stance was found to be slightly less than that of the corresponding saturated compound.

3. The corresponding free energies have also been calculated. The free energy change in dehydrogenation reactions was found to vary greatly, and it is apparent that the effect of unsaturation in determining the free energy value of an organic compound is very specific.

STANFORD UNIVERSITY, CALIFORNIA

[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

THE ALCOHOLYSIS OF CERTAIN 1,3-DIKETONES AND BETA-KETONIC ESTERS

BY WALTER M. KUTZ AND HOMER ADKINS

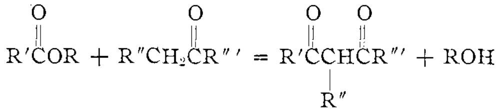
RECEIVED JULY 3, 1930 PUBLISHED NOVEMBER 5, 1930

This investigation was undertaken originally for the purpose of studying the influence of structure on the extent of formation and cleavage of carbon to carbon linkages in organic compounds. The ideal condition for a study of this nature would be a perfectly reversible reaction in which the concentration of various sets of reactants at the equilibrium point could be measured accurately. The quantitative work which has been done previously in connection with this problem has been concerned chiefly with the extent of dissociation of hexa-substituted ethanes. The interpretation of the experimental data in terms of the relation of structure to the strength of the carbon to carbon linkage between the substituted methyl groups is complicated by the fact that the dissociated radical is apparently in equilibrium with compounds having a quinoid structure. In addition to the rather large volume of literature upon the hexa-substituted ethanes there has been, also, a paper by Miss Edith Usherwood[1] upon the position of the equilibrium point in the aldolization of isobutyric aldehyde.

The Claisen or acetoacetic ester condensation since the publication of Dieckmann's work[2] has been considered to be a reversible reaction, and it seemed upon preliminary consideration to be better suited than any other reaction for an investigation of the relationship of the structure of a compound to the strength of carbon to carbon linkages. In general terms the Claisen synthesis may be considered to involve the elimination of a molecule of alcohol through the reaction of the alkoxy group of an ester with a hydrogen on a carbon atom alpha to a carbonyl or other activating group in the presence of such reagents as sodium, sodium ethoxide or sodamide. The type reaction may be represented as

[1] Usherwood, *J. Chem. Soc.*, **123**, 1917 (1923).

[2] Dieckmann, *Ber.*, **33**, 2670 (1900).



$$R'\overset{O}{\overset{\|}{C}}OR + R''CH_2\overset{O}{\overset{\|}{C}}R''' = R'\overset{O}{\overset{\|}{C}}\underset{R''}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}R''' + ROH$$

It is obvious that this simple formulation is very far from giving an adequate picture of this reaction. Sodium ethoxide for example forms addition compounds with the ester and the ketones. The ketones also compete through their enol forms for the metal of the alkoxide. However, these complications do not make it impossible profitably to utilize this action for the study of the relation of structure to the extent of the cleavage of the carbon linkage, although they may make very difficult an interpretation of the results. An attempt was therefore made to determine the concentration at equilibrium of the reactants in the synthesis and alcoholysis of acetoacetic ester.

Higley[3] found that he could obtain acetoacetic ester in a 36% yield (based on the sodium ethoxide) through the reaction of 0.4 mole of ethyl acetate and 0.14 mole of sodium ethoxide. He believed that this represented the concentration of acetoacetic ester at equilibrium. McElvain[4] showed that a 68% yield of the keto ester (based on the sodium ethoxide) could be obtained if the alcohol formed in the condensation were distilled out of the reaction mixture before the ester was isolated. He used 6 moles of ethyl acetate and 0.5 mole of sodium ethoxide. The reaction mixture was not homogeneous after the removal of the alcohol, so that both of these factors tended to drive the condensation toward completion. McElvain's results have been duplicated and the extent of condensation of ethyl acetate in a homogeneous reaction mixture determined both by synthesis and alcoholysis to be from 44 to 50% in so far as this may be judged through the isolation of acetoacetic ester. This last statement is based upon the results of the following experiments in which the homogeneity of the reaction mixture was maintained through the use of a large excess of ethyl acetate.

