THE REDUCTION OF ORGANIC COMPOUNDS BY METAL-AMMONIA SOLUTIONS

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Introduction

THE aims of this Review are to present a picture of the process of reduction, especially as observed in metal–ammonia solutions, and to survey some of the advantages and limitations of these reagents in synthesis and degradation. Several excellent reviews [1] exist of various aspects of metal–ammonia solutions, but they are chiefly concerned with reactions rather than with mechanisms. The theory of the process of reduction itself is very well set out by L. Michaelis and M. P. Schubert.[2] In the present Review no attempt is made to present a complete literature summary; work is included which has a pertinent bearing on the more fundamental aspects of the subject. Other reduction processes are mentioned where it is considered necessary for an understanding of reaction mechanisms. It is hoped to state the problems raised by the subject, if not always to solve them in detail.

To make the following sections comprehensible, it is necessary first to consider briefly the most probable mechanism of reduction by chemical agents. The essential step is the addition of one electron to a molecule to give an anion-radical or an anion and a radical, or of two electrons to give a di-anion or two anions. The charged molecules are associated with positive ions, usually derived from a metal supplying the electrons, so ionised salts may be considered to act as intermediates. Sometimes these salts, even of anion-radicals (*e.g.*, ketyls), can be isolated as stable compounds; in other cases they may exist only momentarily as part of a transition complex. In the following sections the reductions are usually represented in terms of the ions, rather than the un-ionised salts which may be in equilibrium with them, because the ions are the active agents, and because there is considerable uncertainty with some of the mesomeric systems as to where the cations are attached. The cation in most cases mentioned here is that of sodium.

Two types of reaction may be distinguished: * the fission of a molecule, $X\text{–}Y + e \rightarrow X^* + Y^-$ or $X\text{–}Y + 2e \rightarrow X^- + Y^-$; and the opening of a multiple bond, $X{=}Y + e \rightarrow \underbrace{\overset{*}{X}\text{–}\overset{-}{Y}\;\;\overset{-}{X}\text{–}\overset{*}{Y}}$ or $X{=}Y + 2e \rightarrow \overset{-}{X}\text{–}\overset{-}{Y}$. These both involve the breaking of a bond (albeit of different types) and the production of charged centres, so they can be treated on similar lines. The

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[1] See, *e.g.*, C. A. Kraus, *Chem. Reviews*, 1931, **8**, 251; C. B. Wooster, *ibid.*, 1932, **11**, 1; W. C. Fernelius and G. W. Watt, *ibid.*, 1937, **20**, 216; B. K. and K. N. Campbell, *ibid.*, 1942, **31**, 78. Frequent reviews also appear in the *J. Chem. Educ.*, *e.g.*, G. W. Watt and W. B. Leslie, 1941, **18**, 210.

[2] *Chem. Reviews*, 1938, **22**, 437.

* An asterisk is used to denote the odd electron in a free radical.

fission type is somewhat simpler because the fragments are free to move apart, and can usually be examined separately.

It is important to distinguish between one-electron and two-electron addition as the rate-determining step. This is not always easy. Often the uptake of the first electron is the potential-determining stage, although a second electron is then taken up and the products are those derived from the anion, rather than from the radical. The polarographic reduction of polycyclic hydrocarbons shows this clearly.[3] This mechanism is very common, because the radical initially formed is usually more readily reduced than the starting material, and is reduced before it can undergo other reactions, *e.g.*, dimerisation. In some cases it seems that the initial stage demands the addition of two electrons at once. Section I is chiefly concerned with a discussion of such problems.

Section II treats the subsequent stages of the process : the reactions of the charged centres. Protons may be added, *e.g.*, $Ph\cdot CH{=}CH\cdot Ph \rightarrow Ph\cdot\overset{-}{C}H{-}\overset{-}{C}H\cdot Ph \rightarrow Ph\cdot CH_2\cdot CH_2\cdot Ph$; [4] $CH_2{=}CH\cdot CH_2\cdot OH \rightarrow \overset{-}{\overbrace{CH_2 \cdots CH \cdots CH_2}} \rightarrow CH_3\cdot CH{=}CH_2$; [5] an anion-radical may dimerise with the addition of protons, $2Ph_2C{=}O \rightarrow 2Ph\overset{*}{C}{-}\overset{-}{O} \rightarrow Ph_2C(OH)\cdot CPh_2(OH)$,[6] or a radical may dimerise as in the Ullmann reaction, $2PhBr\ (+\ 2Cu) \rightarrow 2Ph^* \rightarrow Ph{-}Ph$. Much the same dimeric products can, however, result from a purely ionic mechanism through the action of an anion on the starting material, *e.g.*, $Ph_2C{=}CH_2 + 2e \rightarrow Ph_2\overset{-}{C}{-}\overset{-}{C}H_2\ \ (+\ Ph_2C{=}CH_2) \rightarrow Ph_2\overset{-}{C}\cdot CH_2\cdot CH_2\cdot\overset{-}{C}Ph_2 \rightarrow Ph_2CH\cdot CH_2\cdot CH_2\cdot CHPh_2$.[7] It is important, if possible, to distinguish between radical and ionic processes, but the controversy between W. Schlenk and E. Bergmann [4, 8] on one hand, and K. Ziegler and his co-workers [7, 9] on the other, illustrates some of the difficulties. Purely chemical methods alone are usually inconclusive.[3] Polymeric materials are sometimes obtained by repetition of the addition of ions to the starting material, and there is good evidence [10] that in the production of Buna rubber, ions not radicals are involved.

The investigation of mechanisms for many reductions is not easy. The processes are often carried out at the surface of a metal dissolving with evolution of hydrogen gas in an excess of an " acid " (including in that term solvents like alcohol or even ammonia), or at the surface of an electrode in a similar solution. H. Burton and C. K. Ingold [11] have postulated that the primary reaction under such conditions is the polarisation of the molecule

[3] S. Wawzonek and H. A. Laitinen, *J. Amer. Chem. Soc.*, 1942, **64,** 1767, 2365; S. Wawzonek and J. W. Fan, *ibid.*, 1946, **68,** 2541.

[4] W. Schlenk and E. Bergmann, *Annalen,* 1928, **463,** 114.

[5] E. Chablay, *Ann. Chim.*, 1917, **8,** 145.

[6] W. E. Bachmann, *J. Amer. Chem. Soc.*, 1930, **52,** 2823.

[7] K. Ziegler and O. Schäfer, *Annalen,* 1930, **479,** 150.

[8] *Ibid.*, p. 78.

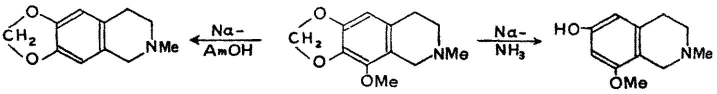
[9] K. Ziegler, H. Colonius and O. Schäfer, *ibid.*, 1929, **473,** 36.

[10] W. Kern, FIAT Review, Preparative Organic Chemistry, Part III, 1948, 179.

[11] *J.*, 1929, 2022.

at the surface and the addition of a proton *followed* by two electrons ; *e.g.*, $C{=}C{-}C{=}C \xrightarrow{H^+} \overbrace{C{\cdots}C{\cdots}C}^{+}{-}C{-}H \xrightarrow{2e} \overbrace{C{\cdots}C{\cdots}C}^{-}{-}C{-}H$. This sequence of events seems unlikely in any but a fairly strongly acid solution,[12] but, as will be seen later, the theory now outlined gives rise to the same kind of intermediate by a slightly different route.

Many reactions can be carried out in *homogeneous* solution in liquid ammonia because it dissolves many organic compounds and most of the alkali and alkaline-earth metals. A theory of the constitution of such metal–ammonia solutions has been put forward elsewhere.[13] Because of the low acidity of ammonia (pK about 34) [14] intermediate organo-metallic salts are often stable enough to be examined, particularly at the low temperatures used (ammonia, b.p. − 33°, m.p. − 80°). The availability of protons can be regulated by the addition of " acids " like alcohols or ammonium salts. Furthermore, the dipolar and associated character of ammonia makes it a very favourable solvent for the production of salts of very weak acids, whether these are derived from the acids by the action of bases or in the course of reduction reactions. The differences between ammonia and other solvents are usually differences in degree, due to the differences in solvation energies of ions, rather than differences in kind.[15] For example, the same dihydroanisoles are obtained from anisoles either with potassium and ethanol or with sodium and ethanol in ammonia, although much more readily with the latter reagent. One divergence in the course of reduction has been observed by D. B. Clayson,[16] which must be due to a difference in the primary reduction stage :



I. Electron-addition Stage

Fission Reactions.—The reductive fission of unsaturated ethers or alcohols is possible where one charge is stabilised by the unsaturation and the other by the electron-affinity of the oxygen, *e.g.*, $Ph{-}O{-}Ph \rightarrow Ph^- + PhO^-$; [17] $CH_2{=}CH{\cdot}CH_2{\cdot}OH \rightarrow \overbrace{CH_2{\cdots}CH{\cdots}CH_2}^{-} + OH^-$.[5] Compounds producing very stable anions, *e.g.*, Cl^-, are reduced more readily,[18] but the effects of altered substitution on reaction rates are not so easily observed for that very reason. More side-reactions also occur, owing to the

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[12] J. W. Baker, W. C. Davies, and M. L. Hemming, *J.*, 1940, 692.

[13] A. J. Birch and D. K. C. MacDonald, *Oxford Science*, 1948, **2,** 1.

[14] S. Makishima, *J. Fac. Eng. Tokyo Imp. Univ.*, 1938, **21,** No. 3, 115.

[15] A. J. Birch, *Nature*, 1946, **158,** 585.

[16] *J.*, 1949, 2016.

