THE CHEMICAL BEHAVIOR OF THE ORGANOALKALI COMPOUNDS[1]

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CONTENTS

I. INTRODUCTION

This review presents a general theory of the behavior of organoalkali reagents,—a theory based on (*a*) the existence and reactions of an ion-pair in a non-dissociating solvent, and (*b*) the presence of a dominant metal ion which has a powerful attraction for electrons. The reactions of the ion-pair are linked with the behavior of all salts in general, and the effect of the metal ion is classed with that of electron-attracting substituents, such as the nitro, ammonium, and other common groups attached to aromatic systems.

Although the formal classification of material is that given in the table of contents, the general understanding of this paper, particularly of the latter half,

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will be made easier by the statement of a simple, yet reasonable, sequence of opinion and argument which has formed the basis for much of the author's reflection on the subject. This series of guiding principles is:

(*1*) Organosodium compounds are salts, an opinion now generally accepted.

(*2*) A great disparity in strength between the two components of the salt exists, and the reactivity usually increases as the disparity increases.

(*3*) This lack of balance results in a display of residual force which emanates from the stronger component, because its affinity is unsatisfied.

(*4*) For a reagent which consists of two components, adjacent to each other but of great inequality in strength, it is the part of common sense to express the reactions as deriving a major impulse from the stronger component, unless unquestioned reasons can be advanced for supporting a contrary view.

(*5*) An exterior force, which is capable of separating the salt into its two parts, may make it possible for each portion to act independently, to an extent depending on the degree of separation and on the potency of single as compared with joint action of the ions.

It will be made clear that one of the principal facts which justify the above sequence is that the conditions under which the organoalkali reagents are prepared and used are, in general, those in which neither of the ions of the salt can move from the vicinity of the other. Hence, while as salts the organoalkali compounds show properties characteristic of salts in general, the differences in strength cause the cation to play a prominent part in all reactions, even those in which the action appears to be localized in the anion.

The above sequence, in general, runs parallel to the table of contents, but the space allotted to the first point, the matter of the salt-like nature of the organoalkali compounds, comprises nearly a third of the paper. The discussion of acidity and salt formation covers a wide range, and extends even to the more common type of the carboxylic acids. The remaining points in the sequence are argumentative in nature, designed to assist in interpreting some of the reactions of organoalkali compounds which now appear to be of an unusual or peculiar nature but which, by this discussion, are brought into line with other well-known reactions or principles in organic chemistry.

The general aim in this review is not to offer a complete bibliography in the field, though the list is of necessity fairly generous, but to present a rational treatment of the chemistry of these compounds, in order to establish a sound basis for interpreting known facts and predicting new ones.

II. THE SALT-LIKE NATURE OF ORGANOALKALI REAGENTS

The salt-like character of organoalkali compounds[2] forms the basis for the discussion presented in this paper. The correctness of this viewpoint is now generally accepted. The electronic formula requires it, conductance measurements support it, and physical properties accord with it.

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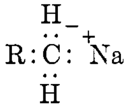
[2] The commonly accepted definition of organoalkali compounds—namely, that they are compounds in which carbon is attached to an alkali metal—is used in this paper.

A. The electronic formula

The electronic formula requires that the valence between carbon and sodium be ionic (11), because an octet of electrons about the sodium ion is complete and the additional electron of the sodium atom forms part of the system of eight that surrounds the carbon atom. The octets about sodium and carbon contain no electrons shared with each other; hence the valence must be an electrostatic one.



$$R:\underset{\underset{\textstyle H}{\cdot\cdot}}{\overset{\overset{\textstyle H\,^{-}}{\cdot\cdot}}{C}}:\ \overset{+}{Na}$$

B. Conductance of salts

Numerous conductance measurements support this idea: ethylsodium in diethylzinc (61); benzylsodium in ether (105); triphenylmethylsodium in ether (106, 32), pyridine (137), and liquid ammonia (78); and the Grignard reagent in ether (77, 19). Conductance in these solutions is low. Dielectric constants of 4.7 for ether, 12.5 for pyridine, and 22 for liquid ammonia, as compared with 81.1 for water, insure that the electrostatic attraction between the ions remains high, particularly so in ether, one of the common solvents. Dissociation of the ions is accordingly much lower than is found in aqueous solutions of the more common salts.

Occasionally a salt fails to conduct the current. Phenylsodium (61), for example, does not conduct the current in dimethylzinc, although phenyllithium does. An explanation for this abnormality is not clear. Fortunately other properties are such that the salt-like nature of this reagent can be accepted.

C. Physical properties

Physical properties of the organoalkali compounds, such as insolubility in organic solvents, decomposition without melting when heated, and non-volatility, accord, in general, with those of the common salts. All organoalkali compounds do not share these properties equally. The variations led Ziegler (133) to divide these compounds into three groups.

(*1*) *Colorless salts*, which are insoluble in organic solvents, are heteropolar in the solid state, and are conductors of an electric current when dissolved in dimethylzinc. Alkyl- and aryl-sodium and potassium compounds are examples of this class.

(*2*) *More or less intensely colored compounds*, often very soluble in organic solvents, which conduct an electric current. The metal is attached to a carbon atom, which is attached also to a double bond or a benzene ring. Benzylsodium, benzyllithium, and phenylisopropylpotassium are examples of this class.

(*3*) *Colorless compounds* which are soluble in organic solvents and which distill or sublime. The physical properties appear analogous to those of the alkylzinc and alkylcadmium compounds of Group II of the Periodic Table. They are non-electrolytes and conduct poorly in zinc alkyls. The alkyllithium compounds are examples.

The first two classes include compounds which are distinctly salt-like; the last includes those of doubtful salt character. The fact that organolithium compounds dissolve in organic solvents and melt without decomposition need not perhaps be surprising in view of the fact that inorganic lithium salts, such as the bromide or iodide, are soluble in ether and that the inorganic lithium compounds, in general, melt appreciably lower than the corresponding sodium or potassium ones. This review, however, makes no distinction between organoalkali compounds of different classes nor seeks any explanation for the absence of some expected properties in one class, because, in a large number of reactions, such a separation serves no useful purpose. Indeed, one aspect of this presentation is the view that the electrostatic bond in the salts has much in common with the covalent bond in the distinctly organic compounds. For the remainder of this paper, all organoalkali compounds are regarded as salts without further regard to fine distinctions which, in our present incomplete state of knowledge, affect the chemical properties slightly, if at all.

The system of naming which designates organoalkali compounds as derivatives of the metal, e.g., ethylsodium, originated before their salt-like character was fully recognized. There is no special name reserved for this class of salts. A few attempts have been made to emphasize the relation to other salts by names, such as sodium methide (12) or sodium ethide, analogous to sodium amide. In the case of amylsodium this system might lead to some confusion with the amine salt, unless the term "sodium pentide" were used. Although the present convention of naming is inconsistent with the well-defined salt-like character of some of these compounds, the use of expressions such as amylsodium, phenyllithium, or phenylisopropylpotassium, that suggest covalence, may after all serve to emphasize the opinion that the distinction is in many cases a physical one and that the chemical properties of these unique salts, under the condition in which they are usable, frequently parallel the properties found in compounds whose bonds are unquestionably of the convalent type.

