Mechanism of the Reaction of Acetylacetone with Diazomethane

George S. Hammond[1] and Robert M. Williams

Department of Chemistry of Iowa State University and from
the Ames Laboratory of the Atomic Energy Commission, Ames, Iowa

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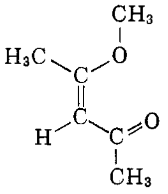
Rates, products, and stoichiometry of the reaction of diazomethane with acetylacetone have been studied. Acid-catalyzed polymerization of diazomethane occurs concomitantly with the methylation reaction without the production of higher alkyl ethers. This result indicates that methylation must involve either a concerted mechanism or tightly bound ion pairs.

From the reaction of acetylacetone and diazomethane in absolute ether Eistert *et al.*,[2] by careful manipulation, were able to isolate two compounds, which they designated *cis*- and *trans*-methyl enol ethers. The higher boiling ether was formed initially and changed into the low boiling isomer at a rate dependent upon conditions. From qualitative observations of the effect of methanol and of clay shards on the rate and products of the reaction, and from the difference in chemical behavior of the two enol ethers with ferric chloride solution and with aqueous sodium hydroxide solution, it was concluded that the initially formed, higher boiling enol ether was the *cis* isomer I.



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Eistert *et al.*[2] felt that diazomethane reacted at the site of the original binding place of the proton. Protonation of the diazomethane molecule was followed by nitrogen loss and subsequent collapse to the product without dissociation into free methyl cations. It was thought that formation of free ions would have resulted in C-alkylation.[3] Arndt[4] also considers that the reaction involves reaction at the site of the acidic hydrogen without separation into discrete ionic species.

A detailed study[5] indicated that diphenyldiazomethane reacts with benzoic acid in ethanol solution without the intervention of free carbonium ions. A recent study of substituent effects on the rate of the reaction can be construed as indicating that ion pairs may be intermediates.[6] In contrast, evidence for the involvement of diazonium ions was adduced from the study of the reaction of ethyl diazoacetate with acetic acid or ethanol (in the presence of strong acid).[7] Curtin and Gerber[8] and Huisgen and Rüchardt[9] have presented and reviewed evidence, based upon occurrence or absence of molecular rearrangement, for and against the incursion of carbonium ion mechanisms in the reactions of diazoalkanes with acids. The net conclusion seems to be that carbonium ions may be involved in reactions in polar solvents, especially those catalyzed by mineral acids, but that reactions in nonpolar media probably involve ion pairs in which one partner is a diazonium ion.

In the present paper we report a preliminary study of the reaction of diazomethane with acetylacetone.

Experimental

Diazomethane.—Solutions of diazomethane were prepared by the method of Arndt.[10] All glassware was washed with concentrated ammonium hydroxide and dried at 140°.[11] Diazomethane solutions were dried over potassium hydroxide[11] for 3 hr. and stored at −15°.

Acetylacetone (2,4-pentanedione, Eastman Kodak Co. white label) was distilled at atmospheric pressure through a tantalum, spiral wire column, 74 cm. × 7 mm. The middle third of the fraction boiling from 134–135° was retained and redistilled. A fraction, constituting the middle third of the redistilled material, was collected and stored at −20° until use (within 3 days). Refractive indices at 25° of three different samples were 1.4516, 1.4496, and 1.4492. Neutralization equivalents, determined by titration with standard *n*-butyltriethylammonium hydroxide in pyridine, were 100.6, 100.0, and 98.9; calcd., 101.1.

***p*-Toluenesulfonic Acid.**—*p*-Toluenesulfonic acid (Eastman Kodak Co., 90%) was recrystallized two to three times from an ether–benzene mixture.

4-Alkoxy-3-penten-2-ones.—4-Methoxy-3-penten-2-one was made by the reaction of diazomethane with acetylacetone in ethyl ether solution. The product was worked up by fractional distillation through the column previously described. A fraction collected at 61–62° at 10–11 mm. had a maximum in its ultraviolet spectrum at 255 mμ, with log ε 4.12.[2] Vapor phase chromatographic analysis showed that the material contained small amounts of acetylacetone and 3-methyl-2,4-pentanedione.

