric hindrance. The effect on the reduction of reactivity of the hydroxyl group by Cl and NO_2 was greater in the meta than in the ortho position; the same conclusion was drawn from the relative reactivities of the acyl chloride with alcohol.

In the preparation of acyl chlorides from acids and thionyl chloride, a molecular quantity of pyridine has been used to assist the reaction.[5] L. F. Fieser and M. Fieser[6] prepared the acyl

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[1] From the thesis submitted by Arthur E. Bearse in partial fulfilment of the requirements for the degree of Doctor of Philosophy, 1936.

[2] Norris and Strain, THIS JOURNAL, **57**, 187 (1935).

[3] Flürscheim, *J. Chem. Soc.*, **95**, 718 (1909); *Phil. Mag.*, **47**, 569 (1924).

[4] Norris and Young, THIS JOURNAL, **57**, 1420 (1935); Norris and Ware, *ibid.*, **61**, 1418 (1939).

[5] Carre and Libermann, *Compt. rend.*, **199**, 1422 (1934).

[6] L. F. Fieser and M. Fieser, THIS JOURNAL, **57**, 782 (1935).

chloride of a derivative of butyric acid by treating the latter, dissolved in ether, with thionyl chloride and a trace of pyridine. The effect of pyridine and its concentration on the rates at which certain of the acyl chlorides were formed was investigated to discover to what extent the substituent in the acid affected the rates. The effect of concentration of the catalyst was studied in the case of benzoic acid. When equal molecular quantities of the acid and of pyridine were used the rate of the reaction at 25° was 97 times that of the uncatalyzed reaction; with 12.5 moles of acid to 1 of pyridine the rate was 82 times; with 25 moles 64, and with 50 moles 36 times. It was evident that pyridine acted as a catalyst and not as a reagent to remove hydrogen chloride. This conclusion was strengthened by the fact that when 12.5 moles of benzoic acid was treated with a large excess of thionyl chloride and 1 mole of N,N-dimethylcyclohexylamine, the rate was increased 91 times and when an equivalent quantity of the hydrochloride of the amine was used the rate increased 67 times. Dimethylaniline in the same concentration increased the rate with benzoic acid only 14 times.

The reactions were carried out in the way used in the case of the uncatalyzed reactions. The results are given in Table II.

TABLE II

Column I, substituent in benzoic acid; Column II, first order velocity constant of catalyzed reaction at 25°; mole conc. of acid to pyridine 12.5 to 1, time in min.; Column III, ratio of constant of catalyzed reaction to constant of uncatalyzed reaction; Column IV, relative rates of catalyzed reactions with benzoic acid = 1; Column V, relative rates of uncatalyzed reactions, benzoic acid = 1.

I	II	III	IV	V
2-Nitro	0.35–0.30	1520	0.6	0.03
2-Chloro	.63	600	1.1	.16
2-Methyl	.66	89	1.2	1.1
Benzoic acid	.54– .55	82	1	1
3-Chloro	.048	77	0.09	0.09
2,6-Dichloro	.042	75	.08	.08
3-Methyl	.67	60	1.2	1.7
4-Methyl	.67	26	1.2	3.8
3-Nitro	.0011	..	0.002	..

The figures in Column III show the great effect of the catalyst in increasing the rate of the reaction between the acids and thionyl chloride. The effect was greatest in the case of the acids containing a substituent in the *ortho* position. From Column V it is seen that the two acids most affected were those that had low reactivity when measured by the uncatalyzed reaction. Columns IV and V show that the relative reactivities measured by the catalyzed and by the uncatalyzed reactions are not the same. The three methyl derivatives are more reactive than benzoic acid when measured in either way and the halogen and nitro derivatives, with the exception of the 2-chloro compound, are less reactive than benzoic acids.

