THE ACETOACETIC ESTER CONDENSATION. III. THE ROLE OF SODIUM IN THE CONDENSATION

BY JOHN M. SNELL AND S. M. McELVAIN

Since the discovery,[1] in 1863, that acetoacetic ester is formed by the action of metallic sodium on ethyl acetate, periodic discussions of the role of the metal in the condensation have appeared in the literature. One group of investigators[2] has advanced the idea that sodium is not the direct cause of the condensation but serves only to generate sodium ethoxide, the active condensing agent, from traces of alcohol in the ester or from other side reactions. Another group[3] has maintained that when sodium reacts with the ester it is the metal itself which is directly responsible for the condensation. The main objections to the formulation of sodium ethoxide as the active condensing agent have arisen from the observation that sodium produces higher yields of acetoacetic ester than does sodium ethoxide,[3b,d] and that ethyl acetate from which all alcohol has been carefully removed reacts with sodium just as readily as does ordinary ethyl acetate.[3e]

A previous study[4] of the reaction of sodium with various aliphatic esters has shown that ethyl acetate and ethyl propionate are unique among this type of ester in that they are not converted by sodium into the corresponding acyloins when they are reacted with the metal in the presence of an excess of the ester. Rather, they undergo the acetoacetic ester condensation. Consequently, a study of the role of sodium in the acetoacetic ester condensation of this type of ester must necessarily be restricted to the use of ethyl acetate or ethyl propionate if complications resulting from acyloin formation are to be avoided.

This paper is a report of a study of the reaction of ethyl acetate with sodium in which a careful determination of the amounts of the reaction products, acetoacetic ester, alcohol and hydrogen, has been made. The amounts of these reaction products were determined in the reaction mixture as directly obtained from the reaction of sodium and the ester as well as after the condensation had been driven to completion as far as possible by

[1] Geuther, *Jahresber.*, 323 (1863).

[2] Claisen, *Ber.*, **20**, 651 (1887); **21**, 1154 (1888); Nef, *Ann.*, **298**, 320 (1897); Higley, *Am. Chem. J.*, **37**, 293 (1907).

[3] (a) Michael, *Ber.*, **33**, 3731 (1900); (b) *ibid..* **38**, 1934 (1905); (c) Tingle and Gorsline, *Am. Chem. J.*, **37**, 438 (1907); (d) *ibid.*, **40**, 46 (1908); (e) THIS JOURNAL, **30**, 1874 (1908); (f) Scheibler and Ziegner, *Ber.*, **55**, 789 (1922); (g) Scheibler and Marhenkel, *Ann.*, **458**, 1 (1927).

[4] Snell and McElvain, THIS JOURNAL, **53**, 750 (1931).

the removal of the alcohol produced in the reaction.   Similar determinations were made with sodium ethoxide as the condensing agent under comparable reaction conditions.   The results which were obtained appear to be strong evidence in favor of Claisen's original postulate that sodium is not the active condensing agent in the acetoacetic ester condensation.

Experimental Procedure and Results

In a 1-liter 3-necked flask fitted with a mercury seal stirrer, a condenser for downward distillation and a coil reflux condenser 20 cm. in length, 11.5 g. (0.5 mole) of sodium was finely powdered by heating under boiling xylene with vigorous stirring.   The xylene, after cooling, was removed from the powdered sodium by decantation and the latter washed with dry ether.   After pouring off this wash ether the sodium was covered with a considerable excess (2.3 moles) of carefully purified ethyl acetate.[5]   The delivery end of the condenser for downward distillation was fitted with a distilling flask as a receiver. By plugging or leaving open the side arm of this receiver the ester in the reaction flask could be caused to reflux from the coil condenser or to distil into the receiver.   From the top of the coil reflux condenser a tube was led to the bottom of a tower filled with porous chips which had been soaked previously in concentrated sulfuric acid.   From the top of the tower a tube was led to a flask for the collection of the hydrogen evolved in the reaction.

The reaction flask was then heated in an oil-bath with stirring until the ester boiled gently.   The reaction appeared to proceed quite slowly for about twenty minutes, but after this time it became so vigorous that it was necessary to remove the heating bath from the reaction flask and to cool the latter periodically with a wet towel.   This more vigorous reaction continued for approximately another twenty minutes, after which time the sodium had completely disappeared and the reaction mixture was homogeneous.   It was during this latter twenty minutes' reaction period that practically all of the hydrogen was evolved from the reaction.   This hydrogen was collected and its volume measured.

