A STUDY OF THE MECHANISM OF CERTAIN CHEMICAL REACTIONS—I

THE MECHANISM OF THE LEUCKART–WALLACH REACTION AND OF THE REDUCTION OF SCHIFF BASES BY FORMIC ACID

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Abstract—The reduction of benzylidene-bis-piperidine by formic acid in organic solvents has been investigated. This is a chain reaction that depends on the nature of the solvent. The rate of the reaction is decreased by the addition of hydroquinone and increased when diphenylamine is added. In the latter case, an intense transient orange-greenish colour appears. These facts indicate that reduction takes place, according to the free-radical mechanism. As this reaction is closely related to the Leuckart–Wallach reaction and to the reduction of imines by formic acid, the hypothesis has been advanced that these reactions occur through the intermediate formation of esters of α-aminoalcohols and formic acid. These esters suffer decarboxylation according to the radical (crypto-radical or free-radical) mechanism. This hypothesis is in contradiction to the common opinion on the ionic mechanism postulated for these reactions.

ALTHOUGH the reducing properties of formic acid have been known for a long time no convincing explanation of the reduction mechanism involved has as yet appeared.

Formic acid has been used in the reduction of a number of organic compounds and, in particular, to the reductive amination of aldehydes and ketones, using the method of Leuckart and Wallach,[1] as well as to the reductive methylation of amines, according to the method of Clarke.[2] Recently, attention has been paid to the formic acid reduction of compounds such as pyridine, quinoline,[3] Schiff's bases,[4–5] enamines,[6] hydrazones and azines.[7]

It is believed that the mechanism involved in the majority of these reductions is essentially the same. This particularly concerns the Leuckart–Wallach reaction, and the reduction of Schiff bases as well as of enamines. According to existing opinion,[8] the Leuckart–Wallach reaction, which may be represented by the equation

$$\diagup\!\!\!\diagdown C{=}O + HN{\diagup\diagdown} \quad \xrightarrow{\text{HCOOH}} \quad \diagup\!\!\!\diagdown CH{-}N{\diagup\diagdown} + CO_2 + H_2O,$$
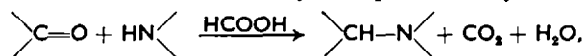
results in the formation of α-aminoalcohols or imines as intermediate products. In the above equation the carbonyl compound may be an aldehyde or ketone, the amine constituent a formate or formyl derivative either of ammonia or of a primary or secondary amine.

[1] R. Leuckart, *Ber. Dtsch. Chem. Ges.* **18**, 2341 (1885); O. Wallach, *Liebig's Ann.* **343**, 54 (1905).
[2] H. T. Clarke, H. B. Gillespie and S. J. Weisshaus, *J. Amer. Chem. Soc.* **55**, 4571 (1933).
[3] A. N. Kost and L. G. Judin, *Zh. Obshch. Khim.* **25**, 1947 (1955).
[4] E. R. Alexander and R. B. Wildman, *J. Amer. Chem. Soc.* **70**, 1187 (1948).
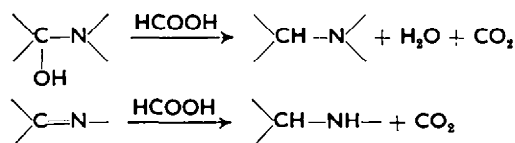[5] R. Baltzly and O. Kauder, *J. Org. Chem.* **16**, 173 (1951).
[6] P. L. de Benneville and J. H. Macartney, *J. Amer. Chem. Soc.* **72**, 3073 (1950).
[7] A. N. Kost and J. J. Grandberg, *Zh. Obshch. Khim.* **25**, 1719 (1955).
[8] M. L. Moore, *Organic Reactions* Vol. V; p. 301. New York (1948).