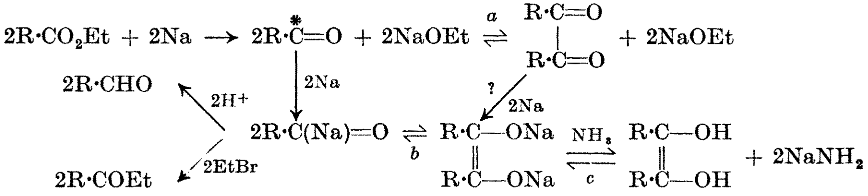
[17] P. Shorygin and S. A. Skoblinskaya, *Compt. rend. Acad. Sci. U.R.S.S.*, 1937, **14,** 505.

[18] P. M. Dean and G. Berchet, *J. Amer. Chem. Soc.*, 1930, **52,** 2823.

attack of the carbon-anion on the starting material, for example in the Wurtz–Fittig reaction.

In order to distinguish between the production of radicals and anions in the rate-determining stage, it is necessary to study the effect on reaction rates of altering the substitution of the system being reduced. It is not sufficient merely to study the *products*, which may correspond to the formation of anions merely because the primarily formed radicals are more easily reduced than the starting material. With readily reduced substances, anions or radicals may be detectable according to the relative concentration of reducing agent and substance; it is clear that in such cases the rate-determining step is radical formation. An example is the reduction of esters with sodium in liquid ammonia.[19]

With one atomic proportion of sodium the ester, $R{\cdot}CO_2R'$, produces a high proportion of the diketone R·CO·CO·R. With two atomic proportions, the ketol R·CO·CH(OH)·R is formed, together with the aldehyde R·CHO in some cases, *e.g.*, $R = CMe_3$ or Ph. The aldehyde is formed through the sodium derivative R·C(Na)=O because the action of an alkyl halide on the solution leads to the alkyl ketone, *e.g.*, $Ph{\cdot}CO_2Et \rightarrow Ph{\cdot}C(Na){=}O \rightarrow Ph{\cdot}COEt$. The evidence favours the occurrence of the reactions:



The reversibility of *a*, *b*, and *c* was demonstrated by acting on the ketol or diketone with sodium ethoxide and sodium amide in ammonia.

Alterations in reaction rate caused by alterations in substitution can be qualitatively predicted by considering the energies of formation of anions and radicals in similar systems. From acidity measurements,[20] it is clear that a negative charge requires an increasing energy of formation as hydrogen atoms are successively replaced by electron-repelling groups like alkyl or methoxyl. Evidence for radicals is more scanty, but indicates that almost any type of substituent in place of hydrogen stabilises the amphoteric unpaired electron.[21] Therefore, if the rate of reduction in a fission reaction is decreased by increasing the degree of alkylation of the system upon which the charge resides, then the potential-determining stage involves anions, provided that in the transition state the two fragments can be treated separately. This last assumption would appear to be justified when one fragment (*e.g.*, OH, Cl) has a much higher electron-affinity than the other.

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[19] M. S. Kharasch, E. Sternfeld, and F. R. Mayo, *J. Org. Chem.*, 1940, **5**, 362.

[20] A. J. Birch, *Faraday Soc. Discussion*, 1947, **2**, 246.

[21] H. S. Taylor and J. O. Smith, *J. Chem. Physics*, 1940, **8**, 543; A. J. Birch, *Faraday Soc. Discussion*, 1947, **2**, 262; M. S. Kharasch, H. C. McBay, and W. H. Urry, *J. Amer. Chem. Soc.*, 1948, **70**, 1269; C. E. H. Bawn, *J.*, 1949, 1042.

On this basis, the reactions of the alcohols and ethers to be considered below involve the addition of two electrons as the primary process.

Another fact in favour of this assumption is that dimeric products are not detectable. The production of dimeric products is not an argument in favour of radical-intermediates because sufficiently reactive anions can attack the starting material, but its absence is somewhat better evidence against the formation of radicals.

The experimental methods so far employed to test the effects of substitution in this series have been comparative rather than absolute. Such methods provide quickly a mass of data from which a general picture can be built up, but direct measurements of velocities and of reduction potentials by polarographic methods will be necessary before quantitative calculations can be made. Quantitative measurements have hardly begun, although it is already clear that polarographic methods can be used in ammonia, and that the homogeneity of many reacting systems in ammonia obviates the difficulties encountered in measuring velocities in poly-phase systems.

Comparison has been made of the extent of reduction of compounds in a series compared with a standard competing reaction, *e.g.*, the dealkylation of aryl alkyl ethers by alkali metals in ammonia in competition with the reaction of metal and ammonia to give hydrogen gas.[22] The extent of reduction of a standard group compared with groups of varying substitution is another method which has been used.[23] For example, there are two competing reactions in the reduction of $\mathrm{Ph{\cdot}CH{=}CH{\cdot}CMe(OH){\cdot}R}$ ($\mathrm{R} = \mathrm{H}, \mathrm{Me}$), the formation of $\mathrm{Ph{\cdot}CH_2{\cdot}CH_2{\cdot}CMe(OH){\cdot}R}$ and hydrogenolysis to the hydrocarbon $\mathrm{Ph{\cdot}CH_2{\cdot}CH{=}CMe{\cdot}R}$ by way of the anion $\mathrm{Ph{\cdot}}\overbrace{\mathrm{CH}\overset{\cdots}{-}\mathrm{CH}\overset{\cdots}{-}\mathrm{C}}^{-}\mathrm{Me{\cdot}R}$. When $\mathrm{R} = \mathrm{H}$, the hydrocarbon predominates, but when $\mathrm{R} = \mathrm{Me}$ the chief product is the dihydro-alcohol. It is evident that the extra methyl group ($\mathrm{R} = \mathrm{Me}$) can only have a second-order effect on the double-bond reduction, but that it has a first-order (destabilising) effect on the mesomeric anion. Another comparative method employs a molecule which is symmetrical apart from the substituents to be studied, *e.g.*, unsymmetrically substituted diphenyl ethers.[24] Information is then obtained from the direction of fission. The use of a limited amount of reducing agent on a mixture of two substances can give an idea of the relative ease of reduction ; *e.g.*, a mixture of benzyl alcohol, $\mathrm{Ph{\cdot}CH_2{\cdot}OH}$, and phenyldimethylcarbinol, $\mathrm{Ph{\cdot}CMe_2{\cdot}OH}$, with a limited amount of sodium in ammonia gives toluene not *iso*propylbenzene (p. 75).[23]

In the fission of ethers : $\mathrm{R{-}O{-}R'} + 2e \rightarrow (\mathrm{R^-} + \mathrm{R'O^-})$ or $(\mathrm{R'^-} + \mathrm{RO^-}) + 2\mathrm{H^+} \rightarrow \mathrm{RH} + \mathrm{R'{\cdot}OH}$ or $\mathrm{R'H} + \mathrm{R{\cdot}OH}$, the direction is decided by which transition state has the lower energy. From the fact that RH (p*K* about 37—40) is a much weaker " acid " than R·OH (p*K* about 16—18) it is clear that the greater part of the energy will be required to form the carbon

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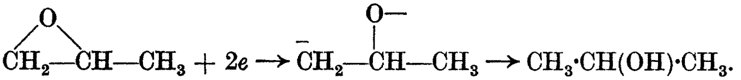
[22] A. J. Birch, *J.*, 1947, 102.

[23] *Idem*, *J.*, 1945, 809.

[24] P. A. Sartoretto and F. J. Sowa, *J. Amer. Chem. Soc.*, 1937, **59**, 603 ; A. L. Kranzenfelder, J. J. Verbance, and F. J. Sowa, *ibid.*, p. 1488 ; F. C. Weber and F. J. Sowa, *ibid.*, 1938, **60**, 94.

anion R^- or R'^-, *i.e.*, that the greater part of the energy of the transition state will be consumed by the carbon system. Furthermore, substituents should produce greater effects on this system since they are directly attached to the atom bearing the charge. In a particular series, therefore, the R-group containing less electron-repelling groups, or more electron-attracting groups, should appear as RH if anions are intermediates. In practice this is found to be so.[25]

The simplest case is the reduction of propylene oxide to *iso*propyl alcohol,[25] the high strain-energy of the three-membered ring evidently assisting a process which is impossible with ordinary saturated ethers. The transition state which is chosen contains CH_2^- rather than CH^-:

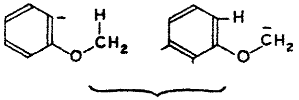


$CH_2—CH—CH_3 + 2e \rightarrow \bar{C}H_2—\overset{O^-}{CH}—CH_3 \rightarrow CH_3{\cdot}CH(OH){\cdot}CH_3$. More extensile evidence is provided by the fission of aryl ethers.[24] The following examples are typical:

$$p\text{-}MeO{\cdot}C_6H_4—O—C_6H_5 \rightarrow p\text{-}MeO{\cdot}C_6H_4{\cdot}OH$$
$$p\text{-}HO_2C{\cdot}C_6H_4—O—C_6H_5 \rightarrow p\text{-}HO_2C{\cdot}C_6H_5(\text{reduced}) + HO{\cdot}C_6H_5$$
$$p\text{-}C_6H_4Me—O—C_6H_5 \rightarrow p\text{-}C_6H_4Me{\cdot}OH\ (75\%) + HO{\cdot}C_6H_5\ (25\%)$$
$$o\text{-}MeO{\cdot}C_6H_4—O—C_6H_4{\cdot}OMe\text{-}p \rightarrow HO{\cdot}C_6H_4{\cdot}OMe\text{-}p$$

Usually the phenolic products were the only ones examined.

The one substituent group so far examined which does not show an immediately obvious relationship between its known electronic character and its influence on reductive fission is the methoxyl group. Its influence on the foregoing diphenyl ether fissions, and on those of the aryl alkyl ethers and benzyl alcohols (below) depends on its position. An *o*-methoxyl is activating (*i.e.*, charge-stabilising relative to hydrogen) and a *p*-methoxyl is strongly deactivating. The dual effect may be related to the known dual electronic character of the group, but this would mean that in an *o*-position the inductive effect, $C \rightarrow OMe$, must predominate, but in a *p*-position the mesomeric effect $\overset{\frown}{C—OMe}$. There are no obvious reasons why this should be so. A more likely explanation is that in the *o*-position there occurs a hyperconjugation which stabilises the charge by transferring it partially to the carbon of the methoxyl group as shown in the inset. The *o*-methyl is found to be less deactivating than the *p*-methyl, which may be due to a small stabilising contribution of the same kind. It is noteworthy that anisoles are invariably metallated *ortho*- to the methoxyl.[26]



The same effects of substituents, including methoxyl, are shown in the fission of aryl alkyl ethers to give phenols, a reaction which is much less

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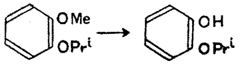
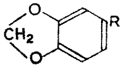
[25] A. J. Birch, *J. Proc. Roy. Soc. N.S.W.*, in the press.

