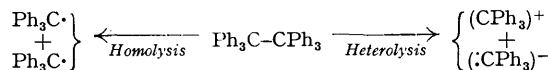## Some Recent Developments in the Chemistry of Free Radicals.

TILDEN LECTURE, DELIVERED IN MANCHESTER ON JANUARY 24TH, 1946, AND IN GLASGOW ON FEBRUARY 15TH, 1946.

By WILLIAM A. WATERS, M.A., Sc.D.

To every organic chemist the term " free radical " calls to mind the reactive substance *triphenylmethyl* and the brilliant researches of Gomberg, which demonstrated the inadequacy of the XIXth Century doctrines of the quadrivalency of carbon. This work finally demonstrated that hexaphenylethane can, and does, dissociate in two ways : *homolytically*, in non-ionising solvents to give " trivalent carbon radicals ", and *heterolytically* in ionising (co-ordinating) solvents to give two ions.

$$\left.\begin{array}{c}Ph_3C\cdot \\ + \\ Ph_3C\cdot\end{array}\right\} \xleftarrow[\textit{Homolysis}]{} Ph_3C\text{--}CPh_3 \xrightarrow[\textit{Heterolysis}]{} \left\{\begin{array}{c}(CPh_3)^+ \\ + \\ (:CPh_3)^-\end{array}\right.$$

We can today define a " free radical " as a product of a homolytic bond fission, and utilise for purposes of diagnosis an inherent property of an unpaired electron—its *magnetic moment*. Whatever their chemical reactivity, free radicals are invariably *paramagnetic* substances (of molecular susceptibility, χ_μ, ca. 1200×10^{-6} e.m.u.), in marked contrast to all normal covalent molecules, and ions, which, except for derivatives of certain transition metals and rare earths,[1] are diamagnetic (of susceptibility, χ_d, -10 to -100×10^{-6} e.m.u.).

The existence of " radical-ions," such as the *aminium salts*, e.g., $(p\text{-Tol}_2\overset{\cdot}{N}\text{--}\overset{\cdot}{N}Tol_2)^+(ClO_4)^-$,[2] thus does not introduce theoretical complexities, for they are paramagnetic salts, whilst again chemical similarities between the simple inorganic molecules, oxygen gas and nitric oxide, and the organic free radicals receive a physico-chemical explanation.

Magnetic susceptibility measurement has, in recent years, become a valuable physical tool, not only for establishing whether or not any substance is a true free radical, but also for examining quantitatively the homolytic dissociability of covalent bonds. Though direct gravimetric methods [3, 4] may give results of more accurate absolute value, the manometric method of inserting one arm of a U-tube between the poles of a powerful electromagnet and observing the shift in level of a solution when the magnetic field is applied is the more convenient for the organic chemist, for he can prepare and examine his products in sealed glass systems [5] and thereby work easily with active radicals, such as triphenylmethyl, which must be handled in the complete absence of oxygen.

Of the many interesting results which have emerged from these magneto-chemical investigations of organic substances, the following have a special theoretical interest :—

1. *Di-radicals* such as (I) can of course exist, but in the *para* series it has often been queried whether the corresponding reactive hydrocarbons were di-radicals (II) or quinones (III). The magnetic studies of Müller [6]
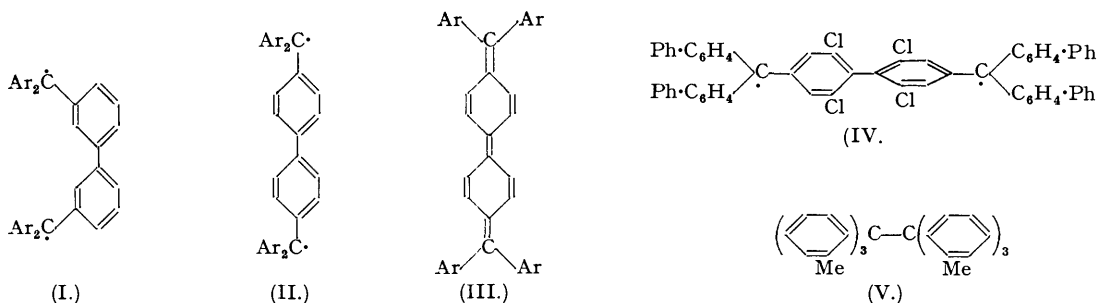
(I.)   (II.)   (III.)   (IV.   (V.)

have shown that the quinonoid structure (III) is the favoured one, rather than (II) or its dimer, but that when the central diphenylyl system is so substituted in the *ortho* positions that free rotation is sterically hindered, and coplanarity of the rings becomes impossible, then a genuine benzenoid di-radical (IV) is formed. This work demonstrates the essential coplanarity of quinonoid systems, such as (III), and affords an excellent justification of Pauling's contention that coplanarity is a pre-requisite for any resonance interchange (*i.e.*, bond formation) between two electron orbits however far apart they may be.