The intermediate α-aminoalcohols and imines are transformed into the corresponding amines under the influence of formic acid and carbon dioxide is evolved.

$$\underset{OH}{\overset{\displaystyle >\!\!C\!-\!N<}{|}} \quad \xrightarrow{\text{HCOOH}} \quad >\!\!CH\!-\!N< + H_2O + CO_2$$

$$>\!\!C\!-\!N\!-\quad \xrightarrow{\text{HCOOH}} \quad >\!\!CH\!-\!NH\!-\! + CO_2$$

Although the α-aminoalcohols are not stable compounds, their intermediate formation in various reactions, is generally accepted (they are assumed—among others—to be the intermediate products during the formation of imines), and a direct reaction between imines and formic acid, leading to the formation of reduction products, has been demonstrated in a number of papers.[5,9,10]

Two hypotheses are known with respect to the reduction by formic acid of imines or of intermediate α-aminoalcohols. According to the opinion of several authors[11] the α-aminoalcohols and formic acid could form esters which suffer decarboxylation on heating. This opinion lacks, however, experimental evidence and has been replaced by an ionic mechanism involving the reduction of imines and α-aminoalcohols by formic acid. The latter mechanism consists of the translocation of an hydride ion in the reduction between an ammonium-carbonium cation, derived either from an imine or an α-aminoalcohol, and a formate anion.[12] The ammonium-carbonium cation results from the attachment of the proton either to the imine nitrogen or to the hydroxylic group of an α-aminoalcohol. In the latter case one molecule of water is formed.

The mechanism of the Leuckart–Wallach reaction and of the reduction of enamines by formic acid has similarly been explained.[13-15] According to the mechanism suggested this ammonium-carbonium cation with resonance hybrid structure forms

$$>\!\!C\!=\!\overset{+}{N}<\quad\longleftrightarrow\quad >\!\!\underset{+}{C}\cdots\overset{-}{N}<$$
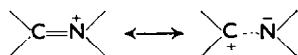
with the formate anion an active complex which decomposes with evolution of carbon dioxide:

$$>\!\!\overset{+}{C}\!-\!N< \quad\longrightarrow\quad >\!\!CH\!-\!N< + CO_2$$
$$\underset{\displaystyle \underset{O \diagdown \diagup O}{C}}{\overset{|}{\underset{|}{H}}}$$
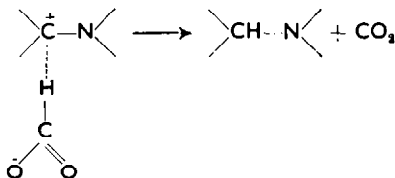
The hydride ion could thus undergo a direct transfer, analogous for example, to the reduction of ketones by the Merwein-Poondorf method.

[9] Z. Eckstein and A. Lukasiewicz, *Bull. Acad. Polon. Sci.* **7**, 789 (1959).
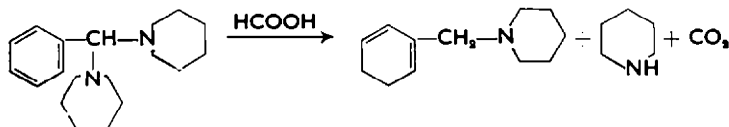[10] A. Lukasiewicz and Z. Eckstein, *Rocz. Chem.* in press.
[11] H. Emde, *Apoth. Ztg.* **44**, 1125 (1929); V. J. Webbers and W. F. Bruce, *J. Amer. Chem. Soc.* **70**, 1422 (1948); P. A. S. Smith and A. J. MacDonald, *Ibid.* **72**, 1037 (1950).
[12] E. Staple and E. Wagner, *J. Org. Chem.* **14**, 559 (1949).
[13] D. S. Noyce and F. W. Bachelor, *J. Amer. Chem. Soc.* **74**, 4577 (1952).
[14] R. R. Sauers, *J. Amer. Chem. Soc.* **80**, 4721 (1958).
[15] N. J. Leonard and R. R. Sauers, *J. Amer. Chem. Soc.* **79**, 6210 (1957).

It was found that both the evolution of carbon dioxide and the formation of the reduction product occur in equivalent quantities[12].

An identical mechanism is proposed for the reduction of enamines:

Leonard and Sauers;[15] while investigating the reduction of enamines by deuterium-labelled formic acid (DCOOH), have found that the hydrogen (deuterium) associated with the carbon of the formic acid suffers association with the α-carbon of the enamine. It is stressed that formate anions favourably influence the reduction of Schiff bases[4] and this fact forms the main argument supporting the ionic mechanism of the formic acid reduction of imines and α-amino-alcohols. An apparent influence of formate anions, as well as anions of other organic acids, on the reduction of Schiff bases—the derivatives of ethylenediamine—has also been observed[9]. The same effect was also noted during the reaction of N,N-diformylethylenediamine with aromatic aldehydes in a formic acid medium.[16] In the previous paper[10] it was also shown that during the reaction between Schiff's bases and formic acid, the decomposition of the base takes place in addition to the reduction of the imine bond, subsequently an aldehyde and formyl derivatives of the amine can form probably through N-formyl-α-amino-alcohols. At the same time the formate anions (or the anions of other organic acids) by retarding these reactions bring about an increase in the rate of reduction. Therefore, the reduction of Schiff's bases excludes the argument that this influence supports the ionic mechanism of this reaction. A hypothesis was formerly advanced[10] that the decomposition of the base into the aldehyde and N-formylamine occurs through the ester of α-aminoalcohol:

