those after forty-five seconds of reaction agreed within 6.5%. Quite probably these average errors can be significantly reduced with a more refined technique such as, for example, the use of a definite quantity of iodine instead of the somewhat arbitrary "crystal of iodine." The rates of some other halides are being measured under more exact conditions.

The authors wish to acknowledge help in some of these experiments from J. B. Dickey.

Summary

n-Butyl bromide reacts more rapidly than bromobenzene with magnesium in ether. This result is of direct value in connection with some theories proposed to account for orientation in the benzene nucleus.

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OXIDATION IN THE BENZENE SERIES BY GASEOUS OXYGEN. IV. MECHANISM OF THE SLOW OXIDATION OF SATURATED HYDROCARBONS

BY H. N. STEPHENS

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Previous papers by the writer[1] have shown that alkyl benzenes are oxidized slowly by gaseous oxygen at a temperature of about 100°. Methylbenzenes yielded mono-aldehydes and the corresponding acids, while hydrocarbons containing two or more carbon atoms in the side chain were attacked only at the α-carbon atom, yielding ketones. When alkyl substituents replaced all of the hydrogen on the α-carbon atom, no oxidation took place under the conditions employed; therefore we must conclude that the linkages between this particular carbon atom and its hydrogen are the points of weakness which are attacked by oxygen.

In studying some of these oxidations it was found that the water formed by the reactions exerted a retarding effect and later, when excess water was used with the hydrocarbons, complete inhibition of oxidation resulted. Important exceptions to this behavior were noted in hydrocarbons which have only one hydrogen atom attached to the α-carbon atom, in which cases no inhibitory action was noted.

In seeking an explanation of the inhibitory action of water, it did not seem to us sufficient merely to classify it under the vague and unsatisfactory term "anticatalysis." Neither did it seem possible to account for the phenomenon on the basis of a protective action in which the water molecules might be assumed to attach themselves loosely to the hydrocarbon molecules, preventing ready access of oxygen to the vulnerable

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[1] Stephens, THIS JOURNAL, **48**, 1824, 2920 (1926).

point. The exceptions to the inhibitory action, which have just been noted, seem to preclude this possibility, as there is no apparent reason why cumene or cymene should not be protected as well as other hydrocarbons.

As has been suggested in previous papers, the simplest and most reasonable explanation seems to lie in the assumption of a reversible stage in the oxidation which involves the elimination of water. In the oxidation of the *iso*propyl group, however, in which only one hydrogen is attached to the α-carbon atom, it has been assumed that the elements of methyl alcohol, instead of the elements of water, tend to be eliminated.

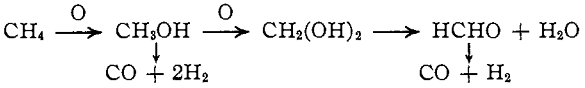
In order to justify such an assumption it was necessary, of course, to obtain additional information about the mechanism of oxidation, the most important problem being to determine the nature of the earlier stages. During the past few years there seems to have been a growing tendency to assume that the oxidation of saturated hydrocarbons passes through all the possible intermediate stages, starting with the alcohol. This view owes its origin chiefly to the work of Bone and his collaborators, which has given rise to the well-known "hydroxylation" theory.

As far as the writer is aware, only one case is on record in which an alcohol has actually been identified as a product of oxidation of a saturated hydrocarbon and in this case the oxidizing agent was ozone.[2] However, this lack of experimental evidence has not been considered a serious drawback to the "hydroxylation" theory, as Bone and Stockings[3] have shown that ethyl alcohol is much more readily oxidized than ethane. Thus it is considered that the alcohol, assumed to be the primary oxidation product, is oxidized further, as rapidly as it is formed.

Another important line of evidence in favor of intermediate formation of alcohols[4] lies in the fact that when methane is exploded with an insufficient supply of oxygen, an increase in the initial pressure of the gases causes a decrease in the proportion of water formed. The interpretation of this fact by Bone and Townsend involves the assumption that at higher pressures the tendency of methane to decompose

$$CH_4 \text{ (1 vol.)} \longrightarrow C + 2H_2 \text{ (2 vols.)}$$

would be repressed; that is, the loosening of the carbon to hydrogen valences which it is necessary to assume in their "hydroxylation" scheme, would be less pronounced. Therefore, in the series of reactions postulated by Bone's theory



$$CH_4 \xrightarrow{O} \underset{\substack{\downarrow \\ CO + 2H_2}}{CH_3OH} \xrightarrow{O} CH_2(OH)_2 \longrightarrow \underset{\substack{\downarrow \\ CO + H_2}}{HCHO} + H_2O$$

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[2] Bone and Drugman, *Proc. Chem. Soc.*, **20**, 127 (1904).

