LX.—*Primary and Associated Results of Replacement of Hydrogen directly attached to 4-Co-ordinated Carbon.*

By WESLEY COCKER, ARTHUR LAPWORTH, and ARTHUR WALTON.

THE substituents NO_2, CN, COR, and SO_2R in attachment to phenyl are meta-directive. In position X, in $X{\cdot}CHR_1R_2$, these substituents render the hydrogen atom labile and, moreover, the compound $X{\cdot}CHR_1R_2$ is able to exist in two "tautomeric" forms. These relations were recognised nearly thirty years ago (compare J., 1901, **79**, 1901).

It is not easy to state when the idea was first advanced that enolisation of a ketonic form originates in a minute degree of ionisation of the hydrogen atom which is attached to the carbon atom in the α-position. It was certainly no later than 1902, when definite schemes based on this idea were proposed for reversible desmotropic changes belonging to the type now commonly called prototropic (J., 1902, **81**, 1508). References were given in this paper to still earlier suggestions, in which conceptions of dissociation had been applied to such phenomena by Brühl, Thiele, and Henrich, and the names of Kekulé, Williamson, Euler, Goldschmidt, Knorr, and others should have been mentioned in any exhaustive treatment.

The conception of the acceleratory influence of an alkali on enolisation as due to the attack of hydroxyl ion on an " incipiently ionised " hydrogen atom in direct attachment to carbon on the ketonic form was formulated in 1920 (*Mem. Manchester Phil. Soc.*, 1921, **64**, 13 and 14).

The above ideas are now widely used, but few of those who have adopted them as working hypotheses appear to be aware that even the most recent of them took definite shape nearly nine years ago.

On the view above described, expressed in terms of current theory, compounds of the type $X\cdot CHR_1R_2$ (X being defined as above) are themselves very feeble acids—too feeble, as a rule, to yield their protons to the very weak base, water, but able to yield them to more potent acceptors.

With the introduction of electronic conceptions it followed naturally, as Lewis himself pointed out, that the affinity of an acid must be associated with the degree of restraint on the bonding electrons of the atom to which the acidic hydrogen, or proton, is attached. Hence, if the above ideas are sound, it follows as a matter of course that each of the substituents NO_2, CN, COR, and SO_2R must exercise some special restraint on the electrons of an attached carbon atom; the case is only one of many covered by scheme 7, in the paper by Allan, Oxford, Robinson, and Smith (J., 1926, 404), in which scheme carbonyl was evidently used to typify all substituents which come in the above category (compare *ibid.*, p. 403, line 8 from bottom). The connexion between electron-restraining properties and meta-directive power had previously been a strong plank in the platform of supporters of " polarity theories " and a passing reference to Robinson's discerning extrapolation from this general basis and his own experiments to the prediction of meta-directive effects in benzylamine salts may serve as a reminder of this. It may therefore be maintained that no date later than that of the paper by Allan, Oxford, Robinson, and Smith may properly be assigned to the complete association of all the above ideas, although much of real novelty has since been written in connexion with the same topics and numerous important extensions have been suggested.

It is, however, not enough to attribute to any given substituent an " inherent " electron-attractive or electron-repulsive power, and then to assume that the apparent contradictions are due to covalency adjustments which are inseparable from a completed chemical change. The present authors are convinced that the idea of interior electron displacements formulated by Lewis (compare "Valence and the Structure of Atoms and Molecules," G. N. Lewis, American Chemical Society Monographs, 1923), though acceptable in many applications and in particular to the strengths of the hydroxides of the elements as bases and acids (*loc. cit.*, p. 138), does not admit of the extension suggested by Lewis himself in his attempt to account for the high ionisation constants of α-, β-, γ-, and δ-chloro-derivatives of saturated aliphatic acids (*loc. cit.*, p. 139). A number of workers have accepted the lead given by Lewis on this point; but it may be noted that in certain schools of thought the mass of indications pointing to the existence of some transmission of effects by interior means is ignored and distances of points from poles are calculated apparently on the assumption that the disturbances are propagated solely through the medium (compare Larsson and Holmberg, *Z. anorg. Chem.*, 1929, **183**, 30).

Insufficient attention has been paid to the possibility, already partly recognised, that even in the resting state of a molecule the effect of a substituent at a given point, even at a considerable distance from the substituent, may be the resultant of at least two simultaneous influences, one reaching the point from the exterior and the other from the interior, that is *via* the electronic system of the adjacent atom, the condition of which, in its turn, is likely to be determined by the resultant of interior and exterior influences. The exterior and interior forces at a given point may operate either in harmony or in opposition according to the nature of the substituent, and possibly also according to other circumstances, and obviously may affect one another to a greater or less extent throughout the whole range of collateral transmission.