The formation of esters of α-aminoalcohols is indicated by the behaviour of Schiff's bases with respect to anhydrous formic acid in some organic solvents (with a stoichiometric quantity of the acid the bases form a homogeneous mixture in slightly polar solvents; with an excess of the acid added an oily phase forms which disappears on addition of further quantities of the base. All these facts indicate the possibility of an ester mechanism for the Leuckart–Wallach reaction and the reduction of Schiff bases by formic acid.

For the present investigation use has been made of the work by Staple and Wagner[12] on the high reactivity of benzylidene-bis-piperidine towards formic acid. The former compound reacts spontaneously with anhydrous formic acid to form N-benzyl-piperidine.

[16] A. Lukasiewicz and Z. Eckstein, *Bull. Acad. Polon. Sci.* **7**, 797 (1959).

In accordance with the ionic mechanism, this would occur via an ammonium-carbonium cation (I).

Similar reactivity is indicated by the ammonium-carbonium cation (II), formed owing to the association of a proton with dibenzal-ethylenediamine, because the structures of these cations are related.
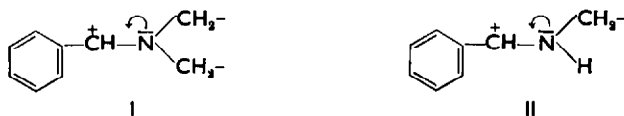
It has been shown, that the rate of reaction between dibenzal-ethylenediamine and formic acid is very slow at room temperature, and this could be an argument against the ionic mechanism for the reaction.

The reaction of benzylidene-bis-piperidine and formic acid has been investigated under anhydrous conditions and with a number of organic solvents. The rate of reduction was determined by the volume of carbon dioxide evolved. The reaction was carried out at room temperature, and at 65°, using two moles of formic acid and one mole of benzylidene-bis-piperidine. The final yield was estimated as N-benzyl-piperidine picrate (Table 2).

The rate of reduction in an organic medium depends on the type of solvent used. At room temperature, the reaction occurs rapidly in bromoform, chloroform, aceto-phenone but slows down in benzene, carbon tetrachloride, ethyl acetate and in tertiary alcohols, but it does not take place in primary or secondary alcohols, cyclo-hexanone and in alkyl formates (Table 1, Fig. 1). The reaction does, however, take place in all these solvents when the temperature is raised (Table 3). The reduction rate is also affected by the concentration of the reagents (Fig. 2) and by addition of large amounts of diphenylamine and hydroquinone. The hydroquinone if soluble in the reaction medium retards the rate (Fig. 3), but if it is insoluble in the solvent used (e.g., in benzene), then brown spots characteristic for quinhydrone appear. Diphenylamine added e.g., in benzene, causes an appreciable increase in the reduction rate (Fig. 4) producing in the initial stages an intense orange-green colour which becomes more green before disappearing. With two moles of anhydrous formic acid benzylidene-bis-piperidine forms a homogeneous mixture in nonpolar organic solvents, e.g., in benzene, but further addition of formic acid, e.g., 3–4 moles causes precipitation of a heavy oil which, in contrast with the homogeneous mixture, is stable at room temperature. Addition of benzylidene-bis-piperidine results in disappearance of the oil and simultaneous evolution of carbon dioxide.

As the rate of reduction depends on the solvent used it may be concluded that a chain reaction is taking place and this is supported by the fact that the reduction occurs rapidly in some solvents at room temperature (e.g., in chloroform or bromoform the reduction is completed within 1 minute—Fig. 1).