The reaction mixture was then subjected to distillation through the other condenser attached to the reaction flask.   As the ethyl acetate was removed by the distillation, pure ethyl acetate was added through the reflux condenser to the reaction mixture and the distillation allowed to proceed slowly until the distillate showed the same refractive index as that of the pure ester.   As the alcohol produced in the reaction was carried out by the ethyl acetate, the reaction mixture lost its homogeneity and a voluminous salt-like precipitate, which could not be taken into solution by the pure ester, settled out.

After all of the alcohol had been removed the reaction mixture, which still had considerable excess ethyl acetate present, was treated with the calculated quantity of 35% sulfuric acid[6] to react with all of the sodium originally put into the reaction.   The ester layer was then decanted from the solid $Na_2SO_4 \cdot 10H_2O$ and this salt washed with a fresh portion of ester.   The combined ester portions were then washed with a solution of potassium carbonate and, after drying with solid potassium carbonate, fractionated. The ethyl acetoacetate fraction, which boiled at 70–75° (10 mm.), was collected and weighed.

Determination of Alcohol in the Distillate.—The amount of alcohol which was present in the distillate from the reaction of sodium ethoxide with various aliphatic esters has been determined from the refractive index of the distillate.[5]   This method did

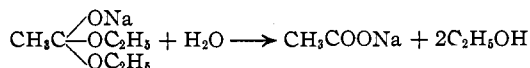[5] McElvain, THIS JOURNAL, **51**, 3128 (1929).

[6] *Cf.* Snell and McElvain, *ibid.*, **53**, 752 (1931).

not seem to be suitable when metallic sodium was used as the condensing agent on account of the presence in the distillate of small but unknown amounts of those liquids, xylene and ether, which were used in the preparation of the powdered sodium. For this reason the following procedure for the determination of the alcohol was adopted.

An accurately weighed aliquot (approximately 1 g.) of the distillate was heated at 100° in a sealed tube with approximately 0.6 g. of phthalic anhydride for four hours. The tube was then cooled and opened and the contents poured into a 125-cc. Erlenmeyer flask and the ethyl acetate evaporated off by heating for a few minutes on a steam-bath. The reaction tube was then washed out thoroughly with hot water and these washings added to the residue in the flask from which the ester had been evaporated. The contents of the flask, amounting to about 50 cc., was heated to boiling for about two minutes until the residue completely dissolved and then titrated with $N/5$ sodium hydroxide using phenolphthalein as an indicator. The titration was carried out as rapidly as possible and stopped when the entire solution showed the characteristic pink color of the indicator for thirty seconds. From the difference between the alkali used for this titration and the alkali equivalent of the phthalic anhydride used in the determination the amount of alcohol in the aliquot was determined. Three test solutions of alcohol in ethyl acetate containing 5.52, 10.50 and 14.25% of alcohol by weight were found by the above procedure to contain 4.51, 9.98 and 13.50% of alcohol, respectively.

The amount of alcohol in the distillates usually amounted to about 10%. All of the determinations of alcohol were made in triplicate. The average deviation from the mean was of the order of 0.05 to 0.10%. It should be pointed out that the alcohol values as determined represented minimum values as is shown by results obtained on samples of ethyl acetate containing known amounts of alcohol. This error is due, no doubt, to a slight amount of hydrolysis of the ethyl acid phthalate during the titration of the excess phthalic anhydride.

The amounts of the products of the reaction of ethyl acetate with sodium and sodium ethoxide are tabulated below. In Runs 1 and 2 the ester (2.3 moles) was allowed to react with 11.5 g. (0.5 atom) of sodium and the alcohol formed in the reaction was removed as described above. In Run 3 the same procedure was followed except that 34 g. (0.5 mole) of sodium ethoxide was used as the condensing agent instead of 0.5 atom of sodium. In Run 4 the same quantities of reactants were used and the reaction was allowed to continue only to the point at which all of the sodium had disappeared. This point was reached in about forty minutes after the ester had reached the boiling temperature. The reaction was stopped by adding a slight excess of dry hydrogen chloride dissolved in ethyl acetate to the reaction mixture. This alteration in the isolation procedure was made in order that the formation of alcohol by the reaction