4-Ethoxy-3-penten-2-one and 4-Butoxy-3-pentene-2-one (ethyl and *n*-butyl ethers of acetylacetone) were pre-

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(1) Present address: Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California.

(2) B. Eistert, F. Arndt, L. Loewe, and E. Ayca, *Ber.*, **84**, 156 (1951).

(3) A. Brändström, *Acta Chem. Scand.*, **4**, 208 (1950), has measured the rates of carbon methylation of acetylacetone by methyl iodide and alkali carbonates in acetone.

(4) F. G. Arndt, "Diazomethane for the Determination of Active Hydrogen," "Organic Analysis," Vol. I, Interscience, New York, 1953, p. 197.

(5) J. D. Roberts, W. Watanabe, and R. E. McMahon, *J. Am. Chem. Soc.*, **73**, 760 (1951).

(6) C. K. Hancock and J. S. Westmoreland, *ibid.*, **80**, 545 (1958).

(7) J. D. Roberts, C. M. Regan, and I. Allen, *ibid.*, **74**, 3679 (1952).

(8) D. Y. Curtin and S. M. Gerber, *ibid.*, **74**, 4052 (1952).

(9) R. Huisgen and C. Rüchardt, *Ann.*, **601**, 1 (1956).

(10) F. Arndt, "Organic Syntheses," Coll. Vol. 2, John Wiley & Sons, New York, N.Y., 1943, p. 165.

(11) J. Goubeau and K. H. Rohwedder, *Ann.*, **604**, 168 (1957).

pared from appropriate diazoalkanes[12] and acetylacetone. Solvent and some acetylacetone were removed by distillation and the crude residues were analyzed directly by vapor chromatography. Each chromatogram indicated the presence of acetylacetone, a major constituent having retention time reasonable for the expected ether, and only traces of other materials. The retention times were used as standards in the scrutiny of chromatograms of mixtures produced from diazomethane and acetylacetone for indication of the presence of higher ethers.

3-Methyl-2,4-pentanedione was prepared in small amounts according to the method of Hauser and Adams.[13] Vapor phase chromatography showed the presence of a trace of a single impurity judged to be 2,4-hexanedione on the basis of its retention time.

Methyl *p*-toluenesulfonate was prepared by reaction of *p*-toluenesulfonic acid with diazomethane in an ether–benzene mixture. Most of the solvents were removed and the residue was analyzed by vapor chromatography. The major product, assumed to be methyl tosylate, had a retention time much longer than that of the *n*-butyl ether of acetylacetone.

Apparatus.—All rates were measured at 27.0 ± 0.03°. Potentiometric titrations were carried out using a Beckman pH meter, Model G. The electrodes were a Beckman general purpose electrode (No. 1190-80) and a Beckman sleeve-type reference electrode (No. 1171-71). The Calomel electrode was modified by replacing the aqueous potassium chloride solution with a saturated solution of potassium chloride in methanol.

Reaction Solvents.—Benzene (Baker and Adamson Co., reagent grade) was dried with sodium ribbon. 1,2-Dimethoxyethane (Ansul Chemical Co., ether product No. 121) was refluxed over sodium for 2 days, distilled, and stored over sodium ribbon. Diethyl ether was Mallinckrodt anhydrous analytical reagent.

Titration Solvents.—Nonaqueous titrations were carried out under nitrogen cover in acetone (Baker and Adamson Co., reagent grade) or in pyridine (Fisher Chemical Co., reagent grade). Blank corrections were made. These varied according to the system being titrated but never exceeded 0.08 ml.

Titrants.—Stansol standard volumetric concentrate was diluted to the appropriate concentration with absolute methanol (Baker and Adamson Co., reagent grade). Benzoic acid and salicylic acid were used as primary standards. Triethyl-*n*-butylammonium hydroxide dissolved in methanol–benzene (1:10) was prepared and used according to the procedure of Fritz and Yamamura.[14]

Determination of Diazomethane.—The concentration of diazomethane in solutions was determined by adding an aliquot to a known excess of salicylic acid. Unchanged salicylic acid was back-titrated with 0.1 *M* triethyl-*n*-butylammonium hydroxide. *p*-Toluenesulfonic acid could not be used to analyze for diazomethane concentration. Less than the theoretical amount of acid (about 10%) was consumed.

