[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WASHINGTON]

The Mechanisms of Hydrogen Peroxide Reactions. II. A Comparison of the Reactivity of Hydroxyl Ion and Hydroperoxide Ion toward Benzonitrile

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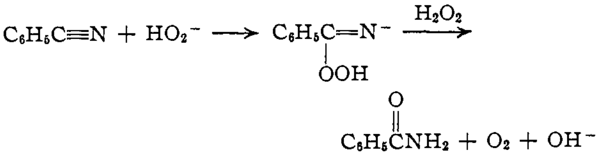
The rates of reaction of hydroperoxide ion and of hydroxyl ion with benzonitrile and three of its ring substituted derivatives have been measured in 50% acetone solution. The reaction of hydroperoxide ion was found to be over 10^4 times as fast as that of hydroxyl ion. The enthalpy of activation for the two ions was about the same, the main difference being found in the entropy of activation. The value of ρ for the reaction with hydroperoxide ion was found to be lower than that for hydroxyl ion. The factors which influence the rate of displacement reactions in some unsaturated systems are discussed.

Introduction

It has been found that the conversion of benzonitrile to benzamide using hydrogen peroxide involves the reaction between benzonitrile and hydroperoxide ion in the rate-determining step.[1]



$$C_6H_5C{\equiv}N + HO_2^- \longrightarrow \underset{\displaystyle OOH}{C_6H_5C}{=}N^- \xrightarrow{H_2O_2} \overset{\displaystyle O}{\overset{\|}{C_6H_5C}}NH_2 + O_2 + OH^-$$

A comparison of the rates of reaction between benzonitrile and several anions indicated hydroperoxide ion to be a particularly effective nucleophilic ion in this reaction. Unfortunately, the data used for the comparison was obtained under different conditions than the benzonitrile–hydrogen peroxide reaction. A comparison has now been made between the reaction of hydroperoxide ion and of hydroxyl ion with benzonitrile and several of its ring-substituted derivatives in 50% acetone solution. The enthalpy and entropy of activation for the two reactions also have been determined.

Experimental

Materials.—The nitriles were purified commercial samples with the exception of *m*-bromobenzonitrile which was prepared from *m*-bromobenzoic acid by conversion to the amide followed by dehydration with phosphorus pentoxide.[2] The hydrogen peroxide was a C.P. grade, with a 3% concentration. The solvent, acetone, was a C.P. grade which was further purified by heating with potassium permanganate, followed by distillation.

Analytical Method. (a) Nitriles.—The concentration of the nitrile in the reaction mixture was determined by adding a 20-ml. aliquot to 30 ml. of saturated sodium chloride solution contained in a separatory funnel, followed by careful extraction with two 10-ml. portions of carbon tetrachloride. The organic solution was distilled from a 50-ml. erlenmeyer flask whose neck had been elongated to 10 cm., until the volume had been reduced to about 5–6 ml. The solution was transferred to a 10-ml. volumetric flask, and diluted to the mark with carbon tetrachloride. The resultant solutions were analyzed by measuring the ratio of the intensities of the 4.38 μ band of carbon tetrachloride and the 4.45 μ band of the nitriles using a Perkin–Elmer model 21 infrared spectrophotometer and a 1.0-mm. fixed cell. The infrared analysis appeared to be quite reproducible, and the main errors were probably associated with the isolation procedure. In order to obtain a calibration for this method, solutions of known nitrile concentration were carried through the above procedure. The calibration curve for *p*-chlorobenzonitrile is shown in Fig. 1.

(b) **Hydrogen Peroxide.**—The concentration of hydrogen peroxide was determined iodometrically using 5-ml. aliquots as described previously.[1]

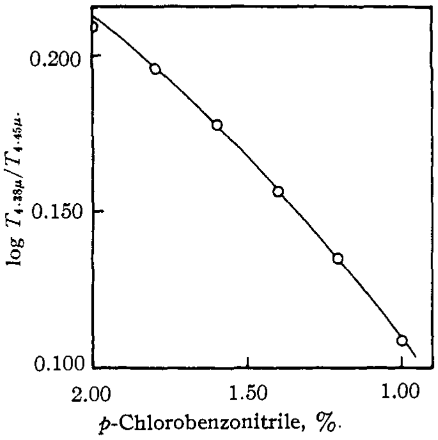


Fig. 1.—Calibration curve for infrared analysis for *p*-chlorobenzonitrile.