1. One-half mole of sodium ethoxide and 6 moles of ethyl acetate were refluxed for periods of from ten to ninety-six hours. The reaction mixture was then acidified with 35 ml. of acetic acid in 70 ml. of water and the aqueous layer extracted twice with 50-ml. quantities of ether after the removal of the layer of acetoacetic ester. The fractionation of the products gave from 32 to 33 g. of ester boiling at 84–87° (25 mm.). This represents a yield of 50 to 51%.

2. One-half mole each of acetoacetic ester, of sodium ethoxide and of ethanol were refluxed for twenty-four hours in six moles of ethyl acetate. The reaction mixture was worked up as described above and from 29 to 30 g. of acetoacetic ester obtained.

3. One-half mole of sodium ethoxide and six moles of ethyl acetate were allowed to react and the alcohol and excess simple ester distilled off as described by McElvain. One mole of ethanol and six moles of ethyl acetate were then added to the solid reaction products and the whole refluxed for twenty-four or forty-eight hours. Upon working up

---

[3] Higley, *Am. Chem. J.*, **37**, 299 (1907).

[4] McElvain, THIS JOURNAL, **51**, 3124 (1929).

the reaction mixture 28.5 to 29 g. of acetoacetic ester was obtained. This is to be contrasted with the yields of from 43 to 44 g. of keto ester obtained if it were isolated before the addition of the ethanol and ethyl acetate or before the second refluxing of the mixture but after the addition of ethanol and ethyl acetate. The last experiment was performed in order to make sure that the higher yields obtained where the alcohol was distilled off were not due at least in part to the greater ease of isolation of the ester.

The condensation of esters other than ethyl acetate with the formation of beta ketonic esters does not lend itself to a study of the relationship of structure to extent of reaction. It is possible to vary one group at a time only through the condensation of dissimilar molecules of ester and this makes possible the formation of two or three different beta ketonic esters in the reaction mixture, thus greatly increasing the difficulties of analysis. In the case of the 1,3-diketones a simple synthesis and alcoholysis is possible only when the ester concerned is incapable of condensation with itself, and the monoketone is of such a structure that it can condense with the ester to form only a single compound. The structures of dibenzoylmethane and its derivatives are such that only simple alcoholysis and synthesis are possible and so these diketones were selected as the basis of study. Broderick in 1927[5] showed that the percentage of diketone present in the reaction mixtures was the same irrespective of whether he started with dibenzoylmethane and alcohol or ethyl benzoate and acetophenone. However, this did not represent a true equilibrium point because of the separation of the solid salt of the diketone. An extensive search has been carried on since that time in order to discover an inert solvent in which homogeneity could be maintained during the synthesis or alcoholysis of a diketone. There has been found no inert solvent in which the sodium, potassium or lithium salt of a diketone was sufficiently soluble to permit determinations of the extent of alcoholysis or synthesis in the presence of a catalyst for the latter reaction. Attention was therefore directed toward the study of the relationship of structure to the rate of alcoholysis in the presence of hydrogen chloride,[6] and of sodium ethoxide.

There are several reasons why the relative rates of alcoholysis of 1,3-diketones cannot be determined and compared as accurately in the presence of sodium ethoxide as when hydrogen chloride is the catalyst. For example, the former reagent catalyzes "side reactions" such as the acetoacetic ester condensation. This may be minimized and it is believed practically eliminated through the use of a large molecular excess of alcohol. However, as may be seen from an inspection of the data shown in the figures, the ultimate percentage of alcoholysis, calculated on the amount of diketone used, is in many cases considerably less than 100%, this despite the fact that with the ratio of one mole of sodium ethoxide to two moles of acetylbenzoylmethane all of the diketone had disappeared after one hun-

---

[5] Ph.D. Dissertation, University of Wisconsin, **1928**.