2. The elucidation of the structural features which influence the dissociability of structures $R_3C\text{--}CR_3$ has engaged the attention of both experimental and theoretical chemists for the past forty years, and though a reasonable qualitative explanation can now be given in terms of the resonance theory,[7] the subject is still too complex for successful quantitative treatment. Recent magnetic measurements [8] have shown that the occurrence of side reactions, such as disproportionation (see below, p. 411), invalidates much of the earlier cryoscopic data, and reveals that the increasing of the number of possible canonical states in the radical $R_3C\cdot$ is not the only structural factor of significance. In addition, the presence of substituents *ortho* to the weak bond, as in (V), favours homolysis most definitely.[9]

It has been suggested, with some physical justification,[10] that this " ortho effect " is steric, and leads to a stretching of the central C–C bond. In this respect theory seems to have come full-circle back to the views of Gomberg and Baeyer; this exemplifies once again how the experimental organic chemist seems to be led instinctively to a conclusion which, much later, is established quantitatively, though with extreme difficulty, by the mathematical physicist.
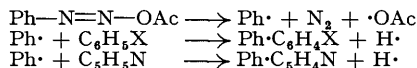
This dissociation problem has another theoretical aspect of importance. Ziegler and his colleagues [11] have shown that the rates of reaction of compounds $R_3C–CR_3$ with nitric oxide, or better with oxygen, can be used for measuring the rate of dissociation of the central C–C link. They find inevitably that the activation energy for the dissociation process is greater than the heat of dissociation, a fact which accords with the view that a tetrahedral group, $R_3C–$, in $R_3C–CR_3$ becomes stabilised as a planar free radical, $R_3C\cdot$, with the unpaired electron in an *s* orbital. Also from investigations of compounds $AlkylCPh_2–CPh_2Alkyl$ they have shown that *both* the " *PZ* " and the " *E* " terms of the Arrhenius equation $k = PZe^{-E/RT}$ are modified by changes in the nature of the alkyl groups.[12] Changes in the " *P*-factor " of the order of 10^2, to as much as 10^6, are by no means unusual. Evidently no comprehensive theory of covalent bond fission can be derived from energy considerations alone

So far, this lecture has dealt with developments in the chemistry of the free radicals of the Gomberg type, but this subject must now be regarded as but one of the many branches of the chemistry of free radicals, for there has developed, within the past twelve years, a whole new subject, termed by Professor D. H. Hey " The New Organic Chemistry," [13] which deals with the participation in organic reactions in solution of short-lived unstabilised radicals, such as free methyl, $CH_3\cdot$, and free phenyl, $C_6H_5\cdot$, which are identical with the active agents of homogeneous gas reactions. So extensive is this subject already that I shall have to confine my attention to synthetic reactions and technical processes of value.

The existence, in the gas phase, of free methyl was first demonstrated in 1929 by Paneth and Hofeditz,[14] who used for diagnosis its reactions with mirrors of metals such as lead, zinc, and antimony, and later with mercury, tellurium, and other elements to give organo-metallic compounds, *e.g.*, $PbMe_4$, $Me_2Sb–SbMe_2$, which could not be formed directly from known stable hydrocarbons. In 1934, Wieland's indications [15] that free radicals were obtained by the thermal decomposition, in solution, of compounds $Ph_3C—N\!\!=\!\!N—R$ (R = Acyl or Aryl) led D. H. Hey [16] to postulate that the spontaneous decomposition of benzenediazoacetate (*N*-nitroso-acetanilide) in aromatic solvents involved the production of *electrically neutral* phenyl radicals (rather than phenyl cations or anions) which immediately attacked vicinal solvent molecules. In support of this he showed (*a*) that the rate of decomposition of benzenediazoacetate was unimolecular and approximately the same in all solvents, and (*b*) that benzenediazoacetate phenylated aromatic solvents, C_6H_5X, in *all three* positions (the *para* and *ortho* products being isolated most easily) in their aromatic rings, irrespective of the polar nature of the group X (and of orientation laws for the substitution of C_6H_5X). Further evidence for the production of neutral phenyl from benzenediazoacetate [17] is (*c*) the regular abstraction of hydrogen from aliphatic solvents, and of halogens from halogenated liquids, and (*d*) reaction with metals to produce organo-metallic compounds which are clearly analogues of products formed by the Paneth technique.

It is extremely interesting to find that *diazonium chlorides* react similarly with metals in suspension in neutral acetone, and to a lesser extent under ethyl acetate and methyl cyanide,[18] but not under many other solvents, and appear therefore to be capable of existence in a covalent " diazo-state," $Ar—N\!\!=\!\!N—Cl$, which decomposes to give a neutral aryl radical and a free chlorine *atom*.

These decompositions of aromatic diazo-compounds have valuable synthetic applications which have not yet been explored in any great detail. Hey's own subsequent studies [19] have shown that diazoacetates and diazohydroxides formed *in situ* can be used extensively for the union of aryl nuclei :

$$Ph—N\!\!=\!\!N—OAc \longrightarrow Ph\cdot + N_2 + \cdot OAc$$
$$Ph\cdot + C_6H_5X \longrightarrow Ph\cdot C_6H_4X + H\cdot$$
$$Ph\cdot + C_5H_5N \longrightarrow Ph\cdot C_5H_4N + H\cdot$$

and are of particular value for the synthesis of unsymmetrical diphenyls and polyphenyls, and also of aryl-substituted pyridines, including useful dyes and substances of some therapeutic value.