Determination of Acetylacetone.—Reaction mixtures were analyzed for residual diketone by titration with *n*-butyltriethylammonium hydroxide in pyridine. Residual diazomethane was first destroyed by addition of an amount of salicylic acid slightly in excess of the residual diazomethane (determined as described above). Potentiometric titration of the resulting mixtures showed two breaks. The first break corresponds to neutralization of strong acid, and the second is the combined end point for neutralization of acetylacetone and methyl salicylate. Methyl *p*-toluenesulfonate is apparently titrated along with the two weak acids.

Acetylacetone determination is of relatively low accuracy because it depends upon taking the difference between two breaks, and because the titer is due to more than one species—*i.e.*, acetylacetone, methyl salicylate and, when applicable, methyl *p*-toluenesulfonate; furthermore, the end point is not sharp and occurs over a range of 0.2–0.3 ml. of titrant.

Determination of *p*-Toluenesulfonic Acid.—Aliquots (quenched with salicylic acid solution if diazomethane were present) were titrated potentiometrically in acetone with methanolic sodium hydroxide. The first break corresponds to *p*-toluenesulfonic acid and is fairly large.

In a reaction mixture containing only *p*-toluenesulfonic acid (0.09 *M*) and diazomethane (0.28 *M*), no strong acid was found to be present after 3 min. Continued titration to high pH showed an end point corresponding to the expected amount of methyl *p*-toluenesulfonate.

General Procedure for Rate Measurements.—Reaction and control mixtures were prepared from stock solutions previously equilibrated at 27.0°. In a typical run, 10 ml. of acetylacetone was mixed with a 90-ml. aliquot from a stock solution of *p*-toluenesulfonic acid in 1,2-dimethoxyethane in a 200-ml. volumetric flask. The reaction was commenced by the addition of 100 ml. of diazomethane in benzene. Aliquots were withdrawn at intervals from the reaction mixture for analysis. The first sample was titrated with methanolic sodium hydroxide to determine the concentration of unchanged *p*-toluenesulfonic acid. Then alternate samples were used for the determination of diazomethane and acetylacetone. The control solutions were also sampled and analyzed for diazomethane at intervals. Titrants and salicylic acid stock solutions were standardized both immediately before and after the run. Initial concentrations of acetylacetone and *p*-toluenesulfonic acid were determined by analysis of a blank solution identical with the reaction mixture except for the absence of diazomethane. The initial concentration of diazomethane was estimated from the rate of decomposition of two control solutions and the diazomethane stock solution.

Vapor Phase Chromatography.—Two instruments were used: a Consolidated Electrodynamics Type 26–201 with a 9-ft. column packed with Apiezon M on firebrick and an instrument built by Dr. D. H. Froemsdorf with a 15-ft. column packed with Apiezon L or M on firebrick.

Reaction Products.—Diazomethane was decomposed in the presence of acetylacetone under various conditions. Solvents were partially removed from reaction mixtures by conventional techniques. Residues were then analyzed by vapor chromatography. Identification of products was based upon comparison of retention times with those compounds of known structure.

Reaction of equimolar amounts of diazomethane and acetylacetone in ethyl ether gave enol ether as the principal product. A few per cent 3-methyl-2,4-pentanedione was formed. Doubling the concentration of diazomethane gave essentially the same results although small amounts of two other compounds having retention times close to that of acetylacetone were formed. Nearly identical results were obtained with a reaction mixture approximating closely that used in the kinetic studies (0.25 *M* diazomethane and 0.48 *M* acetylacetone in 1,2-dimethoxyethane-benzene). A very small amount of polymethylene was formed. A similar reaction mixture, which originally contained 0.11 *M* *p*-toluenesulfonic acid, gave volatile products in the following relative amounts: enol ether, 92%; 3-methyl-2,4-pentanedione, 5%; unknown compound (2,4-hexanedione, ?), 3%. A small peak having a long retention time was probably methyl *p*-toluenesulfonate. A considerable amount of polymethylene was formed. Similar results were obtained in other reactions in which the concentrations of diazomethane and acetylacetone were varied. Increasing the initial concentration of acetylacetone to 5 *M* gave similar ratios of volatile products but reduced the yield of polymethylene to a barely detectable level, even in the presence of toluenesul-

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[12] Nitrosoalkylureas, used to generate the diazoalkanes, were prepared by Mr. W. A. Bappe from the corresponding ammonium chlorides and potassium cyanate.

