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A STUDY ON THE MECHANISM OF FRIES REACTION

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Abstract—The aluminum chloride-catalysed rearrangement of phenyl acetate to *p*- and *o*-hydroxyacetophenones has been carried out in the presence of acetic anhydride-1-C^{14} in petroleum benzine, nitrobenzene or ethylene dichloride as solvent. The analysis of the radioactivities of formed *o*- and *p*-hydroxyacetophenones together with recovered ester suggests a mechanism involving a comparatively fast ester interchange followed by an intramolecular acetyl migration probably via π-complex. The mechanism is also supported by the effect of temperature, solvent and catalyst concentration on the *p*:*o* ratio of hydroxyacetophenones.

SEVERAL investigators have studied on the Fries reaction and they have found that the acyl group of the aromatic ester could migrate to the solvent and or another molecule.[1] However, there seems to be no decisive evidence whether the migration of acyl group is intermolecular[2] or intramolecular[3] or both.[4,5] The intermolecular migration may go by way of an attack of intermediary acyl chloride or acyl cation on the benzene ring,[2a]

$$C_6H_5OCOR + AlCl_3 \rightleftharpoons C_6H_5OAlCl_2 + RCOCl$$

$$C_6H_5OAlCl_2 + RCOCl \rightarrow RCOC_6H_4OH + AlCl_3$$

or by the catalysed bimolecular acylation of ester,[2b] e.g.,

$$C_6H_5OCOR + AlCl_3 \rightleftharpoons C_6H_5OAlCl_2 + RCOCl$$

$$C_6H_5OCOR + RCOCl \rightarrow RCOC_6H_4OCOR + HCl$$

$$RCOC_6H_4OCOR + C_6H_5OAlCl_2 \xrightarrow{HCl} 2RCOC_6H_4OH + AlCl_3$$

The electrophilic attack on the *o*- and *p*-positions of ester should be more difficult

[1] For reviews see, [a] A. H. Blatt, *Organic Reactions* **1**, 342 (1942); *Chem. Rev.* **27**, 413 (1940); [b] Y. Ogata, *Chem Rev., Japan* **9**, 199 (1943).
[2a] S. Skraup and K. Poller, *Ber. Dtsch. Chem. Ges.* **57**, 2033 (1924); [b] K. W. Rosenmund and W. Schnurr, *Liebig's Ann.* **460**, 56 (1928); [c] E. H. Cox, *J. Amer. Chem. Soc.* **52**, 352 (1930); [d] A. W. Ralston, M. R. McCorkle and E. W. Segebrecht, *J. Org. Chem.* **6**, 750 (1941); [e] A. Schönberg and A. Mustafa, *J. Chem. Soc.* 79 (1943); [f] Y. Ogata, R. Kometani and R. Oda, *Bull. Phys. Chem. Research Inst.* **22**, 828 (1943); [g] D. S. Tarbell and P. E. Fanta, *J. Amer. Chem. Soc.* **65**, 2169 (1943); [h] C. R. Hauser and E. H. Mann, *J. Org. Chem.* **17**, 390 (1952).
[3a] O. N. Witt and O. Braun, *Ber. Dtsch. Chem. Ges.* **47**, 3216 (1914); [b] K. Fries and H. Ehlers, *Ibid.* **56**, 1304 (1923); [c] K. Auwers and H. Mauss, *Liebig's Ann.* **464**, 293 (1928).
[4a] D. Klamann, *Liebig's Ann.* **583**, 63 (1954); [b] R. Baltzly, W. S. Ide and A. P. Phillips, *J. Amer. Chem. Soc.* **77**, 2522 (1955).
[5a] N. M. Cullinane, A. G. Evans and E. T. Lloyd, *J. Chem. Soc.* 2222 (1956); [b] N. M. Cullinane and B. F. R. Edwards, *Ibid.* 3016 (1957); [c] N. M. Cullinane, R. A. Woolhouse and B. F. R. Edwards, *Ibid.* 3842 (1961); [d] A'. Furka and T. Széll, *Ibid.* 2312, 2321 (1960).

than that on the same positions of phenol. Therefore, it is less probable that the Fries reaction proceeds through the acylated ester as above.