[3] Bone and Stockings, *ibid.*, **20**, 106 (1904).

[4] Townsend, *Proc. Roy. Soc., London*, **116A**, 652 (1927).

although it is assumed that normally (that is, at ordinary pressures) there is a tendency toward a "non-stop" oxidation of CH_4 to $CH_2(OH)_2$; under the influence of higher pressures greater difficulty is experienced in introducing the second atom of oxygen and there is more tendency for the oxidation to stop at the alcohol stage. Then, as methyl alcohol has been shown to decompose into CO and H_2, the total amount of water formed would be decreased. In passing, it might be pointed out that it is not clear why the introduction of the second oxygen atom should be disfavored rather than the first, as this is not in accord with the fact that ethyl alcohol is oxidized more readily than ethane.

As the assumptions made by the writer to account for the inhibitory action of water do not definitely provide a place for the alcohol stage, it seemed desirable to find out, if possible, whether or not the alcohol stage was an intermediate one in the production of aldehydes and ketones. With this end in view a study of the oxidation of several α-phenyl carbinols was made[5] and it was found, with one exception (that of *iso*propylphenyl carbinol), that a small amount of ketone was formed at 100°. However, in this study and in some later experiments, other evidence was found which argues very strongly against the alcohol stage being an intermediate one in the oxidation of hydrocarbons. Assembling material both from papers already published and from the present paper we may present the following arguments.

1. The main products obtained from alcohols at 100° were high boiling liquids, which were presumably ethers. Also benzoic acid was formed in the oxidation of all secondary alcohols. None of these products was detected in the oxidation of hydrocarbons.

2. Oxidations of xylene and ethylbenzene were carried out in the presence of acetic anhydride in an attempt to get an ester of the intermediate alcohol but in neither case was any ester detected. To eliminate the possibility of the ester being oxidized, xylyl acetate was treated with oxygen under the usual conditions but no toluic aldehyde was formed. The only effect of acetic anhydride was to increase the rate of oxidation, due to the removal of water.

3. Water inhibits the oxidation of all of the alcohols studied. In the hydrocarbons containing normal alkyl groups, the oxidation of which is completely inhibited by water, we must, therefore, assume that the oxidation of hydrocarbon to alcohol is inhibited. In the oxidation of cumene, however, water does not inhibit the reaction, although the oxidation of the corresponding alcohol, dimethylphenyl carbinol, is completely inhibited. In this case, then, it would be expected that the alcohol, if it is an intermediate product, would accumulate and that no acetophenone would be formed. As it has been shown that cumene is oxidized

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[5] Stephens, THIS JOURNAL, **50**, 186 (1928).

directly to acetophenone in the presence of water, with no formation of dimethylphenyl carbinol, the assumption that the alcohol is an intermediate stage seems unjustifiable.

4. Finally, it has been shown that, using equimolecular amounts of ethylbenzene and phenylmethyl carbinol, a much greater yield of acetophenone is obtained in a given time from the hydrocarbon than from the alcohol. In this particular case, then, the non-existence of alcohol in the final products from the hydrocarbon cannot be explained on the basis of the more rapid oxidation of the alcohol. On the contrary, the alcohol would be expected to accumulate, if it were an intermediate oxidation product.