[26] G. Wittig and U. Pockels, *Ber.*, 1939, **72**, 89; G. Wittig and G. Fuhrmann, *ibid.*, 1940, **73**, 1179; H. Gilman, W. Langham, and A. L. Jacoby, *J. Amer. Chem. Soc.*, 1939, **61**, 215.

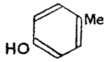
readily performed because one of the groups is saturated. In this case the relevant charge appears, not on carbon but on oxygen. The demethylation of some anisole derivatives with sodium in ammonia under standard conditions gives the following yields of the phenol :[22] anisole 27% ; *o*-Me, 17% ; *m*-Me, 9% ; *p*-Me, 4% ; *o*-OMe, 89% ; *m*-OMe, 71% ; *p*-OMe, 2·5% ; 3 : 4-dimethoxytoluene gives 3-hydroxy-4-methoxytoluene. Alteration of the alkyl group confirms that a methyl ether is more readily cleaved than, for example, an *iso*propyl ether, (I) giving rise to (II).



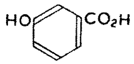
(I.) (II.)



(III.)



(IV.)

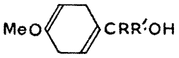


(V.)

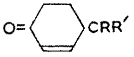
Another interesting transformation involves the direct removal of oxygen from a benzene ring, *e.g.*, (III ; R = Me) gives (IV), while (III ; R = CO_2H) gives (V).[22] Here, as expected, the oxygen *meta* to the electron-repelling methyl, but *para* to the electron-attracting carboxyl, is the one removed.

In the hydrogenolysis of benzyl or allyl alcohol the standard group OH^- is split off in each case, so that only the substitution of the benzyl or allyl system need be considered. The results again agree with the anion hypothesis, the same dual effect of methoxyl also being observed.[25] In some cases the relative energies of the anions can be estimated from " acidity " measurements, *e.g.*, the " acidity " of *iso*propylbenzene is much less than of toluene,[27] which agrees with the fact that benzyl alcohol is reduced in preference to phenyldimethylcarbinol. It may be pointed out that with these weak " acids " the effects of substituents on energies seem to be so great that variations due to probability, *e.g.*, to the number of replaceable hydrogen atoms, are negligible. The *o*- or *m*-methoxyphenylcarbinols (*o*- or *m*-$MeO{\cdot}C_6H_4{\cdot}CRR'{\cdot}OH$; R = R' = H or Me) behave in the same manner as compounds lacking the methoxyl group, and give rise to the *o*- or *m*-alkylanisole (*o*- or *m*-$MeO{\cdot}C_6H_4{\cdot}CHRR'$). The *p*-methoxyphenylcarbinols (VI ; R = R' = H or Me) are reduced instead in the ring to 4-methoxy-2 : 5-dihydrophenylcarbinols (VII ; R = R' = H or Me), hydrolysed and dehydrated by mineral acid to the 4-alkylidene*cyclo*hexenones [25] (VIII ; R, R' = H, Me).

(VI.)



(VII.)



(VIII.)

There is no appreciable difference in the ease of the ring-reduction of *m*- and *p*-tolyl methyl ether, so the conclusion must be drawn that the *p*-methoxyl raises the energy of the charge in the transition state of hydrogenolysis to a prohibitive level. The presence of a hetero-atom, with readily

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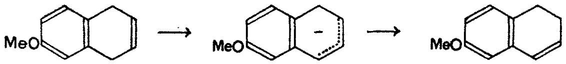
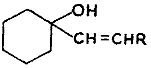
[27] A. A. Morton, J. T. Massengale, and M. L. Brown, *J. Amer. Chem. Soc.*, 1945, **67**, 1260 ; H. Gilman and L. Tolman, *ibid.*, 1946, **68**, 522.

available *p*-electrons engaged in the aromatic resonance of a heterocycle, has a similar deactivating effect relative to the corresponding benzene derivative, *e.g.*, furylbutylcarbinol is little hydrogenolysed under vigorous conditions.[23] Little evidence is available from acidity measurements on methoxylated systems, but the isomerisation of (IX) to (X) shows clearly that an anion is more readily formed by loss of a proton from a methylene group in the *m*-, rather than the *p*-position to methoxyl.[28] 2 : 5-Dihydroanisoles have a comparatively acidic 2-position, *ortho*- to the methoxyl.[29]

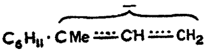


(IX.) (X.)



(XI.)

The allyl alcohol reductions are very sensitive to changes in the substitution of the allyl system. Examples of the reaction are the conversions of geraniol, C_6H_{11}·CMe:CH·CH_2·OH, and linaloöl, C_6H_{11}·CMe(OH)·CH:CH_2, into the *same* hydrocarbon methylgeraniolene, C_6H_{11}·CMe:CH·CH_3.[5, 30] The identity of the products in this case and the bond-shifts which occur in other cases (p. 84) are clear indications that mesomeric systems are involved in the transition; in this case as inset. There are no dimerisation products obtained, which is some evidence against the formation of radicals. The experimental evidence shows [23] that reduction occurs if a CH_2 or a CHPh group is at one or other end of the mesomeric system; which end seems to matter little. The hydroxyl can be directly attached to this group as in geraniol or Ph·CH(OH)·CH:CMe_2, or at the other end as in linaloöl or Ph·CH:CH·CMe_2·OH, presumably because the energy level of the ion is high compared to the difference in energies of the isomeric alcohols. It is clear also from simple theoretical considerations that the substitution of both ends of the mesomeric system must be taken into account in arriving at an estimate of the ease of producing it.


$$\overset{-}{\overbrace{C_6H_{11}\cdot CMe \mathrel{\cdots} CH \mathrel{\cdots} CH_2}}$$

The effect of an alkyl group can be seen by comparing (XI; R = H) with (XI; R = Bu^n); the former is reduced to ethylidene*cyclo*hexane, the latter is not reduced. The alcohol CHMe:CH·$CHBu^n$·OH does give a small amount of an octene under rather vigorous conditions, so the alkylation of both ends of the system is not completely prohibitive.

If mesomeric radicals were the potential-determining intermediates, increased alkylation would probably tend to make reduction easier, as has been pointed out (p. 72). The effect of phenyl groups is no evidence either way, although it is possible that substituted aryl groups might provide valuable information. The experimental evidence available from " acidity "

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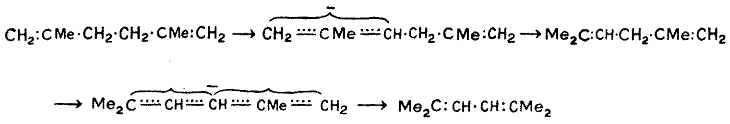
[28] C. T. Beer, D. Phil. Thesis, Oxford, 1948.

[29] A. J. Birch, *J.*, 1947, 1642.

[30] G. Dupont, R. Dulou, and V. Desreux, *Bull. Soc. chim.*, 1939, **6**, 83; J. Dœuvre, *ibid.*, 1939, **6**, 882.

measurements can be correlated with the anion hypothesis. The position from which a proton is removed in the " metallation " of hydrocarbons confirms that increased alkylation of either end of the potential mesomeric anion lowers the " acidity ",[20] and the isomerisation of unsaturated hydrocarbons with sodium or potassium amide in ammonia is an illustration of the same rule. These isomerisations proceed *via* the metal salts, which in some cases are present in high concentration [29] (p. 85). An example of the process is



$$CH_2{:}CMe\cdot CH_2\cdot CH_2\cdot CMe{:}CH_2 \longrightarrow \overbrace{CH_2 \cdots CMe \cdots CH}^{-}\cdot CH_2\cdot CMe{:}CH_2 \longrightarrow Me_2C{:}CH\cdot CH_2\cdot CMe{:}CH_2$$

$$\longrightarrow \overbrace{Me_2C \cdots CH \cdots CH \cdots CMe \cdots CH_2}^{-} \longrightarrow Me_2C{:}CH\cdot CH{:}CMe_2$$

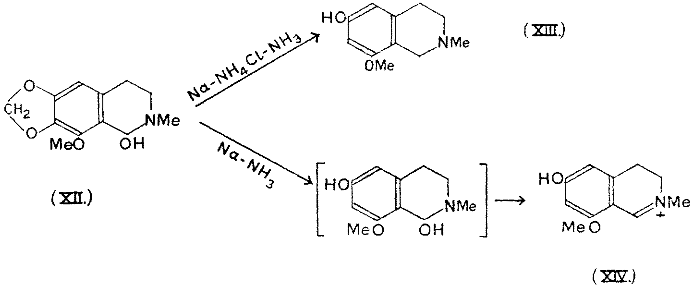
The critical stage with 1 : 5-dienes is obviously the first bond-shift, since the acidity is greatly increased in the 2 : 5-dienes by increased resonance in the ion. It is found that no isomerisation takes place unless the first potential anion has a CH_2 or a CHPh group in the system. Furthermore, the reduction of 1 : 5-dienes with calcium hexammoniate or sodium in ammonia must be preceded by isomerisation to conjugated dienes, and is not observed unless the same conditions are fulfilled.[29, 31] A discussion of other relations between structure, acidity, and ease of reduction, particularly of hetero-systems, will be found elsewhere.[20]

The reductive fission of allyl or benzyl alcohols can be prohibited by placing a negative charge on the oxygen through salt formation. This explains Chablay's observation [5] that only half the allyl alcohol is reduced by sodium in liquid ammonia, unless ethanol is present. The equilibrium $RONa + EtOH \rightleftharpoons ROH + EtONa$ is evidently set up, allowing the (irreversible) reduction of ROH to proceed. Use can be made of the observation to protect hydroxyl groups in such systems while reducing other groups. It has already been pointed out, for example (see p. 73), that $Ph\cdot CH{:}CH\cdot CMe_2\cdot OH$ is reduced in part on the double bond and in part to lose the hydroxyl. The sodium salt with sodium in ammonia gives only the dihydro-alcohol with retention of the hydroxyl.[25] A more complicated case is the reduction of cotarnine (XII). With sodium in liquid ammonia in the presence of ammonium chloride (an " acid " of the ammonia system) the hydroxyl group is lost and the compound (XIII) formed. If the ammonium chloride is replaced by sodium hydroxide the hydroxyl group is retained, and the product can be converted into the metho-salt (XIV).[16] In the second case there seems no doubt that the protection is afforded by formation of the sodium salt of the carbinol.