Kinetic Method.—To a 100-ml. portion of a solution of the nitrile in acetone was added either an equal volume of 0.200 *N* sodium hydroxide solution or an aqueous solution containing 10 ml. of 1.0 *M* dipotassium hydrogen phosphate, 2 ml. of 0.500 *N* hydrochloric acid and the stoichiometric amount of hydrogen peroxide in 100 ml. of solution. All volumes were measured at room temperature, and the solutions were brought to the thermostat temperature before mixing. Aliquots of the solutions were analyzed as described above. The rate constants for the alkaline hydrolysis of the nitriles to the amides were determined by plotting the natural logarithm of the nitrile concentration against time, the slope of the line divided by the hydroxyl ion concentration giving the second-order rate constant. The concentration of the nitrile and of hydroxyl ion was about 0.1 *M* in all cases. The values thus obtained were estimated to have an accuracy of about ±5%. Aliquots also were analyzed for the hydroxyl ion concentration by titration with standard acid to a phenolphthalein end-point. These titers were constant during any given reaction, indicating that hydrolysis of the amide to the acid did not occur. In a number of cases, duplicate determinations were made, and the rate constants thus obtained invariably agreed to better than 5%.

The rate constants for the reaction of the nitrile with hydrogen peroxide were determined by plotting the logarithm of the reciprocal of the nitrile concentration against time, the slope of the line giving the pseudo second-order rate constant at constant *p*H. The nitrile concentration was about 0.1 *M*, and the stoichiometric amount of hydrogen peroxide was used. The *p*H of the solutions was measured using a Beckman model G *p*H meter, and the *p*H was found to be constant ±0.05 *p*H unit. The rate constants were estimated to have an accuracy of ±5%. In the case of benzonitrile at 60° and *p*-chlorobenzonitrile at 50°, the concentration of the nitrile was determined as well as the hydrogen peroxide concentration. The results for *p*-chlorobenzonitrile are shown in Fig. 2. The excellent agreement between the change in nitrile concentration and the change in hydrogen peroxide concentration indicates that no significant amount of independent decomposition of hydrogen peroxide took place under these conditions.

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[1] K. B. Wiberg, THIS JOURNAL, **75**, 3961 (1953).

[2] C. Engler, *Ber.*, **4**, 708 (1871).

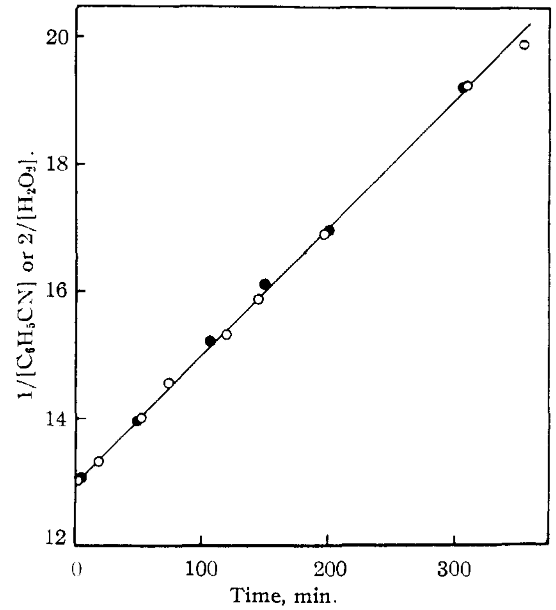

Fig. 2.—Rate plot for the reaction of hydrogen peroxide with *p*-chlorobenzonitrile at 50.0°. Closed circles are for the nitrile and open circles are for hydrogen peroxide.

The Hydrolysis Constant for Hydroperoxide Ion.—The hydrolysis constant was determined by measuring the decrease in rate of the hydrolysis of ethyl acetate in 50% acetone caused by the addition of hydrogen peroxide. The reaction solutions were prepared by mixing equal volumes of a solution of ethyl acetate in acetone, and a solution of sodium hydroxide and hydrogen peroxide in water. The extent of reaction was determined by removing 20-ml. aliquots, which were added to standard acid followed by back titration.

Results

The rates of reaction of benzonitrile and several substituted benzonitriles with both hydroxyl ion and hydrogen peroxide in basic solution have been determined. The rate constants thus obtained are shown in Table I. From these rate constants, one may calculate a value of ρ by plotting the logarithm of the rate constants against the Hammett σ-values.[3] The values thus obtained (Fig. 3) are 2.31 for the reaction with hydroxyl ion and 1.66 for the reaction with hydrogen peroxide.