In the face of the above arguments, it seems impossible to grant that the alcohol stage is an intermediate one in the oxidation of alkyl benzenes to aldehydes or ketones and if this is true for alkyl benzenes, there seems no reason why it should not be true for paraffin hydrocarbons. The retarding action of water on the oxidation of ethane at 415 and 440° has been noted by Bone and Andrews[6] and thus one point of similarity is definitely established. The writer takes the view that the benzene nucleus merely exerts a directive influence without affecting, in any fundamental way, the mechanism of oxidation. Granting this, any theory of the mechanism of oxidation ought to be able to explain oxidations in both classes of hydrocarbons. As Bone's theory assumes the existence of the alcohol stage, which, apparently, is not justifiable and also provides no explanation for the inhibitory action of water, the following scheme is submitted in the belief that it is capable of explaining satisfactorily all of the known facts

$$\begin{tikzcd} \text{Hydrocarbon} + O_2 \arrow[r, rightleftharpoons] & \text{Complex} \arrow[r, rightleftharpoons] & H_2O + \text{unsaturated residue} \arrow[d] \\ & & \text{Aldehyde or ketone} \end{tikzcd}$$

In the oxidation of the alkyl benzenes, it is believed, although not definitely proved, that the reaction takes place chiefly, if not exclusively, in the vapor phase; therefore, the first stage may be considered as a homogeneous gas reaction in which one molecule of hydrocarbon associates with one molecule of oxygen. To call the bimolecular aggregate thus formed a molecular compound might possibly be misleading, as it is considered as being extremely unstable and, consequently, short-lived. On account of the slowness of these oxidations it must be assumed that the majority of these temporary associations are followed by dissociation into the original molecules; that is, the first stage is strictly reversible. It might be mentioned, in passing, that it seems much more reasonable to consider molecular oxygen as the oxidizing agent rather than atomic, as assumed by Bone and his co-workers. At explosion temperatures, the presence of atomic oxygen will be granted, but as the "hydroxylation"

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[6] Bone and Andrews, *J. Chem. Soc.*, **89**, 659 (1906).

theory is applied to slow oxidations as well as to rapid combustions, the existence of appreciable concentrations of oxygen atoms at 100° would have to be assumed, which is apparently contrary to fact.

The Inhibitory Action of Water

Although the majority of the bimolecular aggregates just dealt with are assumed to dissociate again, a small proportion might be expected to decompose, as shown in the second stage of oxidation, with elimination of the elements of water and formation of an "unsaturated residue." Now, if this reaction is reversible, the extremely interesting phenomenon of the inhibitory action of water can be explained in a very simple way. On the other hand, it seems impossible, on the basis of the hydroxylation theory, to devise any simple explanation of this behavior. It will be seen readily that, if this stage is reversed, no permanent oxidation product can be formed.

The final stage of this series of reactions involves a rearrangement, or orientation, of the "unsaturated residue" into the stable form of an aldehyde or ketone and this reaction could hardly be thought of as other than an irreversible one. On this account, the oxidation as a whole would be irreversible and the action of water on an aldehyde or ketone could not be expected to yield the corresponding hydrocarbon and oxygen.

It might be mentioned that the purpose of introducing the "unsaturated residue" is twofold; first, to account for the irreversibility of the reaction as a whole and, second, to take cognizance of the fact that it must take a finite time, however short, for an unsaturated fragment from the decomposition of a molecule or aggregate to orientate itself into a stable configuration. Then, if this residue has a definite life period, the presence of a sufficient concentration of water vapor could cause the second stage of the oxidation to be reversed.

In the oxidation of the *iso*propyl group in cumene, or cymene, the series of reactions shown above would be the same except for the elimination of the elements of methyl alcohol instead of water. In this case, it would be expected that oxidation would accompany, or immediately follow, this elimination and actually the product that is obtained is not methyl alcohol but formic acid. As was anticipated, the presence of methyl alcohol in excess did not inhibit the oxidation of cumene and other work is at present under way to attempt to throw more light on this reaction.

To return once more to the oxidation of methane under high pressure and with a small proportion of oxygen present,[4] it seems quite possible, in accord with the above theory, to grant the correctness of the assumption that some methyl alcohol was formed. Under ordinary conditions (ordinary pressures and with a sufficient supply of oxygen) it seems reasonable to assume that the simplest possible type of reaction will take place, that is, a bimolecular one. However, if the concentration of methane were very high, with respect to that of oxygen, there seems every possibility of two molecules of methane associating with one molecule of oxygen. That is, according to the widely accepted view of Trautz and Schleuter,[7] there would be ample opportunity for a second methane molecule to encounter a bimolecular oxygen–methane aggregate, while the two molecules were still under their mutual sphere of influence. Now, the decomposition of this trimolecular aggregate would be most simply represented by the equation

$$CH_4{\cdot}O_2{\cdot}CH_4 \longrightarrow 2CH_3OH$$

Thus, under these special conditions, the formation of an alcohol from a hydrocarbon seems quite possible. It must be pointed out, however, that the alcohol thus formed is a by-product and not an intermediate in the oxidation of the hydrocarbon.