The effect of the solvent cannot be explained by solvent polarity, though a decrease in the reaction rate could be observed in such solvents as are capable of solvating

TABLE 1. SOLVENTS ARRANGED (DECREASING RATE OF THE REACTION)[*]

$$C_6H_5CH(NC_5H_{10})_2 \xrightarrow[\text{solvent}]{2HCOOH} C_6H_5CH_2(NC_5H_{10}) + CO_2 + C_5H_{10}NH.HCOOH$$
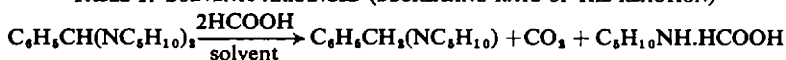
Nr	Solvent	Yields (volumes of CO_2) of the reaction measured as per cents of the theoretical yield, at various time intervals.		
		1 min	5 min	20 min
1	Bromoform	70·0	79·0	80·0
2	Chloroform	62·0	67·0	73·0
3	Acetophenone	30·0	56·0	62·0
4	Benzene	20·0	52·5	64·0
5	Ethyl acetate	21·5	39·5	46·0
6	Carbon tetrachloride	9·0	43·5	62·5
7	Amyl alcohol, tertiary	10·0	28·0	42·0
8	Butyl alcohol, tertiary	10·0	28·0	41·0
9	Butanol-2	1·0	3·5	11·0
10	Butanol-1	—	—	5·0
11	Cyclohexanone	—	3·5	6·0
12	2-Methylcyclohexanol	—	1·5	5·0
13	Isobutyl formate	—	—	3·5
14	Ethyl formate	—	—	—

[*] 2·5 mmoles of benzylidene-bis-piperidine in 5 ml solvent, at 25°.

TABLE 2. A COMPARISON OF THE YIELDS OF THE REACTION ESTIMATED EITHER AS THE VOLUME OF CARBON DIOXIDE EVOLVED OR THE AMOUNT OF N-BENZYLPIPERIDINE PICRATE

Nr	Solvent	Yields as per cents of the theoretical yield for	
		CO_2	Picrate
1	Chloroform	73	65
2	Acetophenone	62	60
3	Benzene	64	61
4	Carbon tetrachloride	64	60
5	Amyl alcohol, tertiary	49	43
6	Butyl, tertiary	44	42

TABLE 3. YIELDS OF THE REACTION IN VARIOUS SOLVENTS AT 65°

Nr	Solvent	Yields of N-benzylpiperidine as per cents of the theoretical yield (reaction time = 1 hr)
1	Butanol-2	60
2	Butanol-1	67
3	Isobutyl formate	55
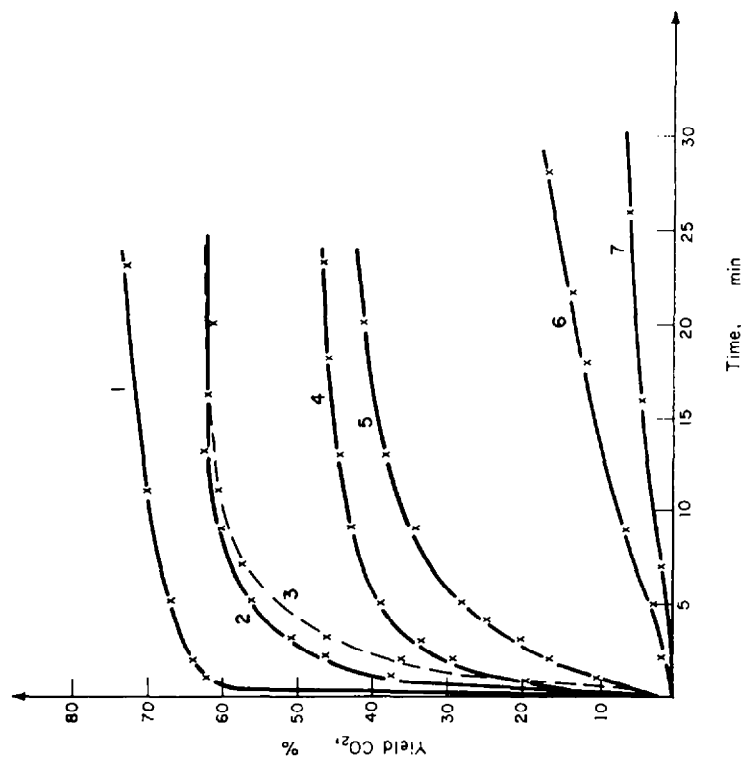
FIG. 1. Effect of solvent on reaction* rate.