Alteration of the connecting atom can also change the ease of fission. From the order of acidities SH > OH > NH (dependent chiefly on decreasing nuclear charge) it appears that the fission of sulphur compounds should be easier, and of nitrogen compounds more difficult, than that of the corresponding oxygen compounds. This expectation is borne out in practice.

[31] A. J. Birch, *J.*, 1946, 593.

Unlike saturated ethers, dialkyl sulphides are reduced readily with sodium in ammonia: *e.g.*, $C_3H_7 \cdot S \cdot C_3H_7 + 2Na + NH_3 \rightarrow C_3H_7 \cdot SNa + C_3H_8 + NaNH_2$.[32] Very few amines undergo fission except under drastic conditions.[33] D. B. Clayson [34] has observed the fission of the tetrahydro*iso*quinoline ring of



laudanosine with potassium in liquid ammonia at room-temperature, and G. R. Clemo and T. J. King [35] have observed an allylamine fission in strychnine derivatives.

The necessity for forming a nitrogen anion in the reaction is avoided by using a quaternary ammonium salt, in which fission is found to occur readily with the production of an electrically neutral amine,[16, 25] *e.g.*, $Ph \cdot \overset{+}{N}Me_3 \rightarrow PhH + NMe_3$; $Ph \cdot CH_2 \cdot \overset{+}{N}Me_3 \rightarrow Ph \cdot CH_3 + NMe_3$. The presence of ethanol in this reaction is beneficial in preventing side-reactions due to the strongly basic amide anion. It is a powerful variant of the well-known Emde reduction using sodium amalgam.[36]

The evidence thus indicates that the potential-determining stage is the addition of two electrons. An examination of the reduction of triarylmethyl radicals with sodium amalgams [37] shows that the free-energy change ($-\Delta F$) is much the same for all of them (about 17—20 kcals.); the resonance energies of a single electron and an electron-pair in the same system are therefore about the same. A slight increase (1—5 kcals.) is observed for the electron pair as the resonance possibilities increase in number. The presence of polarisable groups in the system may, however, alter the picture considerably. A *p*-methoxyl group, as in diphenyl(methoxyphenyl)methyl, shifts the free energy change to more positive values, and although tri(methoxyphenyl)methyl chloride is readily reduced to the radical, the radical itself is not reduced with sodium amalgam. The presence of the methoxyl group thus makes a considerable difference between the resonance energies of the radical and anion.

Two electrons carry twice as much energy as does one electron, so in

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[32] F. E. Williams and E. Gebauer-Fülnegg, *J. Amer. Chem. Soc.*, 1931, **53**, 352.

[33] E. Stoelzel, *Ber.*, 1941, **74**, 982.

[34] Private communication.

[35] *J.*, 1948, 1661.

[36] *E.g.*, H. Emde and H. Kull, *Arch. Pharm.*, 1934, **272**, 469.

[37] H. E. Bent *et al.*, *J. Amer. Chem. Soc.*, 1930, **52**, 1498; 1931, **53**, 1789; 1932, **54**, 1393; 1935, **57**, 1242, 1452; 1936, **58**, 1228.

the absence of high interaction energies (such as may occur when two adjacent negative charges are formed in the reduction of an unsaturated system) and special resonance effects such as above, the addition of two electrons in one stage would appear to be favoured. There are no kinetic difficulties about this, since the reactions occur at a conducting metal surface, or in a conducting ammonia solution. The lower the energy associated with the metal electrons the more is the likelihood of the production of radicals, if the reaction can proceed at all. For example, the Ullmann reaction $2RX + 2Cu \longrightarrow R{-}R + 2CuX$ requires considerable heat energy and probably goes *via* radicals, whereas the Wurtz–Fittig reaction $2RX + 2Na \longrightarrow R{-}R + 2NaX$ is carried out at low temperatures under the driving energy associated with the metal, and goes *via* ions.

The Reduction of Unsaturated Systems.—The isolated carbon–carbon double bond does not undergo reduction with chemical agents,[9, 38] presumably because the intermediate electron-addition products would require an energy which the ordinary reagents cannot reach. It is noteworthy that ethylene reacts with cæsium to give $Cs{\cdot}CH_2{\cdot}CH_2{\cdot}Cs$, decomposed by proton-donors to give ethane.[39]

The simplest double bond which does undergo reduction is that between carbon and oxygen, the energy of formation of the charged intermediates being lower than in a carbon system because oxygen has a greater electron-affinity than has carbon. One or two electrons can be added, depending on concentration factors, *i.e.*, the potential-determining stage is the addition of the first electron. The addition of one atom of sodium in an inert solvent (ether or ammonia) to an aromatic or non-enolisable aliphatic ketone gives rise to a compound $R_2\overset{*}{C}{\cdot}ONa$ called a ketyl.[40] The ketyls were formulated as free radicals by W. Schlenk and his co-workers [41] because of physical and chemical similarities to the triarylmethyls, and they are paramagnetic.[42] Electrical conductivity measurements show that quite a complex series of equilibria exist in the solutions,[43] and these are confirmed by other methods.[44, 45] The equilibria

$$Ph_2\overset{*}{C}{\cdot}ONa \rightleftharpoons Ph_2\overset{*-}{CO} + Na^+ \quad . \quad . \quad . \quad . \quad (1)$$

$$2Ph_2\overset{*}{C}{\cdot}ONa \rightleftharpoons Ph_2C(ONa){\cdot}CPh_2(ONa) \quad . \quad . \quad . \quad (2)$$

$$Ph_2C(ONa){\cdot}CPh_2(ONa) \rightleftharpoons Na^+ + Ph_2C(ONa){\cdot}CPh_2(O^-) \quad . \quad . \quad (3)$$

$$Ph_2\overset{*}{C}{\cdot}ONa + Ph_2\overset{*}{C}{\cdot}\overset{-}{O} \rightleftharpoons Ph_2C(ONa){\cdot}CPh_2(O^-) \quad . \quad . \quad . \quad (4)$$

all exist in solutions of the benzophenone ketyl. Bachmann [44] showed that

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[38] P. Lebeau and M. Picon, *Compt. rend.*, 1914, **159**, 70.

[39] L. Hackspill and R. Rohmer, *ibid.*, 1943, **217**, 152.

[40] E. Beckmann and T. Paul, *Annalen*, 1891, **266**, 1 ; A. E. Favorskii and I. N. Nazarov, *Bull. Acad. Sci. U.R.S.S.*, 1933, 1309.

[41] *Ber.*, 1911, **44**, 1182 ; 1913, **46**, 2840.

[42] S. Sugden, *Trans. Faraday Soc.*, 1934, **30**, 23.

[43] C. B. Wooster, *J. Amer. Chem. Soc.*, 1937, **59**, 377.

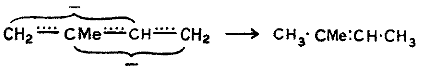
[44] W. E. Bachmann, *ibid.*, 1933, **55**, 1179.

[45] C. B. Wooster, *ibid.*, 1934, **56**, 2436.

(2) exists in ether, and Wooster [45] showed that in liquid ammonia it lies about 85% in favour of the monomeric products. The action of acids gives rise to the pinacol,[44] *e.g.*, $Ph_2\overset{*}{C}\cdot ONa \longrightarrow Ph_2C(OH)\cdot CPh_2(OH)$. The further equilibrium $2R_2\overset{*}{C}\cdot ONa \rightleftharpoons R_2C{=}O + R_2C(Na)\cdot ONa$ was shown not to exist by Wooster,[45, 46] because benzyl alcohol has little action on the ammonia solution of the ketyl, but reacts rapidly with $R_2C(Na)\cdot ONa$ formed by further action of sodium. Absorption spectra confirm this conclusion.[47] However, the equilibrium $Ph_2C\cdot ONa + Ph_3C^* \rightleftharpoons Ph_2C{=}O + Ph_3CNa$ does exist,[48] and is an important demonstration of the comparative stability of the ketyl radical, and also of the reversibility of the electron (*i.e.*, metal) addition.

A considerable body of evidence is available that the addition of both the first and the second electron can be reversed. For example, mercury acts upon $Ph_2C(Na)\cdot ONa$ to form $Ph_2\overset{*}{C}\cdot ONa$ and sodium amalgam,[49] and the reaction can be reversed if sufficiently concentrated amalgam is used.[50] The treatment of $R_2C(Na)\cdot ONa$ with $R_2C{=}O$ may lead to $2R_2\overset{*}{C}\cdot ONa$,[50] and the action of $R_2\overset{*}{C}\cdot ONa$ on $R'_2C{=}O$ can in some cases give $R'_2\overset{*}{C}\cdot ONa$ and $R_2C{=}O$.[51] A similar reversibility is found with the sodium addition compounds formed by many hydrocarbons, *e.g.*, Ph·CHNa·CHNaPh acts as an electron-source by producing a Wurtz product R–R with an alkyl halide R–X, together with the original unsaturated hydrocarbon, *e.g.*, Ph·CH:CHPh.[52] Compounds of this type have even been used as catalysts for the Wurtz reaction.[53] Many sodium-addition compounds can carry out isomerisations characteristic of radicals, not ions, *e.g.*, of *cis-* to *trans-*stilbene.[54] K. Ziegler and H. Wollschitt have also observed the transfer of sodium from one olefin to another.[55] Finally, the polarographic method [3] shows that the potential-determining step for many carbonyl and hydrocarbon reductions is the *reversible* addition of the first electron.

