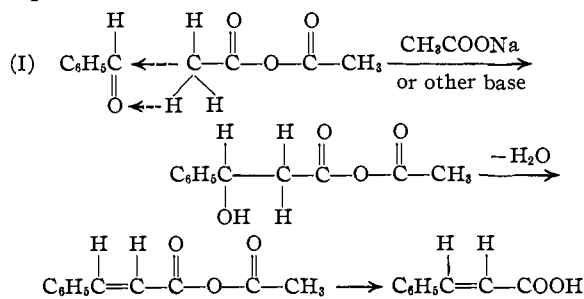


[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF DUKE UNIVERSITY]

Condensations Brought about by Bases. VI. The Mechanism of the Perkin Synthesis¹

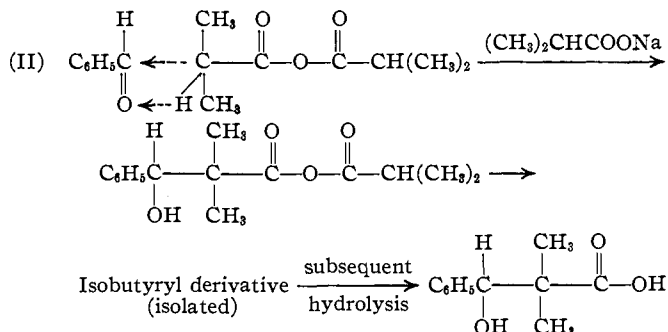
BY CHARLES R. HAUSER AND DAVID S. BRESLOW

The Perkin synthesis of unsaturated acids from aromatic aldehydes, aliphatic anhydrides and salts is generally considered to involve the intermediate formation of an "aldol" which loses water to give the unsaturated acid. Most current texts of organic chemistry represent the "aldolization" between the salt and the aldehyde, but, as shown in a previous paper of this series,² the condensation undoubtedly takes place between the anhydride and the aldehyde, the salt functioning as a basic catalyst. The "aldolization" of acetic anhydride with benzaldehyde, in the presence of sodium acetate or other base, followed by the elimination of water, may be represented as follows

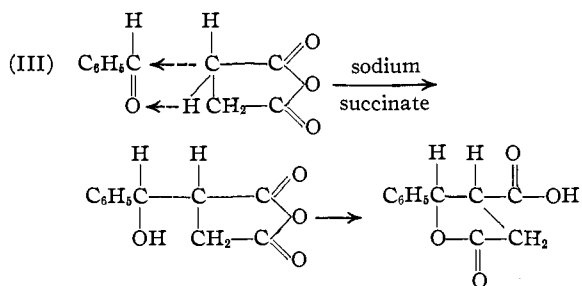


The mixed anhydride, cinnamic-acetic anhydride, that is formed by elimination of water is probably only partly converted to cinnamic acid or its salt during the reaction, but subsequent treatment converts the remainder of the anhydride to cinnamic acid, which is the product isolated in the experiment.

Although the intermediate "aldol" represented in (I) has not been isolated, Fittig³ reported that an "aldol," incapable of losing water, has been obtained from benzaldehyde, isobutyric anhydride and sodium isobutyrate. In this experiment the isobutyryl derivative of the "aldol" was isolated from the reaction mixture, the true "aldol," β -phenyl- β -hydroxypivalic acid, being obtained on subsequent hydrolysis. The reactions may be represented⁴



Fittig⁵ showed also that benzaldehyde, succinic anhydride (or acetic anhydride) and sodium succinate give phenylparaconic lactone; this product is formed presumably through the intermediate formation of the "aldol." The reactions may be represented⁴



Recently, Müller⁶ has carried out a similar reaction with homophthalic anhydride. This anhydride was first converted into its enolate by means of sodium triphenylmethyl, and the enolate condensed with benzaldehyde.