The reactions of diazonium chlorides with metals can be developed into new synthetic methods for the preparation of organo-metallic compounds of mercury, arsenic, antimony, tellurium, and perhaps other elements.[20] The syntheses by Nesmejanow and his colleagues in Russia [21] of aromatic compounds of mercury, tin, and lead, by reducing diazonium double salts in organic solvents, and also the Bart and Schmidt reactions for preparing aryl arsonic and stibonic acids, *e.g.*,

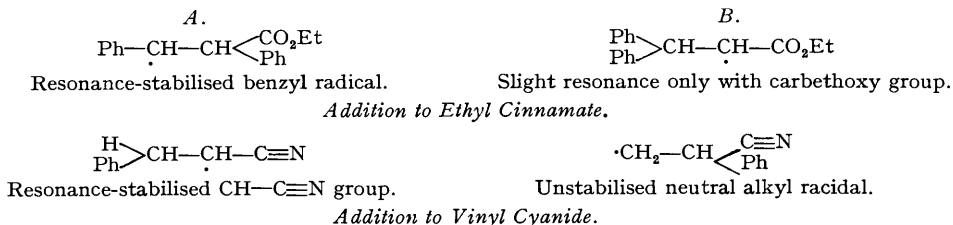$$Ph\cdot N_2\cdot OH + Na_2HAsO_3 \longrightarrow Ph\cdot AsO(ONa)_2 + H_2O + N_2$$
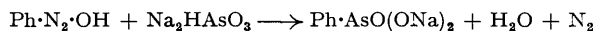
can be explained along these lines.

Besides substituting into aromatic nuclei and abstracting hydrogen from paraffin chains, the free aryl radicals derivable from diazoacetates or diazohydroxides will add on to many olefinic substances, and give eventually *either* arylated olefins *or* long chain polymers. For instance, in 1939, Meerwein, Büchner, and Von Emster [22] showed that diazo chlorides in neutralised aqueous acetone, in the presence of a trace of a cupric salt, would arylate $\alpha\beta$-unsaturated esters, ketones, and cyanides, whilst a similar reaction occurs with quinones and with nitrosophenols.[23] Meerwein and his colleagues believed that the aryl group regularly added on to the double

bond in the α-position to the activating CO or CN group, but more recently Koelsch [24] in U.S.A. has shown that, whereas ethyl cinnamate gives the α-phenyl derivative, ethyl crotonate and vinyl cyanide both give β-phenyl compounds. This is a further indication that th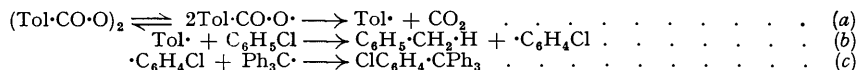e processes are not ionic in character, since the substances concerned are all catio-enoid systems, *e.g.*, $C=C-C=O$, which should in polar addition reactions all give similar products. It follows from the free neutral radical hypothesis, however, that the first addition product to any unsaturated compound will itself be a neutral radical, and since, in each case formulated below, the resonance-stabilisation of the radical is greater in form A than in form B, it will follow that the predominating addition reaction should take a different course in the two cases.

A.

$$Ph—CH—CH{<}^{CO_2Et}_{Ph}$$

Resonance-stabilised benzyl radical.

B.

$$^{Ph}_{Ph}{>}CH—CH—CO_2Et$$

Slight resonance only with carbethoxy group.

Addition to Ethyl Cinnamate.

$$^{H}_{Ph}{>}CH—CH—C{\equiv}N$$

Resonance-stabilised CH—C≡N group.

$$·CH_2—CH{<}^{C{\equiv}N}_{Ph}$$

Unstabilised neutral alkyl radical.

Addition to Vinyl Cyanide.

In many ways the decomposition reactions of the covalent aromatic diazo-compounds are similar to those of the diacyl peroxides, which, in many solvents, eliminate carbon dioxide by decomposing in two successive stages, and liberate free hydrocarbon radicals, *e.g.* :

$$Ph·CO·O·O·CO·Ph \rightleftharpoons 2Ph·CO·O· \longrightarrow Ph· + CO_2.$$
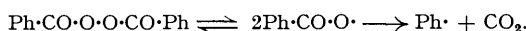
Hey [25] showed that the non-polar phenylation of aromatic nuclei can be effected with dibenzoyl peroxide, whilst Wieland [26] from a more extensive study has shown that when diacyl peroxides decompose in solution there are produced, by hydrogen abstraction, further active radicals which are characteristic of the solvent used. For instance, when di-*p*-toluoyl peroxide is allowed to decompose in chlorobenzene solution containing triphenylmethyl some chlorotetraphenylmethane is formed. Evidently the reaction sequence is :
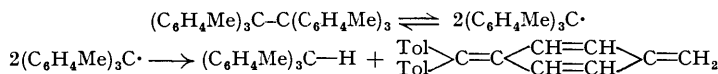
$$(Tol·CO·O)_2 \rightleftharpoons 2Tol·CO·O· \longrightarrow Tol· + CO_2 \quad \cdots \cdots \cdots \quad (a)$$
$$Tol· + C_6H_5Cl \longrightarrow C_6H_5·CH_2·H + ·C_6H_4Cl \quad \cdots \cdots \quad (b)$$
$$·C_6H_4Cl + Ph_3C· \longrightarrow ClC_6H_4·CPh_3 \quad \cdots \cdots \cdots \quad (c)$$