2·5 mM of benzylidene-bis-piperidine in 5 ml solvent, temp — 25°, curve 1—chloroform, 2—acetophenone, 3—benzene 4—ethyl acetate, 5—butyl alcohol, tertiary, 6—butanol-2, 7—isobutanol-1.
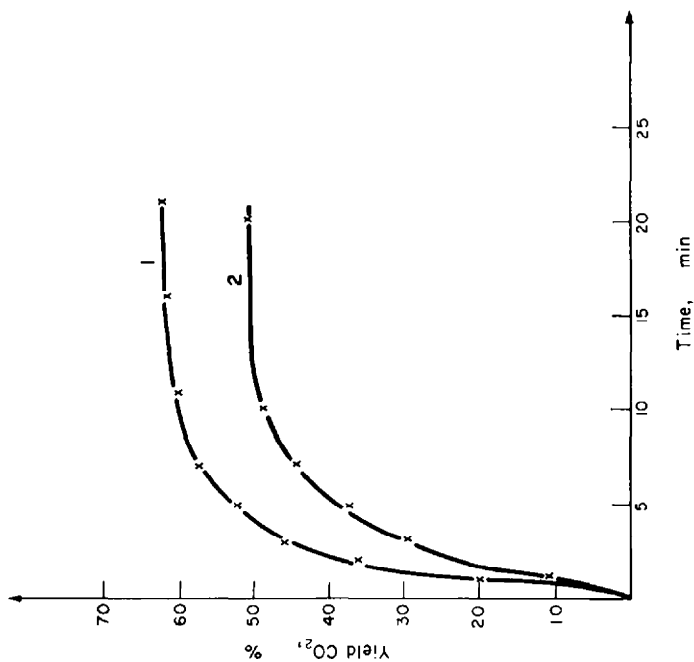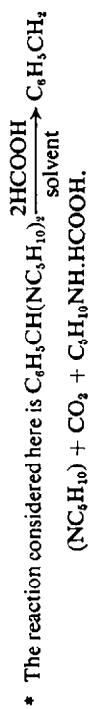
* The reaction considered here is $C_6H_5CH(NC_5H_{10})_2 \xrightarrow[\text{solvent}]{\text{2HCOOH}} C_6H_5CH_2$

$(NC_5H_{10}) + CO_2 + C_5H_{10}NH.HCOOH$.

FIG. 2. Effect of concentration of reagents.