[6] Adkins, Kutz and Coffman, THIS JOURNAL, **52**, 3212 (1930).

dred hours. This failure to obtain a 100% recovery of ester is no doubt connected with the fact that it is impractical to determine how much ester is lost during the analysis, due to saponification or other reactions, as was done in the study of alcoholysis involving the use of hydrogen chloride. Perhaps the most serious obstacle to a precise comparison of the rates of alcoholysis of various diketones is the fact that they differ so greatly with respect to their sensitivity toward the catalyst. This makes it impossible to compare any considerable group of diketones or keto esters under identical experimental conditions.

The rates of alcoholysis at 60° of diacetylmethane, acetylbenzoylmethane, benzyldiacetylmethane, dibenzyldiacetylmethane, ethyldiacetylmethane, benzylacetylbenzoylmethane, ethyl acetoacetate, ethyl ethylacetoacetate, ethyl benzylacetoacetate, ethyl diethylacetoacetate and ethyl dibenzylacetoacetate were measured in ethanol in the presence of various amounts of sodium ethoxide. Approximately 0.01 mole of the diketone or keto ester with the desired amount of sodium ethoxide was dissolved in enough ethanol to make the volume of the reaction mixture 40 ml. The reaction was stopped after the alcoholysis had proceeded for the desired length of time by adding an excess of a normal solution of hydrogen chloride in ethanol. After shaking the mixture, 2 ml. of phenylhydrazine was added to combine with the excess hydrogen chloride and ketones. After standing for two or three hours the ester was distilled out and determined as described in our previous paper. In only one case was any modification of this procedure necessary. Ethyl ethylacetoacetate gave ethyl butyrate as well as ethyl acetate upon alcoholysis so that two 20-ml. portions of propanol were added and distilled out after the normal distillation procedure had been followed.

Diacetylmethane, acetylbenzoylmethane, ethyldiacetylmethane, benzyldiacetylmethane, dibenzyldiacetylmethane and benzylacetylbenzoylmethane were prepared and had the physical constants described in a previous paper. Acetoacetic ester was dried over calcium chloride and fractionated from the commercial products, b. p. 85–87° (25 mm.), d_{25}^{25} 1.012. Ethyl ethylacetoacetate was prepared from acetoacetic ester, using toluene as a medium; the yield was 60% of product boiling at 100–102° (25 mm.), d_{25}^{25} 0.9690. Ethyl diethylacetoacetate was prepared from the monoethyl compound, the yield being 40 to 50%; b. p. 115–117° (25 mm.), d_{25}^{25} 0.9435.[7] Ethyl benzylacetoacetate was obtained in a 58% yield, b. p. 165–170° (25 mm.), d_{25}^{25} 1.050.[8] The ethyl dibenzylacetoacetate after crystallization from ethanol had a melting point of 56–57°.[9] Diethyldibenzoylmethane was prepared in a yield of 35% through the re-

[7] Wislicenus, *Ber.*, 7, 683 (1874).

[8] Ehrlich, *Ann.*, **187**, 12 (1877).

[9] Fittig and Christ, *ibid.*, **268**, 123 (1891).

action of diethyl malonyl dichloride with benzene in the presence of aluminum chloride. The diketone melted at 102–103°.[10]

The rate of alcoholysis of five beta ketonic esters and six 1,3-diketones for various concentrations of sodium ethoxide is shown in Figs. 1, 2 and 3. The molar ratio of sodium ethoxide to diketone or keto ester is shown in parentheses for each curve. The rate of alcoholysis of diacetylmethane and acetylbenzoylmethane was increased by almost 100% when the ratio of sodium ethoxide to diketone was increased from 1:5 to 1:2. A further increase to a ratio of 1:1 brought about what was apparently a small decrease in the rate of alcoholysis but it is believed that this was due to the greater loss in ethyl acetate prior to analysis rather than to a real decrease in the rate of alcoholysis.