including, at stage (*b*), a prompt replacement of the tolyl radical by the chlorophenyl radical $·C_6H_4Cl$, which then persists, in kind though not necessarily in identity, by solvent collisions, such as (*d*)

$$·C_6H_4Cl + H·C_6H_4Cl \rightleftharpoons H·C_6H_4Cl + ·C_6H_4Cl \quad \cdots \cdots \cdots \quad (d)$$
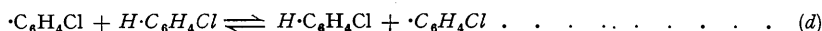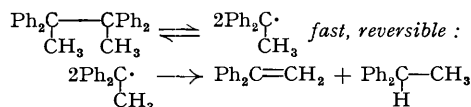
until combination with triphenylmethyl can occur, (*c*). Thus though hydrogen abstraction by free radicals is more particularly characteristic of reactions between free active radicals and aliphatic molecules it still can occur, together with arylation (see above, p. 410), in reactions involving aromatic solvents.

Hydrogen abstraction of this same type is also a common reaction of the more stable radicals of the triarylmethyl series. For instance tri-*p*-tolylmethyl undergoes a first-order disproportionation, which obscures ebullioscopic measurement of dissociability : [27]

$$(C_6H_4Me)_3C–C(C_6H_4Me)_3 \rightleftharpoons 2(C_6H_4Me)_3C·$$

$$2(C_6H_4Me)_3C· \longrightarrow (C_6H_4Me)_3C—H + {}^{Tol}_{Tol}{>}C=C{<}^{CH=CH}_{CH=CH}{>}C=CH_2$$

and tetraphenyldimethylethane reacts as follows : [28]

$$Ph_2\underset{CH_3}{C}——\underset{CH_3}{C}Ph_2 \rightleftharpoons 2Ph_2\underset{CH_3}{C}· \quad fast, \, reversible :$$

$$2Ph_2\underset{CH_3}{C}· \longrightarrow Ph_2C=CH_2 + Ph_2\underset{H}{C}—CH_3$$

Hence no clear line of demarkation can be made between reaction mechanisms of these resonance-stabilised radicals and those of intensely active radicals such as free phenyl.

Just as the diazotates will arylate quinones [23] so also can both diacyl and diaroyl peroxides, as was shown by Fieser and his colleagues in 1942. [29] In carrying out this valuable synthetic reaction for the introduction of alkyl groups it is safer, and often more convenient, to use salts of quadrivalent lead, or, more simply, a mixture of red lead and an anhydrous organic acid. These lead salts decompose smoothly to give either a diacyl peroxide, or, more probably, free carboxylate radicals, and risks of explosions can thereby be avoided, *e.g.* :

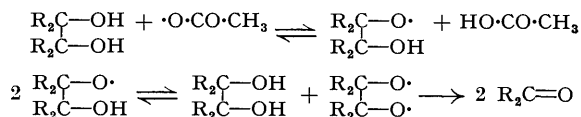$$Pb(O·CO·CH_3)_4 \longrightarrow Pb(O·CO·CH_3)_2 + 2·O·CO·CH_3 \longrightarrow CO_2 + ·CH_3$$
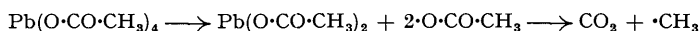
With free methyl radicals produced in solution in these ways, or even by electrolysis, it is possible to methylate aromatic substances such as nitrobenzene, and thus demonstrate the exact similarity between free methyl and free phenyl radicals.
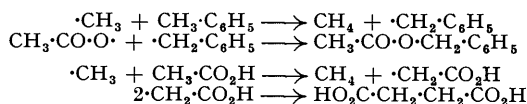
There is no difficulty in explaining all the characteristic reactions of lead tetra-acetate by this free radical mechanism,[30] provided that it is remembered that two different free radicals, (i) neutral acetate, CH_3—CO—O·, and (ii) neutral methyl, ·CH_3, are produced in consecutive stages, and that of these the latter is very much the more reactive, and of short free life, whilst the former (i) can be regenerated by solvent exchange :

$$CH_3—CO—O· + H—O—CO—CH_3 \rightleftharpoons CH_3—CO—O—H + ·O—CO—CH_3$$
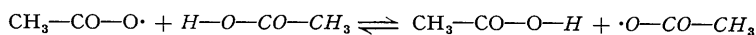
Thus the fission of α-glycols by lead tetra-acetate can be interpreted as a reaction of free acetate radicals, for it occurs without carbon dioxide evolution :

$$\begin{array}{l} R_2C—OH \\ R_2C—OH \end{array} + ·O·CO·CH_3 \rightleftharpoons \begin{array}{l} R_2C—O· \\ R_2C—OH \end{array} + HO·CO·CH_3$$

$$2\begin{array}{l} R_2C—O· \\ R_2C—OH \end{array} \rightleftharpoons \begin{array}{l} R_2C—OH \\ R_2C—OH \end{array} + \begin{array}{l} R_2C—O· \\ R_2C—O· \end{array} \longrightarrow 2\ R_2C{=}O$$
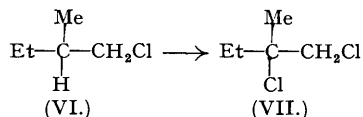
whilst processes involving the dehydrogenation of alkyl groups, such as the acetoxylation of toluene, or the conversion of acetic acid to succinic acid, more probably involve free methyl.