[13] C. R. Hauser and J. T. Adams, *J. Am. Chem. Soc.*, **66**, 345 (1944).

[14] J. S. Fritz and S. S. Yamamura, *Anal. Chem.*, **29**, 1079 (1957).

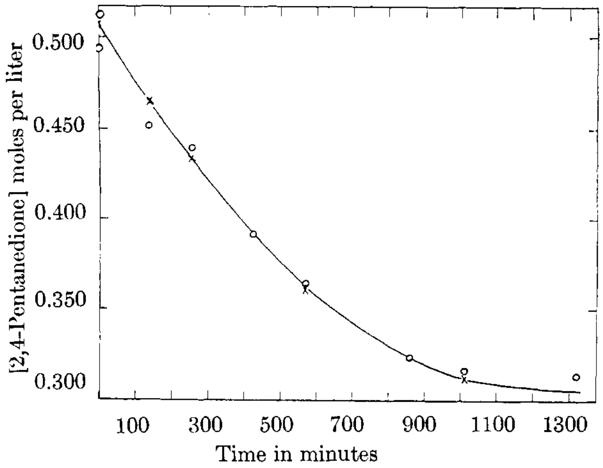


Fig. 1.—Reaction of diazomethane and 2,4-pentanedione in 1,2-dimethoxyethane–benzene at 27.0°. Concentration of 2,4-pentanedione as a function of time. Experimental values are represented by ○. Corrected values used in calculations of rate constants are represented by *x*.

fonic acid. Qualitative observation of the rates of these reactions, as gauged by the evolution of nitrogen, showed that the inclusion of toluenesulfonic acid in the reaction mixtures always accelerated the reaction rate. In benzene the reaction was nearly complete in 4 hr. in the absence of acid, and with acid present nitrogen evolution essentially stopped after 1.5 hr. In 1,2-dimethoxyethane the reaction appeared to be complete in 3 hr.; when acid was originally present, no change was noted after 1 hr.

Analysis of Kinetic Data.—All data were fitted to the second-order rate law using the differential form. Rate constants were calculated from consecutive pairs of experimental points using the analytical values for diazomethane and acetylacetone concentrations at the beginning and end of the individual reaction periods. Rate constants were calculated for the individual periods using the averaged concentrations of the reactants during the interval. The average concentrations of diazomethane were corrected by the assumption that the "spontaneous" decomposition of diazomethane, determined in parallel control experiments, followed the first-order rate law. The corrections were small in comparison with the actual changes in diazomethane concentrations.

In benzene solution with no added strong acid the average second-order rate constant was $1.34 \pm 0.38 \times 10^{-3}$ l. mole^{-1} min.$^{-1}$ for a reaction mixture that originally contained 0.300 *M* diazomethane and 0.975 *M* acetylacetone. A value of $1.29 \pm 0.28 \times 10^{-3}$ l. mole^{-1} min.$^{-1}$ was obtained from a reaction in benzene in which $[CH_2N_2]_0$ was 0.248 *M* and $[Ac_2CH_2]_0$ was 0.473 *M*.

