[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, RUTGERS, THE STATE UNIVERSITY]

Deuterium Isotope Effects in Some Friedel–Crafts Cyclizations of 2-(2-Deuteriophenyl)-benzoyl Chloride

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2-(2-Deuteriophenyl)-benzoyl chloride has been cyclized in various solvents with the catalysts aluminum chloride, stannic chloride and zinc chloride to give fluorenone. The isotope effects observed for these reactions have been found to vary with the nature of the catalyst and the reaction medium, the range of k_H/k_D being from 1.15 to 4.71. The significance of these results is discussed in terms of a general mechanism and the factors which influence the pertinent rate constants.

Recently[2] some deuterium isotope effects have been reported which were observed during the cyclizations of 2-(2-deuteriophenyl)-benzoic acid and some of its derivatives. We now wish to report deuterium isotope effects which arose upon cyclization of 2-(2-deuteriophenyl)-benzoyl chloride (I) to labeled and unlabeled fluorenone (Va and b). In the earlier papers the possible mechanisms for the cyclization of 2-(2-deuteriophenyl)-benzoic acid and some of its derivatives were discussed and the conclusion was reached that the most reasonable path involved formation of a σ-complex, IVa and b, followed by loss of either a proton or a deuteron to give the product, fluorenone. It has been suggested that the isotope effect arises during the final step, and the fact that one observes this effect has been attributed to the ability of IVa and b to return to intermediates similar to II or III.[3] The assumption will be made that the general scheme outlined above is valid and the results obtained will be examined in this framework.[4] The results of these experiments can be found in Table I.

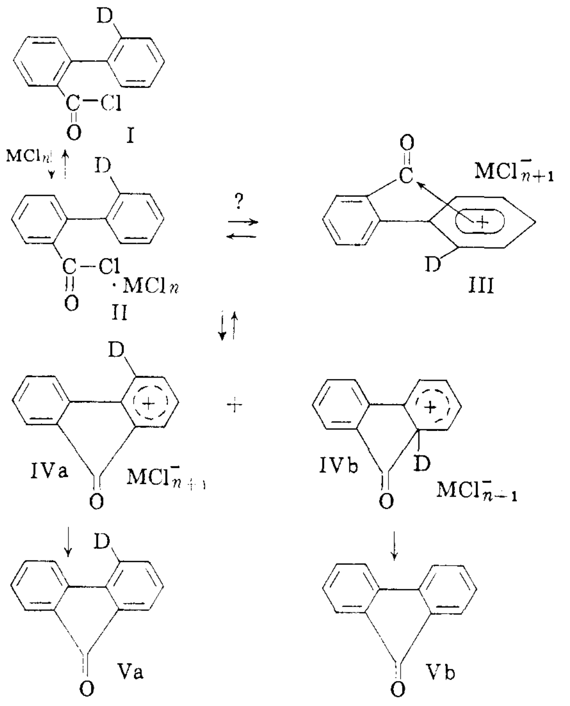

TABLE I

ISOTOPE EFFECTS AS A FUNCTION OF SOLVENT AND CATALYST

Catalyst, chloride	Benzene	Nitrobenzene	Sulfur dioxide
Stannic	1.15 ± 0.03	1.48 ± 0.04	2.15 ± 0.06
Zinc	1.41 ± 0.04[a]		
Aluminum		1.51 ± 0.04	2.88 + ?[b]
Aluminum	2.95 ± 0.14[a]		4.71 ± 0.30[a]

[a] Heterogeneous system. [b] Analyzed mass-spectrometrically by the Esso Research and Engineering Company. The error in this result is about ±0.21.

The stannic chloride, zinc chloride and aluminum chloride catalyzed cyclizations in benzene were allowed to proceed for various times and the products were then analyzed for deuterium. The deuterium content did not change with time, and thus, in these cases, exchange with the hydrogen halide formed in the reaction did not take place. Exchange would have led to a diminution in deuterium content and therefore the apparent isotope effect would have been smaller than the true value. In the aluminum chloride-catalyzed reactions in sulfur dioxide the fact that two different isotope effects were observed makes it seem very unlikely that exchange occurred in this system. The times for these reactions were the same and the status of the reaction mixture was the same at the completion of the reaction, and it seems improbable that exchange would take place in one case and not in the other. Further evidence for the lack of exchange was found by examining the mass-spectra for di-deuterated material in the product. It was found that the maximum amount that could be present was 0.5%.

Table I shows quite clearly that there is considerable variation in the isotope effects. The stannic chloride-catalyzed reactions are unique in that all of them were initially homogeneous and the reaction occurred in solution and not on the surface of the catalyst. The isotope effect increases from benzene to nitrobenzene to sulfur dioxide, and this increase can be explained by a corresponding increase in the stability of IVa and b with respect to loss of hydrogen. Such an increase in stability is

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[1] Alfred P. Sloan Fellow in Chemistry, 1956–1957.