TABLE I

RATE OF REACTION OF THE BENZONITRILES WITH HYDROGEN PEROXIDE AND WITH HYDROXYL ION

Substituent	T, °C.	k $(OH^-)_1$, l. mole^{-1} sec.$^{-1}$	k (H_2O_2) pH 8.75	k (HO_2^-), l. mole^{-1} sec.$^{-1}$	$k_{HO_2^-}/k_{OH^-}$
H	40.0	4.0×10^{-5}	8.0×10^{-5}		
	50.0	1.12×10^{-4}	2.38×10^{-1}	7.3	6.6×10^4
	60.0	3.05×10^{-4}	5.8×10^{-4}		
p-Cl	40.0	2.89×10^{-4}	1.71×10^{-4}		
	50.0	6.8×10^{-4}	4.3×10^{-4}	13.2	2.0×10^4
	60.0	1.75×10^{-3}	9.7×10^{-4}		
p-CH_3	50.0	6.1×10^{-5}	1.13×10^{-4}	3.5	1.9×10^4
m-Br	50.0	9.5×10^{-4}	1.08×10^{-3}	33.0	3.5×10^4

The important rate constant for the reaction with hydrogen peroxide is not the observed rate constant, but rather that for the reaction between hydroperoxide ion and benzonitrile. In order to obtain this value, it was necessary first to determine the hydrolysis constant for hydroperoxide ion in 50% acetone. The most convenient method is that used by Joyner[4] for the measurement of the ionization constant of hydrogen peroxide in water, and involves the measurement of the reduction in rate of the alkaline hydrolysis of ethyl acetate caused by the addition of hydrogen peroxide to the solution. This method was found to give values which were in good agreement with those obtained by other methods, and is based on the lack of reaction between hydroperoxide ion and the ester.

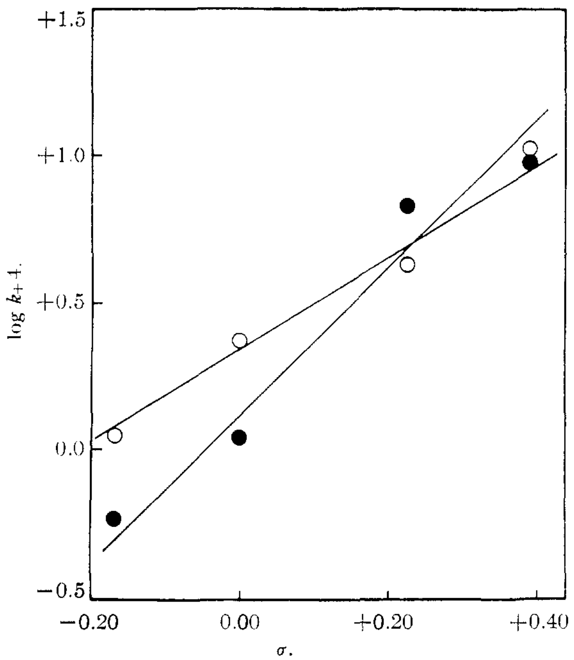

Fig. 3.—Hammett plot for the reaction of benzonitriles with hydroxyl ion (closed circles) and hydroperoxide ion (open circles).

The rate constant is given by equation 1, where $(HO^-)_s$ is the amount of base added, and $[HO^-]$

$$\frac{-d[EtOAc]}{dt} = k[EtOAc][HO^-] = k\frac{[HO^-]}{(HO^-)_s}[EtOAc](HO^-)_s \quad (1)$$

is the actual concentration. Since $(HO^-)_s$ = [EtOAc] in all the experiments, and since the ratio $[HO^-]/(HO^-)_s$ (designated as Q) changes slowly with time (a 10% decrease is obtained at 25% reaction) the quantity kQ may be obtained by plotting 1/[EtOAc] against time and determining the initial slope. Q may be obtained knowing the rate constant found in the absence of hydrogen peroxide. The equilibrium constant is then given by equation 2.

$$K = \left[\frac{(H_2O_2)_s}{1 - Q} - (HO^-)_s\right] Q \quad (2)$$

The data which were obtained are given in Table II.

From these data, the enthalpy and entropy of hydrolysis may be calculated, giving $\Delta F_{40°}$ = 2.9 kcal., $\Delta H = 3.3 \pm 0.6$ kcal. and $\Delta S = 1 \pm 2$

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[3] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 184–193.

[4] R. A. Joyner, *Z. anorg. Chem.*, 77, 103 (1912).