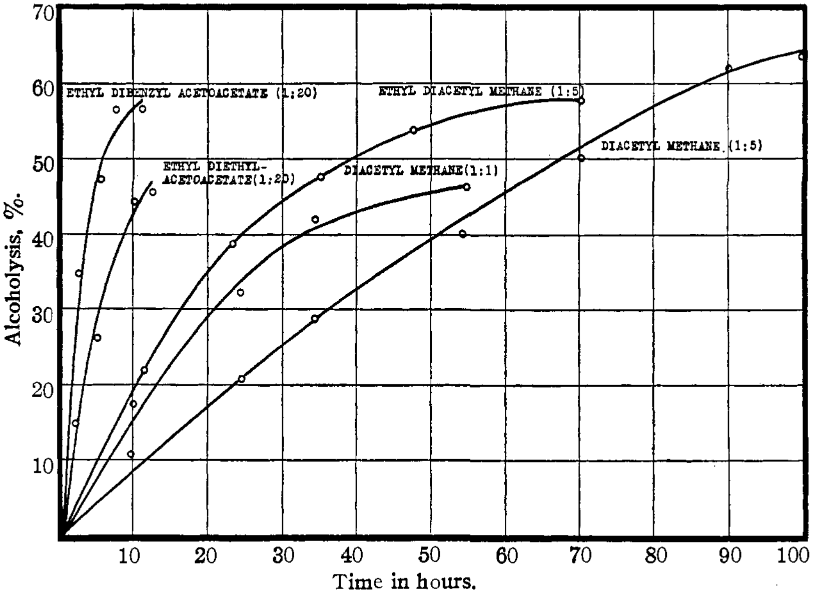


Fig. 1.—Rates of alcoholysis of various 1,3-diketones and β-keto esters. The molecular ratio of sodium ethoxide to dicarbonyl compound is shown in parentheses for each curve.

There was very little difference between the rates of alcoholysis of diacetylmethane and acetylbenzoylmethane irrespective of whether the comparison was made at a ratio of sodium ethoxide to diketone of 1:5 or 1:2.

The keto esters undergo alcoholysis more slowly, for a given ratio of keto compound to sodium ethoxide, than do the 1,3-diketones. This is true irrespective of whether the comparison is made between the unsubstituted compounds or between those in which one or more substitutions have been made on the carbon atom between the carbonyl groups.

[10] Freund and Fleischer, *Ann.*, **373**, 296 (1910).

Substitution of ethyl or benzyl groups on the carbon atom between the carbonyl groups greatly increases the rate of alcoholysis of both keto esters and diketones for a given ratio of keto compound to sodium ethoxide. This may be expressed in another way by saying that it is feasible to cleave a monosubstituted compound, within a given period, with a very much lower ratio of sodium ethoxide to keto compound than is possible in the case of the parent substance. In the case of the disubstituted compounds the rate of alcoholysis is relatively very rapid even where there is only one mole of sodium ethoxide for twenty moles of dicarbonyl compound. However, even a qualitative comparison is perhaps not justifiable, for in the case of the unsubstituted and of the monosubstituted compounds there is the probability that a very considerable portion of the sodium ethoxide reacts with the enol and is thus eliminated as a catalyst. There is no possibility of this in the case of the disubstituted dicarbonyl compounds unless enolization occurs by the migration of a hydrogen from the methyl group at the end of the molecule. Even this is not possible for diethyldibenzoylmethane, which readily undergoes alkaline alcoholysis and hydrolysis.