Although Müller obtained an "aldol" (isolated as the lactone) from homophthalic anhydride and benzaldehyde, he and his co-workers⁷ were unable to duplicate Fittig's experiment with benzaldehyde, isobutyric anhydride and sodium isobutyrate (II). These workers report also that an attempt to produce an "aldol" from benzaldehyde and ethyl isobutyrate using sodium triphenylmethyl as condensing agent likewise failed, although benzaldehyde and ethyl acetate in the presence of this condensing agent readily gave ethyl cinnamate.

(1) This work was supported in part by a grant from the Duke University Research Council.

(2) Breslow and Hauser, *THIS JOURNAL*, **61**, 786 (1939).

(3) Fittig and Ott, *Ann.*, **227**, 61 (1885).

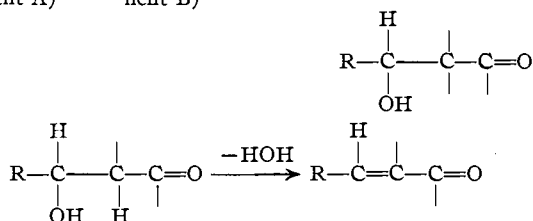
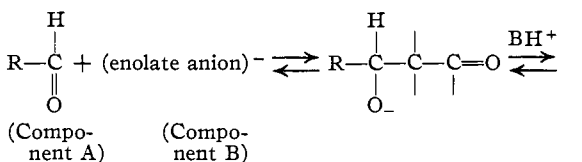
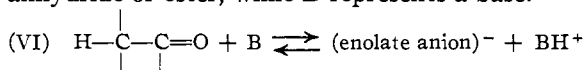
(4) Fittig represented the condensation between the salt and the aldehyde.

(5) Fittig, *Ann.*, **208**, 121 (1881); Fittig and Jayne, *ibid.*, **216**, 100 (1882).

(6) Müller, *ibid.*, **491**, 251 (1931).

(7) Müller, Gawlick and Kreutzmann, *ibid.*, **515**, 97 (1934).

strength of the base¹³ used and upon the "activation" of the anhydride² indicates that in these cases, also, enolates are formed as intermediates. The more complete mechanism¹⁴ for the Perkin type of condensation may be illustrated by the following series of ionic equations (VI), in which the system $\text{H}-\overset{\text{H}}{\underset{|}{\text{C}}}-\overset{\text{H}}{\underset{|}{\text{C}}}-\text{C}=\text{O}$ represents an enolizable anhydride or ester, while B represents a base.



The first equation represents an acid-base reaction, the extent of which (*i. e.*, the equilibrium) depends upon the strength of base B and upon the activity of the hydrogen on the α -carbon atom of the system $\text{H}-\overset{\text{H}}{\underset{|}{\text{C}}}-\overset{\text{H}}{\underset{|}{\text{C}}}-\text{C}=\text{O}$. This reaction, in which an enolate anion is formed, may be considered to involve the removal of the proton from the system $\text{H}-\overset{\text{H}}{\underset{|}{\text{C}}}-\overset{\text{H}}{\underset{|}{\text{C}}}-\text{C}=\text{O}$, accompanied by the formation of a resonance system. The two resonance forms of the enolate anion are represented by (a) $:\overset{\ominus}{\text{C}}-\overset{\text{H}}{\underset{|}{\text{C}}}-\overset{\text{H}}{\underset{|}{\text{C}}}-\text{C}=\text{O}:$ and (b) $\overset{\text{H}}{\underset{|}{\text{C}}}=\overset{\text{H}}{\underset{|}{\text{C}}}-\overset{\ominus}{\text{O}}-\text{C}=\text{O}$.

The second equation represents the condensation of the enolate anion (component B) with component A. In this reaction, resonance form (a) of the enolate anion may be considered to condense with the carbonyl group of component A to form first an anion in which the negative charge is located on the oxygen atom; this anion takes up a proton from the medium forming the true "aldol." If the "aldol" contains a hydrogen on the α -carbon atom, water can be eliminated to give a cinnamic acid derivative, as represented in the last equation.