III. THE ACIDITY OF THE ACID COMPONENT OF THE SALT

If organoalkali compounds are salts, the hydrocarbon portion must be derived in some manner from an acid, and the acidity of this acid must be of an extremely low order. The common expression "pseudo acid" reflects, in part, the general opinion of a lack of true acidic properties in the hydrocarbon from which the salt is, theoretically, derived but often cannot be obtained by direct action with the metal. Within the ranges covered by these compounds, however, the relative acidities are as meaningful as they are with the stronger carboxylic acids. The comparisons will, indeed, be shown to be very striking.

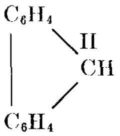
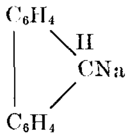
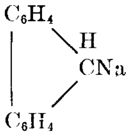
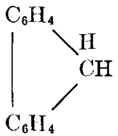
A. The method of measuring the acidity

The general method of measuring the acid strength in this series is one of replacement of a weak acid by a stronger one. Table 1 shows a graded series

TABLE 1

Graded replacement series connecting organometallic salts with the common salts

Increasing reactivity of salts ↑

REACTIVE SALT	+	ACID	(ACIDITY SCALE)	⟶	PRODUCTS LESS REACTIVE SALT	+	WEAKER ACID
$C_5H_{11}Na$	+	C_6H_5H	10^{-39}	$\rightleftarrows$	C_6H_5Na	+	$C_5H_{11}H$
C_6H_5Na	+	$C_6H_5CH_2H$	10^{-38}	$\rightleftarrows$	$C_6H_5CH_2Na$	+	C_6H_5H
$C_6H_5CH_2Na$	+	$(C_6H_5)_3CH$	10^{-33}	$\rightleftarrows$	$(C_6H_5)_3CNa$	+	$C_6H_5CH_2H$
$(C_6H_5)_3CNa$	+		10^{-25}	$\rightleftarrows$		+	$(C_6H_5)_3CH$
	+	C_2H_5OH	10^{-18}	$\rightleftarrows$	C_2H_5ONa	+	
C_2H_5ONa	+	HOH	10^{-14}	$\rightleftarrows$	HONa	+	C_2H_5OH
HONa	+	C_6H_5OH	10^{-10}	$\rightleftarrows$	C_6H_5ONa	+	HOH
C_6H_5ONa	+	CH_3COOH	10^{-5}	$\rightleftarrows$	CH_3COONa	+	C_6H_5OH
CH_3COONa	+	HCl		$\rightleftarrows$	NaCl	+	CH_3COOH

Increasing strength of acids ↓

which illustrates the process and, at the same time, links the salt-like character of the organosodium compounds to the better-known salts of the stronger acids.

The most authoritative study of this point and, indeed, the only one which assigns numerical values to the degree of acidity, is that made by Conant and Wheland (15) and later extended by McEwen (81). These investigators measured, under equilibrium conditions, the direction of change in several ways: a colorimetric one in the case of colored salts, a carbonation process followed by isolation of the respective acids, a spectroscopic method in which etioporphyrin I was used as an indicator, and a polarimetric one with some optically active compounds. They assigned approximate values of strength on the basis of the usual equation for comparing acids

$$\mathrm{p}K_1 - \mathrm{p}K_2 = \log \frac{[\mathrm{R}_1^-]}{[\mathrm{R}_1\mathrm{H}]} - \log \frac{[\mathrm{R}_2^-]}{[\mathrm{R}_2\mathrm{H}]}$$

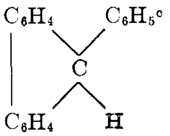
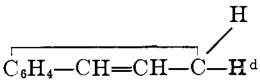
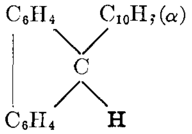
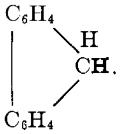
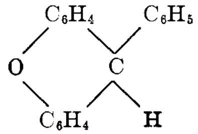
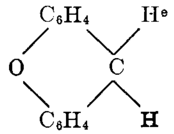
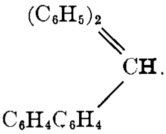
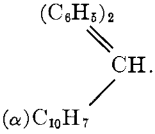
$\mathrm{p}K_1$ and $\mathrm{p}K_2$ are the respective acid strengths, R_1^- and R_2^- are the concentrations of the respective ions, and $\mathrm{R}_1\mathrm{H}$ and $\mathrm{R}_2\mathrm{H}$ are the concentrations of the corresponding acids. The assumptions are that the metallic salts are equally dissociated and that the pseudo acids are not dissociated. The concentrations of the ions of the salt can therefore be substituted for those of the acids. According to this equation the reaction will proceed 90 per cent to completion if the acids differ by 2 pK units when the quantities used are equal. Since a fivefold excess was used in the colorimetric measurements, a difference of 0.4 pK unit could exist. In the series of McEwen (81), the known value of 16 for methanol serves as a reference standard from which approximate values of pK are assigned to the other acids. The results of these studies are listed in table 2, in the order of decreasing strength and with the acidic hydrogen shown in heavy type.

The valuable series given in table 2 can be supplemented by information from replacement reactions in which the tendency to metalate, the comparative yields, and the ease of reaction have been noted. Such measurements are subject to special factors such as the insolubility of one or both of the organoalkali compounds present or the cation used (see Section IV A), and hence are not as suitable for determining the relative acidity as are the experiments made under equilibrium conditions. Nevertheless a surprising degree of unanimity is often found in the results of different investigators, many of whom had no thought of determining relative reactivities. Several examples of this method of judging the order of acid strength can be given.

Schorigin's (107) observation that ethylsodium reacts with benzene, toluene, and diphenylmethane rates ethane as a much weaker acid than any of the other three compounds. Amylsodium (85) attacks benzene, and phenylsodium, in turn, attacks toluene. Potassium amide (129), in liquid ammonia, does not substitute in toluene but does in diphenylmethane. Moreover, the series in table 2 shows that triphenylmethane is a stronger acid than diphenylmethane, from which the inference can be drawn that toluene, in which just one phenyl group is present, is less acidic than diphenylmethane. The reasonable deduction for the order of acid strength is: pentane or ethane $<$ benzene $<$ toluene $<$ ammonia $<$ diphenylmethane.

TABLE 2

Order of acidity as listed by Conant and Wheland and by McEwen

ACID	p*K*
$CH_3O\mathbf{H}$	16
$C_4H_4N\mathbf{H}$[a]	16.5
$(CH_3)_2C(H)O\mathbf{H}$ $C_2H_5O\mathbf{H}$ $C_6H_5CH_2O\mathbf{H}$	18
$(CH_3)_3CO\mathbf{H}$ $C_{10}H_{19}O\mathbf{H}$[b] $C_6H_5C(O)CH_2\mathbf{H}$ $(C_6H_5)_3CO\mathbf{H}$	19
 [c]  [d]  $C_6H_5C{\equiv}C\mathbf{H}$	21
$(C_6H_5)_2N\mathbf{H}$	23
	25
$C_6H_5\overset{H}{N}\mathbf{H}$ $p{-}CH_3C_6H_4\overset{H}{N}\mathbf{H}$ $p{-}CH_3OC_6H_4\overset{H}{N}\mathbf{H}$	27
  [e]	29
	31
$(C_6H_5)_3C\mathbf{H}$	33
	34
$(C_6H_5)_2\overset{H}{C}\mathbf{H}$	35
$(C_6H_5)_2C{=}CH{-}\overset{H_2}{C}\mathbf{H}$	36
$C_6H_5C\mathbf{H}(CH_3)_2$	37
$C_2H_5\mathbf{H}$	[40][f]

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[a] Pyrrole.
[b] Menthol.
[c] 9-Phenylfluorene.
[d] Indene.
[e] Xanthene.
[f] Estimated value.