The intramolecular migration may proceed via an intramolecular σ-complex[4b] or π-complex.[6] Cullinane *et al.* on the basis of their kinetic study postulated a mechanism involving both inter- and intramolecular migration.[5a,5b] The present paper summarizes our results concerning the mechanistic study on the Fries reaction of phenyl acetate by means of the tracer study with added acetic anhydride-1-C^{14} and also on the effect of experimental conditions (temperature, solvent etc.) on the *p*:*o* ratio of the produced hydroxyacetophenones.

Results and discussion

The tracer experiment. The Fries reaction was carried out for appropriate reaction time in the presence of 1/5 equivalent amount of acetic anhydride-1-C^{14} to phenyl acetate. Acetic anhydride has been proved to be an effective acetylation agent like acetyl chloride. Phenyl acetate, *o*- and *p*-hydroxyacetophenones were isolated from the reaction product and the content of radioactive carbon was estimated as shown in Table 1.

TABLE 1. THE DISTRIBUTION OF THE RADIOACTIVE CARBON IN THE FRIES REACTION OF PHENYL ACETATE

Initial conc.: phenyl acetate, 7·3 g ($5{\cdot}30 \times 10^{-2}$ mole); acetic anhydride, 1 ml ($1{\cdot}06 \times 10^{-2}$ mole); $AlCl_3$, 9·8 g ($6{\cdot}90 \times 10^{-2}$ mole) except No. 1 (none) and No. 7 ($13{\cdot}8 \times 10^{-2}$ mole). Solvent: 50 ml.

No.	Solvent	Temp (°C)	Time (hr)	Yield of hydroxy-ketones (%)	Radioactivities (c/m)[d]				Ester inter-change[b] (%)
					Recovered ester	*o*-HOC_6H_4-$COCH_3$	*p*-HOC_6H_4-$COCH_3$	100% inter-change[a]	
1	Petroleum benzine	85	5	0	0	—	—	106	0
2	Petroleum benzine	85	1	0	22	—	—	90	24
3	Petroleum benzine	85	3	10	37	13	—	80	46
4	Petroleum benzine	85	5	48	72	38	33	90	80
5	Petroleum benzine	85	12	69	—	52	47	90	(100)[c]
6	$C_6H_5NO_2$	30	5	20	131	82	81	125	105
7	$ClCH_2CH_2Cl$	50	1·5	41	—	36	40	106	—

[a] "Radioactivities on 100% interchange" means the theoretical radioactivity expected in the products, if the acetyl group in acetic anhydride is interchanged with that of ester instantaneously. For example, in No. 2, acetic anhydride with original activity of 2147 c/m and with the ratio of (ester)/(acetic anhydride) of 5/1 gives the value of $2147 \times [1/(5+1)] \times (2/8) = 90$ c/m. [b] (Radioactivity of recovered ester)/(Radioactivity on 100% interchange). [c] Assumed value. [d] These values are calibrated for their background against standard barium carbonate (6–7 c/m).

[6] M. J. S. Dewar, *The Electronic Theory of Organic Chemistry* p. 229. Oxford Univ. Press, London (1949); *Molecular Rearrangements* (Edited by P. de Mayo) p. 318. J. Wiley, New York, N.Y. (1963).

Petroleum benzine cannot dissolve the aluminum chloride complex, while nitrobenzene or ethylene dichloride can constitute an essentially homogeneous solution. In spite of this difference, the distribution of radioactivity in the products was not influenced by the kind of solvent as shown in Table 1, which imply that a single mechanism is operating in these solvents.

No reaction and also no interchange of acetyl group between ester and acetic anhydride was detected without aluminum chloride, since there was no radioactivity in the recovered ester under these conditions (No. 1 in Table 1).