The practical application of these results is evident, namely, the use of pyridine or dimethylcyclohexylamine as a catalyst in preparing acyl chlorides by means of thionyl chloride. Hans Meyer[7] who applied the reaction to a large number of acids, without a catalyst, reported that certain acids required heating the mixture for several hours. The acid chloride was obtained by removing the excess of thionyl chloride by distillation. In our experiment the catalyzed reaction was complete at 25° in the case of benzoic acid in about ten minutes; the 3-chloro acid required about one hour for complete reaction.

Details of Experiments

The Apparatus Used.—This is sketched in Fig. 1. The vessel in which the reaction took place (A, side view at left) had two arms, 8 cm. long and 3 cm. in diameter and a no. 20 ground glass joint. It was connected through the joint to a tube, attached to a shaking device, and flexible glass bends to the stopcock B. The apparatus up to the cock was placed in a thermostat at 25 ± 0.02°. A tube from B led to cock C and a closed spiral tube (18 turns 2.5 cm. in diameter) to which was sealed a small mirror. The tube and mirror were enclosed in a jacket which was connected with cocks as indicated and a manometer, having two arms, in which the pressure could be adjusted. When the pressure in the reaction vessel increased the spiral would cause the mirror to change its position. The position of the mirror was indicated by a beam of light reflected from it onto a screen. In order to determine the increased pressure in the partially evacuated apparatus, the pressure outside of the spiral was adjusted roughly by letting air in through the cocks, and a final adjustment was made by raising the vessel containing mercury attached to the manometer until the spot of light from the mirror returned to the original zero position. The pressure added to balance the inside pressure was measured on the manometer. This method of measuring the pressure of a corrosive gas was used successfully by Johnson[8] in measuring the vapor pressure of ammonium chloride at high temperatures and by workers in the Research Laboratory of Inorganic Chemistry of this Institute.

In using the apparatus the desired weight of the solid acid was introduced into the weighed reaction vessel A held so that one tube was vertical and the other horizontal Through a short piece of glass tubing placed in the opening

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(7) Hans Meyer, *Monatsh.*, **22**, 415, 477 (1901). See also McMaster and Ahmann, THIS JOURNAL, **50**, 145 (1928), and Clark and Ball, *Trans. Roy. Soc. Can.*, III, **27**, 97 (1933).

(8) Johnson, *Z. physik. Chem.*, **61**, 457 (1907).

was introduced a smaller tube carrying the acid. By tapping the tube the required amount of acid could be dropped into the vertical tube. The reaction vessel A was again weighed. The weight of acid introduced could be determined to 1 mg. The reaction vessel was connected with the rest of the apparatus by means of the ground glass joint which had been treated with "lubriseal," and water was added to the thermostat which was brought to approximately 25°. Enough of the water was then drawn off to permit the removal of the reaction vessel after it had been wiped dry. By means of a calibrated pipet exactly 10 cc. of thionyl chloride was added to the leg of the reaction vessel which did not contain the acid. The reaction vessel was again connected with the apparatus, care being taken to prevent the thionyl chloride from coming in contact with the acid. The water was returned to the thermostat and the shaker and water pumps connected at C and F were started. The system was evacuated until the pressure on the two sides of the spiral manometer was about 140 mm. This required about one and one-half minutes. The cocks C and E were then closed. Shaking was continued for ten minutes to allow the system to come to equilibrium; during this time the temperature of the thermostat was brought to 25 ± 0.02°. The shaker was stopped, the cock B was closed and the reactants were mixed by rotating the reaction vessel through 90 degrees. The time was recorded as zero time. The pressure was measured by adjusting the pressure in the outside of the spiral manometer so that the spot of light reflected from the mirror returned to the zero position. The cock B was opened and the shaker started.