Finally, we might turn to the only case on record in which an alcohol has been detected as an oxidation product of a saturated hydrocarbon, that of the production of ethyl alcohol from ethane by means of ozone.[3] If we assume the same type of reaction as in the case of oxygen, we should expect the bimolecular aggregate thus formed to decompose, giving ethyl alcohol and oxygen.

$$C_2H_6{\cdot}O_3 \longrightarrow C_2H_5OH + O_2$$

Ozone, then, cannot be compared too strictly with oxygen, as the former can give an alcohol through bimolecular impacts, while the latter cannot. One other possibility might be mentioned in this connection. In the work of Bone and Drugman a large excess of ethane was employed and it is conceivable that some trimolecular impacts might occur under these conditions. If this does take place, the resulting aggregates might decompose according to the scheme

$$C_2H_6{\cdot}O_3{\cdot}C_2H_6 \longrightarrow C_2H_5OH + CH_3CHO + H_2O$$

also yielding ethyl alcohol.

To sum up very briefly, the normal primary reaction between a saturated hydrocarbon and oxygen is assumed to depend on bimolecular impacts. Under exceptional conditions, as has just been indicated, trimolecular collisions may take place to some extent. Only in this latter event can any alcohol be formed and the alcohol would thus be considered as a by-product rather than an intermediate oxidation product.

Experimental Part

A. Oxidation in the Presence of Acetic Anhydride

Xylene.—Twenty g. of xylene and 20 g. of acetic anhydride oxidized at 102–104° for twenty-one days yielded 7.85 g. of crude toluic aldehyde, b. p. 78–81° (10 mm.); previously reported, 1.9 g. of aldehyde from 90 g. of xylene in 30 days at 100°.

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[7] Trautz and Schleuter, *Z. anorg. Chem.*, **136**, 1 (1924).

Ethylbenzene.—Twenty-five g. of ethylbenzene and 25 g. of acetic anhydride oxidized for eleven days at 102–104° yielded 9.0 g. of crude acetophenone; previously reported, 9.5 g. of acetophenone from 50 g. of ethylbenzene in twenty-four days at 110–115°.

Xylyl Acetate.—Twelve g. of xylyl acetate, b. p. 103–106° (10 mm.), oxidized for eleven days at 102–104°, yielded no toluic aldehyde.

B. Parallel Oxidation of Ethylbenzene and Phenylmethyl Carbinol

Twenty-five g. of phenylmethyl carbinol, oxidized for eleven days at 122–124° yielded 0.85 g. of acetophenone, isolated as semicarbazone.

Twenty-one g. of ethylbenzene, oxidized as above for eleven days, yielded 6.3 g. of crude acetophenone, b. p. 77–83° (8 mm.).

Summary

A new mechanism of the oxidation of saturated hydrocarbons by gaseous oxygen is proposed, which accounts for the inhibitory action of water in oxidations studied by the writer.

It is shown that the oxidation of a hydrocarbon to aldehyde or ketone does not go through the alcohol stage.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY, No. 578]

THE INTERRELATION OF HYDROGEN-ION ACTIVITY AND CONCENTRATION OF SALT IN THE ACTIVATION OF PANCREATIC AMYLASE[1]

BY H. C. SHERMAN, M. L. CALDWELL AND M. ADAMS

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It has long been known that the presence of electrolyte is essential to the activity of pancreatic amylase, but quantitative data obtained under sufficiently controlled conditions have not been available to afford satisfactory explanations of this influence or to permit strictly quantitative comparisons of different electrolytes.

In view of this fact and of the theoretical and practical importance of the subject, series of investigations to obtain quantitative and comparable data concerning the influence of various electrolytes upon the activity of pancreatic amylase have been carried out in which the influence of the other factors involved has been recognized and eliminated as completely as possible. In this way it was hoped that the magnitude of the influence, if any, exerted by each salt might be quantitatively established, that other interrelated factors might be recognized, that more light might be thrown upon the way in which such influences are exerted and that

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[1] We are greatly indebted to the Carnegie Institution of Washington for grants in aid of this investigation.