Preliminary studies in ethyl ether solution indicated that addition of *p*-toluenesulfonic acid accelerated the rate of disappearance of diazomethane. Detailed studies were made in 1,2-dimethoxyethane–benzene solution. Qualitatively the titrations showed that the strong acid titer dropped very rapidly to an undetectably low level. Quantitatively the data were hard to analyze because of the imprecision in the determination of the concentration of residual acetylacetone. To approximate the rate constants, the analytical values for acetylacetone were plotted against time and a smoothed curve was drawn through the experimental points. Such a curve is shown in Fig. 1. The values of acetylacetone were read from the curve and were used to calculate the values of second-order rate constants, using the differential kinetic law as described above. For a solution originally 0.265 *M* with respect to diazomethane and 0.494 *M* with respect to acetylacetone, the apparent bimolecular rate constant was $4.35 \pm 0.80 \times 10^{-3}$ l. mole^{-1} min.$^{-1}$. For a solution that originally contained 0.11 *M* *p*-toluenesulfonic acid, 0.265 *M* diazomethane, and 0.247 *M* acetylacetone the average value of the rate constant, calculated from points taken after the first, fast decrease in diazomethane concentration, was $11.3 \pm 2.4 \times 10^{-3}$ l. mole min.$^{-1}$. The stoichiometry of the reactions was estimated by plotting $\Delta[CH_2N_2]$ against Δ-$[CH_3COCH_2COCH_3]$. After an initial, very rapid decrease in the concentration of diazomethane, the points scattered about a 45 degree line, indicating the stoichiometry of the reaction was approximately 1:1 during the major part of the reaction.

Discussion

Two kinds of data have been accumulated. First, relative amounts of volatile products formed from the reaction of diazomethane with acetylacetone have been determined by vapor chromatography, and the amounts of polymethylene formed in various experiments have been noted qualitatively. Second, the rates of disappearance of diazomethane and acetylacetone have been followed in a rather approximate manner. Product analysis shows that the only ether of acetylacetone formed in significant amount is the methyl ether. Ethyl and *n*-butyl ethers have been made by independent syntheses; vapor chromatograms show that they are not present in the reaction mixtures. The *n*-propyl ether is also presumed to be absent on the basis of the assumption that it would have a retention time intermediate between those of the ethyl and *n*-butyl ethers.

The kinetic measurements indicate that the principal reaction in the absence of strong acid is a bimolecular reaction between acetylacetone and diazomethane. In the presence of toluenesulfonic acid a very rapid reaction occurs and consumes both diazomethane and the strong acid. Both methyl tosylate and polymethylene are produced. Even after the concentration of strong acid has fallen to an undetectably low level, the rates of disappearance of diazomethane and acetylacetone are faster than those observed in solutions that have never contained strong acid.

The results compel two conclusions: First, diazomethane decomposes in an acid-catalyzed reaction which produces polymethylene without the concomitant formation of significant amounts of higher ethers of acetylacetone. Second, there must be a reaction between acetylacetone and diazomethane, which gives methyl enol ether without the help of acid catalysis since the ether is produced in large amounts in solutions in which virtually no polymethylene is formed. It is also possible that a third reaction, acid-catalyzed reaction of diazomethane with acetylacetone, occurs.

The easiest formulation of the polymerization effected by strong acid involves growing chains that are either diazonium ions or alkyl cations.

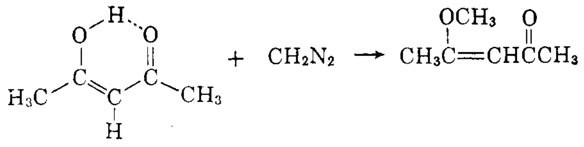
$$CH_2N_2 + H^+ \longrightarrow CH_3N_2^+$$

$$CH_3N_2^+ + CH_2N_2 \longrightarrow CH_3CH_2N_2^+ \xrightarrow{CH_2N_2} \text{polymer}$$

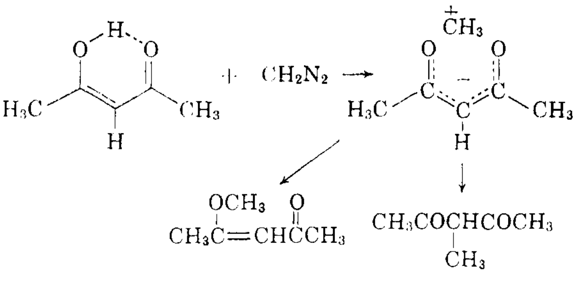
or $CH_3N_2^+ \longrightarrow CH_3^+ + N_2$

$$CH_3^+ + CH_2N_2 \xrightarrow{-N_2} CH_3CH_2^+ \xrightarrow{CH_2N_2} \longrightarrow \text{polymer}$$

Obviously, the intermediate cations react preferentially with diazomethane rather than acetylacetone. Otherwise, a continuous spectrum of alkyl enol ethers would be produced. Methyl enol ether must be formed by some independent mechanism involving reaction between diazomethane and the diketone. The reaction may involve either a concerted Mechanism A or formation of an ion pair (Mechanism B) with predominant collapse of the ion pair to form alkylated products.