A similar series can be arranged from data of Gilman and coworkers. Butyl-, phenyl-, α-naphthyl-, and *p*-methoxyphenyl-lithiums give 55, 12, 7.6, and 0 per cent yields, respectively, of the lithium salt of dibenzothiophene (31). Benzylsodium (39) metalates dibenzofuran. Neither dibenzofuranylsodium (39) nor triphenylmethylsodium (25) will attack dibenzothiophene. The orders, as judged from the data, are (*1*) butane < benzene < naphthalene < dibenzothiophene < anisole (para position) and (*2*) toluene < dibenzothiophene < dibenzofuran or triphenylmethane. The probable acidity of dibenzothiophene is in the neighborhood of 10^{-33} to 10^{-36}.

Other measurements of the same type have been made. Ziegler and coworkers (136) showed that phenylisopropylpotassium introduces a metal in 1,1-diphenylpropenyl, $(C_6H_5)_2C{=}CHCH_3$, and that phenyllithium attacks diethylamine (134). Gilman (25) showed that diphenyl ether is metalated by butyllithium but not by triphenylmethylsodium. By similar studies (27) triphenylmethane is rated weaker than furan, which in turn is weaker than phenylacetylene, rated 10^{-21} (table 2).

It is clear from the foregoing that the interchange of acids in a salt is very common and is virtually the only method now available for measuring the comparative acidities of these weak acids. When such processes can be carried out under equilibrium conditions a reliable opinion can be formed. When carried out in the usual manner the results, while not as accurate, nevertheless offer a satisfactory basis for establishing the probable order of acidity.

B. The effect of substituents on the acidity and the relative order of acid strengths

The evidence that phenyl groups increase the acidity of these hydrocarbo acids is clearly marked. In addition to the increase in the series methane, toluene, diphenylmethane, and triphenylmethane, 9-phenylfluorene is more acidic than fluorene (table 2). Presumably 9-phenylxanthene is more acidic than xanthene, although the method of measurement did not permit a fine distinction. The conclusion appears justified that attachment of a phenyl group to a carbon atom bearing an acidic hydrogen raises the acid strength.

Alkylation of any kind appears to lower the acidity. The comparative strengths of the alkanes may be judged from the fact that amylsodium attacks benzene or toluene more readily than does butylsodium, which in turn acts more readily than propylsodium (96). In fact, toluene can be used as a solvent in the preparation of propylsodium from propyl chloride and the metal. Increasing chain length is accordingly associated with greater reactivity of the salt and, therefore, with less acidity of the acid.

tert-Butyl-, isopropyl-, butyl-, and methyl-lithiums form the lithium salt of dibenzofuran (39) with decreasing ease. *tert*-Butyllithium attacks toluene more readily than does butyllithium (39, 40). These results indicate that alkyl chain branching, as well as chain lengthening, decreases the acid strength.

Confirmatory observations of the decrease in acidity with alkylation come from the greater difficulty experienced in metalation, once alkyl groups are introduced (unless, of course, the alkyl group introduced is itself metalated as in the case of a change from benzene to toluene). For example, *o*-, *m*-, or *p*-xylene is metalated by amylsodium (88) with more difficulty than is toluene; and the ortho isomer is attacked with more difficulty than the other two, probably because of the proximity of the two methyl groups. Butyl- or amyl-benzene is metalated (96) with more difficulty than is toluene. Two methyl groups, introduced into the alkyl portion of toluene (that is, to form isopropylbenzene), so reduce the acidity of the hydrogen on the side chain that the para position of the ring becomes a preferred point for salt formation (89). Furthermore, ethylsodium metalates the side chain with the least number of alkyl groups in *p*-cymene, i.e., the methyl in place of the isopropyl group (107).

These evidences of reduced acidity on alkylation have an interesting parallel in the observations of Ingold and coworkers (58, 72) that the decomposition of tetrasubstituted ammonium salts proceeds less readily when alkyl branching or alkyl chain lengthening occurs on the β-carbon atom. He appropriately attributes the effect to a reduction in the "incipient acidity" of the hydrogen atom on the β-carbon.

All these results confirm the opinion that the tertiary hydrogens in paraffin hydrocarbons are less acidic than the secondary hydrogens and that these in turn are less acidic than primary hydrogen atoms.

The effect of oxygen atoms on the acidity cannot be predicted at the present time with much certainty. As far as ethereal oxygen is concerned, the acidity appears to be raised. For example, xanthene can be regarded as diphenylmethane with an oxygen bridge. According to table 2, the first is a stronger acid than the second, $K_A = 10^{-29}$ and 10^{-35}, respectively. The increase may, however, be more the effect of a union of two rings than an oxygen ether influence, since fluorene is a markedly stronger acid than diphenylmethane.

Furan is metalated by triphenylmethylsodium but not by sodium phenylacetylide (27); therefore its acidity may be between 10^{-21} and 10^{-33}. Dibenzofuran (48) is weaker than dibenzothiophene. Diphenyl ether (25) is metalated by ethylsodium or butyllithium but not by triphenylmethylsodium, and is therefore probably weaker than 10^{-33}. Anisole is metalated by butyllithium, butylsodium, phenylsodium (25), and amylsodium (86). One difficulty in attempting to evaluate the influence of ethereal oxygen is that any effect of oxygen on the acidity may also be influenced by the facility with which organoalkali reagents cleave the ether (Section IV C). The question of the influence of other types of oxygen, such as esters or ketones, will be presented as a part of the next section (III C).

A general over-all order for hydrocarbons and some ring systems may be arranged as follows:

Alkane (tertiary)	$< 10^{-37}$	Diphenylmethane	10^{-35}
Alkane (secondary)		Triphenylmethane	10^{-33}
Alkane (primary)		Xanthene	10^{-29}
Methane		Aniline	10^{-27}
Benzene		Fluorene	10^{-25}
Toluene	near 10^{-37}	Phenylacetylene	10^{-21}

Introduction of phenyl groups into any of these systems will, in general, increase the acidity. Introduction of alkyl groups will decrease the acidity. Oxygen, in the form of ether, possibly strengthens the acidity, other factors being equal.

C. The relationship to other acids and salts

By and large, substituents have the same qualitative effect on acidity whether they are introduced into hydrocarbons, amines, alcohols, or carboxylic acids. The similar character of this effect is very clear in the case of phenyl groups (see table 3). The progressive introduction of the phenyl nucleus in methane has already been shown to cause a decided increase in acid strength. Its introduction into ammonia likewise increases the acidity (81), and conversely decreases the basicity (110). Sodium amide, as predicted from such basicity studies, will metalate aniline (116). The known difference in acidity between phenol (110) and water shows that the phenyl group exerts a similar effect when the acidic hydrogen is attached to oxygen instead of to nitrogen or carbon. The acidity of acetic acid shows a similar trend when phenyl is introduced.