In the presence of aluminum chloride ester interchange occurs[3c] and from our data the ester interchange competes with the acyl migration of ester to benzene ring, the former being faster than the latter, because the value of (ester interchange)/(yield of hydroxyketones) was 2–5 as obvious in Table 1. However, since the products, hydroxyacetophenones, have always less radioactivity than that of corresponding 100% interchange, the acetyl migration is not so slow as to only start after completion of the interchange.

If the acetyl cation from acetic anhydride would attack benzene ring as effective as the acetyl cation from the ester, the radioactivity of the produced hydroxyketones should be the same value as that of 100% interchange, but the data in Table 1 indicate that each observed radioactivity of the product is lower than the corresponding value of 100% interchange; the difference is more apparent at earlier stages of the reaction. (cf. Nos. 3, 4 and 5). Therefore, the labeled carbon in the products, hydroxyketones, is probably introduced via ester interchange followed by the intramolecular migration of acetyl group.

If the reaction proceeds by both intra- and intermolecular acyl migrations as proposed by Baltzly[4b] and Cullinane,[5a,b,c] it is likely that the *ortho* substitution goes preferably by intramolecular migration and *para* substitution by intermolecular way, which should result in the higher radioactivity of *p*-hydroxyketone than that of *o*-isomer. However, their radioactivities agree each other within experimental error, hence the simultaneous occurrence of intra- and intermolecular migrations is less probable.

The para:ortho ratio in the products. The gas chromatographic analysis showed that the reaction product contained *o*- and *p*-hydroxyacetophenones, phenol, phenyl acetate and a trace of tarry material, but no *m*-hydroxyacetophenone. Table 2 shows that the ratio of *p*- to *o*-hydroxyacetophenone in the product is constant at any time during the reaction in spite of the statement of Ralston.[2d] *o*-Hydroxyacetophenone cannot be rearranged to the *p*-isomer on heating with aluminum chloride at 80° for 4 hours in our hands. These facts eliminate the possibility of the successive migration of acetyl group from the ester to *ortho*, *meta* and then *para* positions, and suggest the presence of a common intermediate such as π-complex for the acetyl migration to *ortho* and *para* positions.

The *p*:*o* ratio in the products, hydroxyacetophenones, was influenced by the reaction temperature, solvent and catalyst concentration. As reported by several workers,[1a,2d,4b] the ratio (*p*/*o*) found in our hands decreased with increasing temperature; e.g., 4·01 at 40°, 2·41 at 60° and 1·56 at 80° in a nitrobenzene solution with the reactants composed of equimolar phenyl acetate and aluminum chloride.

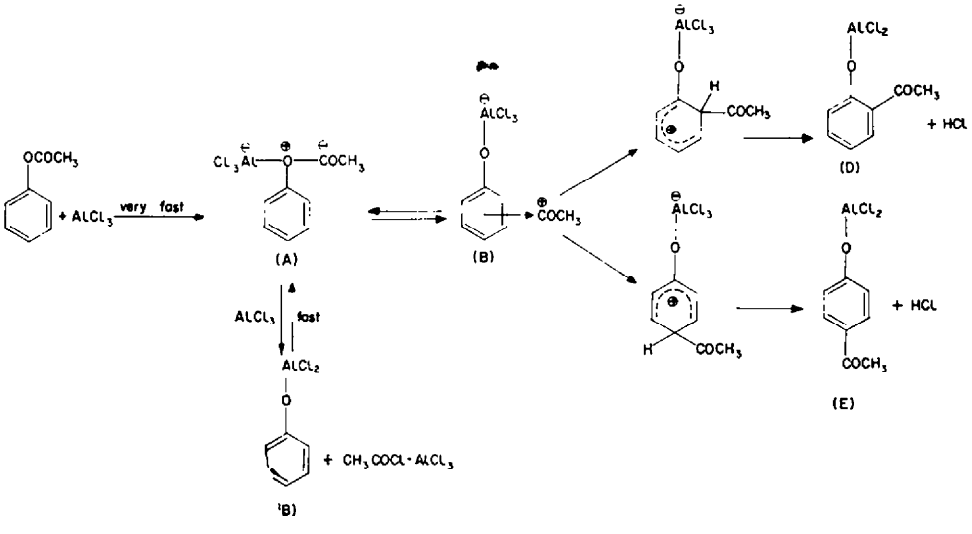
The ratio at 80° with equimolar ester and aluminum chloride decreased with changing solvent in the order: nitrobenzene (*p*/*o* = 1·56), ethylene dichloride (0·41)