Mechanism A



Mechanism B

The fact that small amounts of 3-methylacetylacetone are formed is more easily accommodated by the ion-pair mechanism (Mechanism B). This mechanism also leads easily to an explanation of the fact that trace amounts of polymethylene were formed in all experiments. Separation of a small percentage of the ion pairs would produce a few methyl cations that would react with diazomethane to give high polymer. The stoichiometric relationship in the runs with strong acid present is sufficiently imprecise to allow the assumption that catalysis by strong acid leads only to the formation of polymer.

Evidence for Hydrogen Bonding of Peroxy Radicals. The Autoxidation of 2,4-Pentanediol and Related 2,4-Pentanes

F. F. RUST AND E. A. YOUNGMAN

Shell Development Company, Emeryville, California

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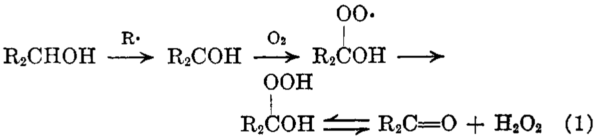
A distinctive characteristic of 2,4-dimethylpentane oxidation is the unusual efficiency with which the two tertiary hydrogen atoms can be replaced in a single reaction sequence (intramolecular oxidation). The same phenomenon is shown by 2,4-dimethoxypentane. However, if either a single methyl or methoxy group is replaced by a hydroxyl group, oxidation is limited to the carbinol moiety and hydrogen peroxide and ketone are formed semiquantitatively. In the case of 2,4-pentanediol, where both substituent groups are hydroxyl, relatively minor amounts of peroxide are produced and no intramolecular oxidation occurs. This absence of intramolecular peroxy radical attack in molecules presumed to be configurationally favorable to such a process is concluded to be a consequence of hydrogen bonding between the peroxy radical and an hydroxyl group with resultant redirection of the point of attack.

When hydrocarbon destruction by oxidation is viewed as a procession of transformations terminating in oxides of carbon and water, it becomes apparent that no real understanding of hydrocarbon oxidation is possible without much greater insight into the reaction characteristics of the many intermediate compounds which are way stations to the end result. Considerable information has been accumulated on the initial sequence of radical reactions involved in the autoxidation of paraffin hydrocarbons, but very little is known concerning subsequent reaction steps which lead to the destruction of primary reaction products. Even such a seemingly simple reaction as hydroperoxide formation can be complicated by the proximity of a second tertiary carbon atom in the molecule. Thus, the finding that 2,4-dimethylpentane can give semiquantitative yields of the dihydroperoxide[1] by an intramolecular process, emphasizes the significance of difunctionality in the over-all oxidation picture.

Inasmuch as a hydroxyl group is essentially equivalent spatially to a methyl group, and since secondary alcohols can give high yields of hydrogen peroxide *via* peroxidation of the "tertiary" carbon atom,[2] the substitution of 2,4-dihydroxypentane for



$$R_2CHOH \xrightarrow{R\cdot} R_2COH \xrightarrow{O_2} R_2\overset{OO\cdot}{C}OH \longrightarrow R_2\overset{OOH}{C}OH \rightleftharpoons R_2C{=}O + H_2O_2 \quad (1)$$

2,4-dimethylpentane in an autoxidation system could be expected to give a substantial yield of 2,4-pentanedione and hydrogen peroxide. The results are notably otherwise.

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[1] F. F. Rust, *J. Am. Chem. Soc.*, **79**, 4000 (1957).

[2] F. F. Rust (to Shell Development Co.), U. S. Patent 2,871,104 (January 27, 1959).