TABLE II

DETERMINATION OF THE HYDROLYSIS CONSTANT FOR HYDROPEROXIDE ION

T, °C.	[Et-OAc]	$(NaOH)_0$	$(H_2O_2)_0$	k_1	Q	$K_h \times 10^3$
0.2	0.0213	0.0206	....	1.10×10^{-2}	..	....
.2	.0213	.0206	0.0173	4.64×10^{-3}	0.42	3.9
.2	.0213	.0206	.0237	3.39×10^{-3}	.31	4.2
					Ave.	4.1 ± 0.2
25.0	.0208	.0215	....	4.88×10^{-2}	..	....
25.0	.0208	.0215	.0160	2.67×10^{-2}	0.55	7.8
25.0	.0208	.0215	.0213	2.05×10^{-2}	.42	6.4
25.0	.0208	.0215	.0315	1.54×10^{-2}	.32	7.9
					Ave.	7.3 ± 0.7
40.0	.0205	.0203	....	1.31×10^{-1}	..	....
40.0	.0205	.0201	.0228	5.7×10^{-2}	0.42	8.1
40.0	.0205	.0197	.0455	3.2×10^{-2}	.24	9.6
					Ave.	8.9 ± 0.8

e.u. In water, the corresponding values are $\Delta F = 3.2$, $\Delta H = 4.9$ and $\Delta S = 5.6$.[5] The values obtained are quite reasonable since Bertin[6] has found that neutral and negatively charged acids become weaker in going from water to acetone–water mixtures, whereas the ion product of water remains essentially constant.

The observed *p*H of the solutions was 8.75. However, it is known that a glass electrode will not give the correct *p*H in mixtures of water and organic solvents. Swain and Scott[7] found their glass electrode to read 1.2 *p*H units high when used in 50% acetone, and the electrode used in this work gave a value 1.21 units high in 10^{-3} *M* sodium hydroxide in 50% acetone. The correct *p*H would then be 7.54. The same buffer in water gave a *p*H of 7.87, and since negatively charged acids were found to be weaker in acetone–water than in water alone,[6] one would expect a higher rather than a lower *p*H. It was then important to determine whether the actual *p*H was higher or lower than 7.87. This was done by comparing the colors of several indicators in a *p*H 7 buffer in water, and in the phosphate buffer in acetone–water and in water. The indicators used were thymol blue (*p*H range 8.0–9.6), brom thymol blue (6.0–7.6) and phenol red (6.4–8.0). With each of the indicators, the color of the buffer in acetone–water was between that of the *p*H 7.00 buffer and the 7.87 buffer. Thus the correct *p*H will be assumed to be 7.54. It also was assumed that the buffer *p*H was constant over the *p*H range studied, since it has been shown that phosphate buffers in water give essentially no change in *p*H with temperature between 40 and 60°.[8]

TABLE III

ENTHALPY AND ENTROPY OF ACTIVATION

Substituent	Reacn. with HO^-		Reacn. with H_2O_2[a]		Reacn. with HO_2^-[b]	
	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
H	20.5 ± 0.7	−13 ± 2	18.9 ± 0.7	−17 ± 2	22 ± 1	5 ± 4
p-Cl	18.0 ± .7	−17 ± 2	17.3 ± .7	−21 ± 2	21 ± 1	1 ± 4

[a] Apparent values based on rate constants at *p*H 7.54.
[b] Based on calculated third-order rate constants.

Using the value of the hydrolysis constant calculated for 50° from the above data and the van't Hoff equation (1.07×10^{-2}) and a *p*H of 7.54 ($[HO^-] = 3.5 \times 10^{-7}$), the rate constants in the third column of Table I were calculated. It was then possible to determine the enthalpy and entropy of activation which are given in Table III.

Discussion

The reaction of hydroperoxide ion with benzonitrile has been shown to be over 10^4 as fast as that of hydroxyl ion. This difference in rate suggests that hydroperoxide ion is more nucleophilic than hydroxyl ion, since the latter is the stronger base. If an ion will contribute to the stabilization of the transition state in some unique manner, because of its higher polarizability or some other factor, then one would expect that the influence of substituents on an aromatic ring attached to the reaction site would be lower with this ion, than with one which does not have this possibility of stabilization. In the present case, the hydroperoxide ion was found to give a lower value of ρ than did hydroxyl ion, as would be expected on this basis.