TABLE 3

Effect of introducing phenyl groups into acids

NUMBER OF PHENYL SUBSTITUENTS	pK				
	CH_4	NH_3		H_2O	CH_3COOH
	K_A	K_A	K_B	K_A	K_A
None	?		1.85×10^{-5}	1.0×10^{-14}	1.75×10^{-5}
One	$<10^{-35}$	10^{-27}	5.0×10^{-10}	1.0×10^{-10}	4.88×10^{-5}
Two	10^{-35}	10^{-23}	*		11.5×10^{-5}
Three	10^{-33}				

* Too weak to measure in water (52).

There are many other instances of increase in acidity caused by introducing phenyl groups. Phenylhydrazine ($K_B = 1.6 \times 10^{-9}$) is more acidic than hydrazine ($K_B = 3 \times 10^{-6}$) and is metalated by sodium amide in liquid ammonia to give $C_6H_5N(Na)NH_2$ (3). Phenylacetylene (25) is stronger than acetylene, judged by metalation studies. Two phenyl groups substituted in propene, $(C_6H_5)_2C{=}CHCH_3$, raise the acidity so as to permit substitution by phenylisopropylpotassium (133). Thiophenol is a stronger acid than hydrogen sulfide. It is clear from all this evidence that the introduction of phenyl into the system H_nXH, where X is either a bi-, tri-, or tetra-valent atom, or into any system where the acidic hydrogen is in a position conjugated with X, as in the above-mentioned propene compound, will invariably increase the acidity of the hydrogen. The introduction of a phenyl group into any position of a molecule does not, however, necessarily raise the acidity of carboxylic acids, since benzoic acid (110) is weaker ($K = 6.3 \times 10^{-6}$) than formic acid ($K = 1.76 \times 10^{-4}$) and β-phenylpropionic acid is not appreciably different from propionic acid (18). In a similar way 1,1,1-triphenylethane (129), $(C_6H_5)_3CCH_3$, is not acidic enough to be affected by potassium amide in liquid ammonia. The activating influence is realized when the phenyl group is attached directly or through a vinyl system to the atom which holds the acidic hydrogen or acid-functioning group (128). When it is otherwise situated, the effect need not be the same.

The vinyl group, like the phenyl, confers marked acidity on acids. The fact that the ionization constant (110) of vinylacetic acid is a little less (3.8×10^{-5}) than that of phenylacetic acid (5.4×10^{-5}) suggests that substitution in the hydrocarbo acids would be a little more difficult when the activation is by a vinyl rather than a phenyl group. In agreement with this expectation, propene is not metalated as readily as is toluene. When two vinyl groups are present and are connected with each other, the activation is appreciable. Cyclopentadiene (53) is metalated by such a mild reagent as ethylmagnesium bromide; pyrrole, also, has a hydrogen which is acidic enough to be detected by the Grignard reagent (132) in pyridine solution at 85°C. The marked activity of the hydrogen atoms in fluorene in the reaction with a Grignard reagent (52, 132) is readily explained on the basis that a divinyl system, activated by two benz groups, is present.

A similar parallelism, in an opposite direction, can be shown to result from the introduction of alkyl groups. The weakening of the acidity in the nitrogen series is seen by the increase of the basicity (inverse of the acidity) (20) and the decrease of the ionization potential (114) of ammonia as alkyl groups are introduced. Similarly, the acidity becomes weaker as water (10^{-14}), methanol (10^{-16}), and ethanol (10^{-18}) are compared (81). The series methanol, isopropyl alcohol, and *tert*-butyl alcohol likewise shows decreasing acidity (table 2). The same alkyl influence is found in changing from acetic to trimethylacetic acid (18).

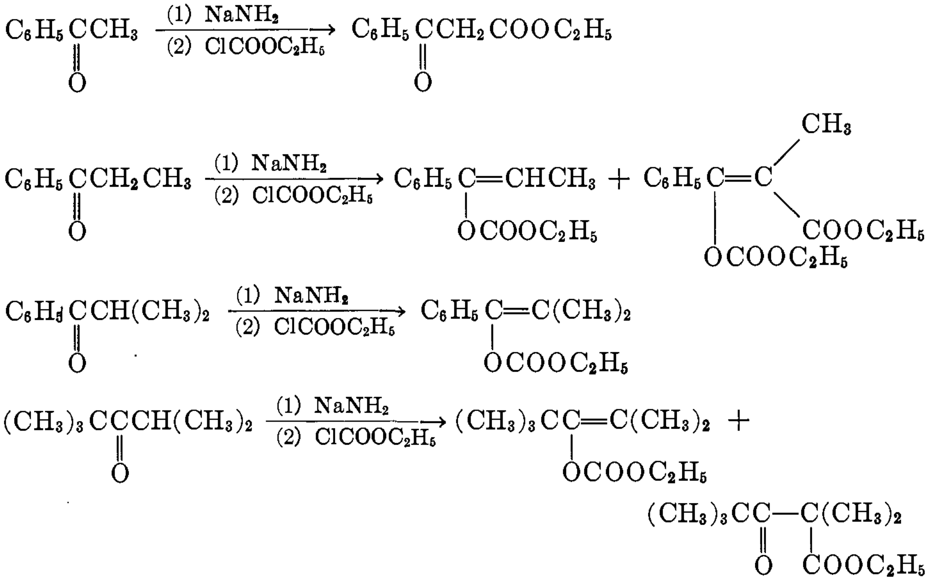
Exceptions to this general rule of decreased acidity with increased alkylation are few in number. The ionization constants of carboxylic acids show some irregularity with chain lengthening, which Dippy (18) ascribes to chelation of the hydrogen on the γ-carbon atom with the carbonyl oxygen. Heptylacetylene (25) is stronger, rather than weaker, than acetylene, judged by metalations with the lithium salt. Sodium isobutyrate (85) is metalated more readily by amylsodium than is sodium caproate, a circumstance that may be related to the difficulty of adequate contact in a mixture in which both reagents are insoluble.

The remarkable similarity in the effects of phenyl or alkyl groups in hydrocarbo, ammono, or carboxylic acids suggests that similar parallel effects will be encountered for carbethoxy or other groups. That is to say, since a carbethoxy group will raise the acidity of a carboxylic acid, it should also raise the acidity of a hydrocarbo acid. Such reasoning leads to the opinion that the hydrogen in ethyl acetate or ethyl malonate is acidic. Practical results indicate that the acidity of ethyl acetate is of a relatively high order, comparable with that of ethyl alcohol, for the reaction of sodium ethoxide with ethyl acetate is an equilibrium process. This view is advanced by Chelintzev (14) and by Hauser (59, 60) as preferable to the older view of Claisen of an addition product between the ester and the alcoholate:

$$NaOC_2H_5 + CH_3COOC_2H_5 \rightleftarrows HOC_2H_5 + NaCH_2COOC_2H_5$$

This opinion is in accord, also, with the fact that as an alkylated ester is used, i.e., as ethyl propionate and higher members are treated with sodium ethoxide, the acidity of the ester is weaker and the equilibrium lies further toward the left. Hence the reaction to the right needs to be forced by volatilization of the ethyl alcohol formed in the process (11). Moreover, with esters which are more difficult to convert to the sodium salt, the use of the more reactive triphenylmethylsodium (K_A of $(C_2H_5)_3CH$ is 10^{-33}) has been shown by Hauser (59) to be preferable to sodium ethoxide (K_A of C_2H_5OH is 10^{-18}). Even in this case alkylation, superimposed on the carbethoxy effect, reduces the acidity, for the metalation of the ester should and does, in some cases at least, proceed with more difficulty as the chain is lengthened. For example, triphenylmethylsodium metalates ethyl diethylacetate, $(C_2H_5)_2CHCOOC_2H_5$, in 30 min. and ethyl isobutyrate, $(CH_3)_2CHCOOC_2H_5$, in 5 min. (59). According to the principles which have been presented earlier, the first compound would be a weaker acid than the second and, therefore, harder to metalate.