It is almost certainly erroneous to suppose that the net effect of a substituent, Y, in say, $Y{\cdot}CHR_1R_2$, on the electrons of the carbon atom to which it is directly attached is always in the same sense as its net effect on the electrons of more remote atoms. It so happens that, if attention be restricted to the meta-directive substituents above specified, no glaring discrepancy is revealed, for not only does each of these substituents exercise, in the light of the above ideas expressed in terms of Lewis's theory of proton expulsion, a marked restraining effect on the electrons of any carbon atom to which it is directly attached, but it also displays consistent restraining effects on the electrons of atoms more remote, as shown by the large ionisation constants of all carboxylic acids in which these substituents occur. With a number of other substituents, however, and more especially with some of the powerfully ortho-para directive ones, no such consistency obtains.

Discussion of even the most elementary issues involved in this complicated question requires a clear understanding as to the implication of terms used. In view of this, the electropolar effect of a substituent is now defined for the present purpose and without references to any particular hypothesis, as that effect which, when the substituent occurs at the α-, β-, γ- and more remote positions in a saturated aliphatic acid, leads consistently to a rise or consistently to a fall in the ionisation constant of the acid, and diminishes as the distance from the substituent increases. The rate of diminution in the series of saturated fatty acids is given approximately by Derick's logarithmic rule (*J. Amer. Chem. Soc.*, 1911, **33**, 1152).*

The authors prefer to use the description " electropolar " effect or factor, due to Flürscheim, rather than " electron affinity " (Lewis), because the latter expression has been applied (*a*) to the restraint which an atom exercises over its own electrons, (*b*) to interior electron displacements consequent thereon, and (*c*) to true electropolar effects, which, in the view of the present authors, have often been confused with (*b*). The description " general polar," originally suggested (1921) as equivalent to Flürscheim's " electropolar," has since been used to specify not only true electropolar effects but also effects of interior electron displacements as conceived by Lewis.

Significant connexions which have appeared from the work of Bjerrum and others between electropolar effects and dipole moments, combined with the circumstances that electropolar effects make themselves felt at considerable distances from their point of origin even when a long saturated chain of carbon atoms intervenes, lead the authors to accept the view that the electropolar effect of a substituent, Y, is essentially the manifestation of a change in the electrical fields immediately exterior to the chains of atoms on the molecule. They imagine that the substitution ordinarily produces a change in the external field which is equivalent to the superposition of a new external field on the original one, and that this superimposed field increases in intensity as the substituent is approached from distant parts of the molecule. At some point, at a very small distance (measured in atomic diameters) from the point of substitution, it is, however, presumed that the superimposed field may be extremely complex, so that neither its intensity nor its sign can be deduced from a knowledge of the distribution of that field at points more remote—or at least not until that knowledge is far more exact than can be claimed at the present time. The precise distance at which the exterior effects may be treated as

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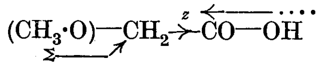
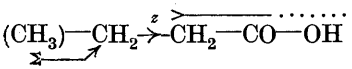
* Admittedly the criterion can strictly be applied only when the influence of " steric " factors has been eliminated.

mathematically separable from the primary and its interiorly transmitted effects is likely to remain as an outstanding difficulty; but on the view advanced by Lapworth and Manske (J., 1928, 2536, 2537) its point must be somewhere *beyond* the atom at which substitution takes place. Assuming, for simplicity, that this point in saturated systems lies immediately beyond the electrons of the atom in question and that " steric " effects may be treated as irregularities in an otherwise regularly diminishing, exterior field beyond this point, the opposite electropolar factors of $O{\cdot}CH_3$ and CH_3 may be suggested by the arrows placed above the two figures



$$\underset{\Sigma\longrightarrow\nearrow}{(CH_3{\cdot}O)-CH_2}\overset{z\;\longleftarrow\cdots\cdots}{\succ CO-OH}$$



$$\underset{\Sigma\longrightarrow\nearrow}{(CH_3)-CH_2}\overset{z\;\succ\!\longrightarrow\cdots\cdots\cdots}{\succ CH_2-CO-OH}$$

To the left of these two upper arrows it is postulated, not that an exterior field is non-existent, but that, whatever its direction may be, it is, by definition (J., 1928, 2536), only one of the factors in the primary effect, $\Sigma\longrightarrow CH_2\succ$, of the substituent on the electrons of the carbon atom to which it is directly attached, and may not be counted twice.

This interpretation of the facts, however, demands that in the two cases just specified, the displacements implied by the $\succ$ signs are very small, which is consistent with remarks which are made later in this paper on transmission by a single bond in a saturated carbon system (p. 450). The sign z is used to imply that the value, $>$, is almost zero.

