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THE NATURE OF THE CATALYST IN THE PERKIN CONDENSATION

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The conclusion that the catalyst in the Perkin condensation may be a sodium compound other than the salt of a fatty acid has been re-examined in the light of fresh evidence.

The difference of opinion which existed amongst workers at the close of the last century as to the respective rôles of the acid anhydride and the sodium salt of the fatty acid (1, 2) has been resolved in recent years, and it is now held that condensation occurs between the acid anhydride and the aldehyde, the salt acting as a basic catalyst. A considerable amount of evidence has been offered in support of this view. Kalnin (3) showed that the sodium salts of fatty acids were not specific as catalysts in this condensation, and that the reaction would also proceed in the presence of the stronger tertiary organic bases, and of carbonates, phosphates, sulfites, and sulfides of sodium and potassium. In consequence of this evidence Kalnin (3) proposed a mechanism for the reaction involving the addition of the aldehyde to the enolized anhydride, followed by enolization of the condensation product, and subsequent elimination of a molecule of fatty acid to give the unsaturated product.

Therefore it is to be expected that other basic catalysts will serve to bring about the change, and further evidence has been provided by the work of Kuhn and Ishikawa (4) and Bakunin and Pecerillo (5), who also confirmed that organic tertiary bases were effective in catalyzing the reaction, although differing somewhat with the views of Kalnin as to the mechanism involved. An intensive study of the mechanism was later made by Breslow and Hauser (6) who showed that by heating the sodium salt and the anhydride of unlike fatty acids an equilibrium was established (confirming indications by earlier workers), so that in the presence of benzaldehyde a mixture of two cinnamic acids was obtained, the relative proportions of which varied with changing temperature. In the light of these facts the catalytic function of the sodium salt of the organic acid is rendered acceptable and a general basic mechanism for aldolization processes is extended to this reaction (7, 8); further proof was furnished by the isolation of the intermediate aldol product in the condensation of benzaldehyde with ethyl isobutyrate in the presence of sodium triphenylmethyl.

We have successfully repeated Kalnin's experiments using a tertiary organic base and have added sodium borate, sodium formate, and disodium tartrate to the list of effective condensing agents. In the case of sodium and potassium carbonates and sodium sulfite, however, we have demonstrated that carbon dioxide or sulfur dioxide is evolved in the course of the condensation, and that in each case sodium or potassium acetate must really be the catalyst. Although sodium formate appears to be a catalyst it rapidly loses carbon monoxide during reaction and sodium acetate is produced in quantity.

Independent experiments have been conducted in the absence of benzaldehyde. The greatest care was taken to remove all traces of acetic acid from the acetic anhydride and to exclude the ingress of moisture to the anhydrous reagents, because, as water is formed in the Perkin condensation, it was important to see if reaction between the two components could be initiated in its absence. We are satisfied, therefore, that with sodium and potassium carbonates the carbon dioxide arises in the manner indicated by the following equation:—

$$Na_2CO_3 + (CH_3CO)_2O \rightarrow 2\ CH_3COONa + CO_2$$

In the case of sodium carbonate, quantitative yields of carbon dioxide and sodium acetate were obtained, but with potassium carbonate, although the correct amount of carbon dioxide was evolved, the solid product was shown to be a double compound of potassium acetate and acetic anhydride the proportions of which appeared to vary appreciably. Separate experiments with potassium acetate and acetic anhydride alone at room temperature and at 100° led to the double compound of variable composition.