$$CH_3C\underset{\overset{|}{\underset{OC_2H_5}{}}}{\overset{\overset{ONa}{|}}{\underset{}{-}OC_2H_5}} + H_2O \longrightarrow CH_3COONa + 2C_2H_5OH$$

which has been shown to take place when the reaction mixture is decomposed with 35% sulfuric acid, might be prevented. The ethyl acetate and alcohol were then distilled through a fractionating column from the reaction flask, and the amount of alcohol present in the distillate was determined by phthalic anhydride. The residue in the reaction flask was treated with water, to dissolve the sodium chloride, and ether to dissolve the acetoacetic ester. The ether layer after drying was fractionated. Run 5 was made under the same conditions as to time of reaction and method of decomposition of the reaction mixture as Run 4 except that sodium ethoxide was the condensing agent instead of metallic sodium.

The last column in the table shows the amount of residue which remained after the distillation of the acetoacetic ester.

Run	Condensing agent	Hydrogen Moles per atom of Na	%	Alcohol Moles per atom of Na	%	Ethyl acetoacetate Moles per atom of Na	%	Residue, g.
1	Na (0.5 atom)	0.080	16	1.30	130^a	0.74	74	5
2	Na (0.5 atom)	.088	17.6	1.30	130^a	.754	75.4	5
3	NaOC$_2$H$_5$ (0.5 mole)	..	..	1.86^b	93^c	.74^b	74	4
4^d	Na (0.5 atom)	.078	15.6	0.96	96^a	.49	49	4
5^d	NaOC$_2$H$_5$ (0.5 mole)	..	..	..	..	.55^b	55	1

^{a} Calculated on the basis of 1 Na producing 1C$_2$H$_5$OH, the ratio expected from the acetoacetic ester condensation when Na is the condensing agent. ^{b} Moles per mole of NaOC$_2$H$_5$. ^{c} Calculated on the basis of 1NaOC$_2$H$_5$ producing 2C$_2$H$_5$OH, the ratio expected from the acetoacetic ester condensation when NaOC$_2$H$_5$ is the condensing agent. ^{d} Reaction allowed to proceed for forty minutes.   No alcohol removed from the reaction mixture and the latter decomposed with dry hydrogen chloride.

Discussion of the Experimental Results

The most striking feature of the results that are summarized in the above table is the relative amounts of alcohol and acetoacetic ester which are obtained when sodium reacts with ethyl acetate. When the alcohol is removed from the reaction (Runs 1 and 2), the ratio of alcohol to acetoacetic ester is about 1.7 to 1 and in the case (Run 4) where the alcohol is not removed the ratio is about 2 to 1. Obviously the simple equation
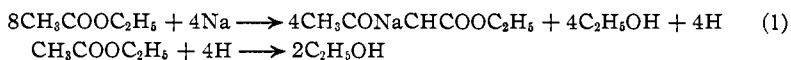
$$2CH_3COOC_2H_5 + Na = CH_3CONaCHCOOC_2H_5 + C_2H_5OH + H$$

which is often used to express the course of the reaction is inadequate, for · according to this equation the ratio of alcohol to keto ester is 1 to 1. The alcohol in excess of that which is produced by the acetoacetic ester condensation must be formed by the reduction of some of the excess ethyl acetate. The low yield of hydrogen (about 16% of the theory) supports such a conclusion.[7] The sodium equivalent of the hydrogen that is given off from the reaction is obviously lost for reduction, but from the remainder of the sodium the amount of alcohol produced by reduction can be estimated if it be assumed that it is derived from ethyl acetate. Thus in Run 1, since a 16% yield of hydrogen is obtained, only 84% of the sodium that was used in the reaction is available for reduction. Therefore 0.42 mole of alcohol per atom of sodium should have been formed through reduction. There is left 1.30–0.42 = 0.88 mole of alcohol per atom of sodium which is due to the acetoacetic ester condensation. This yield (88%) of alcohol is quite comparable to the yield (93%) of alcohol obtained when sodium ethoxide was the condensing agent (Run 3). Similarly it is seen from Run 4

[7] Von Meyer and Friessner [*J. prakt. Chem.*, **65**, 528 (1902)] reported a 33% yield of hydrogen from the action of sodium on ethyl acetate and concluded that the missing hydrogen, by reduction, induced side reactions that lowered the yield of acetoacetic ester.   The lower yields of hydrogen obtained in the present work were due, no doubt, to the fact that very finely divided sodium was used in the reaction.

that approximately 0.42 mole of alcohol per atom of sodium is produced by reduction, leaving 0.96 − 0.42 = 0.54 mole of alcohol per atom of sodium which may be attributed to the acetoacetic ester condensation. This yield (54%) of alcohol parallels quite closely the yield (49%) of acetoacetic ester in this particular run. Obviously, the method of determination of the amounts of acetoacetic ester formed in these reactions is not as accurate[8] as the method used for the alcohol determination, so it is not surprising that the yields of the latter compound are generally somewhat higher than those of the former.