Proton is admittedly unique; and there is strong physical evidence, largely but not wholly spectroscopic, that proton can enter very deeply into the electronic systems of other atoms (compare Knorr, *Z. anorg. Chem.*, 1923, **129**, 109; Müller, *Z. Elektrochem.*, 1924, **30**, 493; 1925, **31**, 46, 143; Lederle and Rieche, *Ber.*, 1929, **62**, 2576). The presence of hydrogen in direct combination with another non-metallic atom may then be equivalent to an increase in the central restraining charge of that atom, and this would lead, algebraically, to a corresponding decrease in restraint when the hydrogen is replaced. This factor is doubtless not the only one operative, and electrostatic attraction between the nucleus of one atom and the electrons, especially if " unshared," of another atom in the sense of theories previously used by Stark, Robinson, Lapworth and others is consistent with numerous data and is not excluded by electronic theory. It remains, however, as a striking fact that, with the exception of some, like $NMe_3\oplus$, which themselves contain an additional positive charge, and others, like NO_2, which contain a qualitatively equivalent dipole, nearly all the familiar substituents produce, on 3-co-ordinated carbon, chemical effects which correspond with those to be anticipated from a virtual decrease in the central charge of the carbon atom (compare Lapworth and Manske, J., 1928, 2536). Examples of this include such diverse substituents as NH_2, NMe_2, OMe, Cl, and Alk, some (*e.g.*, Cl) with electron-restraining and others (*e.g.*, Alk) with electron-releasing electropolar factors.

On the evidence of the ionisation constants of substituted acetic, propionic and butyric acids, the electropolar factors for OH and $O{\cdot}CH_3$ attached to 4-co-ordinated carbon are definitely *electron-restraining*; moreover, *m*-hydroxybenzoic acid is stronger than benzoic acid, and there is strong evidence that the electropolar effect is usually the dominant one in the meta-position (compare, *inter alia*, J., 1929, 2547, lines 7—9). Nevertheless, OH, or $O{\cdot}CH_3$, when replacing H attached to an aromatic nucleus, confers on some electrons of the nucleus a greatly *decreased* restraint; and when OH replaces the H of the kation, $H{\cdot}CO_2\ominus$, of formic acid, the product, $HO{\cdot}CO_2\ominus$, has a very greatly increased affinity for proton, connoting a greatly *decreased* restraint on the electrons of the carboxyl oxygens. In these two cases, however, the OH has replaced H attached to 3-co-ordinated carbon and the view has already been expressed by Lapworth and Manske (J., 1928, 2536), that this occurrence is undoubtedly associated, in the case of OH, with a greatly decreased restraint on the carbon electrons, which restraint can be transmitted in turn, by electron displacements (Lewis), to other atoms in the molecule, the intensity and extent of transmission varying very greatly with structural conditions.

It is perhaps desirable at this juncture to state that the present view accommodates the case of initiation of electron displacement at points remote from the substituent by the operation of the electropolar effect on a plastic system, such as a double bond, a 1 : 3-diene system, or a carbon–halogen linkage. The slight polarisation of the ethylenic linkage in stearolic acid, demonstrated by Robinson and Robinson (J., 1926, 2204), is regarded by the present authors as a case coming within this category; such effects might suitably be called " imported," in contrast to " transmitted."

A 1 : 3-diene, or an aromatic, system, when acted upon either by an imported or a transmitted strain, may display " alternate effects " of several kinds. The problem of the mechanism of " static " alternate effects such as those indicated by study of dissociation constants of aromatic carboxylic acids and cyanohydrins must be approached from the standpoint of a sound theory of the more elementary phenomena associated with substitution.

The question whether a given substituent operates on 4-co-ordinated (or " saturated ") carbon in the same mode as it operates on 3- and 2-co-ordinated carbon was touched on very lightly by Lapworth and Manske, in view of the paucity of convincing evidence bearing thereon (*loc. cit.*, p. 2537). The substituents NO_2, CN, COR, and SO_2R offer no difficulty from the qualitative point of view, their primary interior factors (*ibid.*, p. 2536) and electropolar factors being, as previously stated, clearly and consistently electron-restraining, no matter to which type of carbon atom they are attached. It has been shown in the preceding pages that the conjunction of Lewis's theory with the idea of incipient ionisation in the derived systems, $X{\cdot}CHR_1R_2$, implies that these substituents exercise a restraining effect on the electrons of 4-co-ordinated carbon, thus facilitating the removal of the hydrogen atom as proton by suitable acceptors. In the following pages an attempt is made to show that some of the more powerfully ortho-para directive substituents exert precisely the opposite effect on the electrons of directly attached, 4-co-ordinated carbon, so that when the latter is also associated with an atom or group, which either *per se* or by association with a suitable acceptor, can act as an anion, a state of " incipient ionisation " is brought about in the sense opposed to that induced by the meta-directive substituents NO_2, CN, COR and SO_2R, when occupying similar positions.