Curve 1—2·5 mM of benzylidene-bis-piperidine in 5 ml benzene, curve 2—2·5 mM of the base in 10 ml benzene.
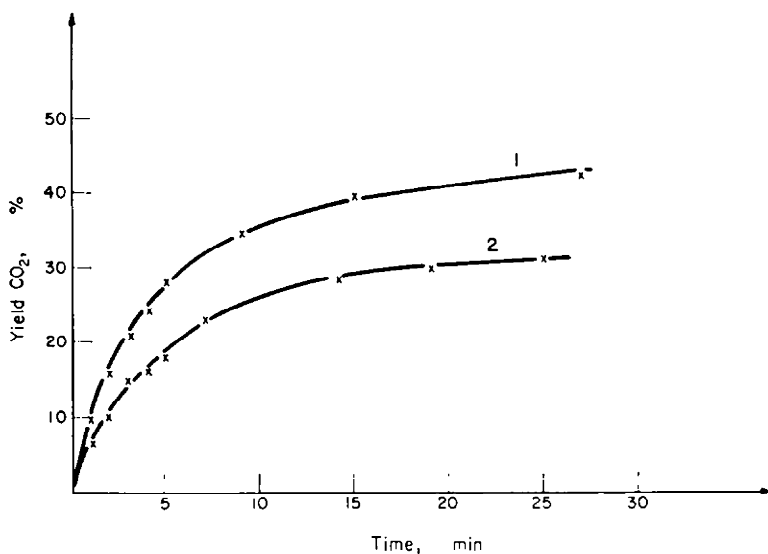
FIG. 3. Effect of addition of hydroquinone.
2·5 mM of the base in 5 ml amyl alcohol, tertiary at 25°, curve 1—no hydroquinone added, curve 2—0·25 g hydroquinone added.
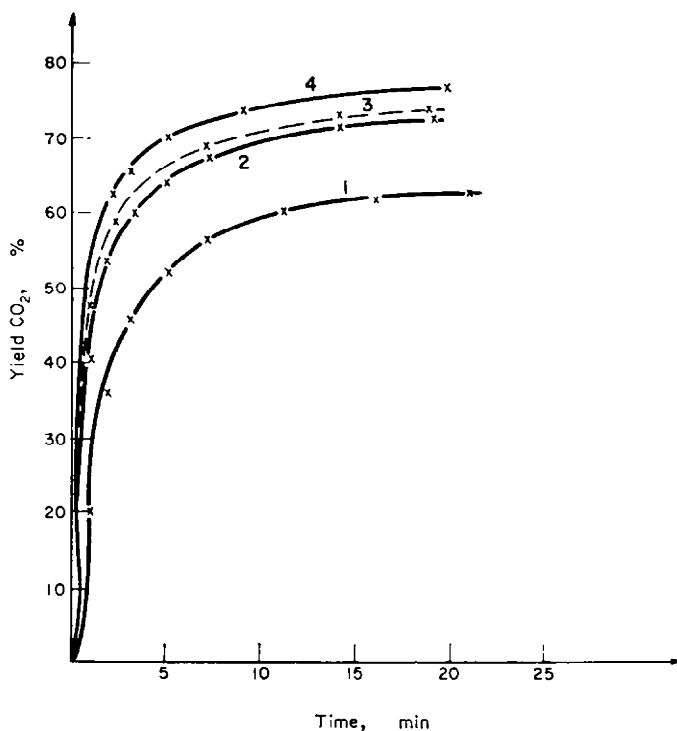
FIG. 4. Effect of addition of diphenylamine.
2·5 mM of the base in 5 ml benzene, temp 25°, curve 1—the reaction in the solvent alone, curve 2—0·5 g diphenylamine added, curve 3—1 g diphenylamine added, curve 4—2 g added.

ions. The rate of the reaction distinctly depends on the chemical character of the solvent used (Table 1). A free radical mechanism is indicated by the fact that the rate is influenced by the addition of hydroquinone and diphenylamine. Despite the fact that diphenylamine and hydroquinone are often regarded as inhibitors for radical reactions, it may be assumed that in the case of diphenylamine the $(C_6H_5)_2N$ radicals are links in the reacting chains. In fact, the temporary appearance of the colour corresponds to the colour described for the $(C_6H_5)_2N$ radicals.

It should be noted that in the chain course of reduction only an ester of α-amino-alcohol can take part and not the ammonium-carbonium cation. Precipitation of the heavy oil from the benzene solution, may as in the case with Schiff bases, be explained by formation of an ester salt in the presence of the acid in excess.

The ester in a solvent capable of solvating may be in equilibrium with the ionic form (ammonium-carbonium formate). This may provide an explanation for the fact that the reduction rate decreases in such solvents (Table 1):
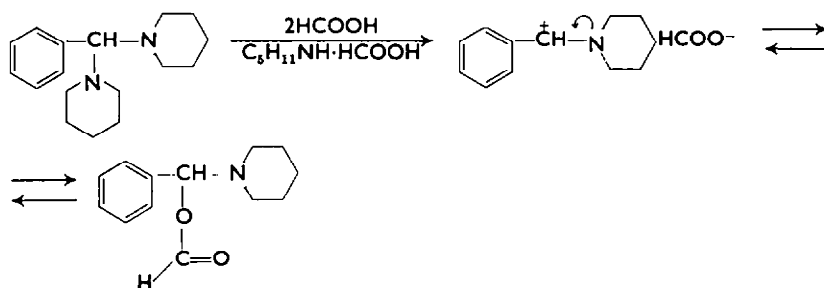
The chain course of the reaction may be represented as follows:
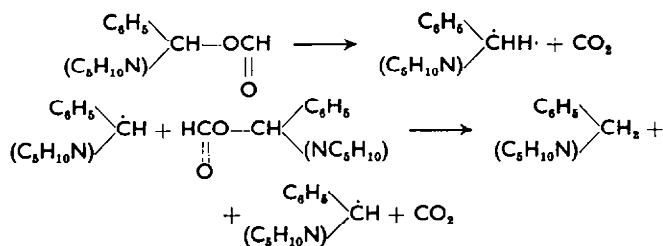
If the radical $C_6H_5\overset{\cdot}{C}H(NC_5H_{10})$, which follows the thermal decomposition of the ester, were to react with the ester molecule before it could associate with the hydrogen radical, the reaction chain would start. The break of the latter may be due to the reaction between the radical $C_6H_5\overset{\cdot}{C}H(NC_5H_{10})$ and the solvent. However, it is necessary to take into account the possibility of incorporation of the radical, resulting from the solvent molecule (presumably due to its sufficient stability) in the reaction chain, similarly as it is evident from the case with diphenylamine.