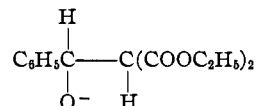
The equations given above illustrating the

(13) Kalnin, *Helv. Chim. Acta*, **11**, 981 (1928).

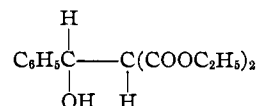
(14) See Arndt and Eistert, *Ber.*, **69**, 2386 (1936).

mechanism for the Perkin type of synthesis also represent the general course of the Knoevenagel condensation,¹⁵ although the detailed mechanisms for the two types of syntheses may be different. In the Knoevenagel condensation, component B would be a methylene compound, such as malonic ester, acetoacetic ester or cyanoacetic ester, while component A could be an aldehyde or ketone. These and other types of condensation will be discussed further in a later paper. Before closing this paper, however, we wish to discuss briefly Müller's result^{7,14} with the pure sodium enolate of ethyl malonate and benzaldehyde. He reported that, although ethyl malonate and benzaldehyde condense in the presence of a basic catalyst, the pure enolate of ethyl malonate, when heated with benzaldehyde (in benzene), does not condense; instead, the benzaldehyde undergoes the Cannizzaro reaction. We have found that the pure sodium enolate of ethyl malonate, when heated with benzaldehyde, gives, in addition to Cannizzaro reaction products, a small yield of the condensation product, ethyl benzalmalonate. We also obtained generally an appreciable amount of high-boiling oil, which appeared to be a Michael condensation product. The latter should be expected, since unchanged sodium ethyl malonate could condense easily with the ethyl benzalmalonate first formed.

On the basis of the above equations (VI), the condensation of an enolate with benzaldehyde could not proceed to completion under ordinary conditions in the absence of a proton donor. The condensation of the enolate of ethyl malonate with benzaldehyde should give the anion (C)



but this could either not eliminate hydroxyl to form ethyl benzalmalonate, or eliminate hydroxyl only with difficulty. If there is a proton donor present in the medium, however, (C) could take up a proton to form the true aldol (D)



which could eliminate water easily forming ethyl benzalmalonate. Certainly, (D) should form ethyl benzalmalonate more easily than (C).

(15) See Cope, *THIS JOURNAL*, **59**, 2327 (1937); also see ref. 14.

It is obvious from equations (VI) that, in the reaction of ethyl malonate with benzaldehyde in the presence of basic catalysts B, a proton donor BH^+ is formed in the formation of the enolate; consequently, the reaction can proceed to completion giving ethyl benzalmalonate. On the other hand, when the enolate of ethyl malonate (formed, for example, from sodium and the ester) is allowed to react with benzaldehyde in the *absence* of a proton donor, the anion (C) is formed, but, as pointed out above, the reaction cannot proceed to completion. The fact that considerable amounts of Cannizzaro reaction products are obtained in the latter reaction is not surprising, since (C) is in equilibrium with the starting materials, the enolate of ethyl malonate and benzaldehyde. It should be noted that only after the formation of Cannizzaro products (proton donors) can (C) take up a proton forming (D), which can eliminate water to give ethyl benzalmalonate.

Experimental¹⁶

Preparation and Purification of Materials.—Sodium isobutyrate was prepared by adding a slight excess of isobutyric acid to a solution of sodium hydroxide in water and evaporating the mixture to dryness. The salt was dried for four hours at 180°.

Isobutyric anhydride was prepared according to the method of Fittig and Ott.³ Anhydrous sodium isobutyrate (108 g., 1.0 mole) was placed in a 500-cc. Claisen flask and 96 g. (0.9 mole) of isobutyryl chloride (Eastman) added. There was a vigorous evolution of heat and the flask had to be cooled slightly to prevent loss of the chloride. After the reaction mixture had cooled to room temperature, it was distilled with a constantly moving free flame up to 190°. The distillate was then redistilled using a short Widmer column. The fraction boiling at 175–185° (uncorrected) was collected and redistilled; b. p. 183–186°, yield 62 g. (44%).