It is well known that the halogen in α-chloroalkyl oxides such as monochlorodimethyl ether, $CH_3{\cdot}O{\cdot}CH_2Cl$, is exceptionally labile. Contrasting $CH_3{\cdot}O{\cdot}CH_2Cl$ with $H{\cdot}CH_2Cl$, it may be said with confidence that the replacement of H by $O{\cdot}CH_3$ does not lead to any of the results to be anticipated from a virtual increase in the central charge of the carbon atom of the CH_2 group. Such results would be, for example, a more ready reducibility of the chloro-compound to the hydride, or a tendency to react with water in accordance with the scheme $R{\cdot}Cl + HOH \longrightarrow R{\cdot}H + HOCl$ (compare the properties of NCl_3 and NH_2Cl with those of chloro-derivatives of methane). On the contrary, there is observed a greatly increased tendency for the halogen atom to appear as chloridion; moreover, the group $CH_3{\cdot}O{\cdot}CH_2$ has apparently so small an affinity for its bonding electrons that it can replace proton, even in presence of free hydrochloric acid, as in the facile reaction of the chloride $CH_3{\cdot}O{\cdot}CH_2Cl$ with methyl alcohol :

$$CH_3{\cdot}O{\cdot}CH_2Cl + HO{\cdot}CH_3 \longrightarrow CH_3{\cdot}O{\cdot}CH_2{\cdot}O{\cdot}CH_3 + HCl$$

(Henry, *Ber.*, 1893, **26**, 933, *Ref.*).

The extraordinary facility of the transformations of this chloride and the consistent relative " polarities " of its two parts, $CH_3{\cdot}O{\cdot}CH_2$ and Cl, as well as the comparatively small heat changes involved, are well illustrated by its behaviour towards water, alkali and concentrated hydriodic acid respectively. In each case hydrolysis occurs quickly, the chloro-ether, at first insoluble, dissolves within a few seconds when shaken vigorously with the cold aqueous liquid. In the case of the strong, aqueous hydriodic acid, the heat display is so small that, with equal volumes of acid and chloro-ether, the rise of temperature is only about 7°. No free iodine is liberated even if the compound is added to the hot acid. From the work of Henry (*loc. cit.*) and others there is good reason to conclude that in each of the three cases the change which takes place is simply a reversal of that on which the ordinary method of preparing the ether is based :

$$CH_2O + CH_3{\cdot}OH + HCl \longleftrightarrow CH_3{\cdot}O{\cdot}CH_2Cl + H_2O.$$

Monochlorodimethyl ether acts almost instantaneously on tertiary bases (Litterschied, *Annalen*, 1901, **316**, 161), forming quaternary salts :

$$CH_3{\cdot}O{\cdot}CH_2Cl + NR_3 \longrightarrow CH_3{\cdot}O{\cdot}CH_2{\cdot}\overset{\oplus}{N}R_3\}\overset{\ominus}{Cl}.$$

The present authors have observed that although, as found by Litterschied, these salts are also formed almost instantaneously in presence of an alcoholic solvent, such as amyl alcohol or *cyclo*hexanol, they may subsequently react with the alcohol on warming in presence of excess of the tertiary base, the methoxymethyl residue evidently leaving the nitrogen atom and replacing the proton of some of the alcohol. Thus with pyridine and amyl alcohol :

$$C_5H_5N + C_5H_5\overset{\oplus}{N}(CH_2{\cdot}O{\cdot}CH_3)\}\overset{\ominus}{Cl} + C_5H_{11}{\cdot}OH \longrightarrow$$
$$C_5H_5\overset{\oplus}{N}H\}\overset{\ominus}{Cl} + C_5H_5N + C_5H_{11}{\cdot}O{\cdot}CH_2{\cdot}O{\cdot}CH_3.$$

It may be worth while to point out that these reactions do not seem to differ in any essential feature from those which occur during the well-known process, due to Einhorn, for acylation of alcohols by means of acyl chlorides and tertiary amines (*Annalen*, 1898, **301**, 95), though the yields obtained are less satisfactory, owing in some cases to less complete reaction and in others to formation of products of higher molecular weight in which methoxyl has been replaced. In both cases quaternary salts are formed in the first instance by direct union of amine and acid chloride (compare Dennstedt and Zimmermann, *Ber.*, 1886, **19**, 75) and there is no sufficient reason to assume that there is an essential distinction between the two mechanisms. The authors infer that both acyl groups and α-alkyloxymethyl groups can function much as protons do; that is to say, while probably not capable of separate existence in solution as kations, they are readily detached from their bonding electrons and thus, in the same sense as such protons, occur in the state frequently described as "incipient ionisation."