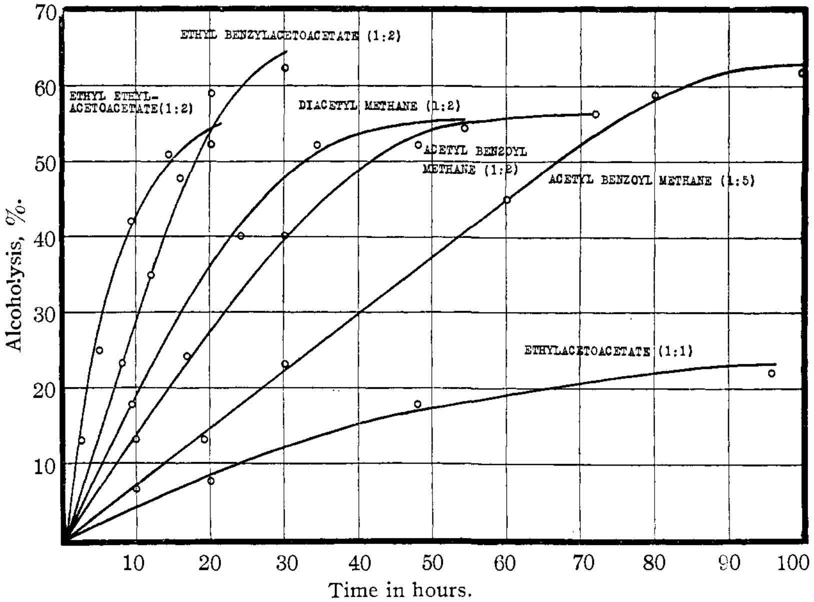


Fig. 2.—Rates of alcoholysis of various 1,3-diketones and β-keto esters. The molecular ratio of sodium ethoxide to dicarbonyl compound is shown in parentheses for each curve.

Two grams of this diketone dissolved in 50 ml. of ethanol was allowed to undergo alcoholysis at 60° for twelve hours in the presence of an equimolecular amount of sodium ethoxide. Acidification with 50 ml. of dilute aqueous hydrochloric acid did not give a crystalline precipitate and it was considered that the diketone had been completely split into ethyl benzoate and the corresponding monoketone. The reaction mixture was then made alkaline with solid sodium hydroxide and the ester saponified. After evaporation to dryness, the residue was dissolved in 200 ml. of water and

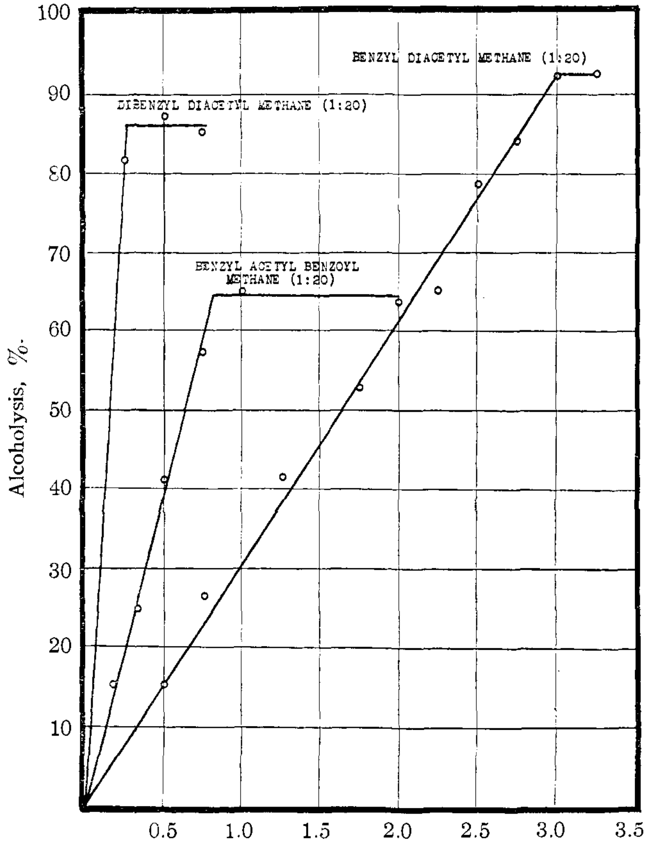


Fig. 3.—Rates of alcoholysis of three 1,3-diketones.

washed with ether. Evaporation of the water solution to a small volume, acidification with hydrochloric acid and cooling precipitated out 0.819 or 94% of the theoretical amount of benzoic acid. One and four-tenths grams of diethyldibenzoylmethane was hydrolyzed at 60° for ten hours in 75 ml. of a 1% solution of sodium hydroxide in 80% ethanol. After evaporation to dryness, the residue was dissolved in 200 ml. of water, washed with ether and 0.5960 g. of benzoic acid precipitated with sulfuric acid. The yield was thus 98% of the theoretical.

The high reactivity of the substituted keto esters in alkaline alcoholysis as compared with the unsubstituted esters is in accord with the qualitative experiments of Dieckmann[11] on the cleavage of substituted acetoacetic esters. However, his inference from these experiments with regard to the concentration at equilibrium of acetoacetic ester and its derivatives is unjustified by any experimental work, and in so far as it applies to the non-condensation of isobutyric ester has been shown by McElvain to be incorrect.