The manner in which the reduction of the ester takes place is of considerable interest. If it is assumed that "nascent hydrogen" can cause such a reduction, then there can be no argument against the contention that sodium is the direct cause of the acetoacetic ester condensation when ethyl acetate is reacted with the metal, for the sodium could in some manner condense the ester with the liberation of "nascent hydrogen" which would reduce more of the ester, thus

$$8CH_3COOC_2H_5 + 4Na \longrightarrow 4CH_3CONaCHCOOC_2H_5 + 4C_2H_5OH + 4H \quad (1)$$
$$CH_3COOC_2H_5 + 4H \longrightarrow 2C_2H_5OH$$

Such a formulation, however, does not seem probable in view of some recent work on the mechanism of sodium reductions. Willstätter, Seitz and Bumm[9] have demonstrated that the mechanism of the reduction of phthalic acid by sodium amalgam in aqueous solution does not proceed with the "nascent hydrogen" but rather it involves the primary addition of the alkali metal to the carbon to carbon double bond followed by the hydrolysis of the organo-alkali compound. More recently, Wooster and Smith[10] showed that a similar mechanism was followed in the reduction of naphthalene by sodium or potassium in liquid ammonia. If sodium assumes such a role in the reduction of a carbon to carbon double bond it would seem safe to conclude that it functions similarly in the reduction of the carbon to oxygen double bond of an ester. As a matter of fact, the formation of an acyloin by the action of sodium on an ester is a reduction that follows such a mechanism.[4]
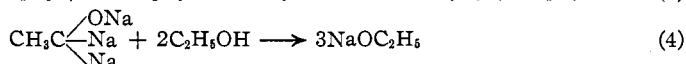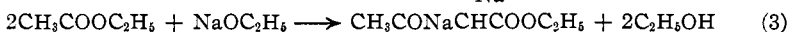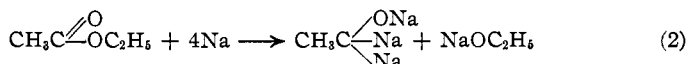
On the basis of such a conclusion it is difficult to see how sodium can be directly responsible for the acetoacetic ester condensation. It would seem more in accord with the experimental facts to postulate the condensation as taking place through the agency of sodium ethoxide resulting from the

[8] The residue left after the distillation of the acetoacetic ester represents a considerable loss in the yield of the keto ester, since it undoubtedly results from the self-condensation of some of the acetoacetic ester during distillation into β-(β'-ketobutyryloxy)-crotonate and dehydroacetic acid [cf. Adkins and Connor, THIS JOURNAL, 52, 5193 (1930)].

[9] Willstätter, Seitz and Bumm, Ber., 61, 871 (1928).

[10] Wooster and Smith, THIS JOURNAL, 53, 179 (1931).

reduction of the ethyl acetate by metallic sodium. The steps in the condensation could be represented as follows

$$CH_3C\diagup_{OC_2H_5}^{O} + 4Na \longrightarrow CH_3C\diagdown_{Na}^{ONa} + NaOC_2H_5 \tag{2}$$

$$2CH_3COOC_2H_5 + NaOC_2H_5 \longrightarrow CH_3CONaCHCOOC_2H_5 + 2C_2H_5OH \tag{3}$$

$$CH_3C\diagdown_{Na}^{ONa} + 2C_2H_5OH \longrightarrow 3NaOC_2H_5 \tag{4}$$

$$6CH_3COOC_2H_5 + 3NaOC_2H_5 \longrightarrow 3CH_3CONaCHCOOC_2H_5 + 6C_2H_5OH \tag{5}$$

At present there is no experimental evidence for reactions (2) and (4). They simply represent the reduction of the ester through the intermediate formation of an organo-sodium compound followed by alcoholysis in accordance with the suggestion of Willstätter, Seitz and Bumm.[9] It may be that (2) represents the sum of two or more previously occurring reactions.[11]