$$·CH_3 + CH_3·C_6H_5 \longrightarrow CH_4 + ·CH_2·C_6H_5$$
$$CH_3·CO·O· + ·CH_2·C_6H_5 \longrightarrow CH_3·CO·O·CH_2·C_6H_5$$
$$·CH_3 + CH_3·CO_2H \longrightarrow CH_4 + ·CH_2·CO_2H$$
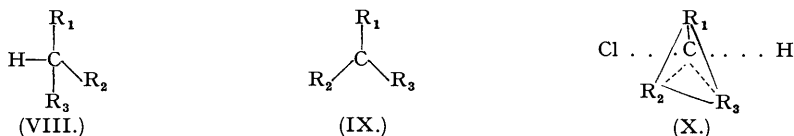$$2·CH_2·CO_2H \longrightarrow HO_2C·CH_2·CH_2·CO_2H$$

It is significant that these latter reactions are not quantitative, require heating, and occur with noticeable gas evolution.

Dehydrogenations such as the above are undoubtedly the chain-initiating processes in most of the " peroxide catalysed " addition and substitution reactions which have been disclosed by Kharasch and his colleagues at Chicago [31] and which will undoubtedly have wide applications in organic synthesis. In the case of " atomic " chlorination by means of sulphuryl chloride, which is one of the most striking of these catalysed reactions, the formation of a *free* hydrocarbon radical by this initial process of hydrogen abstraction has been proved most conclusively by Brown, Kharasch, and Chao [32] by showing that the chlorination of optically active amyl chloride (VI) yielded *inactive* 1 : 2-dichloro-2-methylbutane (VII).

$$\begin{array}{ccc} \overset{\displaystyle Me}{\underset{\displaystyle H}{Et—C—CH_2Cl}} & \longrightarrow & \overset{\displaystyle Me}{\underset{\displaystyle Cl}{Et—C—CH_2Cl}} \\ (VI.) & & (VII.) \end{array}$$

Only if an optically active substance (*e.g.*, VIII) loses hydrogen to form the separated free planar radical (IX), with the odd electron in a spatially symmetrical, *s*, orbital, will such a substitution as this lead to a complete loss of optical activity. Any bimolecular reaction, in which the active chlorine attacked the central carbon atom, would lead to a Walden inversion, by way of a transition complex (X).

$$\begin{array}{ccc} \overset{\displaystyle R_1}{\underset{\displaystyle R_3}{H—C{\diagdown}R_2}} & \overset{\displaystyle R_1}{\underset{R_2\diagup\ \diagdown R_3}{C}} & Cl\ .\ .\ \overset{\displaystyle R_1}{\underset{R_2\diagdown R_3}{\diagup\ .C\diagdown}}\ .\ .\ .\ .\ H \\ (VIII.) & (IX.) & (X.) \end{array}$$

The homolytic, rather than the heterolytic, mechanism for all these peroxide-catalysed processes can confidently be inferred from the fact that they are all chain reactions which proceed only so long as there is free peroxide in the reaction mixture.

Free radical addition to one end of an olefinic link is, quite definitely, the process involved in the peroxide catalysed polymerisation of unsymmetrical olefins, R—CH=CH$_2$, such as styrene, methyl methacrylate and vinyl chloride, though it may not be the process involved in catalysis by such reagents as stannic chloride or boron trifluoride which probably form ionic complexes. In connection with this process of chain polymerisation it is significant to note that C. C. Price and his colleagues,[33] by using *p*-bromobenzoyl peroxide, or tribromobenzoyl peroxide, have shown that the aryl group of the catalyst remains as part of the resultant high polymer. They have also shown that the aromatic diazo-compounds can be used as polymerisation catalysts, though with these substances only the aryl radical seems to enter the structure of the final polymer.[34] Polymerisations in halogenated hydrocarbons, or in solvents such as nitrobenzene, have again shown that radicals produced from solvent molecules may play a part in the reaction process, and that oxygen acts as an inhibitor by adding on to the ends of the growing radical chains.

Since it was Tilden who first discovered the polymerisation of isoprene to a synthetic rubber, it should certainly be pointed out that atomic sodium, by giving up its one valency electron, acts in a similar manner as a catalyst for radical-chain polymerisation,

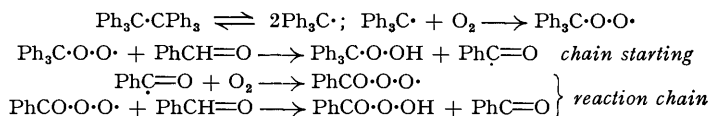$$Na· + CH_2{=}CMe—CH{=}CH_2 \longrightarrow \overset{+}{Na}\ \ :\overset{-}{C}H_2—CMe{=}CH—CH_2·\ \ etc.$$
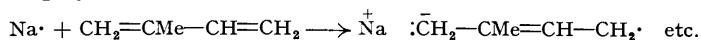
Many other reactions of free metals may have this same feature, though it is impossible to decide, in most cases, whether any solid or liquid metal yields up its electrons singly or in pairs. The formation of the metallic ketyls is of course a typical example of one-electron release.

More recently it has been established by Baxendale, Evans, and Park [35] that the free neutral hydroxyl radical plays a similar part in emulsion polymerisation. This not only confirms the Haber–Weiss theory of the iron-catalysed decomposition of hydrogen peroxide,[36] but indicates that true homolytic reactions can occur in aqueous media.