With the use of sodium sulfite and sodium formate the chief interaction with acetic anhydride in each case is set out in the equations:

$$Na_2SO_3 + (CH_3CO)_2O \rightarrow 2\ CH_3COONa + SO_2$$
$$2\ HCOONa + (CH_3CO)_2O \rightarrow 2\ CH_3COONa + 2\ CO + H_2O$$

In cases where the resultant acid anhydride is not gaseous, *i.e.* with sodium borate and disodium tartrate, an equilibrium is doubtless established between acetic anhydride and the salt added as condensing agent [*cf.* (6)] and, on this basis, the condensation which occurs in the presence of all the salts heretofore described, may be attributed to the intervention of sodium (or potassium) acetate. The production of this salt is also implied if sodium alkoxide and sodium triphenylmethyl are employed as condensing agents, but we and Muller (9) have used the latter compound under customary experimental conditions without conclusive results Nevertheless it must be borne in mind that Hauser, *et al.* (6, 7) have employed sodium triphenylmethyl to bring about a Perkin type of reaction involving the ester of a fatty acid as the second component in place of the anhydride; it is also noteworthy that the conditions were much milder than in the orthodox reaction using sodium acetate as catalyst.

The experiments described in the present paper have helped to place in their proper perspective the pieces of evidence that have accrued in favor of the application of the theory of general basic catalysis to the Perkin reaction. Without in any way doubting the validity of this viewpoint, it must be recognized that the supporting evidence is confined to the observed catalytic effects of certain tertiary organic bases, and presumably to the limited successful use of sodium triphenylmethyl. It cannot now be doubted that sodium (or potassium) acetate is formed when the alkali metal salts of weak inorganic and organic acids are used to promote the Perkin reaction. This in no way implies that any specific catalytic influence is to be ascribed to sodium (or potassium) acetate; it means simply that the production of this salt in such cases is unavoidable and that the experiments in question do not themselves provide valid support for the application of the general basic mechanism to the Perkin reaction.

According to this mechanism, acetic anhydride is not a necessary second component, and so other sources of the acetyl group might be used to advantage. It is significant, therefore, that we have succeeded in utilizing diacetanilide and acetamide as alternatives in this connection, namely, in preparing specimens of cinnamic acid from benzaldehyde in the presence of anhydrous sodium acetate.

EXPERIMENTAL

Perkin reaction under anhydrous conditions. The Perkin condensation between benzaldehyde and acetic anhydride under the influence of various catalytic agents was conducted with scrupulously dried materials.

Benzaldehyde (0.091 mole), acetic anhydride (0.15 mole), and the anhydrous catalyst (0.06 mole) were heated together under reflux for eight hours at 180°, the product was then cooled and added to water (150 ml.). After removing benzaldehyde by steam-distillation, the residue was boiled with charcoal, filtered, acidified, and cooled. The deposited acid was recrystallized from water, and the yields of purified cinnamic acid produced by the various condensing agents are set out below. It is noteworthy that with the borate a homogeneous melt was produced but contrary to anticipation a superior yield of acid was not obtained.

CONDENSING AGENT	YIELD, %
Sodium acetate (fused)	54
Sodium formate	48
Disodium tartrate	17
Sodium borate (fused)	19
Sodium sulfite	12
Sodium carbonate	32
Potassium carbonate	21
Pyridine	1.4

In the progress of the condensations, evolution of carbon dioxide was observed where carbonates were the condensing agents, and of sulfur dioxide where sodium sulfite was employed. During the experiment in which sodium formate was used, copious evolution of carbon monoxide occurred in the first hour of heating; in the absence of benzaldehyde this also happens, and sodium acetate (confirmed by qualitative and quantitative analysis) was obtained in good yield as an end product. From the experiment employing disodium tartrate no evolution of gas was noted.

PURIFICATION OF REAGENTS

Acetic anhydride. Acetic anhydride (500 g.) was allowed to stand over phosphorus pentoxide (50 g.) for three hours, decanted and allowed to stand over ignited potassium carbonate for a further three hours. The supernatant liquid was then distilled, the fraction b.p. 136–138° being collected. After standing over phosphorus pentoxide for a further twelve hours the anhydride was shaken with ignited potassium carbonate, when no detectable reaction occurred. The product was finally distilled through a five-section Young and Thomas' fractionating column, and the distillate b.p. 136.0–138.0° refractionated, the final cut being collected in a weighing-burette, b.p. 137.8–138.0°/759.