The sum of (2), (3), (4) and (5) would be the same as the sum of the reactions shown above in (1), *viz.*

$$9CH_3COOC_2H_5 + 4Na \longrightarrow 4CH_3CONaCHCOOC_2H_5 + 6C_2H_5OH \tag{6}$$

The hydrogen which is given off in the reaction would result from the following reaction

$$2C_2H_5OH + 2Na \longrightarrow 2C_2H_5ONa + H_2 \tag{7}$$
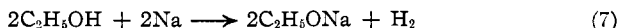
It is seen from reaction (6) that 1.5 moles of alcohol are produced in the reaction for each mole of acetoacetic ester. As pointed out above the acetoacetic ester condensation went to the extent of 88% on the basis of the alcohol yields and about 75% on the basis of the keto ester yields in Runs 1 and 2. If, however, the residue obtained in these runs after the distillation of the acetoacetic ester is considered as derived from acetoacetic ester (*cf.* footnote ref. 8), the yield of keto ester would be raised to about 0.85 mole per atom of sodium[12] (85%). Thus the ratio of alcohol to keto ester obtained from the reaction mixture would be 1.30/0.85 = 1.53 to 1, which compares quite closely to the ratio established by reaction (6).

In the above discussion an attempt has been made to show that a semi-quantitative consideration of the reaction products in the light of the most probable mechanism of sodium reductions leads to the conclusion that

[11] It is quite probable that such a reduction mechanism could be tested experimentally if it were possible to find an acetate, CH_3COOR, of such a nature that $RONa$ did not cause the acetoacetic ester condensation of it. Work along this line is now in progress in this Laboratory.

[12] The question might well arise as to why it is not possible to raise the yield of keto ester even higher if the alcohol produced in the condensation is removed. A very probable reason why this is not possible is that as the alcohol is removed from the reaction mixture the sodium salt of acetoacetic ester precipitates and in so doing carries with it some of the active condensing agent, sodium ethoxide, possibly as the addition product, $CH_3CONaCHC\diagdown_{OEt}^{ONa}$OEt.

sodium is not directly responsible for the acetoacetic ester condensation, but serves only to generate sodium ethoxide, which is the active condensing agent. In further support of this contention another important observation should be emphasized, *viz.*, that sodium ethoxide produces practically the same amount of condensation (Runs 3 and 5) and just as readily (Run 5) as does metallic sodium. This observation is not in agreement with the findings of some of the earlier investigators of the reaction, but it is in accord with the results recently reported by Kutz and Adkins.[18]

Summary

A study of the reaction of sodium and ethyl acetate has been made in which the amounts of the reaction products, acetoacetic ester, alcohol and hydrogen have been determined. The amount of alcohol found in the reaction mixture is approximately the sum of that produced by the acetoacetic ester condensation and that resulting from the reduction of the ester by the sodium used in the reaction. It has also been shown that sodium ethoxide brings about the condensation just as readily and completely as does metallic sodium. These results lead to the conclusion that the role of sodium in the acetoacetic ester condensation is to generate, by reduction of the ester, sodium ethoxide, which is the real condensing agent.

MADISON, WISCONSIN

A QUANTITATIVE STUDY OF THE INFLUENCE OF ACETATE AND OF PHOSPHATE UPON THE ACTIVITY OF THE AMYLASE OF ASPERGILLUS ORYZAE

BY M. L. CALDWELL AND M. G. TYLER

Recent work[1] has emphasized anew the importance of maintaining the optimal hydrogen-ion activity in studies of enzyme action and has also shown that this is not necessarily a fixed value, but may and often does differ with changes in the environmental conditions under which the enzyme acts. Important among the factors which have been found to influence enzyme action is the kind and concentration of electrolyte present. The experiments reported briefly here were undertaken to establish quantitatively the relations of acetate and of phosphate to the saccharogenic activity (formation of reducing sugar, chiefly maltose)[2] of the amylase

[18] Kutz and Adkins, THIS JOURNAL, **52**, 4393 (1930).

[1] (a) Sherman, Caldwell and Adams, *ibid.*, **49**, 2000 (1927); **50**, 2528, 2529, 2535 (1928); (b) Sherman, Caldwell and Boynton, *ibid.*, **52**, 1669 (1930); and other references therein contained.

[2] Sherman and Punnett, *ibid.*, **38**, 1878 (1916).