In the authors' view the conditions which give rise to the modes of reaction of monochlorodimethyl ether are to be regarded as pre-existent in the resting molecules, $CH_3{\cdot}O{\cdot}CH_2Cl$, and it is not necessary to assume complete conversion of the molecules into desmotropic forms prior to interaction with the agents. Oxonium chemistry certainly indicates that reversible changes such as $CH_3{\cdot}O{\cdot}CH_2Cl \longleftrightarrow CH_3{\cdot}\underset{\oplus}{O}{\vdots}CH_2\}\underset{\ominus}{Cl}$ might take place readily; but the existence of such reversible relations in itself connotes comparatively small free energy differences between the molecular configurations in the two isomeric forms, and such forms are probably subject to similar interior distortions, demanding comparatively small "activation" increments of energy for transformation in either direction. It is on this basis, and not on the hypothesis of one ion common to both forms, that the authors would approach the theory of isodynamic isomerism; the observations of Leuchs (*Ber.*, 1913, **46**, 2438) and of Kuhn and Albrecht (*Ber.*, 1927, **60**, 1297), with optically active compounds, strongly support the idea that the ions of the so-called "pseudo-acid" forms have individual existence.

The present authors would represent the interior effects which they believe to be produced by the conversion of $H{\cdot}CH_2Cl$ into $CH_3{\cdot}O{\cdot}CH_2Cl$, by the strain-symbol, $\underset{\Sigma\longrightarrow\nearrow}{CH_3{\cdot}O{-}CH_2}{\rightarrow}{-}Cl$, where, in contrast to the case of $CH_3{\cdot}O{\cdot}CH_2{\cdot}CO_2H$ (p. 444), the transmitted effect is considerable (in the plastic $C{\rightarrow}{-}Cl$ bond) and has more influence on the properties of the compound than has the electropolar effect

$$CH_3{\cdot}O{-}CH_2{-}\overset{\longleftarrow\cdots\cdots}{Cl}$$

The extremely variable lability of CN directly attached to carbon seems strongly to support the general ideas above advanced. Ordinarily, CN directly attached to carbon cannot be removed as cyanidion. Even cyanohydrins $HO{\cdot}CR_2{\cdot}CN$ are mostly quite stable in this respect at the ordinary temperature, providing that appreciable ionisation of the hydroxyl hydrogen be prevented, as by addition of a trace of mineral acid (Lapworth, J., 1901, **79**, 1268; 1906, **89**, 948; Ultée, *Rec. trav. chim.*, 1909, **28**, 248, 257); on the other hand, partial breaking down, with attainment of equilibrium, takes place extremely quickly at the ordinary temperature if the conditions are on the alkaline side, thus permitting of a small amount of ionisation of the acidic cyanohydrin (J., 1904, **85**, 1206):

$$\ominus O{\cdot}CH_2{\cdot}CN \longleftrightarrow O{\vdots}CH_2 + CN\ominus$$

The instability of α-amino-nitriles is well known, and the authors have observed that the compound $NEt_2{\cdot}CH(CH_3){\cdot}CN$ decomposes at the ordinary temperature in presence of water; free hydrogen cyanide is formed and if this be allowed to escape from the system complete decomposition takes place ultimately at the ordinary temperature. The reactions involved are again reversals of those followed during the ordinary method of preparing the compound:

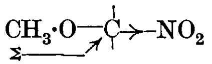
$$NEt_2{\cdot}CH(CH_3){\cdot}CN + H_2O \longleftrightarrow NEt_2{\cdot}CH(CH_3){\cdot}OH + HCN$$

(*not necessarily* by way of the desmotropic form $\overset{\oplus}{N}Et_2{:}CH(CH_3)\}\overset{\ominus}{C}N$). The compound $NEt_2{\cdot}CH(CH_3){\cdot}OH$ then breaks down much in the same way as a cyanohydrin does, giving $NHEt_2$ and $CH(CH_3){:}O$. The case of cyanodihydroberberine is closely comparable with this (compare Robinson and Robinson, J., 1917, **111**, 966).

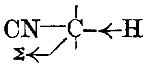
Compounds having the structure $CH_3{\cdot}O{\cdot}CR_1R_2{\cdot}CN$, unlike cyanohydrins themselves and unlike α-amino-nitriles, are exceedingly stable compounds, and do not yield their cyanidion under most drastic treatment.

It seems clear, therefore, that in respect to their efficiencies in promoting the withdrawal of CN from the same carbon atom, the order of four important substituents is $\ominus O$, $NAlk_2$, OH, $O{\cdot}CH_3$. The last of these is here quite ineffective, and even OH is usually effective only at temperatures above the ordinary, in which circumstances almost any ketone cyanohydrin can lose hydrogen cyanide; menthone cyanohydrin when exposed cannot be prevented from doing so slowly even at the ordinary temperature and in presence of stabilising hydrogen chloride (Lapworth, Manske, and Robinson, J., 1927, 2054). It may be noted that the order of the four substituents above deduced is the same as that accepted for ortho-para directive powers, which order, however, is not necessarily always the same as that for " static " or average primary effects. Aromatic substitution, as Robinson has constantly maintained, is no doubt very largely a phenomenon connected with specially energised molecules in the system and not with the average molecules, and the nitroso-group affords a striking example of a substituent the " static " primary effect of which on carbon is in one sense (electron-restraining, like $CO{\cdot}R$ or NO_2) and nevertheless does not too effectively oppose the formation of energised forms in which it is in effect operating in the opposite sense (ortho-para directive and electron-releasing) (compare Robinson, *Chem. and Ind.*, 1925, 456). Such an associated function may be termed a " permissive " property of the substituent.