The carbonyl group, also, has a pronounced effect on acidity. Sodium amide (estimated value of K_A for NH_3 is 10^{-30}) metalates (57) acetophenone ($K_A = 10^{-19}$) and like compounds. The salt produced is one in which the anion exists in two resonance forms, judged by the fact that a subsequent reaction with ethyl chloroformate sometimes produces a carbon derivative and at other times an oxygen derivative. Introduction of alkyl groups into the ketone, as seen below, favors the oxygen form; and this fact would be expected, since alkyl groups reduce the acidity of the hydrogen on the carbon atom to which the groups are directly attached.



$$C_6H_5\underset{\underset{O}{\|}}{C}CH_3 \xrightarrow[(2)\ ClCOOC_2H_5]{(1)\ NaNH_2} C_6H_5\underset{\underset{O}{\|}}{C}CH_2COOC_2H_5$$

$$C_6H_5\underset{\underset{O}{\|}}{C}CH_2CH_3 \xrightarrow[(2)\ ClCOOC_2H_5]{(1)\ NaNH_2} C_6H_5\underset{\underset{OCOOC_2H_5}{|}}{C}{=}CHCH_3 + C_6H_5\underset{\underset{OCOOC_2H_5}{|}}{C}{=}C\begin{matrix}\diagup CH_3\\ \diagdown COOC_2H_5\end{matrix}$$

$$C_6H_5\underset{\underset{O}{\|}}{C}CH(CH_3)_2 \xrightarrow[(2)\ ClCOOC_2H_5]{(1)\ NaNH_2} C_6H_5\underset{\underset{OCOOC_2H_5}{|}}{C}{=}C(CH_3)_2$$

$$(CH_3)_3C\underset{\underset{O}{\|}}{C}CH(CH_3)_2 \xrightarrow[(2)\ ClCOOC_2H_5]{(1)\ NaNH_2} (CH_3)_3C\underset{\underset{OCOOC_2H_5}{|}}{C}{=}C(CH_3)_2 + (CH_3)_3C\underset{\underset{O}{\|}}{C}{-}\underset{\underset{COOC_2H_5}{|}}{C}(CH_3)_2$$

This problem of metalation of compounds which contain carbethoxy or carbonyl groups is complicated by the fact that the reagent can add as well as substitute, a mixture of effects which will be met later in this paper (Section IV B). In order to emphasize the relationship between the hydrocarbon and other types of acids, the influence of such groups, and for that matter of nitrile and nitro groups, will be expressed as a labilizing of the acidic hydrogen, and the structure of the ionized form will be regarded as a resonance hybrid between the carbon atom and the negative pole of the activating group.

A number of interesting summaries can now be made. Table 4 lists (*a*) some of the common acids, including hydrocarbon, alcoholic, and carboxylic; (*b*) the group which influences the acidity of each acid; (*c*) the salt commonly used for metalation; and (*d*) the position in the anion where the metal ion is attached. The table is arranged in order of increasing acidity of the acid which reacts with the metal salt. The acid strength increases as the activating group changes from phenyl to carbonyl or carbethoxy and cyano, and increases further as the hydrogen shifts from a position on carbon to one on oxygen, and still further to one on a carboxyl group. Correspondingly, the salt required to metalate the acid need be less and less reactive, and the product becomes more and more stable.

TABLE 4

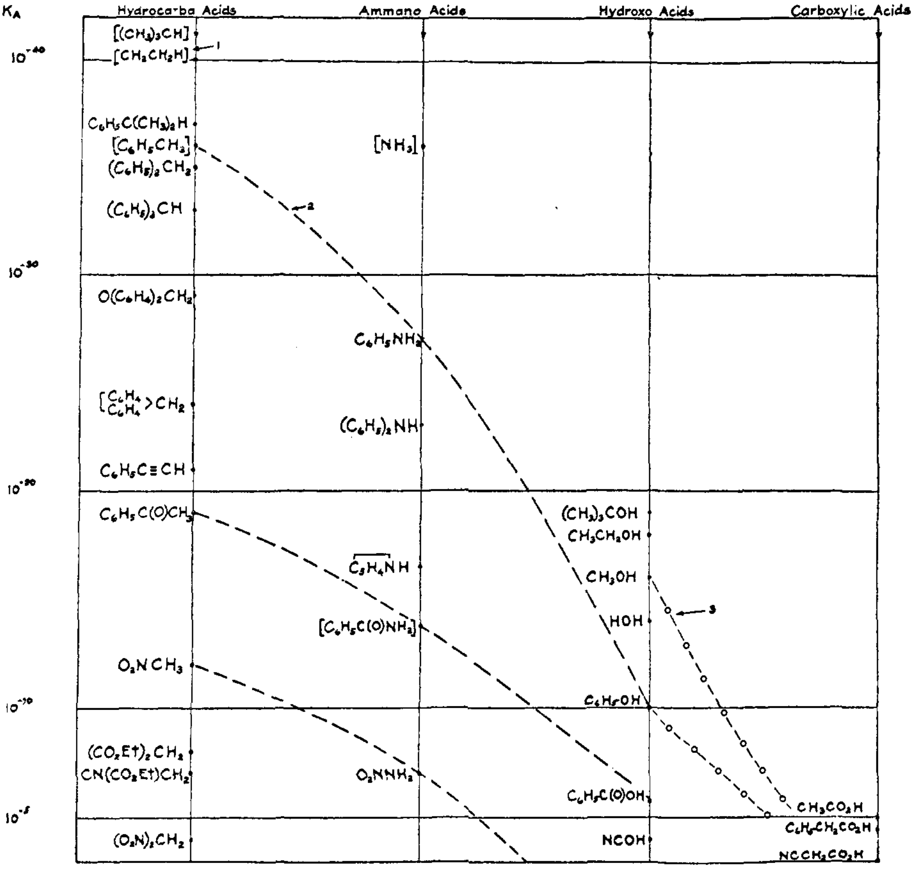
Acids, activating group, and reagent used for replacement of hydrogen

ACID	GROUP ACTIVATING THE ACID	SALT COMMONLY REQUIRED FOR SUBSTITUTION	ATTACHMENT OF THE METAL ION IN THE PRODUCT
Alkanes	Alkyl groups	None so far known	
Benzene or toluene	Benzene ring	Alkylsodium compounds	Metal attached solely to carbon
Acetophenone	Carbonyl group	Sodium amide	Metal attached to a resonance hybrid between carbon and oxygen
Ethyl acetate	Carbethoxy group	Triphenylmethylsodium	
Ethyl acetoacetate	One carbonyl and one carbethoxy group	Sodium ethoxide	
Acetonitrile	Cyano group	Lithium amides, sodium ethoxide	Metal attached to a resonance hybrid between carbon and nitrogen
Alcohols	Alkoxy radical	Sodium acetylide, Grignard reagents. Equilibrium with salts of hydroxides	Metal attached solely to one oxygen
Carboxylic acids	Carboxyl radical	Alkaline hydroxides	Metal attached to resonance hybrid of two oxygen atoms