The reduction of carbon–carbon unsaturated systems is possible when the multiple bonds are conjugated, because the charges are stabilised by resonance. Isoprene, $CH_2{:}CMe\cdot CH{:}CH_2$, is reduced by sodium in ammonia through the di-anion : [56]



$$\overset{-}{\overbrace{CH_2 \cdots CMe \cdots CH}} \cdots CH_2 \;\; \underset{-}{\underbrace{CMe \cdots CH \cdots CH_2}} \longrightarrow CH_3\cdot CMe{:}CH\cdot CH_3$$

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[46] *J. Amer. Chem. Soc.*, 1929, **51**, 1858.

[47] H. E. Bent and A. J. Harrison, *ibid.*, 1944, **66**, 969.

[48] C. B. Wooster and J. G. Dean, *ibid.*, 1935, **57**, 112.

[49] W. E. Bachmann, *ibid.*, 1933, **55**, 1183.

[50] H. E. Bent and W. B. Keevil, *ibid.*, 1936, **58**, 1367.

[51] W. Schlenk and A. Thal, *Ber.*, 1913, **46**, 2840.

[52] W. Schlenk and E. Bergmann, *Annalen*, 1928, **463**, 1.

[53] O. L. Talmud, *Acta Physicochim. U.R.S.S.*, 1938, **8**, 27.

[54] *Annalen*, 1930, **479**, 130.

[55] " Handbuch der Katalyse ", Bd. VI, Ed. G.-M. Schwab, Springer Verlag, Vienna, 1943, p. 109.

[56] T. Midgley and A. L. Henne, *J. Amer. Chem. Soc.*, 1929, **51**, 1293.

Conjugation with aromatic systems has the same stabilising effect, *e.g.*, $Ph{\cdot}CH{:}CHPh \rightarrow Ph{\cdot}\bar{C}H{\cdot}\bar{C}H{\cdot}Ph \rightarrow Ph{\cdot}CH_2{\cdot}CH_2{\cdot}Ph$.[4] Aromatic rings in polycyclic systems are reduced by sodium in ammonia to give dihydro-derivatives as the initial products, *e.g.*, naphthalene and diphenyl. This happens despite the high resonance stabilisation of the aromatic system, because of the large number of resonance possibilities in the electron-addition products. Unless there are electron-stabilising groups present like carboxyl,[57] the mono-benzenoid compounds are not reduced except under special conditions to be considered later. The high resonance energy, due to the special configuration of six electrons, is not compensated in such cases by any *correspondingly* high resonance energy in the electron-addition product. The presence in the ring of a hetero-atom in place of carbon, *e.g.*, nitrogen, which can provide a more stabilising site for a negative charge, assists the reduction process. For example, pyridines are readily reduced even with sodium and alcohol.[58] The evidence from polarographic reduction [3, 59] and equilibria with amalgams [37] shows that for polycylic systems, including polycyclic ethylenes, the potential-determining stage is the addition of the first electron, although the products in most cases are derived by the addition of another electron.

The acetylene triple bond is reducible,[60] the products from dialkylacetylenes being the *trans*-ethylenes : $-C{\equiv}C- \rightarrow -\bar{C}{=}\bar{C}- \rightarrow -CH{=}CH-$. That this reduction takes place, and that the reduction of a double bond does not, is probably to be explained on the basis of the greater free-energy change in passing from a triple to a double bond than in passing from a double to a single bond. Furthermore, there is a greater stabilisation of an electron in the more electron-deficient system. This may be correlated with the known acidity $C{\equiv}CH > CH$.[20] Sodium acetylides are not reduced, presumably because of the negative charge.[61]

The effects of altering the solvent in the reduction of naphthalene by sodium are of great interest. N. D. Scott, J. F. Walker, and V. L. Hansley [62] found that naphthalene in ethylene glycol dimethyl ether, or in dimethyl ether itself, reacts with sodium to take up *one* atom per molecule and form a ketyl-like compound (also observed in diethyl ether with anthracene [50]). Dilution of the solution with *diethyl* ether causes the deposition of sodium metal, and naphthalene is left in solution. In liquid ammonia, naphthalene readily takes up two atoms of an alkali metal per molecule.[63] The reducing power of the sodium therefore varies with the ability of the solvent to stabilise the electron-addition products by solvation : the higher its polarity the further to the right is the equilibrium $C_{10}H_8 + 2e \rightleftharpoons C_{10}H_8{}^{*-} + e \rightleftharpoons C_{10}H_8{}^{--}$.

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[57] A. J. Birch, *J.*, in the press.

[58] B. D. Shaw, *J.*, 1937, 300.

[59] I. M. Kolthoff and J. J. Lingane, " Polarography ", Interscience, N. Y., 1941, Part V.

[60] K. N. Campbell and L. T. Eby, *J. Amer. Chem. Soc.*, 1941, **63,** 216, 2683 ; K. W. Greenlee and W. C. Fernelius, *ibid.*, 1942, **64,** 2505.

[61] A. L. Henne and K. W. Greenlee, *ibid.*, 1943, **65,** 2020.

[62] *Ibid.*, 1936, **58,** 2442.

[63] W. Hückel and H. Bretschneider, *Annalen*, 1937, **540,** 157.

This equilibrium is also illustrated by the fact that the mono-sodium compound behaves chemically as the di-sodium compound.

The effects of substitution on the reduction of an unsaturated system are somewhat more complicated than with the fission reactions already considered, because the two charged atoms remain attached to each other. It is evident, however, that substituents should affect the bivalent anions in a similar way to the univalent anions, with an additional factor due to charge interaction. Even with the addition of one electron to give an anion-radical, it is clear that the essential step is the addition of a *negative* charge, so the ease of reduction should be affected by substituents in the same way. Moreover, the reduction of radicals [37] shows that the resonance effects of a system are more pronounced on a negative charge than on a radical, even when it is a hydrocarbon system, and with the introduction of more readily polarisable groups like methoxyl the difference between negative charge and radical is even more pronounced. Electrochemical reductions provide direct evidence on the point; *e.g.*, the potential for styrene, $Ph{\cdot}CH{:}CH_2$, is $-$ 2·343 v., and for methylstyrene, $Ph{\cdot}CH{:}CHMe$, under the same conditions, it is $-$ 2·537 v.[3] Similar differences are noted in the reduction of *p*-substituted benzaldehydes.[12]

The electron-addition step has been treated so far as if it were completely divorced from the proton-addition step. In many cases this treatment appears to be justified, in others it is not. The reduction potential of the carbonyl group is known to be greatly influenced by pH,[59] but in this and similar cases it is probably the cation formed by the addition of a proton, rather than the substance itself, which is reduced. At the dropping-mercury electrode, the potentials of hydrocarbons are not affected by pH, at least on the alkaline side,[3] and W. C. E. Higginson, in preliminary experiments, has also observed that the reduction potential of anthracene in liquid ammonia is unaffected by the presence of alcohol.[64]

The presence of alcohols in ammonia solutions does, however, exercise a profound influence on the course of reduction of monocyclic benzene derivatives. In its absence, sodium does not reduce benzene hydrocarbons noticeably, and it dealkylates phenyl ethers.[22, 65] Wooster [66] found that in presence of water or alcohols reduction takes place; *e.g.*, benzene gives 1 : 4-dihydrobenzene. From the fact that the hydrogen gas given off is less by about two atoms per molecule of substances like toluene or anisole, he concluded that they also give 1 : 4-dihydro-derivatives. It was later shown by A. J. Birch [65] that the reaction leads to 2 : 5-dihydro-derivatives, *e.g.*, 2 : 5-dihydroanisole from anisole. The reasons for this profound influence of water or alcohols are still not completely clear, but it is evident from the identity of products obtained when a reduction is carried out by electron-addition followed by proton-addition (where this is possible) or by simultaneous addition, that no fundamentally new mechanism is involved

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[64] Private communication.

[65] A. J. Birch, *J.*, 1944, 430.

[66] C. B. Wooster and K. L. Godfrey, *J. Amer. Chem. Soc.*, 1937, **59,** 586; C. B. Wooster, U.S.P., 1939, 2,182,242.

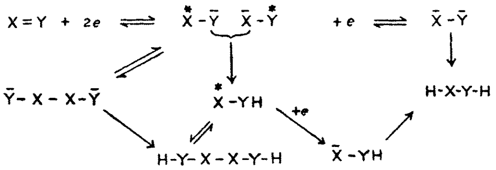
for the latter process. For example, it is unlikely that atomic hydrogen or metal hydrides intervene.

The most likely explanation is that the equilibrium $X + 2e \rightleftharpoons X^{*-} + e \rightleftharpoons X^{--}$ is present, but is far to the left because of high resonance energy in the benzene ring and the small number of resonance possibilities in the charged products, together with the high charge-interaction energy in the di-anion. It is known that sodium reacts surprisingly slowly with alcohol in ammonia to give hydrogen, but that anions react very rapidly, so it is possible that the reaction is forced to the right by removal of the ions as the conjugate "acid," even though the instantaneous concentration of ions is small. Another explanation, somewhat similar to the last, is that the exothermic proton addition and endothermic electron addition may occur in one stage, the energy of the former assisting the latter. However, if this were true, compounds which can be reduced by a two-stage mechanism might be expected to take an easier path in presence of alcohol and be reduced at a (numerically) lower potential. Higginson's preliminary results [64] indicate that this is not so, but a further examination of mono-benzenoid compounds is necessary.