When alcoholic potassium cyanide acts on polynitro-derivatives of the aromatic series, the group O·CH_3 enters the molecule at the carbon atom from which the NO_2 radical is displaced; the group CN, when it enters, is found on a carbon atom to which H was originally attached (Bruyn and others; compare Kenner, J., 1914, **105**, 2730). The opposite primary interior effects of O·CH_3 and CN are doubtless here foreshadowed or utilised in some way at intermediate stages,



$CH_3{\cdot}O{-}C{\rightarrow}NO_2$



$CN{-}C{\leftarrow}H$

⊖NO_2 being "loosened" in the former case and ⊕H in the latter (compare "Summary" of present paper).

On considering all the evidence now available it seems clear that the statement made by Lapworth and Manske to the effect that the influence of substituents on 4-co-ordinated carbon is "certainly small" (J., 1928, 2537) was unfortunate, and a more accurate statement would have been that the changes produced by substitution of H attached to 4-co-ordinated carbon are "certainly more difficult to detect" than with 3-co-ordinated carbon.

This difficulty seems to be due in the main to the circumstance that changes in the restraint on the electrons of 4-co-ordinated carbon are transmitted, if at all, only to a very feeble extent to another carbon atom; thus even the considerable effect of the substituent O·CH_3, which is manifest in the properties of $CH_3{\cdot}O{\cdot}CH_2Cl$, does not suffice to cause loss of the CN group from $CH_3{\cdot}O{\cdot}CH_2{\cdot}CN$ or $CH_3{\cdot}O{\cdot}CH(CH_3){\cdot}CN$ (compare Robinson, on resistance offered by a saturated carbon atom, *Chem. and Ind.*, 1925, 118).

Owing to the difficulty of detection and comparison of static primary effects on 4-co-ordinated carbon, except in special cases such as those above discussed, it would be premature to maintain that the sequence of substituents in this connexion is the same as the sequence for static primary effects on 3-co-ordinated carbon. On *a priori* grounds it would seem possible that such might be the case, at least for substituents which contain no double-bonded structure adjacent to the point of attachment. Comparison of the properties of $(Cl){\cdot}CH_2Cl$ and $(CH_3){\cdot}CH_2Cl$ with those of $(H){\cdot}CH_2Cl$ clearly indicates that the "primary" influence of Cl or CH_3 on 4-co-ordinated carbon is very much smaller than that of O·CH_3, and this again is broadly in agreement with effects already deduced on 3-co-ordinated carbon. Whatever may transpire hereafter, it now seems beyond reasonable doubt that when substituents are arranged in the order of their "static" (or average) primary effects on directly attached, 4-co-ordinated carbon, that order will be quite different from the electropolar sequence (order of " electron affinities ") and will correspond much more closely with Flürscheim's " quantitative " sequence, though, as already explained (p. 449), with certain modifications connected with the mechanism of aromatic substitution. It is doubtful whether the precise order, even if there be such, for static primary effects of substituents can be deduced from chemical reactions, but the authors assume that facile and reversible reactions provide the most trustworthy indications. The study of equilibrium constants furnishes a basis for comparing average free energies over a large number of molecules; but " primary " effects are not the only factors involved.

There is yet another complication, as there is reason to believe that with certain substituents which have comparatively small primary effects, even the sense of their primary effects is not wholly independent of the nature of the other substituents present on the same atom. Thus the successive replacement of hydrogen atoms in ammonia by methyl groups causes at the first step a rise and at the last a fall in the basic affinity constant. Again the capacity of the CCl_3 group to pass, together with its bonding electrons, from one state of combination to another (as from proton in chloroform to depleted carbon in acetone) suggests that the joint primary (*i.e.*, totalised) effect of the three chlorine atoms on the carbon is electron-restraining, whereas the primary effect of Cl on carbon of the aromatic nucleus or of carbonyl appears consistently electron-releasing (compare J., 1928, 2547); on the other hand, a " permissive " effect might be concerned here.

Section II.

This section deals only with observations of which a more detailed account than has been given in the preceding pages seems desirable.