Table 5 presents the acidity relationship from another angle. A limited number only of acids are indicated, but the relative positions of acids activated by similar groups are shown by dotted lines. It is clear that there is a gradual drop in acid strength as the hydrogen is attached to carbon, nitrogen, oxygen, or carboxyl. It is also true that in all series, the acidity increases as the possibility of resonance increases, as judged by the effect of such unsaturated systems

TABLE 5

Approximate relative positions of corresponding acids in different series



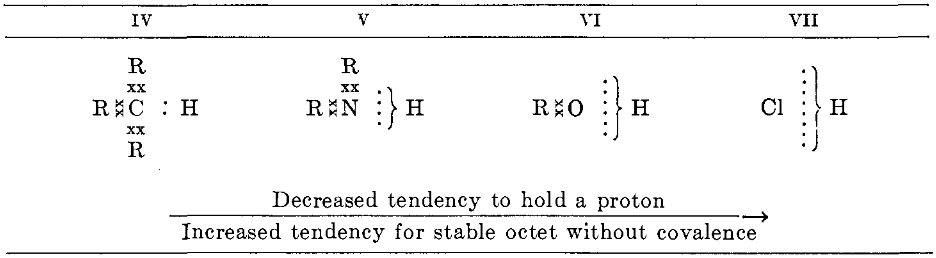
Positions of compounds enclosed in brackets are estimated. Ammonia is placed above diphenylamine because of the observation of Wooster (128), that the hydrogen in a benzohydryl type compound was replaced by metal in reaction with potassium amide. If the position of ammonia is correct, the values for methane, ethane, and trimethylmethane may be considerably less than indicated.

Dotted lines connect the corresponding acids in different series.

Dashes and circles, rather than dotted lines, connect the hydroxo acids to members of the carboxylic acid series, because the latter do not represent a truly different series, but merely hydroxo acids, activated by an adjacent carbonyl group.

as carbethoxy, carbonyl, nitrile, and nitro groups. Dinitromethane, for example, is acidic enough to be measured by conductance (110).

The relationship can also be presented by the electronic picture below, which emphasizes the positions of carbon, nitrogen, oxygen, and chlorine in the Periodic Table:



The ionization increases progressively as the number of electrons to which the proton can be attached increases; or, expressed in another way, the chance of a proton being separated becomes greater as the anion becomes able to maintain a stable octet without the assistance of covalence with the proton and other radicals. This chance is at a minimum for carbon and at a maximum for chlorine.

In the carbon, nitrogen, and oxygen series of acids, the acids become stronger as the system is fortified by resonance. For example, the alcoholic acid is strengthened by another oxygen atom, as in the carboxylic acids, and the latter is still further strengthened by a nitrile group. Similarly, the hydrocarbon acids are strengthened by nitrile or nitro groups.

The description of these relationships is greatly simplified. There are unquestionably some factors, peculiar to each series, which would prevent an exactly parallel effect. At the present moment, however, the scheme serves to show the broad principles involved and to indicate that, within the region where the hydrocarbon acids react, the acidity relationships, and hence the salt-like character of many reactions of the organometallic compounds can be as real as those which prevail among the better-known acids and salts.

IV. THE COMMON REACTIONS

A. Substitution

One of the common reactions of the organoalkali compounds is substitution. This reaction, as far as replacement of hydrogen is concerned, has already been discussed at some length in the section dealing with the measurement of the acidities of the acids, and will be mentioned frequently in other portions of this paper.

The potency of an organometallic reagent in such a reaction might reasonably be regarded as related to the difference in strength between the anion and cation, for if acids vary in strength and bases vary in strength, the various combinations of acids and bases (known as salts) must also vary according as the respective strengths are compensated; the differences will be made manifest by different reactivities of the salts, leading toward greater compensation of the forces involved. The cause of this difference is not known. The electrical charge is theoretically neutralized, for whether the salt is amylpotassium, amylsodium, sodium amide, or sodium chloride, the cation and the anion have charges represented by the loss and the gain of one electron, respectively. The disposition of the electrons in each ion, however, must have a great influence. Although it is possible to speculate on the relation of mass, volume, electron orbits, and the like to the comparative activities of lithium, sodium, potassium, and other cations, and to ponder on the influence of groups on the stability of the system of eight electrons in the anion when one pair is without the fixing influence of a covalence, this review is concerned primarily with the manifestations, rather than the cause, of variable activity.

It has already been made clear that the activity increases as the acid to which the anion is related becomes weaker, the cation at the same time being constant. It is equally true that the reactivity increases as the cation changes. The Grignard reagent attacks anisole (13) only at high temperature; butyllithium metalates it near room temperature. Butyllithium in turn will introduce one metal atom only into furan and has a limited action (15 per cent yield) on benzene (39); amylsodium will introduce two sodium atoms into furan (91), one sodium atom into benzene at around 25°C., and two sodium atoms into benzene (88) at 55–60°C. Ethyllithium, ethylsodium, and ethylpotassium attack dibenzofuran with increasing ease (46). The last two reagents cause dimetalation. The comparatively weak salt, ethylmagnesium bromide, reacts with toluene (64) only under special conditions, such as in hot toluene in the presence of *p*-isopropylbenzyl chloride, to give the disubstituted ethane, $(CH_3)_2CHC_6H_4\text{-}CH_2CH_2C_6H_5$. Alkyllithium compounds, however, metalate toluene (42) readily; amylsodium does so with great rapidity. Amylpotassium (87), but not amylsodium, will metalate 1-pentene easily.

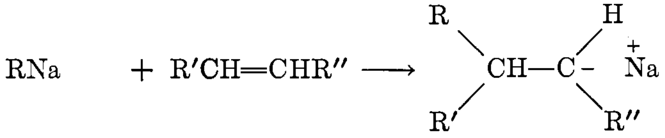
These changes in reactivity accord with the view that the salt becomes more active as the difference in strength between cation and anion increases. The order for the strength of anions, as outlined in the previous section, might not be altered by a change in the cation, but the possibility of metalation when the two pseudo acids involved are near each other in acidity appears to be improved as the cation becomes stronger. This fact, undoubtedly, is important in any attempt to arrange an order of acidity for hydrocarbon acids on the basis of metalation experiments under non-equilibrium conditions, since a failure to metalate with a given salt may merely mean that the cation lacks sufficient strength to bridge the resistance toward a reaction which could otherwise take place.

B. Addition

At first thought the process of addition might be expected to be a very easy one. The fact that halogens add instantaneously to olefins, but substitute slowly in hydrocarbons, has contributed to the tradition that addition reactions are invariably preferred and that, if substitution does take place in a compound where double bonds are present, an addition process may have been its precursor. In spite of the facility with which addition to unsaturated systems occurs, organometallic reagents do not appear to add invariably to olefins, and there are reasons why, in certain instances, they might not be expected to add very readily. The problem of addition is, in fact, complicated by the strong tendency toward substitution.