The restraining influence on the reaction rate manifested by primary and secondary alcohols may be due to the reaction between the radical $C_6H_5\overset{\cdot}{C}H(NC_5H_{10})$ and the alcohol α-hydrogen which is apt to be attacked. This reaction readily occurs in tertiary alcohols which do not possess the α-hydrogen. In the case of esters of formic

acid, the $C_6H_5CH(NC_5H_{10})$ radical may attack the hydrogen of the formyl group (the reaction readily occurs, for example, in ethyl acetate at room temperature).

In cases when the chain reaction cannot develop (e.g., in primary or secondary alcohols) the reduction occurring at elevated temperature, apparently consists in decarboxylation of the ester, according to the crypto-radical mechanism. The latter may probably be ascribed to the Schiff bases, which form esters due to the association of formic acid with the imine bond. The decreased reactivity of the bases towards formic acid may be due to the formation of a chelate ring in the molecule of ester, containing a secondary amine group:

$$
\begin{array}{c}
-CH-N- \\
| \quad\ | \\
O \quad\ H \\
| \\
C=O \\
| \\
H
\end{array}
$$
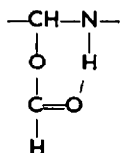
It appears from the literature[2] that a higher reactivity towards formic acid is also demonstrated by other methylene-bis-amines.
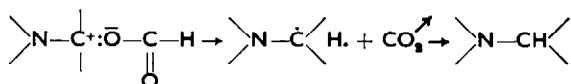
In other reductions with formic acid a similar mechanism may be involved. This is indicated by the behaviour of formic acid towards some inorganic substances. For instance, on mixing aqueous solutions of sodium formate and silver nitrate a precipitate of silver formate is formed. This precipitate decomposes quickly on heating with evolution of gas, and with precipitation of metallic silver. The course of this reaction may be the following:

$$
\begin{array}{ccc}
HC-O: Ag^+ & \rightarrow & HC-O + Ag \\
\| & & \| \\
O & & O \searrow \\
& & CO_2 + H
\end{array}
$$
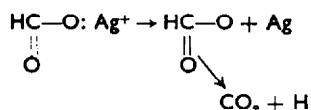
The transfer of the electron from the formate anion to the silver cation and the decomposition of formoxyl radical may occur simultaneously. If the silver cation takes off an hydride ion from the formate anion then silver hydride should result which, in the presence of water, decomposes to form hydrogen and silver oxide. The formate anions reduce, for example, bromine in aqueous solutions. Anhydrous formic acid readily reacts with a bromine complex, with dioxane or an amine. The possible mechanism of the reaction may be represented by:

$$Br_2 \rightleftarrows Br^+ + Br^-; \quad HCOO^- + Br^+ \rightarrow Br. \ + H. + CO_2;$$
$$Br. + H. \rightarrow HBr.$$
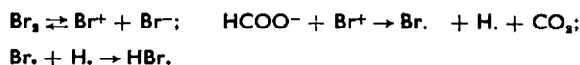
The reduction of both Schiff bases and α-aminoalcohols by formic acid may also be represented as the reaction between the ammonium-carbonium cation and formate anion as follows:

$$
\begin{array}{l}
>N-\overset{|}{\underset{|}{C}}{}^+:\bar{O}-\overset{}{\underset{\|}{C}}-H \rightarrow\ >N-\dot{C}\big\langle{}^{H.} + CO_2\nearrow\ \rightarrow\ >N-CH<
\end{array}
$$

Thus a full analogy can be seen between the reduction of the ammonium-carbonium cation and the silver and bromine cations by formate anion; in both cases the mechanism of the reductive action of formic acid is, in principle, the same. It is noteworthy that during the reduction of ammonium-carbonium cations, the condition on which

the transfer of an electron from the formate anion to the reduced positive carbon depends, is the formation of a covalent bond between the carbon and the oxygen. This bond arises due to the influence of a free electron pair, easily polarizable, that enables both homolytic and heterolytic bond rupture. This is consistent with the opinion that in many cases the more polarizable the bond, the more easily radical bond rupture occurs.[17]

EXPERIMENTAL

The benzylidene-bis-piperidine, m.p. 81–82°, was prepared by heating benzoic aldehyde with two moles of piperidine, and purified by repeated crystallization from ethanol.