and petroleum benzine (0·077). The fact is explicable by assuming that the solvent which can form complex more easily is more *p*-directing because of the higher steric hindrance with *o*-substituent. The analogous solvent effect on the *p*:*o* ratio has been observed with the reaction of phenol and capryl chloride, i.e., nitrobenzene > paraffin > ethylene dichloride > carbon disulfide.[7]

Furthermore, the *p*:*o* ratio was influenced by the concentration of aluminum chloride. For example, the *p*:*o* ratio varied with the molar ratio of aluminum chloride to phenyl acetate written in parenthesis: 2·93 (0·5), 2·41 (1) and 10·1 (2) at 60° in nitrobenzene. The fact that an increase of the molar ratio over 1 resulted in a sudden rise of the *p*:*o* ratio may be explained by assuming that the increase results in the complex formation of aluminum chloride with migrating acyl group in addition to that with phenolic group and hence causes a marked increase of the steric hindrance in the *ortho* acylation.

Cullinane *et al.*[8] and also the present authors confirmed that the Fries reaction and the acylation of phenol gave analogous products against a number of investigators[9,10] who had reported that they gave different products. The *p*:*o* ratio of the Fries reaction of phenyl acetate was found to be similar to that of the acetylation of phenol with acetyl chloride under the same conditions (ester: $AlCl_3$ = 1:1 at 60° in nitrobenzene), e.g., 2·41 and 2·34, respectively. It has been reported that the rate of formation of ester was much faster than that of the Fries reaction.[5] These phenomena suggest that the Fries reaction and the acylation of phenol go by way of a common intermediate i.e., a complex of phenyl acetate with aluminum chloride.

The over-all mechanism. The above findings suggest a mechanism for the Fries reaction of phenyl acetate:



[7] A. W. Ralston, M. R. McCorkle and S. T. Bauer, *J. Org. Chem.* **5**, 645 (1940).
[8] N. M. Cullinane and B. F. R. Edwards, *J. Appl. Chem.* **9**, 133 (1959).
[9] K. Fries and G. Finck, *Ber. Dtsch. Chem. Ges.*, **41**, 4271 (1908); K. Fries and W. Pfaffendorf, *Ibid.* **43**, 212 (1910).
[10] K. Auwers and H. Mauss, *Ber. Dtsch. Chem. Ges.* **61**, 1495 (1928).

It has been known that the formation of coordination complex (A) is very rapid. The step from (A) to π-complex (C) is probably reversible, while the steps (C) to hydroxyacetophenones (D) and (E) are irreversible, since the ketones cannot be converted to the ester. There is no interconversion between (D) and (E). The step from (A) to complexed phenol (B) seems to be reversible, because acetyl chloride and phenol in the presence of aluminum chloride forms (A); however, the presence of a considerable amount of phenol (4–15%) after the completion of Fries reaction implies the evaporation or some other way of removal of acetyl chloride out of the system. Intermediate (A) seems to give rise to the ester interchange and the acylation of the solvent and or another molecule, while the following species such as (C) do not probably participate with these reactions.

TABLE 2. VALUES OF *p/o* IN THE FRIES REACTION AT 60°

Initial conc.: phenyl acetate, $7{\cdot}94 \times 10^{-2}$ mole; $AlCl_3$, $7{\cdot}94 \times 10^{-2}$ mole; nitrobenzene, 50 ml.