The simplest case that can be considered is the possibility of addition to an olefin, such as ethylene or a substituted ethylene. The products would be a long-chain or a branched-chain alkylmetal compound as indicated below:

$$\mathrm{RNa} + \mathrm{H_2C{=}CH_2} \longrightarrow \mathrm{RCH_2{-}CH_2Na}$$



$$\mathrm{RNa} + \mathrm{R'CH{=}CHR''} \longrightarrow \overset{\mathrm{R}}{\underset{\mathrm{R'}}{\diagdown\!\!\diagup}}\mathrm{CH{-}}\overset{\mathrm{H}}{\underset{\mathrm{R''}}{\mathrm{C}^-}}\ \overset{+}{\mathrm{Na}}$$

$$\text{Reactive salts} + \text{Olefins} \longrightarrow \text{More reactive salts}$$

According to the principles discussed in a previous section, alkyl branching and alkyl-chain lengthening will reduce the acidity of the pseudo acid. Hence such addition will produce a salt more active than the reagent employed. This fact need not of course prevent the reaction, since, if the two acids in question are near enough in strength, an observable equilibrium might theoretically exist; and, because the carbon–carbon bond in the product is not labile, the process would be an inrreversible one and would proceed to completion. If, however, substitution were possible at some position in the olefin—and the vinyl group will activate a hydrogen for replacement—the product would be a less reactive salt than the reagent. Therefore, unless the velocity of substitution is extremely slow compared to that of addition (admittedly a very important provision), or unless some other factor, such as insolubility, intervenes, substitution rather than addition would be the rule.

Experiment confirms the above deductions concerning addition reactions to *simple* olefins. 2-Phenylisopropylpotassium does not react with ethylene (133). The more reactive amylpotassium (87) reacts with 1-pentene, but the process is one of substitution, not of addition.

$$\mathrm{C_2H_5CH_2CH{=}CH_2 + C_5H_{11}K \rightarrow C_2H_5CHKCH{=}CH_2 + C_5H_{12}}$$

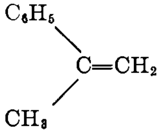
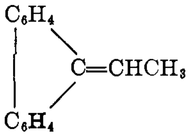
The chances of addition become more favorable when one of the carbon atoms of the olefin has a phenyl or aromatic system attached. Such a group, as mentioned before, increases the acidity of acids; and the product of addition would have a better chance of being a salt of less reactivity than the reagent. In spite of this assistance the tendency to add is by no means dominant. Table 6 shows the results obtained by Ziegler (133) and coworkers in the reaction of phenylisopropylpotassium with a number of olefins. It is apparent that addition will take place in every instance where there is only one phenyl group attached to carbon, except in one compound where two methyl groups are connected vinylogously to the activating ring; and, incidentally, that compound is also one in which a maximum amount of branching would have been present had addition occurred. Addition takes place also when the fluorene group is present.

The margin between addition or substitution, however, must be close, because the presence of two phenyl groups on the carbon atom in question causes substitution to be favored in every instance, even though the activating influence has to be transported through a vinyl group in order to make substitution possible. The presence of two phenyl groups on one carbon atom may retard but does not prevent an addition reaction, because unsymmetrical diphenylethylene, in which no very acidic hydrogen is present, adds the potassium reagent readily. It is clear, therefore, that in these examples substitution is preferred to addition.

When the activating group is a nitrile, carbonyl, or carboalkoxy group, the condition is different from that present in the reaction with olefins, because the activating group is also the one to which addition occurs. On the one hand the probability of substitution is enhanced because the acidity promoted by a nitrile or carbonyl group is greater than that by a phenyl group. (The ionization constants (110) of cyanoacetic, glyoxylic, and phenylacetic acids are 3.7 × 10^{-3}, 4.7 × 10^{-4}, and 4.88 × 10^{-5}, respectively.) On the other hand, the addition process may overcome this advantage by the higher velocity with which addition to an unsaturated, and comparatively strongly polar, system may occur.

TABLE 6

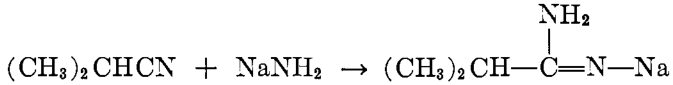
Reaction of phenylisopropylpotassium with various unsaturated hydrocarbons

ADDITION REACTIONS	SUBSTITUTION REACTIONS*
$C_6H_5CH{=}CH_2$	$C_6H_5CH{=}C(C\mathbf{H}_3)_2$
$(C_6H_5)_2C{=}CH_2$	$(C_6H_5)_2C{=}CHC\mathbf{H}_3$
 $\begin{array}{l} C_6H_5 \\ \qquad C{=}CH_2 \\ CH_3 \end{array}$	$(C_6H_5)_2C{=}C(C\mathbf{H}_3)_2$
$C_6H_5CH{=}CHCH_3$	$(C_6H_5)_2C{=}CHC\mathbf{H}_2CH_3$
 $\begin{array}{l} C_6H_4 \\ \qquad C{=}CHCH_3 \\ C_6H_4 \end{array}$	$(C_6H_5)_2C{=}CHC\mathbf{H}_2C_6H_5$

* The hydrogen replaced is shown in heavy type.

The very reactive salts, that is, the salts of extremely weak acids as represented by some organosodium, organolithium, and Grignard reagents, invariably add rather than substitute. The reactions are too common to list.

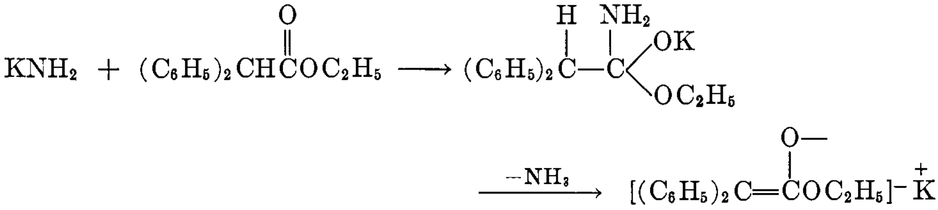
The less reactive salts, such as sodium amide, sodium alkoxides, and triphenylmethylsodium, will sometimes add, but they very frequently substitute, or at least undergo a process the net result of which is equivalent to substitution. For example, addition of sodium amide to a nitrile (135), as in the equation below, produces a salt of an amidine, but reaction of lithium amide or lithium diethylamide with the same compound results in substitution.



$$(CH_3)_2CHCN + NaNH_2 \rightarrow (CH_3)_2CH\text{—}\overset{NH_2}{\overset{|}{C}}\text{=N—Na}$$

$$(CH_3)_2CHC{\equiv}N \xrightarrow[LiN(C_2H_5)_2]{LiNH_2 \text{ or}} (CH_3)_2C(Li)C{\equiv}N$$

The mechanics of the substitution process are not known with sureness. A plausible explanation, frequently offered, is that addition takes place first, followed by elimination, so that the result is equivalent to substitution. This opinion is supported by the isolation of addition products in certain reactions. Potassium amide forms an intermediate with ethyl diphenylacetate (113); when heated, this intermediate liberates ammonia to form a potassium salt in which the metal is presumably attached to the resonance form of the ion.