Though I have already reviewed briefly a large number of different free radical reactions of synthetic and technical value, I have still to refer to what will undoubtedly prove to be the most important group of them all; *i.e., oxidation processes.*

It has for many years been known that oxidation by atmospheric oxygen (" autoxidation ") involved the formation of peroxides, which subsequently broke down in a rather complicated manner. The first definite proof that free radicals were involved in processes of this type is due to Ziegler, who, in 1933,[37] showed that triphenylmethyl would initiate the chain oxidation of many aldehydes and olefins, such as anisaldehyde, styrene, and indene. He also showed that " anti-oxidants," such as pyrogallol, were chain-breakers with easily available hydrogen atoms, and not necessarily decomposers of peroxide molecules.
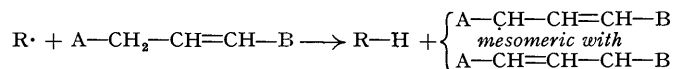
The reaction sequence which he established is as follows :

$$Ph_3C\cdot CPh_3 \rightleftharpoons 2Ph_3C\cdot ; \quad Ph_3C\cdot + O_2 \longrightarrow Ph_3C\cdot O\cdot O\cdot$$

$$Ph_3C\cdot O\cdot O\cdot + PhCH{=}O \longrightarrow Ph_3C\cdot O\cdot OH + Ph\dot{C}{=}O \quad \textit{chain starting}$$

$$Ph\dot{C}{=}O + O_2 \longrightarrow PhCO\cdot O\cdot O\cdot$$
$$PhCO\cdot O\cdot O\cdot + PhCH{=}O \longrightarrow PhCO\cdot O\cdot OH + Ph\dot{C}{=}O \Big\} \textit{reaction chain}$$

The fact that radical-producing agents, such as dibenzoyl peroxide and benzene diazoacetate, are effective catalysts for the autoxidation of many hydrocarbons shows that Ziegler's mechanism can be generalised for the autoxidation of any C–H bond. Again, experimental evidence is steadily accumulating to show that the initial products of nearly all organic autoxidation reactions at moderate temperatures are hydroperoxides, though these often break down very easily in a manner which is not yet fully understood. Though the detailed kinetics of autoxidation is never simple, the very fact that it is invariably a chain-reaction process indicates that free radicals are always involved. The thermal decomposition of the hydroperoxides produced by the oxygen uptake cycle (instanced above for benzaldehyde) may give rise to fresh active radicals, and hence it is now clear why so many autoxidations are auto-catalytic.

By developing reaction mechanisms along these lines it is now becoming possible to co-ordinate theories of gaseous combustion with those of liquid phase reactions.

Besides the evident connection between autoxidation and chain polymerisation, which is a characteristic feature of the autoxidation of olefinic substances, recent demonstrations of the α-methylenic activity of unsaturated substances, such as *cyclo*hexene [38] and the " drying oils ", are of noteworthy theoretical significance. By hydrogen abstraction from these substances there is produced, in the first instance, a resonance-stabilised mesomeric radical,

$$R\cdot + A{-}CH_2{-}CH{=}CH{-}B \longrightarrow R{-}H + \begin{cases} A{-}\dot{C}H{-}CH{=}CH{-}B \\ \textit{mesomeric with} \\ A{-}CH{=}CH{-}\dot{C}H{-}B \end{cases}$$

and it is this stabilisation of the radical which contributes significantly in making the autoxidation of olefins a process which is much more facile than the autoxidation of paraffins. With paraffins the ease of hydrogen abstraction seems to be tertiary CH > secondary CH_2 > primary CH_3, a sequence which accords with the superior " anti-knock " characteristics of branched chain paraffins in combustions at higher temperatures.

The concept of oxidation by the initial abstraction of hydrogen *atoms* from organic molecules is of very wide applicability. Many years ago Wieland [39] drew attention to the fact that a very large number of oxidation reactions, such as the conversion of alcohol into aldehyde, were essentially hydrogen abstractions rather than oxygen additions, and it is more than possible that in the majority of these reactions the primary process is one of homolytic bond fission.

Lead tetra-acetate and dibenzoyl peroxide, which I have already instanced as radical-forming reagents, are by no means the only oxidising agents for which is available evidence of action by the dehydrogenation mechanism. Apparently such simple inorganic oxidisers as chromium trioxide, potassium permanganate, and periodic acid can abstract atomic hydrogen from organic molecules and thereby form free radicals, for they are all immediate catalysts of the autoxidation of tetralin.[30] On similar evidence it can be argued that high temperature dehydrogenation reactions, *e.g.,* by disulphides, quinones, sulphur, selenium, or catalytically active metals, may also proceed by the hydrogen abstraction mechanism, though one could scarcely talk of a " free " radical as an immediate product of a surface-catalysed reaction.