Other observations [7] are important in demonstrating the rôle of an "acid" in ammonia solutions. 1 : 1-Diphenylethylene is reduced by sodium in ammonia to tetraphenylbutane, evidently by the route $Ph_2C{:}CH_2 + 2e \longrightarrow Ph_2\bar{C}{-}\bar{C}H_2\ (+\ Ph_2C{:}CH_2) \longrightarrow Ph_2\bar{C}{\cdot}CH_2{\cdot}CH_2{\cdot}\bar{C}Ph_2\ (+\ 2H^+) \longrightarrow Ph_2CH{\cdot}CH_2{\cdot}CH_2{\cdot}CHPh_2$. In the presence of indene (an "acid") a different course is taken: $Ph_2\bar{C}{-}\bar{C}H_2\ (+\ 2H^+) \longrightarrow Ph_2CH{\cdot}CH_3$. Indene itself is almost unaffected by sodium in ammonia, so its rôle must be confined to that of a supplier of protons to the primary anion, which it must do more rapidly than the anion can add to another molecule. Hydrogen from the indene cannot accept an electron *before* reduction occurs; *i.e.*, atomic hydrogen or some equivalent cannot be involved. Moreover, no di-indenyl is formed, so hydrogen is not abstracted from it as the atom.

II. Nature of the Products

The products are determined not only by the position of the electron-addition equilibrium, but also by the rates of secondary reactions, *e.g.*, proton additions or dimerisation, and by secondary equilibria, *e.g.*, between monomeric and dimeric ions :



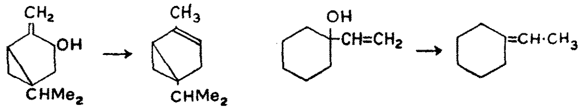
The proton-additions can be either reversible or irreversible, according to the conditions (see Section III); the primary products are those of irreversible addition. Addition to anions, uni- or bi-valent, seems to be more rapid than to anion-radicals, presumably because resonance stabilisation of the latter increases the acidity of the conjugate "acid" $\overset{*}{X}{-}Y{-}H$ [compare the slow and incomplete action of benzyl alcohol on $Ph_2\overset{*}{C}{\cdot}ONa$ with its rapid action on $Ph_2C(Na){\cdot}ONa$ [46]]. Therefore, if the di-anion is present in the equilibrium to any appreciable extent, the products might be expected to result principally by addition of protons to its two charges.

Two problems remain to be solved if the products of reduction are to be explained on the basis of proton addition to mesomeric anions. It is necessary to determine the effects of structure on the position in the mesomeric system taken up by a proton; and to see whether two protons are added simultaneously or successively to a bivalent anion.

The experimental evidence with mesomeric carbon-anions shows that proton-addition occurs at the point of highest charge-density; [20, 22] *e.g.*, $R{\cdot}\overbrace{CMe \cdots CH \cdots CH_2}^{-} \longrightarrow R{\cdot}CMe{=}CH{\cdot}CH_3$ The conversion of sabinol (XV) into α-thujene (XVI) and of (XVII) into (XVIII) are other examples where addition occurs to the least alkylated end of the ion. The conversions show that

$$Ph{\cdot}CH(OH){\cdot}CH{=}CMe_2 \text{ or } Ph{\cdot}CH{=}CH{\cdot}CMe_2{\cdot}OH \longrightarrow Ph{\cdot}\overbrace{CH \cdots CH \cdots CMe_2}^{-} \longrightarrow Ph{\cdot}CH_2{\cdot}CH{=}CMe_2$$

addition occurs adjacent to the charge-stabilising phenyl group. With hetero-enoid systems, *e.g.*, $\overbrace{C \cdots C \cdots O}^{-}$ the charge is chiefly concentrated on the hetero-atom because of its greater electron-affinity, but it is often difficult to find conditions where proton-addition is truly irreversible. When this can be done, *e.g.*, by the use of very low temperatures, the enols result.



(XV.) (XVI.) (XVII.) (XVIII.)

It has been pointed out elsewhere [20] that the reaction of an addendum with the point of highest charge-density is to be expected only if it requires little activation energy—as apparently does the proton reaction—and if it is irreversible. The products of *reversible* addition are governed by an equilibrium dependent on the free energies of the possible products, not on the rates of addition at the various positions carrying a free charge.[20, 67] The equilibrium is $AH \rightleftharpoons \underbrace{\bar{A}\;\bar{B}} \rightleftharpoons BH$, where $\bar{A}$ and $\bar{B}$ are the canonical forms representing the resonating ion. The following examples [57] are of considerable importance to an understanding of the nature of the primary reduction products of benzene rings, and also the secondary products con-

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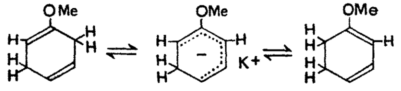
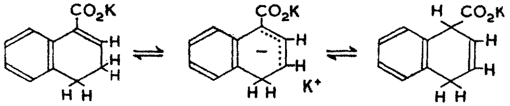
[67] P. B. D. de la Mare, E. D. Hughes, and C. K. Ingold, *J.*, 1948, 17.

sidered in the next section. To avoid confusion in these and subsequent formulæ, only the relevant hydrogen atoms are shown.



(XIX.) (XX.) (XXI.)



(XXII.) (XXIII.)

If a small molecular proportion of potassium amide in ammonia acts upon the unconjugated 2 : 5-dihydroanisole (XIX), the potassium salt (XX) acts merely as a turntable to set up the equilibrium and the conjugated (lower-energy) 2 : 3-dihydroanisole (XXI) results. The conditions are those of *reversible* proton addition. If a large relative amount of potassium amide is used, the potassium salt (XX) is the preponderating substance present, and if protons are added to it by the rapid action (*irreversible*) of alcohol or ammonium chloride, the unconjugated (XIX) results. This is true whether the salt is made from (XIX) or (XXI). The proton is added most rapidly at the 2-position, which should be the position of greatest charge-density, since it is in the middle of the mesomeric system and *ortho* to the methoxyl group. A similar conversion of 3 : 4-dihydro-1-naphthoic acid (XXII) into 1 : 4-dihydro-1-naphthoic acid (XXIII) can be produced through the dipotassium salt in ammonia. Again addition occurs to the point of highest density in the middle of the system and adjacent to the charge-stabilising CO_2K group. Whatever the theoretical interpretation of these results, they are experimental facts which must be accepted.

The production of ions of this type in a reduction reaction would obviously lead to the $\alpha\delta$-dihydro-derivatives (unconjugated) encountered in practice, if protons can be added irreversibly. This is undoubtedly possible if an " acid " strong compared with the hydrocarbon " acid " formed in the reduction is present. Alcohols (p*K* about 16—18) fulfill this condition, but ammonia itself (p*K* about 34) does not.

Originally,[23] it had been assumed that protons are added *simultaneously* to a bivalent mesomeric anion formed by the addition of two electrons to a benzene ring, in order to explain by mutual charge repulsion the $\alpha\delta$-positions taken up by the protons. If one proton comes from the ammonia and one from the alcohol, this would not be improbable from a kinetic point of view, but the results above make it unnecessary. Examples of successive addition are to be found in reactions like $Ph_2C{=}CH_2 \rightarrow Ph_2C{-}\overset{-}{C}H_2 \rightarrow Ph_2\overset{-}{C}{-}CH_3$ (compare Wooster's " benzhydryl rule "),[68] where the unstabilised charge

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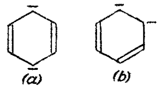
[68] C. B. Wooster and N. W. Mitchell, *J. Amer. Chem. Soc.*, 1930, **52**, 688 ; C. B. Wooster and J. F. Ryan, *ibid.*, 1932, **54**, 2419.

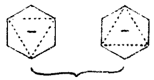
corresponding to the weakest " acid " is the first to abstract a proton from the solvent. From this, and on general grounds, it seems likely that if two charges are present in a molecule the one which reacts first will be that corresponding to the weakest " acid ", *i.e.*, the one whose reaction produces the greatest free-energy change. This assumes that purely steric effects are negligible, which appears to be true for the systems considered. In fact, using the results already arrived at, it is possible to predict with considerable detail the products obtained by the reduction of substituted benzenes. This is strong support for the whole theory.

The rule of addition of hydrogen atoms to a benzene ring based on the experimental evidence is as follows: [65] the atoms are added in positions $\alpha\delta$-to each other, avoiding carbon atoms carrying electron-repelling groups in the order NMe_2,OMe > alkyl, and being attracted to carboxyl groups. The last influence outweighs all others so far investigated, presumably because it acts by a mesomeric mechanism which can stabilise the charge on an oxygen, while the others act by a mere electron-repelling tendency.

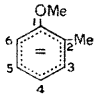
In the last section, it was shown that even if the potential-determining stage is the addition of one electron, the products will almost certainly correspond to the addition of two electrons. Two-electron addition may even be obligatory for monobenzenoid compounds. The products are therefore discussed on the assumption that they are determined by addition, in successive stages, of two protons to bivalent mesomeric anions, of which (XXIV, *a* and *b*) are canonical forms.



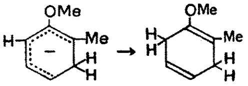
(XXIV.)



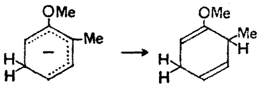
(XXV.)



(XXVI.)



(XXVII.) (XXIX.)



(XXVIII.) (XXX.)