The reaction of benzonitrile with hydroxyl ion was found to give a fairly negative entropy of activation. This is commonly observed in the hydrolysis of esters and nitriles,[9] although it would seem that no completely satisfactory explanation for this effect has been proposed as yet.[10] The reaction of hydroperoxide ion with benzonitrile was found to have about the same enthalpy of activation, and the difference in rate is accounted for by the large difference in entropy of activation. If the reason for the low entropy factor in the alkaline hydrolysis were known, one would be able to decide whether the observed effect of hydroperoxide ion were reasonable on the basis of the proposed mechanism, or if this mechanism required revision. In the absence of additional information, it does not seem profitable to discuss the difference at any length.

It is interesting to note that the basis of the method of determining the hydrolysis constant of hydroperoxide ion is that this ion will not react with ethyl acetate, whereas its reaction with benzoyl chloride is quite rapid, and is the basis for the preparation of diacyl peroxides. A tabulation of some similar reactions is shown in Table IV, in which a plus sign indicates that reaction does occur. If the reaction of all of these compounds involves an intermediate,[11] then the rate of reaction will depend on both k_1 and on the ratio k_2/k_{-1}. The first should be primarily affected by the nucleo-

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(5) Calculated using the data of Joyner, ref. 4, and the data in S. Glasstone, "Thermodynamics for Chemists," D. Van Nostrand Co., Inc., New York, N. Y., 1947, p. 507.

(6) C. Bertin, *Anal. Chim. Acta*, **7**, 105 (1952).

(7) C. G. Swain and C. B. Scott, THIS JOURNAL, **75**, 141 (1953).

(8) G. G. Manov, *J. Assoc. Offic. Agr. Chemists*, **30**, 500 (1947).

(9) B. S. Rabinovitch and C. A. Winkler, *Can. J. Research*, **20B**, 185 (1942), found the alkaline hydrolysis of propionitrile to have an entropy of activation of −18 e.u. Similar values are obtained in the hydrolysis of ethyl benzoates, benzyl acetates and related compounds (E. Tommila and C. N. Hinshelwood, *J. Chem. Soc.*, 1801 (1938)).

(10) E. A. Moelwyn-Hughes, "The Kinetics of Reactions in Solution," Oxford University Press, 1933, pp. 250–252, suggested that the low entropy of activation could be accounted for by a mechanism involving a ternary collision between the ester, the catalyst and water. It is difficult to see why this should be the preferred mode of reaction rather than a bimolecular reaction, and the implications of such a mechanism with respect to reaction of other anions have not been considered as yet.

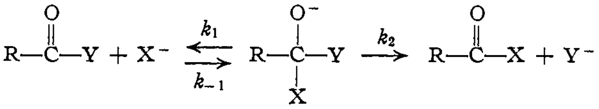
(11) M. L. Bender, THIS JOURNAL, **73**, 1626 (1951).

TABLE IV

THE REACTION OF SOME ANIONS WITH ACID DERIVATIVES

Compound	HO^-	HO_2^- [a]	C_3H_7-CO_2^- [b]	I^- [c]
Ethyl acetate	+	−	−	−
Phenyl benzoate	+	+	−	−
Acetic anhydride	+	+	+	−
Benzoyl chloride	+	+	+	+

[a] Ethyl acetate is known not to react with hydroperoxide ion (ref. 4). Phenyl benzoate has been found to react rapidly (unpublished results), and both acetic anhydride and benzoyl chloride react with hydroperoxide ion to give acetyl and benzoyl peroxides, presumably through the peracid (A. M. Clover and G. F. Richmond, *Am. Chem. J.*, **29**, 182 (1903); H. v. Pechmann and L. Vanino, *Ber.*, **27**, 1511 (1894)). [b] The reaction of ethyl acetate and phenyl benzoate with butyrate ion would give an anhydride and ethoxide or phenoxide ion. Thus, the reaction goes in the reverse rather than forward direction. Acetic anhydride reacts with butyrate ion to give butyric anhydride (A. Michael and R. Hartman, *Ber.*, **34**, 918 (1901)) and mixed anhydrides are commonly prepared by the reaction of carboxylic acid salts with benzoyl chloride (L. Chiozza, *Ann.*, **84**, 108 (1852)). [c] The reaction of esters or anhydrides with iodide ion would give an acyl iodide and an alkoxide or carboxylic acid salt. Thus, the reaction goes in the reverse rather than forward direction. Benzoyl iodide has been prepared by the reaction of iodide ion with benzoyl chloride (H. Staudinger and E. Anthes, *Ber.*, **46**, 1423 (1913)).



$$R-\overset{\overset{\displaystyle O}{\|}}{C}-Y + X^- \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} R-\underset{\underset{\displaystyle X}{|}}{\overset{\overset{\displaystyle O^-}{|}}{C}}-Y \xrightarrow{k_2} R-\overset{\overset{\displaystyle O}{\|}}{C}-X + Y^-$$

philicity of the attacking ion, whereas the latter should be in some measure a function of the relative basicity of X^- and Y^-. Thus, if X^- is a weaker base than Y^-, the reaction should not proceed. But, if X^- is a stronger base than Y^-, the reaction should proceed and the rate of reaction should be largely a function of the nucleophilicity of X^-.