So far I have been indicating free radical mechanism of oxidation for which some experimental justification can already be instanced, but to conclude this lecture I should like to speculate more widely, and to suggest that free radical mechanisms may have even a still wider applicability in fields of biological chemistry, for, as Wieland emphasized,[39] most biological oxidations occur only in the presence of enzymes which have a *dehydrogenase* or hydrogen-abstracting character. Free radical mechanisms for catalysed biochemical oxidations, such as the
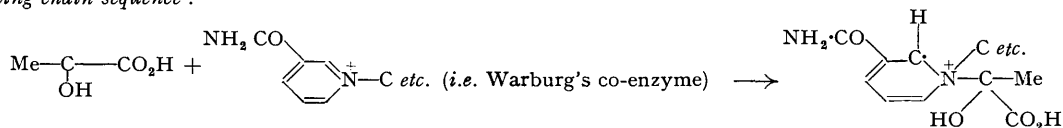
D D

lactate–pyruvate or succinate–fumarate systems, concordant with the oxidation processes which I have been discussing, can easily be postulated.[40]   Thus the lactate–pyruvate system can be represented as follows :
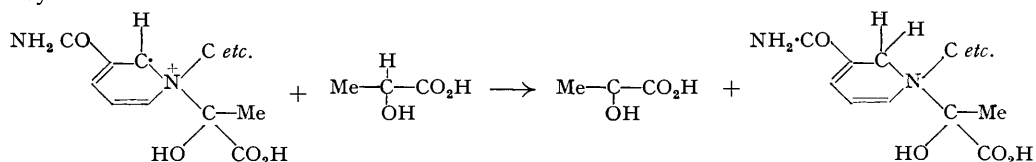
Chain initiation :

$$CH_3—\underset{OH}{CH}—CO_2H + \phi\cdot \longrightarrow CH_3—\underset{OH}{\overset{\cdot}{C}}—CO_2H + H—\phi$$
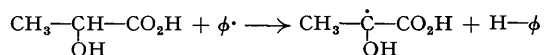
a hydrogen abstraction by a chain starting (enzyme) catalyst $\phi\cdot$ which behaves as a free radical, such as methyl or phenyl.

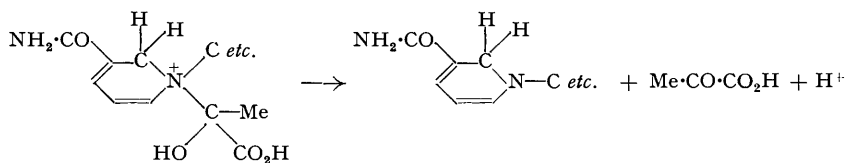*Repeating chain sequence* :

$$Me—\underset{OH}{\overset{|}{C}}—CO_2H + \quad \text{(NH}_2\text{CO / N}^+\text{—C etc.)} \quad (i.e.\ \text{Warburg's co-enzyme}) \quad \longrightarrow$$

followed by

and finally by hydrolysis of the reduced co-enzyme complex, which has an aldehyde-ammonia type of structure, to give free pyruvic acid.
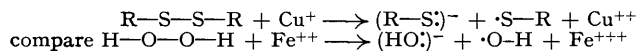
Similarly, one can represent the succinate–fumarate system as a dehydrogenation of succinic acid, followed by a disproportionation of the initial product.

In all such schemes the co-enzyme plays an integral part as a generator of an active radical in a reaction chain, whilst the active prosthetic group of the enzyme catalyst itself is represented (as $\phi\cdot$ in the above scheme) as the provider of the initial free radical.

As yet these hypotheses can be supported only (*a*) by pointing out that many enzyme processes have kinetic resemblances to chain reactions, and (*b*) by instancing the occurrence, or possible occurrence, of undoubted free radicals in the prosthetic groups of certain dehydrogenase enzymes.   In connection with (*b*) the magneto-chemical evidence of the formation of radicals by the partial reductions of riboflavin and the bacterial pigment pyocyanine is particularly cogent.

Again, in connection with other biochemical oxidations, our present evidence [30] showing that thiol radicals, produced by the reversible dissociation of disulphides, can abstract hydrogen atoms from other molecules is of great significance, for disulphide radicals are present in most enzyme proteins.   Disulphides may of course be converted into free thiol radicals by one-electron transference from metallic ions, such as ferrous or cuprous cations, just as the free hydroxyl radical can be produced by the action of ferrous or cobaltous cations upon molecular hydrogen peroxide, *e.g.* :

$$R—S—S—R + Cu^+ \longrightarrow (R—\overset{..}{S}\colon)^- + \cdot S—R + Cu^{++}$$
$$\text{compare } H—O—O—H + Fe^{++} \longrightarrow (H\overset{..}{O}\colon)^- + \cdot O–H + Fe^{+++}$$

In this way the " trace-metals " of many biological systems, and the essential metallic atoms of porphyrins, etc., may play a part analogous to that of the oil-soluble salts of cobalt or manganese in promoting the autoxid-ation of the drying oils.

In the sphere of industrial chemistry, the vulcanisation of rubber may be another radical-chain reaction in which free thiol radicals are concerned.

Today, however, we know so little about the chemical reactions in solution either of the free hydroxyl radical or of free thiol radicals, that it would be premature for me to suggest more than that these active, short-lived, entities should be capable of bringing about, in neutral solution at biological temperatures, many of the oxidation processes which can as yet be effected only by enzyme catalysts.   It is true, however, to say that the transient free neutral radicals constitute the only known types of oxidation catalysts of simple structure which can possibly have sufficient intrinsic energy to be able to break down, at body temperatures, stable organic molecules such as fats and other foodstuffs.