In such a mesomeric anion the electron-distribution can be estimated qualitatively without much difficulty. The two charges cannot reside on the same carbon atom without violating the octet rule, or on carbon atoms *meta* to each other without introducing very improbable ions containing three-membered rings. They must therefore be disposed among alternate carbon atoms as in (XXV), one charge to each set of three carbons.* The truth of this can easily be confirmed by writing out the various canonical forms. The effects of substituents are best illustrated by examples. Two electrons added to *o*-methylanisole will be distributed one between the 1 : 3 : 5- and the other between the 2 : 4 : 6-positions (XXVI). Both

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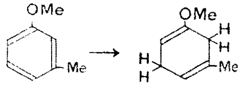
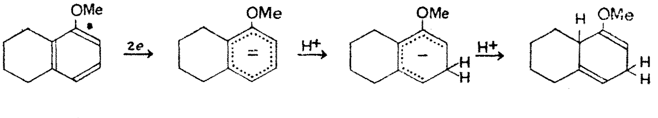
* The complete charge is distributed between the carbon atoms at the corners of the triangle.

substituents raise the energy of the system to which they are attached, but the effect is greater in the 1 : 3 : 5-system because of the greater electron-repulsive power of the methoxyl group. In addition, the 2 : 4 : 6-charge will be stabilised by the *ortho*-influence of the methoxyl group (p. 74). The 1 : 3 : 5-charge must therefore react first, and its point of highest charge-density will be at the unsubstituted 3- or 5-position. Neither of these carries a substituent, but they are not equivalent because of the effect produced by charge-repulsion in the 2 : 4 : 6-system. In the latter, the charge-density is evidently higher in the 6- than in the 2-position because of the methyl group. This means that the 3-position will carry the greater charge, but since the effect is a second-order one, the difference between the 3- and the 5-position is probably not very pronounced. The expectation is therefore that addition will be initiated chiefly in the 3-position, to give (XXVII), and to a lesser extent in the 5-position to give (XXVIII). These will then react according to the experimental results above to give respectively (XXIX) and (XXX). These two substances are in fact obtained,[65] with a preponderance of (XXIX).



(XXXI.) (XXXII.)



(XXXIII.) (XXXIV.)

An alkyl group in a *m*-position, *e.g.*, with *m*-tolyl methyl ether (XXXI), exercises a *primary* influence on the addition of the first proton, since it is directly attached to the 1 : 3 : 5-system. Accordingly, only one product is to be expected, in this case 2 : 5-dihydro-*m*-tolyl methyl ether. A particularly interesting case is that of 5-methoxy-1 : 2 : 3 : 4-tetrahydronaphthalene (XXXIII), for which there was originally no basis on which the course of the reaction could be predicted.[65] It is now clear that the product should be (XXXIV), obtained experimentally.

Where addition of the second proton must take place in a position occupied by an alkyl group (or a saturated carbon atom) in order to give αδ-reduction, some αδ-reduction to give a conjugated diene might be expected as well. 5-Methoxytetralin (XXXIII) is a good test-case, and, in fact, the further reduction products of the expected conjugated diene (XXXV)—9 : 10-octalin (XXXVI) and (after acid hydrolysis) 1-ketodecalin, corresponding to (XXXVII)—could be detected in the crude product of reduction by sodium and ethanol in ammonia.[69] With anisole itself only a trace of methoxy*cyclo*hexene accompanies the methoxy*cyclo*hexadiene formed in this process.

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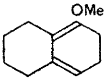
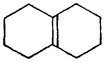
[69] A. J. Birch, unpublished work.

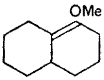
In the reduction of benzene rings containing electron-attracting groups like carboxyl, the di-anion has a high electron concentration in the vicinity of the CO_2Na group, due to its ability to stabilise the negative charge by the resonance $\overset{-}{\mathrm{C}}\text{—}\mathrm{C}(\underbrace{\mathrm{ONa}){=}\mathrm{O}\ \ \mathrm{C}{=}\mathrm{C}(}\mathrm{ONa})\text{—}\overset{-}{\mathrm{O}}$. This concentration repels the other (less stabilised) charge to the *p*-position, which accordingly forms



(XXXV.)



(XXXVI.)

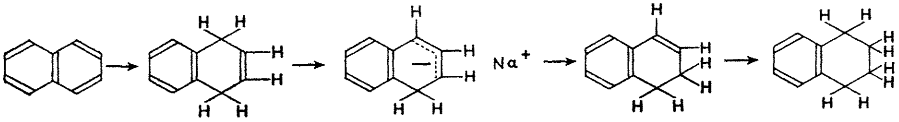


(XXXVII.)

the seat of initial reaction. The product on this basis should be the experimentally found 1 : 4-dihydrobenzoic acid.[57] Other electron-attracting groups like carbonyl are usually reduced in preference to the ring. Where the effect of carboxyl would require a negative charge to occupy a position on a carbon bearing methoxyl, this is eliminated as an anion, presumably because of the greater electron affinity of oxygen than of carbon. The product is the reduced benzoic acid.[69] The elimination of methoxyl observed below in the reduction of 2 : 3-dihydroanisoles (*e.g.*, XXI) is probably for the same reason.

III. Secondary Processes

What may for convenience be termed primary reduction products are those obtained under conditions of irreversible proton addition, whereas secondary products are those obtained when proton addition is reversible. To illustrate the difference we may take the example of naphthalene. In the reduction of naphthalene with sodium in ammonia at the boiling point,[70] it was found that four atoms of sodium are taken up per molecule, the eventual product being 1 : 2 : 3 : 4-tetrahydronaphthalene. It was assumed that a tetrasodium addition product was formed. Later,[63] it was shown that the initially-formed disodium addition product abstracts protons from the ammonia to give 1 : 4-dihydronaphthalene (XXXVIII) which is



(XXXVIII.)

(XXXIX.)

isomerised by the sodium amide formed in the process to the conjugated 1 : 2-dihydronaphthalene (XXXIX) through the sodium salt. The 1 : 2-di-hydronaphthalene is then reduced further by two more sodium atoms to tetrahydronaphthalene. The conjugated isomer is formed because the conditions favour reversible proton-addition, and it is then reducible because of the conjugation.

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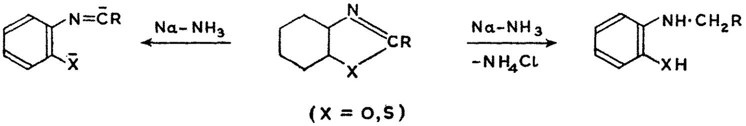
[70] C. B. Wooster and F. B. Smith, *J. Amer. Chem. Soc.*, 1931, **53**, 179.

Reversible proton-addition can occur only if the initial reduction product is an " acid " comparable in strength with the strongest " acid " present in the solution—in this case ammonia itself. If a stronger acid is present, *e.g.*, ethylaniline, the primary reduction product is obtained, and if the product is the strongest " acid " in the solution it is again unchanged, because it is protected as its sodium salt until the reaction mixture is worked up. An example of the latter is the reduction of 2-naphthol to 2-tetralone in up to 80% yield by sodium and alcohol in ammonia.[65, 69] It may seem surprising that a ketone can escape reduction under such vigorous conditions, but it is evidently protected by the negative charge on the enolate ion. The enol forms of the ketones are probably fairly stable at the low temperatures used, and unlike the keto-forms, their acidity must be quite high (of the order p*K* 10). Even nitroparaffins are not reduced by sodium and ammonium bromide in ammonia, presumably because they form stable ammonium salts of the *aci*-form.[71] Another good example of the stabilisation of an unsaturated compound by salt formation can be seen in the contrast between the following reactions (ammonium chloride is an " acid " on the ammonia scale) :[72]



The presence of ammonium salts may assist reactions by removing the strongly basic compounds (sodium hydroxide or amide) formed. For example, nitroguanidine goes smoothly to aminoguanidine in the presence of ammonium bromide, but not in its absence.[73]

The production of tetrahydrobenzenes from benzenes by the action of calcium hexammine, $Ca(NH_3)_6$, observed by Kazanskii and his co-workers,[74] is to be explained on the basis of secondary reductions. The primary products are undoubtedly the same as those obtained from the sodium–alcohol–ammonia reduction—unconjugated dihydrobenzenes—and these are then conjugated probably by the influence of calcium amide, and then further reduced. The original discoverers of the reaction [75] in fact obtained from benzene the 1 : 4-dihydrobenzene, although later workers, presumably using slightly different conditions, were unable to repeat the preparation. Anisole derivatives often give rise chiefly to di- rather than tetra-hydro-derivatives.[29, 31]

The reaction can be imitated by using sodium–ammonia solutions in several stages.[29] The first stage is with sodium–alcohol–ammonia to form

[71] G. W. Watt and C. M. Knowles, *J. Org. Chem.*, 1943, **8**, 540.

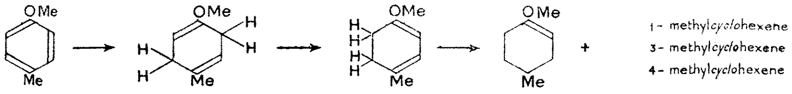
[72] C. M. Knowles and G. W. Watt, *ibid.*, 1942, **7**, 60

[73] L. P. Fuller, E. Lieber, and G. B. L. Smith, *J. Amer. Chem. Soc.*, 1937, **59**, 1150.

[74] B. A. Kazanskii and N. F. Glushnev, *J. Gen. Chem. Russia*, 1938, **8**, 642 ; *Bull. Acad. Sci. U.R.S.S.*, 1938, 1061, 1065 ; B. A. Kazanskii and N. V. Smirnova, *ibid.*, 1937, 547.

[75] A. V. Dumanskii and A. V. Zvyereva, *J. Russ. Phys. Chem. Soc.*, 1916, **48**, 994.

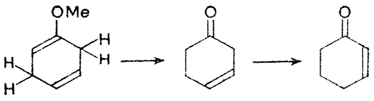
the unconjugated dihydro-derivative. This can then be reduced to tetrahydrobenzenes by the action of sodium in ammonia, the sodium amide formed in the reaction acting as the conjugating agent. Alternatively, the unconjugated dihydrobenzene can be conjugated first by the action of metal amide in ammonia, and then reduced by sodium in ammonia. An example is *p*-tolyl methyl ether, the principal stages being :



Phenols may be obtained by the Kazanskii method from phenol ethers which are difficult to reduce, *e.g.*, 2 : 6-dimethylanisole, but owing to the complex mixture of products the reactions are not of much value. Good yields of 1-methoxy*cyclo*hexenes can be obtained from resorcinol dimethyl ethers,[69] and benzsuberan has been reduced to its tetrahydro-derivative as a preparative method.[76]

IV. Applications in Synthesis and Degradation

From the reactions already mentioned, it is clear that the reagents are likely to have many applications. Work up to the present has, however, been concerned mainly with an exploration of properties and mechanisms. Applications may be based on such properties as lack of steric hindrance ; [77] the formation of *trans*-ethylenes from acetylenes [60] (catalytic methods give chiefly *cis*-) ; but above all on their combination of great power with structure-specificity. The formation of αδ-dihydrobenzenes shows that the sodium–alcohol–ammonia reagent is powerful enough to reduce a benzene ring, but specific enough to add only two hydrogens. The dihydrobenzenes are intrinsically interesting, and can also be converted into compounds inaccessible by other methods. For example, the dihydroanisoles are the enol methyl ethers of ketones, and can be converted by acid hydrolysis first into the βγ- and then into the αβ-unsaturated ketones.[65, 31] This method was the chief one used to identify the products of such reductions. Anisole itself gives 2 : 5-dihydroanisole (XL), which is hydrolysed first to *cyclo*hex-3-enone (XLI) and this is converted into *cyclo*hex-2-enone (XLII).