Time	Recovered ester (%)	Phenol (%)	Hydroxyacetophenones (%)	*p/o*
11 min	81·0	5·8	13·4	2·30
30 min	63·3	6·9	30·7	2·40
1 hr	41·2	7·0	51·8	2·52
3 hr	15·8	6·9	77·3	2·38
12 hr	2·4	7·4	90·0	2·43
				Av. 2·41

EXPERIMENTAL

Materials. The reaction of phenol and acetic anhydride gave phenyl acetate, b.p. 194–195°, which was found to contain 0·3% phenol by gas chromatography. Solvents, nitrobenzene, dichloroethane and petroleum benzine (b.p. 60–80°) were purified according to their standard methods.[11] *m*-Hydroxyacetophenone was prepared from acetophenone by its nitration, reduction and diazotization followed by the decomposition in water, m.p. 96° (lit.[12] m.p. 96°). Acetic anhydride-1-C^{14} was prepared from barium carbonate-C^{14} via its reaction with methylmagnesium iodide to form $CH_3C^{14}OONa$ followed by the dehydration with tosyl chloride.[13,14] Aluminum chloride was of guaranteed grade.

Typical procedure for the tracer study of Fries reaction of phenyl acetate. A mixture of phenyl acetate (7·3 g) and radioactive acetic anhydride (1 ml) was introduced to a stirred mixture of petroleum benzine (50 ml) and aluminum chloride. After appropriate time, the solvent was distilled off, the residue being added with 2N HCl and extracted with ether. The extract was washed with 2N NaOH aq. The separated ethereal layer was washed with water, dried and distilled, giving unreacted phenyl acetate, which was identified by gas chromatography. The aqueous layer of the alkaline extract was acidified and steam-distilled; the distillate was added with semicarbazide hydrochloride to isolate *o*-hydroxyacetophenone (semicarbazone, m.p. and lit.[12] m.p. 210°), while the residue of distillation yielded *p*-hydroxyacetophenone, recrystallized from water, m.p. 109° (lit.[12] m.p. 109°). The yields of the products were shown in Table 1. The same work up was employed in the case of ethylene

[11] J. A. Riddick and E. E. Toops, Jr., *Organic Solvent* pp. 415, 432. Interscience, New York, N.Y. (1955).

[12] S. I. Heilbron and H. M. Bunburg, *Dictionary of Organic Compounds* Vol 2, p. 712. Eyre. & Spottiswoode, London (1953).

[13] J. D. Cox and H. S. Turner, *J. Chem. Soc.* 3167 (1950).

[14] M. Calvin, C. Heidelberger, J. C. Reid, B. M. Tolbert and P. E. Yankwich, *Isotopic Carbon* pp. 92, 175 and 200. J. Wiley, New York, N.Y. (1949).

dichloride as the solvent, while phenyl acetate was hydrolysed to sodium acetate in the case of nitrobenzene as the solvent.

Measurements of radioactivity. All radioactive organic materials were converted to radioactive barium carbonate with Van Slyke–Folch wet oxidation method.[15] The activity was measured by 2π-gas flow counter with thin window as that of corresponding barium carbonate of infinitely thick layer.

Kinetic experiment and gas chromatography of the reaction products. Nitrobenzene (50 ml) and aluminum chloride (10·6 g) were placed in a flask fitted with a reflux condenser, a gas inlet tube and a tube suitable for withdrawing samples and the flask was immersed in a thermostat maintained at 60°. After complete dissolution of aluminum chloride, phenyl acetate (10 ml) was rapidly introduced. Aliquots (each 5 ml) were pipetted out at regular intervals of time, poured into 2N HCl aq and then extracted with ether. The extract was washed with water, dried and analysed by gas chromatography employing a Yanagimoto Model GCG-220 operated with a 1·3 m column packed with Silicone DC 703 on Celite 545 using a flow rate of 40 ml helium per min at 198°. Retention times were: phenol, 1·7 min; phenyl acetate, 2·6 min; nitrobenzene, 3·8 min; *o*-hydroxyacetophenone, 4·8 min; *p*-hydroxyacetophenone, 17 min. All quantitative determinations were made using biphenyl as an internal standard.

[15] D. D. Van Slyke and J. Folch, *J. Biol. Chem.* **136**, 509 (1940); D. D. Van Slyke, J. Pllazin and J. R. Weisiger, *Ibid.* **191**, 299 (1951).