Sodium carbonate and potassium carbonate. The carbonates of Analar quality were heated for one hour at 270° and stored *in vacuo* over phosphorus pentoxide for fourteen days.

Sodium sulfite. Hydrated sodium sulfite of Analar quality was dried *in vacuo* over phosphorus pentoxide for fourteen days. The loss in weight was theoretical and the satisfactory purity of the sulfite was established by volumetric analysis.

Sodium formate. The salt, freshly prepared from aqueous formic acid and sodium hydroxide, was dried at 90° under reduced pressure for two hours, and then stored over phosphorus pentoxide for one day (the purity was established by a sodium estimation).

Sodium tartrate. This salt was prepared in the same manner as for sodium formate, and gave a satisfactory sodium analysis.

Benzaldehyde. Benzaldehyde (250 g.) was shaken with dilute sodium carbonate solution, dried over calcium chloride, and distilled under reduced pressure. Further drying and refractionation gave pure benzaldehyde (b.p. 177.5–178.0°/767) collected in a weight-burette.

Apparatus for studying the reaction of acetic anhydride with anhydrous condensing agents. The reaction vessel consisted essentially of a flask (100 ml.) with a side-neck closed by a ground-glass stopper. Into the main neck was fitted a spiral water-cooled condenser closed at the end by a two-way stopcock, one exit connected to a calcium chloride tube and the other to a Mohr absorption apparatus containing aqueous potassium hydroxide (30%) fitted with a drying tube. A short inlet-tube closed by a stopcock passed through the main neck of the flask, so as to be just above the surface of the reactants, for flushing out the apparatus with carbon dioxide-free air. After thorough drying, the apparatus was quickly assembled and a current of dry, carbon dioxide-free air was passed through the apparatus. The Mohr absorption apparatus was then connected, and showed no change in weight over several hours.

Acetic anhydride (5 g. approx.) was next introduced into the flask from the weight-burette *via* the side-arm against a counter current of dry air and the side neck closed. The apparatus was connected by the two-way stopcock to the Mohr absorption apparatus, the flask was then immersed in an oil-bath at 150°, and a slow stream of dry air passed through the apparatus. Several experiments were conducted using different speeds of flow for the gas and it was found that the most satisfactory rate was 500 ml. per hour.

Volume of gas passed through the apparatus (ml).	*Wt. of acetic anhydride carried over (mg).*
500	27.0
1000	49.2
1750	82.2
2250	99.8

Mean weight of acetic anhydride carried over per 500 ml. of gas at 150° = 23.3 mg.

The corrections for experiments relating to other temperatures (110° and 145°) were also determined in this way.

Reaction of condensing agents with acetic anhydride. The dried reagents were introduced into the apparatus as previously described, a large excess of acetic anhydride being employed. The flask was placed into an oil-bath and raised to the required temperature, and when this point was reached a stream of dry air (500 ml./hr.) from the aspirator was passed through the apparatus. The carbon dioxide absorption vessel was weighed at intervals, and heating was continued until the absorption apparatus showed no further increase in weight. When the reaction was complete the contents of the flask were diluted with dry ether (50 ml.), filtered, the solid residue washed with ether, dried, weighed, and analysed both qualitatively and quantitatively.

Details of the experiments are given below.

Sodium carbonate. Sodium carbonate, 0.9666 g.; acetic anhydride, 5.8200 g.; temperature of reaction, 150°. There was no apparent reaction between the carbonate and anhydride until a temperature of 90° was reached; reaction was quite rapid at 150°.