[2] D. B. Denney and P. P. Klemchuk, THIS JOURNAL, **80**, 3285, 3289 (1958).

[3] A more complete discussion of this reasoning can be found in reference 2 and the papers cited there.

[4] In this scheme the structures of II and III have been deliberately written in a rather vague manner since this work makes no direct contribution to the proof of their structures. For example whether II involves coördination of MCl$_n$ with the carbonyl oxygen or the chlorine is not answered by these experiments. With regard to III, a presumed π-complex, these experiments make no contribution as to its existence, since the only requirement is that IVa and b be able to return to an intermediate symmetrical with respect to the two *ortho* carbon atoms.

certainly reasonable since it parallels the solvating power of the solvents.[5] An increase in the free energy of activation for conversion of IVa and b to Va and b shifts the transition states toward products. Such a shift means that there will be an increase of C–H bond stretching in the transition state and therefore a larger isotope effect will result.[6] Whether or not the rate of return of IVa and b to II or III is affected by the change in solvent is hard to decide, since one does not know whether the charge is being dispersed or neutralized in this return step. If neutralization is taking place then an increase in dielectric constant of the solvent will slow down return; on the other hand, if concentration of charge is taking place as one might expect if IV returns to III then an increase in dielectric constant of the medium would favor return.[7] In order for the proposed scheme to accommodate the data it is necessary to postulate that the rate of return is not as adversely affected as is the rate of proton loss,

Within the aluminum chloride-catalyzed series there were several interesting observations. The isotope effects found in the heterogeneous reactions were considerably different from those found in the homogeneous reactions. In the case of benzene and one run in sulfur dioxide, the reactions were heterogeneous. Under these conditions rather large isotope effects were observed, 2.95 for benzene and 4.71 for sulfur dioxide. When aluminum chloride was used in a solution of sulfur dioxide, the isotope effect dropped to 2.88. Clearly this difference must be caused by the change in the reaction conditions. At least two explanations can be offered for this striking difference; one is that when the reaction takes place on the surface of the solid catalyst IVa and b are stabilized with respect to proton loss by the polar character of the catalyst and the interface surrounding it. On the other hand, the ease with which some base can approach the intermediate may also be diminished when the reaction takes place on this surface.[8] When zinc chloride and benzene were used, again the reaction was heterogeneous and also very slow compared to the aluminum chloride reaction. In this case the isotope effect was much lower, 1.41. This is probably due to the fact that the σ-complex is inherently less stable with respect to proton loss in this system than in the aluminum chloride system, and therefore less bond breaking is required in the product-forming step thereby leading to a smaller isotope effect.

A comparison of the homogeneous reactions using the two catalysts stannic chloride and aluminum chloride is interesting. In nitrobenzene, the isotope effects were practically identical. This indicates that the nature of the anion does not have an appreciable effect on the pertinent rate constants in this solvent. Some difference, 0.73, is noted between the two catalysts in sulfur dioxide, although the isotope effects are closer together than might have been expected. It is also interesting to note that both effects are larger than those in nitrobenzene, which again points to the greater solvating power of the sulfur dioxide.

All of these results fit reasonably well into the proposed scheme even though the number of variables is large. The values of the isotope effects should not be taken as those that would necessarily be found in any Friedel–Crafts reaction under the same conditions, since several factors operate in this system which would not be found in other Friedel–Crafts reactions. For example the cyclization of I is somewhat unique in that during the loss of a proton or deuteron from IV a biphenyl is being formed and some stabilization of the transition state should occur by resonance between the two rings. On the other hand, in order to gain this resonance energy the two *ortho* hydrogens must be brought closer together. The non-bonded interactions of these hydrogens will tend to increase the activation energy. It was suggested[2] that the net effect is to increase the activation energy for proton loss over that which would be observed in a more conventional system.

Experimental

Deuterium Analysis.—The analytical procedure for the determination of deuterium has been described in reference 2.

Reagents and Solvents.—Thionyl chloride was purified according to the procedure of Fieser and Fieser.[9] Benzene was purified according to the procedure of Kraus and Vingee[10] and was distilled from sodium prior to use. Nitrobenzene (Fisher, C.P.) was distilled from phosphorus pentoxide *in vacuo*. Sulfur dioxide (Matheson, anhydrous) was used without further treatment. Zinc chloride (Merck, reagent), was fused prior to use and was pulverized in a dry-box under nitrogen. Stannic chloride (Baker, reagent) was distilled from mossy tin. Aluminum chloride (Matheson) was sublimed from aluminum powder at atmospheric pressure.