(1) *Action of Methoxymethylpyridinium Chloride on Hydroxy-compounds.*—(a) *Benzyl alcohol.* Chlorodimethyl ether (40 g.) was slowly added to purified pyridine (100 c.c) dissolved in dry ether (500 c.c.) cooled in ice-water, the crystalline quaternary salt which at once separated being then collected rapidly on a Buchner funnel, washed with ether, and transferred to a dry flask. A small sample of the chloroplatinite was prepared and had m. p. 180—182° (efferv.) (compare Litterschied, *Annalen*, 1901, **316**, 168). The bulk of the salt was heated with dry benzyl alcohol (54 g.) and pyridine (80 c.c.) at 90—95° for 6 hours, after which time addition of ether to a sample of the cooled mixture led to precipitation of pyridine hydrochloride (chloroplatinite, m. p. 238—240°). In working up the product, the latter was cooled and mixed with water, made slightly acid, and extracted twice with ether (400 c.c. in all), which was then washed

with dilute hydrochloric acid and water successively, dried over sodium sulphate, and evaporated. From the residual liquid, a main portion (40 g.), b. p. 205—215°, and a less volatile portion (5 g.) were obtained. To remove benzyl alcohol, the former was shaken repeatedly with a concentrated aqueous solution of sodium salicylate * until it suffered no further appreciable diminution in bulk and was then refractionated. A fraction (25 g.), b. p. 208—211°, was obtained, consisting of *methoxymethyl benzyl ether*, $C_6H_5 \cdot CH_2 \cdot O \cdot CH_2 \cdot O \cdot CH_3$.

The ether is obtained in better yield (about 36 g.) by simply mixing benzyl alcohol (54 g.), chlorodimethyl ether (40 g.), and dry pyridine (50 g.) slowly but without special cooling, and working up the product as before. It is a colourless oily liquid, b. p. 208—211°/756 mm., having a fragrant fruity odour (Found : C, 70·8; H, 7·9. $C_9H_{12}O_2$ requires C, 71·1; H, 8·0%).

In each of the following cases, the alcohol was warmed with the mixture of chlorodimethyl ether and pyridine for several hours, and the product worked up as above.

(b) cyclo*Hexanol.* The yield of *methoxymethyl* cyclo*hexyl ether* was so poor that a homogeneous product could not be isolated. Most of the alcohol was recovered unchanged, and from 50 g. of *cyclo*hexanol only 1·8 g. of oil (b. p. 190—210°) were obtained (Found : C, 67·3; H, 11·2. $C_8H_{16}O_2$ requires C, 66·6; H, 11·2%). About 2·5 g. of higher-boiling product (b. p. 255—274°) accompanied this.

(c) sec.-β-*Octyl alcohol.* From 65 g. of this alcohol were obtained 5 g. of *methoxymethyl* sec.-*octyl ether*, as a liquid with a fragrant odour; b. p. 188—190° (Found : C, 69·2; H, 12·7. $C_{10}H_{22}O_2$ requires C, 69·0; H, 12·6%).

(d) "*Amyl alcohol.*" A commercial amyl alcohol, b. p. 131—132°, being used (44 g.), a fraction representing methoxymethyl "amyl" ether was obtained in fair yield (15 g.). This product had a very powerful, not unpleasant odour, reminiscent of amyl alcohol (Found : C, 63·5; H, 12·2. $C_7H_{16}O_2$ requires C, 63·6; H, 12·7%).

The action of methoxymethylpyridinium chloride on amyl alcohol appears to be much less energetic than on benzyl alcohol. In the latter case the heat disengaged in admixture is sufficient to ensure completion of the reaction, but in the former it was found that most of the amyl alcohol is recovered unchanged unless the mixture is heated on the steam-bath before it is worked up. No special trials were made to find the minimum time necessary.

(e) *Phenol.* No reaction appeared to take place with the quater-

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* A solution of sodium salicylate seems to have been used in industry for the separation of alcohols from mixtures of these with non-alcoholic compounds.

nary pyridinium salt, and no neutral product boiling above 100° was detected. A sample of the recovered phenolic material was carefully fractionated in order to ascertain whether any alkylation in the nucleus had taken place, but nothing boiling appreciably higher than phenol could be isolated. The expected ether, $C_6H_5{\cdot}O{\cdot}CH_2{\cdot}O{\cdot}CH_3$ boils at 188—189°/760 mm. (compare *Centr.*, 1909, I, 1681).

This inertness of phenol is doubtless associated with its acid character, having a parallel in the difficulty which is experienced in the alkylation of nitrophenols or carboxylic acids by means of aqueous alkali and methyl sulphate.

The order of the hydroxy-compounds examined as to the facility with which they react with methoxymethylpyridinium chloride appears to be: benzyl alcohol, amyl alcohol, *sec.*-octyl alcohol, *cyclo*hexanol, phenol, and a close relation with the order of their acidities may be suspected.

(2) *Observations on some α-Substituted Nitriles.*—(a) *α-Diethylaminopropionitrile.* This compound, which has already been made by Klages (*J. pr. Chem.*, 1902, **65**, 196), is readily produced by slowly mixing diethylamine with a slight excess of acetaldehyde and liquid hydrogen cyanide in the required proportion. There is considerable heat development and careful cooling is therefore necessary. The product, after exposure in a vacuum for a short time, forms a mobile liquid, stable in absence of water at the ordinary temperature (Found: N, 21·9. Calc. for $C_7H_{14}N_2$: N, 22·2%).