Ethyl isobutyrate (Eastman) was washed with 10% sodium carbonate solution, dried over Drierite, and distilled; b. p. 110–111°.

Ethyl acetate was washed thoroughly with a 10% sodium carbonate solution, then with water until neutral, and dried over calcium chloride for several days. It was then shaken for an hour with a fresh supply of the anhydrous salt, filtered and distilled; b. p. 76.7–77.0°.

Sodium triphenylmethyl solution was prepared from 63 g. (0.226 mole) of triphenylchloromethane and 1500 g. of a 1% sodium amalgam according to the directions of Hauser and Renfrow.¹⁷

Benzaldehyde was purified as previously described.²

Ethyl malonate was washed with 10% sodium carbonate solution, dried over calcium chloride and distilled under reduced pressure; b. p. 95–97° at 20 mm.

Condensation of Benzaldehyde, Isobutyric Anhydride and Sodium Isobutyrate.—This experiment was carried out essentially as described by Fittig and Ott.³ Isobutyric anhydride (31.6 g., 0.20 mole), sodium isobutyrate (22.0 g., 0.20 mole) and benzaldehyde (21.2 g., 0.20 mole) were placed in a 200-cc. round-bottomed flask connected to a reflux condenser to which was attached a drying tube. Under an atmosphere of dry nitrogen (purified by passing through an alkaline pyrogallol solution), the mixture was heated for eight hours on a boiling water-bath. The reaction mixture was a pale yellow liquid when hot and solid when cold. After adding water, the reaction mixture was made alkaline with sodium carbonate and extracted with ether. The treatment of the carbonate solution (A) is described below. The ether solution was evaporated and the residue steam-distilled long enough to remove any benzaldehyde (about 500 cc. of distillate was collected). The oily material that did not steam-distill was separated from the water present (by an ether extraction) and refluxed an hour and a half with 100 cc. of 33% sodium hydroxide solution. The alkaline solution was acidified with dilute sulfuric acid, chilled and the precipitate filtered off. The filtrate (acidic solution) yielded nothing but isobutyric acid on extraction with ether. The solid in the funnel, after recrystallization from hot water, gave 7.41 g. of phenylhydroxypivalic acid (α,α -dimethyl- β -phenyl- β -hydroxypropionic acid), melting at 132.5–134.5°. A mixed melting point with an authentic sample of this substance (m. p. 133–134°) was the same.

The original carbonate solution (A) was acidified and the oil that separated extracted with ether. The oil obtained on evaporation of the ether could not be made to crystallize. Fittig stated that the oil, presumably the isobutyryl derivative of phenylhydroxypivalic acid, was difficult to crystallize. The oil was purified as follows. An ether solution of the oil was shaken with water to remove alcohol and dried over Drierite. On evaporation of the ether, 7.3 g. of the isobutyryl derivative was obtained. Calculated as phenylhydroxypivalic acid, the yield was 5.4 g., which, added to the phenylhydroxypivalic acid obtained as described above, gave a total yield of 12.8 g. or 33% of the theoretical amount (based on the benzaldehyde used).

From these results it would appear that no appreciable amount of hydroxy compound was present after the completion of the reaction. Apparently the hydroxy compound (phenylhydroxypivalic acid) was present only as the isobutyryl derivative, both in the form of the free acid and in the form of the mixed anhydride.

Condensation of Benzaldehyde with Enolate of Ethyl Isobutyrate.—Ethyl isobutyrate (20.5 g., 0.177 mole) was added to a sodium triphenylmethyl solution prepared as described above, the mixture shaken and allowed to stand at room temperature. After five minutes, 18.8 g. (0.177 mole) of benzaldehyde was added. The mixture immediately turned dark brown and evolved some heat. After standing twenty minutes longer, the mixture was acidified with 20 cc. of glacial acetic acid in 75 cc. of ether. Sufficient water was added to dissolve the precipitate of sodium acetate and the ether layer separated. The ether solution was washed with sodium carbonate until alkaline and dried over Drierite. After evaporating the ether,

(16) Unless otherwise stated all melting and boiling points are corrected.