VOL. OF GAS PASSED THROUGH APPARATUS, ML.	INCREASE IN WT. OF ABSORPTION BULBS, MG.	CORRECTED WT., MG.	CO_2 EVOLVED, %
500	427.8	392.8	97.9
1000	450.0	391.7	97.6
1500	473.2	391.6	97.6
2000	498.4	393.5	98.0
2500	523.8	395.6	98.5

Weight of solid from reaction, 1.5027 g. (100.4 %, based on sodium acetate). Qualitative tests showed the residue to be sodium acetate and this was confirmed as follows:—
200.4 mg. of the residue on ignition gave sodium carbonate (128.6 mg.; 99.5%) which on treatment with sulphuric acid gave sodium sulfate (182.6 mg.; 99.7%) and barium sulfate (675.5 mg.; 96.6%).

Sodium sulfite. Sodium sulfite, 1.2416 g.; acetic anhydride, 5.9585 g.; temperature of reaction, 145°. Reaction commences at 90–95°, and proceeds only slowly at 145°.

Vol. of gas passed through apparatus, ml.:	500,	1000,	1500,	2000,	(3000),	4270,	6000.
SO_2 evolved, %:	44,	61,	78,	82,	(90),	89,	89.

Weight of solid from reaction, 1.6885 g. (98.0% based on sodium acetate). The residue was shown to be sodium acetate by qualitative tests and by satisfactory gravimetric determinations as in the experiments with sodium carbonate.

Potassium carbonate. Potassium carbonate, 1.5352 g.; acetic anhydride, 3.6230 g.; temperature of reaction 110°. The reaction commences at 100° and above this temperature becomes vigorous. At 150° excessively large quantities of acetic anhydride are swept over, and so it was necessary to conduct the experiment at a much lower temperature.

Vol. of gas passed through apparatus, ml.:	500,	1000,	1500,	2000,	2500,	3000.
CO_2 evolved, %:	46,	70,	81,	92,	96,	100.

Weight of residue in flask, 2.6215 g. Theoretical weight of potassium acetate, 2.180 g. Qualitative tests indicated that the brown crystalline residue in the flask was a complex compound of potassium acetate and acetic anhydride. The ratio of the two molecules in the complex did not appear to be constant as quantitative analyses of specimens derived from four separate preparations did not give good agreement. It is noteworthy that a product of the same character is obtained by shaking a mixture of the two components themselves for two days at room temperature or for eight hours at 100°. The solid obtained is washed with ether and dried under reduced pressure. Analysis yielded results similar to those for the products obtained in the earlier experiments with potassium carbonate.

The proportion (by weight) of potassium acetate in the specimens examined, (which varied from 49% to 89%) was estimated by (a) calculation from the weights of potassium carbonate used and of solid residue formed, (b) gravimetric analysis of the residue (for potassium), and (c) electrometric titration of the residue (for acetic anhydride).

Perkin reaction using diacetanilide. Diacetanilide (14.0 g.; 0.08 mole), benzaldehyde (6.0 g.; 0.06 mole), and sodium acetate (3.2 g.; 0.04 mole) were heated under reflux for eight hours at 180° in an atmosphere of nitrogen. After cooling the mixture was steam-distilled to remove the excess benzaldehyde, the residue was made alkaline by the addition of sodium carbonate, any solid was removed, and the alkaline solution was extracted with ether. After acidification of the aqueous layer, cinnamic acid was precipitated (after purification, 1.5 g. *i.e.* 18% yield).

Perkin reaction using acetamide. Acetamide (12 g.; 0.21 mole), benzaldehyde (10 g.; 0.1 mole), and sodium acetate (5 g.; 0.06 mole) were heated as in the last experiment. After diluting with water and steam-distilling, the product was basified and extracted with chloroform. The aqueous layer was acidified and, on standing, an impure solid deposited; this upon purification (including sublimation) yielded cinnamic acid (0.12 g.).

SUMMARY

Many of the experiments providing support for the application of a general theory of basic catalysis to the Perkin condensation utilize alkali metal salts of weak acids as condensing agents. It has now been established that in these experiments acetic anhydride gives rise to sodium (or potassium) acetate, and the validity of the general mechanism can no longer rest on this kind of evidence. It is not doubted, however, that the Perkin condensation does proceed under the catalytic influence of certain organic tertiary bases.

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