A sample so prepared was added to a solution of silver nitrate acidified with nitric acid and yielded silver cyanide corresponding with 1·3% of free hydrogen cyanide, the nitrile itself (or rather its salt) being stable to this reagent. The total CN present in the same sample was determined by shaking with excess of dilute sodium hydroxide solution and silver hydroxide and then adding excess of dilute nitric acid. The total CN found was 23·1%; hence the combined CN was 21·8% (theory requires CN, 20·4%).

On distillation of the nitrile under reduced pressure, a portion, b. p. 72—77°/17 mm., amounting to about at least 60% of the whole is obtained. This appears to consist mainly of the original nitrile, but is decidedly more viscous, and some decomposition products are probably present.

The nitrile can also be obtained, though in smaller yield (about 30% of the theoretical), by adding diethylamine and acetaldehyde in equimolecular proportion to a concentrated aqueous solution of potassium cyanide and extracting the product with a large bulk of ether. Here potassium hydroxide must be formed:

$$NHEt_2 + CH_3{\cdot}CHO + KCN \longleftrightarrow NEt_2{\cdot}CH(CH_3){\cdot}CN + KOH.$$

When the amino-nitrile is left with water, the odour of hydrogen cyanide becomes perceptible within a few minutes. If the hydrogen cyanide formed is continuously removed by exposure of the vessel in a vacuum desiccator over a solution of sodium hydroxide, the layer of oily nitrile gradually disappears and, after several days, only a scum of tarry product can be seen on the surface of the water, though even then a faint odour of hydrogen cyanide is perceptible.

The picrate is best made from the nitrile before distillation, a solution of picric acid in cold dry ether being used. It is deposited as long prisms, m. p. 99·5—102°; Klages (*loc. cit.*) gives m. p. 102°. As its melting point was appreciably lowered by recrystallisation, the crude salt was analysed (Found: C, 44·2; H, 4·8; N, 22·3, 19·7. Calc. for $C_{13}H_{17}O_7N_5$: C, 43·9; H, 4·8; N, 19·7%).

(b) *Methoxyacetonitrile.* This was made by the method of Polstorff and Meyer (*Ber.*, 1912, **45**, 1911) from formaldehyde, potassium cyanide, and methyl sulphate. Its identity was confirmed by its boiling point (120—122°) and other properties (Found: CH_3·O, 42·7. Calc. for $CH_3·O·C_2H_2N$: CH_3·O, 43·6%), as well as by the properties and composition of the methoxyacetamide prepared from it; needles, m. p. 96·5—97° (Found: CH_3·O, 34·8. Calc. for $CH_3·O·C_2H_4ON$: CH_3·O, 34·8%).

The nitrile does not yield detectable traces of hydrogen cyanide or metallic cyanide when heated alone, with alkalis, with solid sodium hydroxide at its boiling point, with potassium in boiling toluene, or with silver nitrate and dilute nitric acid.

(c) *Methoxypropionitrile.* This compound is most readily made by the method used by Polstorff and Meyer in preparing the lower homologue, the formaldehyde being replaced by an equivalent amount of acetaldehyde. It has previously been made by Gautier from the corresponding chloro-ether (*Ann. Chim. Phys.*, 1909, **16**, 315).

The product obtained by the present authors had b. p. 128—130°/758 mm. (Found: CH_3·O, 30·0. Calc. for $CH_3·O·C_3H_4N$: CH_3·O, 30·1%). It was readily converted into the corresponding amide (needles, m. p. 83°, from light petroleum) by means of alkaline hydrogen peroxide. It yielded no hydrogen cyanide nor metallic cyanide under the most drastic treatment.

Summary.

The electron displacement theory of G. N. Lewis, in its application to phenomena associated with results of introducing substituents into the molecules of carbon compounds, is accepted only in part.

It is shown that there is good reason to believe that the substituents ⊖O, $NAlk_2$, OH and O·CH_3, in descending order of

efficiency, greatly increase the electron fugacity of directly attached, 4-co-ordinated carbon, and thus form a group in complete contrast to the carbonyl and nitro-radicals.

There is no simple relation between such effects (" primary " effects) and the so-called electron affinities (" electropolar " factors) of substituents. There is a close general connexion, however, between the former and the ortho-para directive powers (" quantitative " factors).

The tendency of a radical to enter into combination with a given carbon atom or/and to replace another radical attached thereto, is influenced not only by the nature of the radicals already attached to the carbon atom but also by those properties of the entrant radical which determine what the sign and the magnitude of the " primary " effect of that radical will be after such combination has taken place.

Evidence is cited that, at least with a substituent which has a comparatively small " primary " effect, even the sign of that effect is not always independent of the nature of the other radicals attached to the atom.

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