If the " New Organic Chemistry " of free radicals does develop on the lines of these last speculations then the

organic chemist may in future even challenge the concepts of vitalism, and give more substance to some of the formless ideas of Paracelsus. From the way in which the concept of the transient existence of free neutral radicals in solution has, in the last ten years, led to the discovery of a surprising number of new chemical reactions it is, however, quite clear that we have still very much to learn in the laboratory of the possible behaviour of very simple molecules, and any experimentalist who is interested in tracing out reaction mechanisms is still confronted with an embarrassing choice of research problems.

[1] See Sugden, *J.*, 1943, 328 (Liversidge Lecture on Magnetochemistry).
[2] Weitz and Schwechten, *Ber.*, 1927, **60**, 1203; Müller and Wiesemann, *ibid.*, 1936, **69**, 2157.
[3] Sugden, *J.*, 1932, 167; 1943, 328.
[4] Angus and Hill, *Trans. Faraday Soc.*, 1943, **39**, 185.
[5] Compare Roy and Marvel, *J. Amer. Chem. Soc.*, 1937, **59**, 2622.
[6] *Ber.*, 1939, **72**, 2563; 1941, **74**, 807; *Annalen*, 1935, **517**, 134.
[7] Compare Pauling's monograph " The Nature of the Chemical Bond."
[8] Marvel *et al.*, *J. Amer. Chem. Soc.*, 1939, **61**, 2775; 1940, **62**, 1551; 1941, **63**, 1892; 1942, **64**, 1824; Selwood, *J. Amer. Chem. Soc.*, 1939, **61**, 3168; 1941, **63**, 2509.
[9] Marvel *et al.*, *J. Amer. Chem. Soc.*, 1939, **61**, 2009, 2775; 1942, **64**, 1824.
[10] Morris, Byerly, and Selwood, *J. Amer. Chem. Soc.*, 1942, **64**, 1727; Ziegler, *Annalen*, 1942, **551**, 127.
[11] Ziegler, Orth, and Weber, *Annalen*, 1933, **504**, 131; Ziegler *et al.*, *ibid.*, pp. 162, 182; 1942, **551**, 150.
[12] Ziegler, *Annalen*, 1942, **551**, 161.
[13] Hey, *Nature*, 1945, **156**, 36.
[14] *Ber.*, 1929, **62**, 1335.
[15] Wieland, *et al.*, *Annalen*, 1926, **446**, 31; 1927, **452**, 1; 1934, **514**, 145.
[16] Grieve and Hey, *J.*, 1934, 1797, 1966.
[17] Waters, *J.*, 1937, 113.
[18] Waters, *J.*, 1937, 2007; 1938, 1077; 1939, 864, 1792.
[19] For summaries see Hey, *Ann. Reports*, 1940, **37**, 250; 1944, **41**, 181.
[20] Waters, *J.*, 1939, 864; Makin and Waters, *J.*, 1938, 843.
[21] *Ber.*, 1929, **62**, 1010, 1018; 1935, **68**, 1877.
[22] *J. pr. Chem.*, 1939, **152**, 237.
[23] Kvalnes, *J. Amer. Chem. Soc.*, 1934, **56**, 2478. Borsche, *Ber.*, 1899, **32**, 2935.
[24] Koelsch, *J. Amer. Chem. Soc.*, 1943, **65**, 57; Koelsch and Boekelheide, *ibid.*, 1944, **66**, 412.
[25] Hey, *J.*, 1934, 1966.
[26] Wieland, Ploetz, and Indest, *Annalen*, 1937, **532**, 166; Wieland and Meyer, *Annalen*, 1942, **551**, 249.
[27] Marvel *et al.*, *J. Amer. Chem. Soc.*, 1939, **61**, 2769.
[28] Ziegler, Whitney, and Herte, *Annalen*, 1942, **551**, 187.
[29] Fieser *et al.*, *J. Amer. Chem. Soc.*, 1942, **64**, 2043, 2052, 2060.
[30] Waters, *Trans. Faraday Soc.*, 1946, **42**, 184.
[31] For reviews, see *Ann. Reports*, 1939, **36**, 219; 1940, **37**, 288; 1944, **41**, 186; *Chem. Reviews*, 1940, **27**, 351.
[32] *J. Amer. Chem. Soc.*, 1940, **62**, 3435.
[33] Price *et al.*, *J. Amer. Chem. Soc.*, 1942, **64**, 1103; 1943, **65**, 517, 757, 2380, 2508.
[34] Blomquist, Johnson, and Sykes, *ibid.*, 1943, **65**, 2446.
[35] *Trans. Faraday Soc.*, 1946, **42**, 155.
[36] Haber and Weiss, *Proc. Roy. Soc.*, 1934, *A*, **147**, 333.
[37] Ziegler and Ewald, *Annalen*, 1933, **504**, 162; Ziegler and Gänicke, *ibid.*, 1942, **551**, 213.
[38] Criegee, Pilz, and Flygare, *Ber.*, 1939, **72**, 1562; Farmer *et al.*, *J.*, 1942, 121, 513; this vol., p. 10; *Trans. Faraday Soc.*, 1942, **38**, 340.
[39] Compare Wieland's Pedler Lecture, *J.*, 1931, 1055.
[40] Waters, *Trans. Faraday Soc.*, 1943, **39**, 145.