2-(2′-Deuteriophenyl)-benzoyl Chloride (I).—Several samples of I were prepared in the following manner: 2-(2-deuteriophenyl)-benzoic acid,[2] 4.0 g. (0.020 mole) containing 9.86 ± 0.06 atom % D, and 20 ml. of thionyl chloride were heated at mild reflux for 15 min. and then cooled quickly to 25°. The thionyl chloride was removed *in vacuo*, and the resulting oil was stirred *in vacuo* at room temperature for one hour. The pale lemon-yellow acid chloride was diluted to 40 ml. with benzene.

A 5-ml. aliquot of the benzene solution was evaporated to dryness *in vacuo* and the residue was hydrolyzed by heating with 10 ml. of 10% sodium hydroxide solution for 30 min. on a steam-bath. Acidification with 6 *N* hydrochloric acid precipitated colorless acid which was filtered, washed with water and dried. The acid, 0.420 g., was crystallized twice from 1:9 acetone–hexane and then was sublimed; m.p. 112.0–113.5°.

Anal. Found: 9.88 ± 0.08, 9.84 ± 0.06 atom % D.

General Procedure.—For each cyclization a 5-ml. aliquot of the benzene solution containing 0.0025 mole of acid

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[5] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 53, summarizes the unique ability of sulfur dioxide to solvate carbonium ions and compares this solvent to the poorer nitrobenzene.

[6] G. S. Hammond, THIS JOURNAL, **77**, 334 (1955).

[7] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 345.

[8] Little has been said in our discussion of the role of base in converting IVa and b to the products. H. Zollinger, *Helv. Chim. Acta*, **38**, 1597, 1617 (1955), has demonstrated that base is necessary to convert analogous intermediates to products during diazo coupling reactions, and the same should be true here. However, because of the wide variety of possible bases Cl^-, $AlCl_4^-$, solvent, etc., it is not possible at present to know which one or ones are operating. It has been pointed out by the referee that if the base is an anion then the rate of conversion of IV to products will be slowed down by an increase in the dielectric constant of the solvent, since there will be neutralization of charge in the transition state. This effect would most probably cause an increase in the isotope effect.

[9] L. F. Fieser and M. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1955, p. 345.

[10] C. A. Kraus and R. A. Vingee, THIS JOURNAL, **56**, 511 (1934).

chloride was taken. In the case of reactions conducted in benzene, the 5-ml. aliquot was added with stirring to the appropriate quantity of catalyst in 5 ml. of benzene. After the required time, the reaction mixture was hydrolyzed by adding to ice. The fluorenone was extracted with ether. The ethereal solution was extracted with water, dilute aqueous sodium carbonate solution, dilute ammonia solution, and finally with water. After drying with anhydrous magnesium sulfate, the ether was evaporated to leave a residue of fluorenone. The fluorenone was recrystallized from hexane (0.5 ml. of solvent/0.1 g. of fluorenone) and sublimed. In most instances the resulting product had the proper melting point 83–84°; the few samples which had low melting points were purified by chromatography on silica gel.

In the case of reactions conducted in solvents other than benzene, the 5-ml. aliquot was evaporated *in vacuo* to remove benzene. The residual acid chloride was dissolved in 5 ml. of nitrobenzene or *ca.* 20 ml. of liquid sulfur dioxide and allowed to react with the catalyst in 5 ml. of nitrobenzene or *ca.* 20 ml. of sulfur dioxide.

The products from reactions conducted in nitrobenzene were separated from the nitrobenzene after the usual hydrolysis by chromatography on silica gel.

The yields of fluorenone were good in all instances: an average of about 80% of theory was obtained from evaporation of the ether solutions.

The quantities of catalyst used for each 5-ml. aliquot of acid chloride solution (0.0025 mole of acid chloride) were: 0.67 g. (0.005 mole) of aluminum chloride, 1.30 g. (0.005 mole) of stannic chloride, 0.68 g. (0.005 mole) of zinc chloride.

The first aluminum chloride-catalyzed cyclization in sulfur dioxide was conducted by adding the catalyst to the acid chloride in the solvent. Since the time required to dissolve the catalyst was greater than the reaction time this experiment is classed as heterogeneous. In the second experiment, the aluminum chloride was dissolved in sulfur dioxide and the acid chloride dissolved in sulfur dioxide was added: this experiment is classed as homogeneous.