(17) Hauser and Renfrow, *THIS JOURNAL*, **59**, 1825 (1937).

the residue was distilled under reduced pressure, collecting all material boiling up to 195° at 15 mm. The distillate was distilled at atmospheric pressure through a short Widmer column, 4.9 g. (23.9%) of ethyl isobutyrate, b. p. 108–112°, being recovered. The residue was then fractionated at 12–13 mm. The first fraction (6.8 g.), boiling up to 115°, apparently consisted mostly of benzaldehyde. The second fraction (12.5 g.), boiling at 155–165° (most of it came over at 155–156°), was shown to consist mostly of ethyl β -phenyl- β -hydroxypivalate. This ester is reported¹⁸ as boiling at 155–156° at 11 mm. A small portion (1.62 g.) of the crude ester (b. p. 155–165°) was dissolved in 10 cc. of alcohol and the solution chilled. A small precipitate of triphenylmethane formed. The clear solution was decanted from the triphenylmethane and mixed with 10 cc. of ligroin (30–60°). On cooling the mixture, a precipitate of the ester (ethyl phenylhydroxypivalate) separated. The liquid was decanted and the ester dried *in vacuo*. It melted at 39–40°. The melting point of ethyl phenylhydroxypivalate is reported¹⁹ as being 39°. The yield obtained was 1.15 g., which corresponds to a total yield of 8.87 g. (29.5% based on ethyl isobutyrate used minus that recovered).

The identity of the ester was further established by hydrolysis to the corresponding acid. A sample (2.5 g.) of the crude ester was refluxed with 25 cc. of 33% sodium hydroxide for two and a half hours on a boiling water-bath. The solution solidified on cooling to a yellow solid. Water was added, the solution acidified with dilute sulfuric acid and the mixture cooled. The precipitate was filtered off and recrystallized from an alcohol-water mixture. A little triphenylmethane separated first; this was filtered off, water added and the solution cooled. Phenylhydroxypivalic acid (0.82 g.), melting at 133–134°, was obtained. This agrees with the melting point recorded in the literature.¹⁸ Neutral equivalent found: 194.7; neutral equivalent calculated for $C_{11}H_{14}O_3$, 194.1.

Condensation of Benzaldehyde with Enolate of Ethyl Acetate.—In this experiment a mixture of 15.6 g. (0.177 mole) of ethyl acetate and 18.8 g. (0.177 mole) of benzaldehyde in 20 cc. of ether was added to the sodium triphenylmethyl solution (prepared as described above). The solution boiled vigorously, and within less than a minute the deep red color of sodium triphenylmethyl changed to orange. After standing for one minute at approximately 35° (boiling point of ether), 20 cc. of glacial acetic acid in 75 cc. of ether was added to the mixture. The mixture was made alkaline with dilute aqueous sodium carbonate, the ether layer separated and dried over Drierite. Acidification of the aqueous carbonate solution gave approximately 0.6 g. of solid material (m. p. 102–111°), which was presumably a mixture of cinnamic and β -phenyl- β -hydroxypropionic acids. The dried ether solution was evaporated at room temperature to a small volume, the remaining solution cooled and the precipitate of triphenylmethane filtered off. The filtrate was evaporated on a water-bath to remove the remainder of the ether. The residue was fractionated at 6–7 mm. Very little material passed over below 110°, indicating that little, if any, ethyl acetoacetate was present. The fraction boiling at