The rate of alcoholysis of six of the diketones has been determined in the presence of both hydrogen chloride and sodium ethoxide. As previously reported, these compounds in the order of decreasing reactivity are as follows: diacetylmethane, ethyldiacetylmethane, acetylbenzoylmethane, benzoyldiacetylmethane, benzylacetylbenzoylmethane and dibenzyldiacetylmethane. This is also the order of reactivity (with one exception) of the diketones with respect to sodium ethoxide except that it is one of *in*creasing reactivity. The exception to this statement is acetylbenzoylmethane, which is slightly less reactive in the presence of sodium ethoxide than would be expected on the basis of its reactivity in the presence of hydrogen chloride. There can be no doubt that in general this reversal of reactivity with respect to the two conditions of alcoholysis holds true and that the differences in reactivity are quite large. For example, taking the end members of the series referred to above, it was found that in the presence of hydrogen chloride, diacetylmethane was in the vicinity of ten times as reactive as its dibenzyl derivative, while in the presence of sodium ethoxide the dibenzyl derivative was one or two hundred times as reactive as the parent substance. A similar comparison cannot be made for the keto esters because experimental conditions have not as yet been found in which these compounds undergo alcoholysis in the presence of hydrogen chloride.

It was previously pointed out that there seemed to be a parallelism between the extent of enolization of a 1,3-diketone and its reactivity toward alcoholysis in the presence of hydrogen chloride. Since the order of reactivity of the 1,3-diketones is the opposite in alkaline alcoholysis to that in acid alcoholysis, it seems reasonable to consider this as evidence in support of the hypothesis of Bradley and Robinson that the cleavage of diketones in alkaline medium takes place through the keto rather than the enol compound. This view is also in accord with the very high reactivity in alkaline alcoholysis of the disubstituted 1,3-diketones and keto esters which are incapable of enolization. It is quite possible that cleavage also occurs through the enol compound since Fieser[12] has shown that a fixed enol of a 1,3-diketone readily undergoes cleavage.

---

[11] Dieckmann, *Ber.*, **33**, 2678 (1900).

[12] Fieser, This Journal, **51**, 940 (1929).

Summary

It has been shown that the amount of acetoacetic ester to be obtained from the reaction mixture is the same irrespective of whether it is synthesized from ethyl acetate and sodium ethoxide or remains from the alcoholysis of an amount of acetoacetic ester molecularly equivalent to the amount of sodium ethoxide used in the synthetic reaction. All attempts to make similar determinations on the synthesis and alcoholysis of 1,3-diketones have failed because no conditions have been found under which homogeneity would be maintained during the synthesis and alcoholysis.

The rates of alcoholysis of six 1,3-diketones and five beta keto esters have been determined at 60° in the presence of various ratios of sodium ethoxide. The keto esters were found to be more stable than the diketones toward alcoholysis for a given ratio of sodium ethoxide. Substitution on the carbon atom between the two carbonyl groups very considerably increased the rate of alcoholysis in the presence of sodium ethoxide. This effect reached its maximum in the case of the diacyl dialkyl methanes, which underwent alcoholysis hundreds of times as rapidly as the diacyl methanes.

When the six diketones whose reactivity was measured in the presence of both hydrogen chloride and sodium ethoxide were arranged in the order of decreasing reactivity with respect to alcoholysis in the presence of hydrogen chloride, they were found to be arranged (with one exception) in the order of increasing reactivity toward alcoholysis in the presence of sodium ethoxide. Diethyldibenzoylmethane, which is incapable of enolization, readily underwent alkaline alcoholysis and hydrolysis. These facts taken in conjunction with the parallelism between extent of enolization and rate of acid alcoholysis offer support to the hypothesis of Bradley and Robinson that alkaline cleavage of 1,3-diketones takes place through the reaction of the carbonyl rather than of the enol form of the diketone.

MADISON, WISCONSIN