TABLE II

Catalyst, chloride	Solvent	Time	Temp., °C.	Atom % D
Zinc	Benzene[a]	5 hr.	29	7.21 ± 0.09, 7.18 ± 0.04
Zinc	Benzene[a]	24 hr.	35	7.26 ± .05, 7.21 ± .05
Stannic	Benzene[b]	30 min.	36	6.59 ± .04, 6.57 ± .05
Stannic	Benzene[b]	60 min.	29	6.51 ± .05, 6.61 ± .04
Stannic	Benzene[b]	90 min.	36	6.60 ± .05, 6.61 ± .04
Stannic	Nitrobenzene[b]	20 min.	26	7.34 ± .05, 7.37 ± .05
Stannic	Sulfur dioxide[b]	20 min.	−10	8.45 ± .05, 8.38 ± .05
Aluminum	Benzene[a]	5 min.	5	9.22 ± .06, 9.17 ± .05
Aluminum	Benzene[a]	10 min.	5	9.23 ± .05, 9.19 ± .05
Aluminum	Benzene[a]	15 min.	5	9.13 ± .04, 9.11 ± .05
Aluminum	Nitrobenzene[b]	10 min.	5	7.41 ± .05, 7.42 ± .05
Aluminum	Sulfur dioxide[a]	15 min.	−10	10.14 ± .06, 10.20 ± .06
Aluminum	Sulfur dioxide[b]	15 min.	−10	9.15 ± .10

[a] Heterogeneous system. [b] Homogeneous system.

The data for the several experiments are summarized in Table II.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSAL OF ILLINOIS]

Formation of Cyclohexadienones by Direct Alkylation of Phenols with Saturated Alkyl Derivatives[1]

BY DAVID Y. CURTIN AND ROBERT R. FRASER[2]

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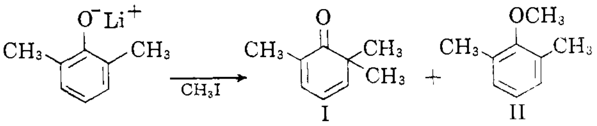
Factors affecting the position of methylation of salts of 2,6-dimethylphenol in non-polar medium have been investigated. It has been found that, in toluene, methyl iodide alkylates sodium 2,6-dimethylphenoxide with a ratio of attack on oxygen relative to attack in the *ortho* positions some 30 times as great as the corresponding ratio with benzyl chloride. It is estimated also that benzyl iodide undergoes alkylation several hundred times faster than methyl iodide. The aluminum and bromomagnesium salts of this phenol react too slowly to be useful. The alkylations of lithium phenoxide and *o*-cresoxide have also been found to lead to mixtures of carbon- and oxygen-alkylated products. Comparison of the ratios in methyl iodide medium indicates that the phenol salt undergoes attack in each *o*-position at about the same rate as attack on oxygen while the *o*-cresol salt undergoes attack at the unsubstituted *o*-position and at the oxygen at about the same rate, but attack at the methyl-substituted position about one-third as fast. It is concluded in agreement with the work of Zagorevsky[11,12,14] that a halide which reacts by a more nearly limiting mechanism gives more carbon alkylation under the conditions employed. However, methyl *p*-bromobenzenesulfonate with sodium 2,6-dimethylphenoxide gives only oxygen alkylation.

The demonstration by Claisen, Kremers, Roth and Tietze[3] that sodium salts of phenols undergo alkylation in an *o*-position when treated with allyl and benzyl halides recently has been extended[4] to 2- or 2,6-substituted phenol salts which yield alkylcyclohexadienones on alkylation in suitable non-polar solvents.

It was implied by Claisen and has since been generally accepted[5] that carbon-alkylation was peculiar to benzylic and allylic halides when monocyclic monohydroxylic phenol salts were being alkylated. It has been reported recently[6] in preliminary communication,[6] however, that the lithium salt of 2,6-dimethylphenol reacts with methyl iodide at 150° without solvent, forming 2,6,6-



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[1] Supported in part by the Office of Ordnance Research, U. S. Army. Abstracted from the Ph.D. Thesis submitted to the University of Illinois, by Robert R. Fraser, June, 1958. This work was partially described in a preliminary communication [D. Y. Curtin and R. R. Fraser, *Chemistry & Industry*, 1358 (1957)].

[2] Texas Company Fellow, 1957–1958.

[3] L. Claisen, F. Kremers, F. Roth and E. Tietze, *Ann.*, **442**, 210 (1925).

[4] (a) See D. Y. Curtin, Robert J. Crawford and M. Wilhelm, THIS JOURNAL, **80**, 1391 (1958); (b) D. Y. Curtin and M. Wilhelm, *J. Org. Chem.*, **23**, 9 (1958).

[5] See, for example, L. F. Fieser, "Organic Chemistry," edited by H. Gilman, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 190; R. H. Thompson, *Quart. Revs.*, 29 (1956).

[6] (a) D. Y. Curtin and R. R. Fraser, *Chemistry & Industry*, 1358 (1957); (b) T. L. Brown, D. Y. Curtin and R. R. Fraser, THIS JOURNAL, **80**, 4339 (1958).