This hypothesis is borne out in the case of phenyl benzoate. Here, phenol is a stronger acid than hydrogen peroxide, and therefore this ester should react with both hydroxyl ion and hydroperoxide ion, and the rate of reaction should be larger for the latter ion. This has been found to be the case.[12] Another test may be found in the reaction of benzoyl chloride with various ions because of the wider range of useful groups. A study of this type is now planned.

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[12] The details of this investigation will be published in a later communication.

SEATTLE, WASHINGTON

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

The Mechanisms of the Fries Reaction[1]

BY RICHARD BALTZLY, WALTER S. IDE AND ARTHUR P. PHILLIPS

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The Fries reaction is interpreted as proceeding through a complex of phenol ester and aluminum chloride which, when sufficiently polarized, becomes capable of acylating a different molecule or of rearranging. The former process follows the usual rules of orientation while the latter affords only *o*-hydroxy ketone. As a rule the rearrangement is favored only at high temperatures, but it is facilitated by electron-repelling groups in the phenolic portion and can predominate even at low temperatures if those groups activate an *ortho* position. It has been found that conditions favoring formation of *p*-hydroxy ketone also favor reaction with a competitor substance, in this case diphenyl ether. Under other conditions both of these processes can be minimized or suppressed.

The present communication describes work carried out over a period of several years and intended to decide whether or not the *ortho* shift of the Fries reaction is in substantial degree the result of an intramolecular rearrangement. During the investigation our view-point has been altered materially and it appears most expeditious to state at the beginning the conclusions we have reached, thereafter relating the experimental findings to these conclusions.

It is perhaps well to state at this point that, although it was our constant desire to devise and perform a critical experiment settling this question no single experiment devised to that end has given a decisive result. The failure of these efforts is itself a datum and it is therefore an important characteristic of the mechanism to be presented that no critical experiment should in fact be possible. Despite this disadvantage, we believe the cumulative effect of the evidence to be presented is sufficient to establish a general picture of the Fries reaction.[2]

In the presence of a sufficient excess of aluminum chloride, phenol esters may be considered to be completely coördinated and there is reason to believe that the reaction rate is of first order with respect to this conjugate acid.[3] This coördination complex may be represented by the scheme shown wherein the covalent complex Ia and the ion-pair I_∞ are obviously limiting states which may never be approximated and between which not one but many intermediate stages (symbolized by Ia) of increasing polarization may intervene.[4] The states of lower polarization may be presumed to

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[1] Presented in part before the Organic Division of the American Chemical Society, Chicago, Ill., Sept., 1953.

[2] General reviews of the literature up to 1943 have been published by A. H. Blatt, *Chem. Revs.*, **27**, 429 (1940); "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 342.

[3] R. Baltzly and A. P. Phillips, THIS JOURNAL, **70**, 4191 (1948). Parallel experiments to the same effect have been reported in some detail with boron fluoride catalyst (Kästner, Thesis, Marburg, 1937, in "Newer Methods of Preparative Organic Chemistry," First American Edition, Interscience Publishers, Inc., New York, N. Y., 1948, pp. 284–291).

[4] It is obvious that similar polarized but not ionized complexes may be the reagents in the Friedel–Crafts reaction itself. The Friedel–Crafts reaction proceeds more rapidly than the Fries reaction, so one may expect that polarization is more facile with $Cl_3Al\cdot\cdot ClCOR$ than with $Cl_3Al\cdot O(Ph)\cdot COR$. It is arguable also that discrete oxo-carbonium ions ought to attack compounds such as nitrobenzene and *o*-dichlorobenzene that are notoriously not affected by Friedel–Crafts reagents. Unfortunately only relatively stable oxo-carbonium ions have been demonstrated unambiguously as having discrete existence (*cf.* H. P. Treffers and L. P. Hammett, THIS JOURNAL, **59**, 1708 (1937)). Nitrobenzene does not appear to be attacked appreciably by mesitylenecarboxylic acid dissolved in 100% sulfuric acid.