(XL.) (XLI.) (XLII.)

The syntheses of the sesquiterpenes α-, β-, and γ-curcumene, (XLIII), (XLIV), and (XLV), illustrate some important characteristics of the

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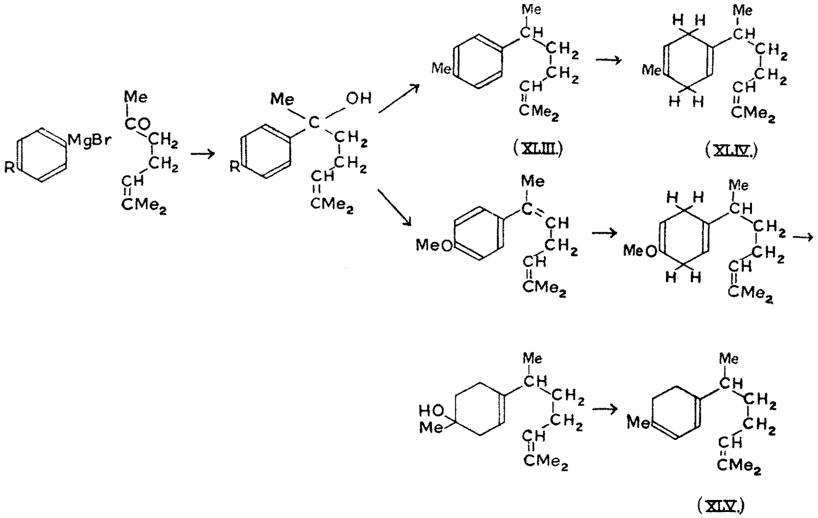
[76] P. A. Plattner, *Helv. Chim. Acta*, 1944, **27**, 808.

[77] H. L. Lochte, J. Horeczy, P. L. Pickard, and A. D. Barton, *J. Amer. Chem. Soc.*, 1948, **70**, 2012.

reagent.[78] The production of α-curcumene (XLIII) shows that a benzyl alcohol can be hydrogenolysed without noticeable reduction of the ring, but that the ring can be reduced (production of XLIV) by sufficient reagent. The *p*-methoxy-compound employed in the synthesis of γ-curcumene (XLV) cannot be hydrogenolysed directly, but after dehydration the double bond can be hydrogenated because of its conjugation with the ring. In none of these compounds is the isolated double bond in the side chain affected.



(XLIII.) (XLIV.) (XLV.)

One of the greatest difficulties encountered in synthesis is that many compounds are but little soluble in ammonia, particularly if their molecular weight is greater than about 150. Several methods can be applied to overcome the difficulty, at least in part. Rise in temperature greatly increases solubility, as can be seen from the example of cholesterol [79] (mg./100 c.c.) : − 38°, 0·00 ; 0°, 6·16 ; 49°, 545·0. To utilise this requires, however, work under pressure with considerable mechanical difficulty. A more practical method which can be used with phenol ethers is to use side chains containing hydroxyl groups, which render the molecule soluble.[78, 80] Hydrolysis of the reduced material gives a ketone with removal of the side chain, so that its nature does not matter. The following syntheses have been accomplished : thymyl 2-hydroxyethyl ether (XLVI) to piperitone (XLVII) ; α-œstradiol 1-glyceryl ether (XLVIII) in several stages to nortestosterone (XLIX), and hexœstrol bis-(2-hydroxyethyl) ether (L) to (LI) and (LII). A further advantage of such side chains is that the products are readily separated from any unchanged starting material by distillation or chromatography. According to G. F. Pope,[81] it is necessary to have about 10% of alcohol in

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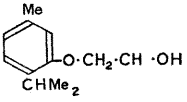
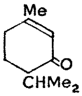
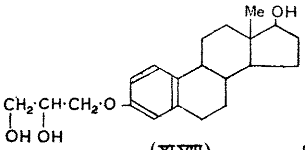
[78] A. J. Birch and S. M. Mukherji, *J.*, 1949, 2531 ; A. J. Birch, *J.*, 1950, 367.
[79] R. G. Gustavson and J. B. Goodman, *J. Amer. Chem. Soc.*, 1927, **49**, 2526.
[80] A. J. Birch and S. M. Mukherji, *Nature*, 1949, **163**, 766.
[81] Private communication.

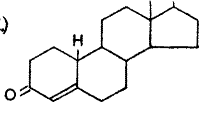
the ammonia to ensure reduction with the hexœstrol derivative. The use of mixed solvents merits further investigation.

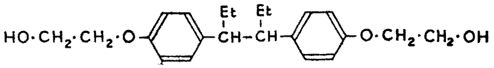
Another useful property of the solutions is that they can be used with sulphur compounds which poison metallic catalysts. Amino-acids containing thiol groups are readily prepared by the reduction of benzylthio-derivatives.[82] Penicillamine (LIII) and some of its *N*-alkyl derivatives (LIV) have been similarly prepared.[83] Another sulphur compound conveniently prepared is B.A.L. (British Anti-Lewisite) (LV),[84] 2 : 3-dimercaptopropanol.

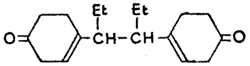

(XLVI.)

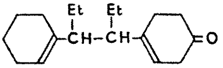

(XLVII.)


(XLVIII.)


(XLIX.)


(L.)

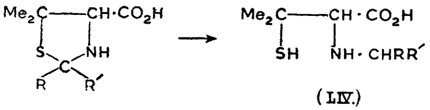

(LI.)

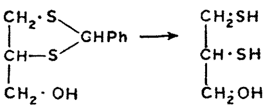

(LII.)

An outstanding problem for synthetic work is the protection of reducible groups while others are undergoing reduction. The carbonyl group can often be protected by conversion into an acetal or an enol ether, *e.g.*, (LVI) can be converted into (LVII), the benzene ring reduced, and the carbonyl group recovered by the action of acid to give (LVIII).[85] An aryl ketone cannot usually be so protected, because the acetal undergoes hydrogenolysis, and an $\alpha\beta$-unsaturated ketone cannot be protected as its enol ether, because this contains conjugated bonds capable of reduction. Fortunately, a complementary method can often be employed in such cases, because the


$Me_2C(SCH_2Ph)\cdot CH(NH_2)\cdot CO_2H \longrightarrow Me_2C(SH)\cdot CH(NH_2)\cdot CO_2H$

(LIII.)


(LIV.)


(LV.)

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[82] V. du Vigneaud *et al.*, *J. Biol. Chem.*, 1935, **108**, 753 ; **109**, 97 ; **112**, 149 ; etc.

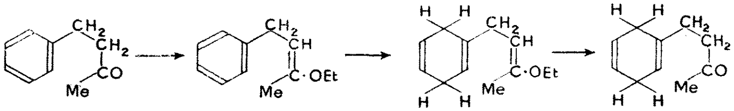
[83] " The Chemistry of Penicillin ", Princeton Univ. Press, 1949, 16, 460.

[84] L. A. Stocken, *J.*, 1947, 593.

[85] A. J. Birch and S. M. Mukherji, unpublished.

enol salts of unsaturated ketones, unlike the saturated ones, are often stable enough in ammonia to protect the group even when the reduction demands the presence of an alcohol.[69]

The general problem is still under investigation, but the principles are clear : the unsaturated group must be converted (reversibly) into a saturated one, or into one containing only an isolated carbon–carbon double bond, or else it must be charged negatively by salt formation.



(LVI.) (LVII.) (LVIII.)

Few uses have been made of the reagents for the investigation of natural products, although their properties suggest a number of possible applications. The fission of aryl or benzyl ethers has been tentatively applied in the investigation of lignin.[86] K. Freudenberg and his co-workers found that aryl-, but not alkyl-, glucosides are split by potassium in ammonia, and from the fact that lignin is almost entirely removed from intact wood, they conclude that any links between lignin and carbohydrate are of the aryl-glucoside type. Other workers [87] obtained about 80% of products of low molecular weight from a similar lignin treatment, which confirms that most of the linkages between units are through oxygen rather than carbon. A determination of the nature of the products may give further information on the structure of lignin. Methylated acacia tannin also gives a proportion of products of lower molecular weight.[88] The fission of quaternary ammonium salts (Emde reaction type) may well prove a useful tool in alkaloid investigations.[16]

Ammonia is cheap, and the mechanical difficulties encountered when working at atmospheric pressure are small because the latent heat of vaporisation is large and the boiling point not unduly low. Ordinary apparatus can be used, with or without " dry-ice " baths and condensers. Dewar flasks are useful, but not essential ; the chief requisite is a good fume-chamber. Excess of sodium can be destroyed catalytically by a trace of ferric nitrate [68] or chemically by sodium nitrate.[89]

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[86] K. Freudenberg, K. Engler, E. Flickinger, A. Sobek, and F. Klink, *Ber.*, 1938, **71**, 1810 ; K. Freudenberg, W. Lautsch, and G. Piazolo, *ibid.*, 1941, **74**, 1879.

[87] N. N. Shorygina and T. Y. Kefeli, *J. Gen. Chem. U.S.S.R.*, 1947, **17**, 2058.

[88] A. J. Birch and A. M. Stephen, unpublished work.

[89] N. O. Kappel and W. C. Fernelius, *J. Org. Chem.*, 1940, **5**, 40.