Readings of pressure were made at intervals of time that depended on the rate at which the reactions were taking place. When a reading was made the cock B was closed and the shaker stopped. In order to avoid a possible leak in the apparatus, the two sides of the glass joint that connected the reaction vessel with the rest of the apparatus were held in position during the shaking by a wire around projections sealed to the two parts of the joint. Shaking was continuous during the first hour except when pressure readings were made; thereafter the shaker was run only for ten minutes preceding a reading. The adjustments in the outside pressure were made through the three-way cock F; air was either withdrawn by the pump or admitted through the cock.

Calculation of the Velocity Constants.—The constants were calculated from the formula

$$K = \frac{2.303}{t} \log \frac{P}{P - p}$$

in which P is the final pressure and p is the pressure at time t. By plotting the log terms against t a straight line was obtained up to a high percentage conversion in the case of most of the acids. The slope of the line is a measure of the constant. In certain cases the line did not cut the axis of time at zero and the time correction, determined in the usual way, was used in calculating the constant.

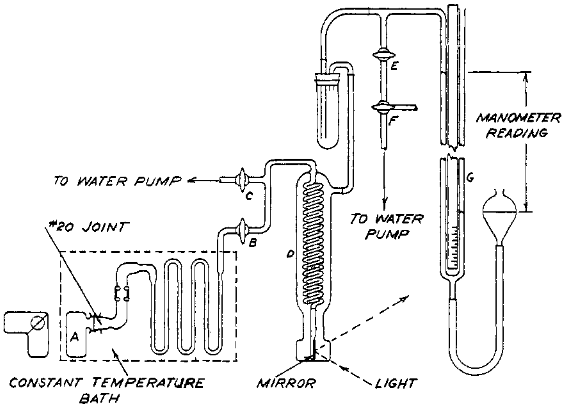

Fig. 1.—Apparatus for measuring pressure increase.

The method of calculation required the determination of the pressure when the reaction was complete (P). This value was determined in the case of benzoic acid and the acids more reactive than benzoic. It was found to be nearly constant since equivalent weights of the acids were used. In the case of the less reactive acids the experimental values found with benzoic acid were used for P.

In the case of certain of the inactive acids the following formula was used as a check

$$K = \frac{2.303}{t_2 - t_1} \left(\log \frac{P}{P - P_2} - \log \frac{P}{P - P_1} \right)$$

Control experiments in which thionyl chloride without an acid was used showed that a pressure was developed slowly. This probably was due to the slow diffusion of the chloride into the parts of the apparatus outside the thermostat. In order to correct for this added pressure four runs were made; they agreed well and furnished average values to be used in calculating the real increase in pressure due to the reaction. The correction increased from 1 mm. to 10 mm. at the end of three hundred minutes. In the case of benzoic acid and the acids that were more reactive, the correction was a small percentage of the observed pressure; the constants were calculated from times less than one hundred and forty minutes. In the case of the very inactive acids the correction amounted to from 10 to 30 % of the observed reading.

The Reagents Used.—The acids were purified by crystallization until the melting points were constant and checked closely the best values in the literature. They were dried in an oven and finally in a vacuum desiccator over activated aluminum for at least twelve hours before use.

The 2,6-dichlorobenzoic acid was prepared from 2,6-dichlorotoluene by a convenient method which has not been described. The method is given in detail because we were unsuccessful in preparing the acid by the direct oxidation of the toluene derivative with potassium permanganate.[9] Attempts to prepare the acid by oxidation of the toluene derivative with alkaline or acid permanganate, chromic acid and sulfuric acid in acetic acid, and potassium dichromate and sulfuric acid did not give satisfactory results.