110–160° at 6–7 mm. was collected. It weighed 12.5 g. and presumably consisted mainly of ethyl phenylhydroxypropionate. Apparently a little of the latter was decomposed during the distillation to give a little ethyl cinnamate. The hydroxy ester was hydrolyzed in the following manner. A portion (1.82 g.) of the distillate (b. p. 110–160° at 6–7 mm.) was dissolved in 50 cc. of 1 *N* 50% alcoholic sodium hydroxide. On standing at room temperature, a small precipitate formed after an hour and the mixture turned yellow. More alcohol was added to the mixture at the end of twenty-four hours in an attempt to precipitate the sodium salt of the hydroxy acid, but no appreciable amount was obtained. The mixture was acidified with hydrochloric acid and evaporated at room temperature in an air draft. The residue was treated with absolute alcohol and the sodium chloride filtered off. On evaporating the alcohol at room temperature, 1.55 g. of crude hydroxy acid was obtained. In order to separate the small amount of cinnamic acid present, the material was shaken with 30 cc. of water at room temperature and filtered. The precipitate of impure cinnamic acid was dissolved in ether, the ether extracted with sodium carbonate and the alkaline solution acidified; in this way 0.11 g. of cinnamic acid, m. p. 133–134°, was obtained. The aqueous solution of the hydroxy acid was evaporated at room temperature, 1.12 g. of solid material (m. p. 70–80°) being obtained. Great difficulty was experienced in recrystallization of the hydroxy acid because of its extreme solubility in water. After two recrystallizations from warm water, 0.63 g., melting at 92–93.5°, of β -phenyl- β -hydroxypropionic acid was isolated. The melting points recorded in the literature for this compound range from 92 to 96°. Neutral equivalent found, 167.7; neutral equivalent calculated for $C_9H_{10}O_3$, 166.1.

The total yield of ethyl β -phenyl- β -hydroxypropionate based on the crude hydroxy acid (m. p. 70–80°) isolated was 9.0 g. or 26.2% of the theoretical amount.

Condensation of the Enolate of Ethyl Malonate with Benzaldehyde.—The enolate was prepared by treating 24.0 g. (0.15 mole) of ethyl malonate in 200 cc. of benzene with 3.45 g. (0.15 mole) of sodium wire. On refluxing for one hour, a copious white precipitate of sodium ethyl malonate was formed. To the enolate was added 15.9 g. (0.15 mole) of benzaldehyde. The mixture turned brown and most of the sodium salt went into solution. After refluxing for eight hours, the mixture was cooled and acidified with glacial acetic acid. The mixture was then extracted with sodium carbonate until alkaline and dried over Drierite. The alkaline solution yielded no precipitate on acidification. The solvent was distilled off from the dried benzene solution and the residue distilled at 8–9 mm. The first fraction, boiling up to 100°, yielded 1.12 g. (7%) of benzaldehyde as the sodium bisulfite addition product. The second fraction (approximately 10 g.), boiling at 100–200°, was hydrolyzed by refluxing for three hours with a mixture of 13 g. of barium hydroxide and 100 cc. of water. A yellow precipitate was formed. The mixture was acidified with hydrochloric acid and the cloudy solution resulting extracted with ether. The ether solution was evaporated and the oily residue remaining treated

(18) Blaise and Herman, *Ann. Chim. Phys.*, [8] **23**, 532 (1911).

(19) Dain, *J. Russ. Phys.-Chem. Soc.*, **26**, 162 (1896).

(20) Beilstein, "Handbuch der organischen Chemie," 4th ed., 1927, Vol. X, p. 249.

with a small amount of cold benzene. The precipitate formed was filtered off, and, after another benzene treatment, 2.16 g. of benzalmalonic acid, m. p. 187–192° (with decomposition), was obtained.²¹ This compound was not further purified because of its high solubility in water and its tendency to decompose.