Commercial organic solvents were of chemical or analytical grade and were additionally purified by dehydration (using suitable hygroscopic substances) and by distillation. The middle fraction boiling within 1° was used.

The anhydrous formic acid was prepared from a commercial product (~90%), twice distilled under red. press. from an anhydrous mixture of formic acid and sulphuric acid at 30°. The formic acid was trapped, using a freezing mixture: isopropanol + solid carbon dioxide. The anhydrous formic acid (99·8–100%) obtained was redistilled under normal pressure.

Reduction of benzylidene-bis-piperidine by formic acid

The experiments were carried out in the apparatus shown in Fig. 5. Benzylidene-bis-piperidine (0·65 g; 2·5 mmoles) was dissolved in 5 ml of the solvent used in a beaker *a*, placed in a water bath
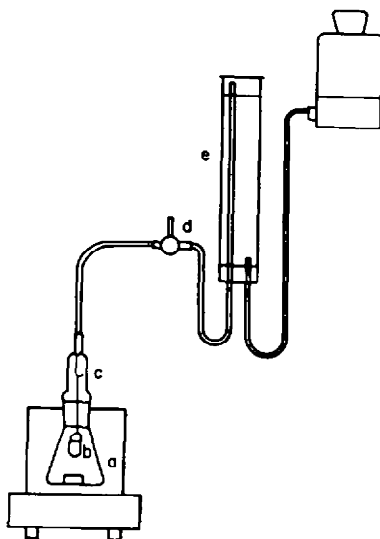

FIG. 5

the temperature of which was controlled to within 1°. In a tube *b* hanging from the closing stopper *c* 0·23 g (5 mmoles) of formic acid was introduced, a magnetic stirrer was set in motion and the temp of the bath adjusted at 25°. After 10 min stirring the level of liquid in the gas-meter *e* was equilized using the stopcock *d*. The latter was closed and the tube containing the formic acid was broken by sharply jerking the apparatus. The volume of carbon dioxide evolved was read at intervals in the gasmeter at room temp, and equated to standard conditions. The same apparatus was also used for experiments at 65°. When the reaction was complete (the volume in the gasmeter having subsided) 3 ml water and 2 ml conc hydrochloric acid were added. The mixture was then shaken in a separatory funnel and the aqueous layer separated and basified with a 10% solution of sodium hydroxide.

[17] W. Heller and M. Polanyj, *Trans. Faraday Soc.* **32**, 633 (1936).

In the case of polar solvents (e.g., alcohols) after addition of hydrochloric acid, the excess of solvent was distilled off under red. press. as a solvent-water azeotropic mixture. The remaining aqueous layer was basified as described above. The oil, which was brought down by alkalization of the acidic layer, was extracted with ether (3 × 5 ml), the etheral layer being dried (Na_2SO_4). The ether was removed and then piperidine *in vacuum* at room temp and 1 g picric acid in 10 ml ethanol added to the residue. The precipitate of picrate was filtered off and washed with ethanol.

Example. Benzylidene-bis-piperidine (0·65 g) and 1 g diphenylamine were dissolved in 5 ml benzene and 0·23 g anhydrous formic acid added to a stirred solution. This was almost immediately accompanied by vigorous evolution of gas, while the solution became intensely orange with a greenish shade. After 1 min the solution became yellowish-green, after 3 min it was completely colourless and the evolution of gas was insignificant. After 20 min, 3 ml water and 2 ml conc hydrochloric acid were added. A white precipitate formed and filtered off. The filtrate was shaken in a separatory funnel; the aqueous phase was basified and the precipitated oil treated as described above yielding 0·68 g picrate. The crude product m.p.180°–182°, after recrystallization from ethanol melted at 181°–182° (uncorr.). (Found: N, 13·75 Calc. for $C_{18}H_{20}O_7N_4$: N, 13·85%).