Twenty grams of 2,6-dichlorotoluene was placed in a 300-cc. flask having two necks to which were attached a reflux condenser and a separatory funnel the end of which was just above the liquid. The flask was heated in an oil-bath at 170° and 19.8 g. of bromine was added slowly through the funnel at such a rate that no bromine escaped. When the reaction was complete and the flask was cold, the contents were transferred to a 1-liter flask fitted with a mercury seal stirrer, and a reflux condenser. A solution of 6 g. of sodium hydroxide in 500 cc. of water was added and the mixture heated to boiling with the stirrer running. Powdered potassium permanganate was added in small portions through the condenser and washed down with a little water. When the color disappeared more permanganate and small amounts of a solution of sodium hydroxide to keep the mixture alkaline were added. After 24.8 g. of the permanganate had been used during about two hours the color persisted. This was removed by alcohol and the mixture was distilled with steam; about 0.7 cc. of the chlorotoluene was recovered. The material in the flask was filtered and the solid washed with water. The filtrate was concentrated to about 150 cc. and enough hydrochloric acid added to precipitate the 2,6-dichlorobenzoic acid. The acid was digested with water, dried and crystallized from a mixture of equal volumes of benzene and ligroin. The yield of pure acid which melted at 143–144° was 57% of the theoretical amount calculated from the 2,6-dichlorotoluene used. A similar method could be applied probably to other hydrocarbon derivatives which resist ordinary oxidizing agents.

The method was based on information from the du Pont Company, that 2-chloro-6-nitrotoluene could be brominated readily in the side chain at 170°, whereas a higher temperature is required for chlorination and the resulting yield is very small.

In an attempt to prepare 2-chloro-6-nitrobenzoic acid from the corresponding aldehyde by means of the Cannizzaro reaction, it was found that the aldehyde group was removed and nearly the theoretical yield of *m*-chloronitrobenzene was obtained.

Purification of Thionyl Chloride.—The material used (Eastman Kodak Company, No. 246, b. p. 75–76°) was fractionally distilled in an all glass apparatus with a Davis column. The several fractions were used in test experiments with benzoic acid. The value of the velocity constant for the reaction varied from 0.0103 to 0.0131. It was evident that a small amount of impurity was present which increased the rate and could not be removed by fractionation. A portion of the original sample (50 cc.) was treated with 1 g. of benzoic acid and allowed to stand twelve hours. The excess of thionyl chloride was then distilled off, fractionated, and tested by determining the velocity constant of the reaction with benzoic acid. This was found to be less than before treatment. Four such treatments, followed by fractionation, caused a marked decrease in the constant. Four additional treatments caused only a slight decrease. Four more treatments changed the constant only within the experimental error of the process. All determinations were made with thionyl chloride that had been subjected to twelve treatments with benzoic acid and subsequent fractionation in which the first part of the distillate was rejected. Two separate preparations gave products which yielded constants that checked within less than 3%. The purification did not appreciably affect the boiling point of the thionyl chloride. The samples used boiled at 74.8–75.6° (751 mm.). The recorded boiling point is 75° (746 mm.).[10]

Summary

1. The relative reactivities of the acidic hydroxyl groups of a number of derivatives of benzoic acid have been determined by measuring the rates at which the acids react with thionyl chloride.

2. The results show that the acids which have the more reactive hydroxyl groups have the less reactive acidic hydrogen atoms.

3. Acids which have methyl, ethyl or methoxy groups in the two positions ortho to the carboxyl group have very reactive hydroxyl groups; the acids having chlorine or the nitro group in these positions have very inactive hydroxyl groups.

4. A study of the effect of pyridine and of N,N-dimethylcyclohexylamine on the rates of the reaction showed that the latter were greatly increased by the catalysts. The acids which contained the substituent in the ortho position were most affected; the rate with *o*-nitrobenzoic acid was increased 1520 times, *o*-chlorobenzoic acid 600 times, and *o*-methylbenzoic acid 87 times when the concentration of the catalyst was 1 mole to 12.5 moles of the acid.

CAMBRIDGE, MASS.

RECEIVED JANUARY 6, 1940

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[9] Claus and Stanenhagen, *Ann.*, **269**, 224 (1892). Cohen and Dakin, *J. Chem. Soc.*, **79**, 1132 (1901), report failure with this method.

[10] Arri, *Chem. Abs.*, **24**, 277 (1930).