The benzene solutions were evaporated, the oily residue treated with dilute sodium carbonate and the alkaline solution extracted with ether. The alkaline solution yielded 0.5 g. of cinnamic acid, m. p. 130–132°, on acidification and subsequent recrystallization of the precipitate from hot water. The total yield of ethyl benzalmalonate, based on both the crude benzalmalonic and cinnamic acids, was 3.6 g. (9.7% of calcd.). It is probable that more ethyl benzalmalonate was formed in the reaction but was decomposed to benzaldehyde and malonic acid during the hydrolysis.²¹

This experiment was repeated several times under varying conditions, and in every case some condensation apparently occurred, although it was not always possible to isolate the products. In addition to ethyl benzalmalonate, a high-boiling oil generally was obtained in considerable amount. This was presumably a Michael condensation product, formed by the reaction of unchanged sodium ethyl malonate with ethyl benzalmalonate. In every case considerable amounts of Cannizzaro reaction prod-

(21) Claisen and Crismer [*Ann.*, **218**, 136 (1883)] give 195–196° as the melting point of this compound.

ucts, benzyl alcohol and benzoic acid, were obtained, as previously reported by Müller and co-workers.⁷

Summary

1. Contrary to the result of other workers, we have confirmed Fittig's original result with benzaldehyde, isobutyric anhydride and sodium isobutyrate, in which the isobutyryl derivative of the "aldol" is formed.

2. Ethyl isobutyrate (as enolate) has been condensed with benzaldehyde by means of sodium triphenylmethyl to form ethyl phenylhydroxy-pivalate.

3. The condensation of ethyl acetate with benzaldehyde, brought about by sodium triphenylmethyl, has been arrested at the "aldol" stage, and ethyl phenylhydroxypropionate isolated from the reaction mixture.

4. It has been found that the sodium enolate of ethyl malonate condenses with benzaldehyde in the presence of a proton donor.

5. The mechanism of the Perkin type of condensation is discussed.

DURHAM, N. C.

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[CONTRIBUTION FROM THE LABORATORY OF THE UNION PRODUCING COMPANY]

The Theory of Absolute Reaction Rates and the Polymerization of Ethylene

BY FRANCIS P. JAHN

It is well known that the simple collision theory of reaction kinetics is not in accord with the rate of the homogeneous thermal polymerization of ethylene.¹ Pease¹ has shown that the rate calculated from the collision number and the experimental energy of activation is about two thousand times greater than the experimental rate. Rice and Gershinowitz² have accounted for the rates of this and three other well-known bimolecular association reactions by a method which is essentially the same in principle as that used in this paper. It seemed worth while, however, to emphasize by a set of calculations that the rate of the ethylene polymerization may be satisfactorily predicted over the experimental temperature range by means of the somewhat more straightforward assumptions of the theory of absolute reaction rates as set forth by Eyring.³ Wynne-Jones and Eyring⁴ have used the same

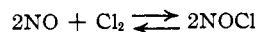
method in calculating a steric factor of 10^{-6} for the formation of cyclopentane and methyl radical from *n*-hexyl radical, thus justifying the assignment of F. O. Rice.

The expression for the rate constant of a reaction is, in the thermodynamic form⁴

$$K = \kappa \frac{kT}{h} e^{\Delta S^*/R} e^{-\Delta H^*/RT} \quad (1)$$

where κ is the transmission coefficient and ΔS^* and ΔH^* are, respectively, the entropy and heat of activation.

Welinsky and Taylor in a study of the rates of the nitric oxide-chlorine combination and the nitrosyl chloride decomposition have shown that the difference between the entropies of activation of the forward and reverse reactions at a given temperature is equal to the standard entropy increase for the equilibrium



when this entropy increase is evaluated for the standard state corresponding to the concentration

(1) Pease, *THIS JOURNAL*, **53**, 613 (1931).

(2) O. K. Rice and Gershinowitz, *J. Chem. Phys.*, **2**, 853 (1934).

(3) Eyring, *ibid.*, **3**, 107 (1935).

(4) Wynne-Jones and Eyring, *ibid.*, **3**, 492 (1935).