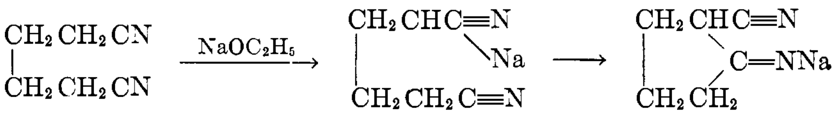


Sodium methoxide, also, forms an addition compound with ethyl benzoate (119). Adickes (1), however, failed to find evidence that such compounds were present with reagents used in preparations leading to compounds of the ethyl acetoacetate type.

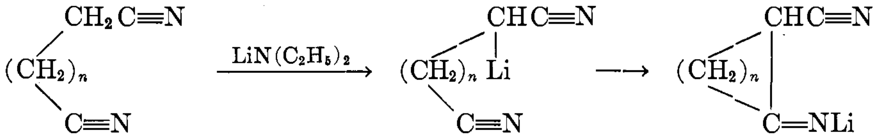
In the present state of knowledge it is impossible to distinguish between a direct substitution and an indirect process by an addition mechanism when the final product contains a metal in place of hydrogen. Suitable pen and paper pictures can be constructed easily for either possibility.

Whatever the governing factor, substitution occurs readily with the less reactive reagents, and numerous processes rely upon a sequence of substitution followed by addition. For instance, the preparation of cyclic compounds from dinitriles by use of alkaline reagents shows both steps (see below). For making five- and six-membered rings, Thorpe (115) used sodium ethylate; for large rings, Ziegler (134) used lithium diethylamide.

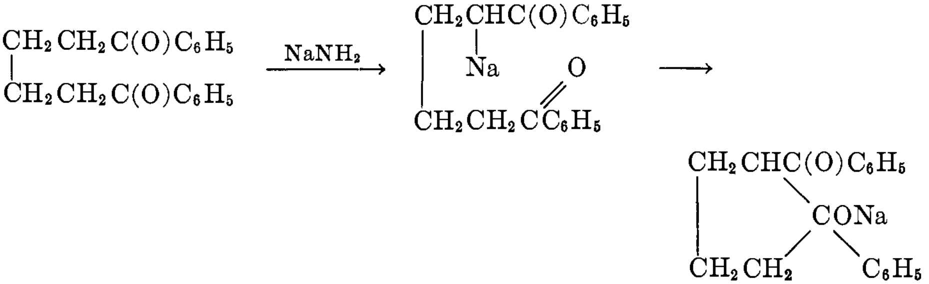
Thorpe:



Ziegler:

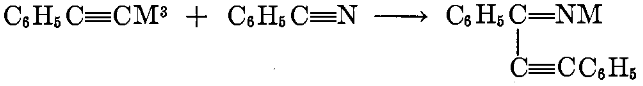


Similar ring formation occurs when the activating group is carbonyl (56).



The well-known formation of ethyl acetoacetate has been interpreted (2, 14, 59, 60) as one of initial substitution in an equilibrium process, followed by addition. The alcohol formed in the first step can be removed by distillation (11) or by metallic sodium. When sodium alcoholate is the condensing agent, the first phase is not readily isolable because the alcohol produced is so acidic that an equilibrium exists. When triphenylmethylsodium (66) is used with dialkyl-substituted acids, the triphenylmethane is so weakly acidic, or the intermediate substitution product is so stable, that the reaction proceeds to the completion of the formation of substitution product in place of the self-condensation. The reagent which will induce a proper sequence of substitution and addition varies (109) with the substance being condensed. Sodium amide is not effective with ethyl acetate, whereas sodium alkoxide is. Sodium or potassium amide or isopropylmagnesium bromide induce the condensation in ethyl phenylacetate or in *tert*-butyl acetate.

When addition takes place, the velocity appears proportional to the strength of the cation as long as the anion remains constant. The times required for completion of the reaction of phenylacetylides (49) with benzonitrile were found



$$C_6H_5C{\equiv}CM^3 + C_6H_5C{\equiv}N \longrightarrow \begin{array}{l} C_6H_5C{=}NM \\ \quad\;\; | \\ \quad\;\; C{\equiv}CC_6H_5 \end{array}$$

to be 2.9, 3.9, 4.4, 6.8, 60 and 86 hr., respectively, for the cesium, rubidium, potassium, sodium, lithium, and magnesium bromide salts.

The effect of a variation in the strength of the anion cannot be foretold with certainty, for two factors are at work: one the increased reactivity of the reagent salt as salts of weaker pseudo acids are employed, and the other the decreased strength of acid in the product salt caused by branching. In other words,

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[3] M = a metal ion.

the anions in the reagents and in the product do not compete by interchange of a proton and an alkali cation, but unite in an irreversible process. The result is that the order found in the replacement studies is not always followed in the addition processes. For example, Ziegler (133) and coworkers noted that the reactions of ethyl-, propyl-, and butyl-lithiums with unsymmetrical diphenylethylene at 50°C. were as 1.5 to 3.4 to 2.8, respectively; Gilman, Moore, and Baine (39) found that the percentage of addition to the same compound after 8 hr. in benzene with *sec*-butyl, isobutyl-, and butyl-lithium was 82, 13, and 12, respectively. These results are approximately in the order of greater reactivity as rated by the replacement series (Section III B) (although Ziegler's results showed a maximum value for propyllithium). On the other hand, the addition of the Grignard reagent to benzonitrile (42) showed roughly the opposite trend of less reactivity with more reactive salts, *tert*-butyl, *sec*-butyl-, butyl-, ethyl-, and phenyl-magnesium bromides requiring 25.5, 11.65, 4.57, 0.85, and 0.31 hr., respectively, for completion of the addition process. These orders are the inverse of that based on reactivity in replacement reactions. The variations are not the result of using benzonitrile in place of diphenylethylene, because similar irregularities can be found in each type of compound. Amyllithium added less readily than butyllithium to *as*-diphenylethylene, contrary to expectation; and the time required for addition to benzonitrile decreased in the series phenyl-, *p*-tolyl-, and mesityl-magnesium bromides from 0.31 to 0.10 to 0.01 hr., respectively, in agreement with the order of expected increase in reactivity. In general, the processes of addition do not furnish as reliable an index of reactivity as do those of substitution where, under certain conditions at least, equilibrium conditions exist and where the changes involve only a replaceable hydrogen in the pseudo acid, not a complete change by fusion of the anion with the pseudo acid.

C. Cleavage

It is characteristic of salts that they will cleave organic compounds wherever a more stable salt will form and the reagent has sufficient reactivity. Ethers are accordingly cleaved by some organometallic reagents, the products being metallic alkoxides or phenoxides. Amines are cleaved with more difficulty, for the metallic amide formed is in general a more reactive salt than is the alkoxide. The carbon–carbon bond is broken only when the bond is greatly activated by carbonyl and carboalkoxy groups. For example, ethyl acetoacetate is cleaved by such a comparatively mild reagent as sodium ethoxide, one of the products being the less reactive acetate.

Ordinary ether can be cleaved easily. Ethylsodium (107) reacts with it to form sodium ethoxide, ethane, and ethylene. Amylsodium cleaves ether so readily that it cannot be used as a solvent in reactions of that organoalkali reagent. *Sec*- and *tert*-alkyllithiums (30) react with ethyl ether rather rapidly. In contrast to the behavior of these reactive salts, methyllithium, which is, according to Section III, a very much weaker salt than the *sec*-, *tert*-, and *n*-alkyllithium reagents, can be kept in refluxing ether for 11 days without any action taking place. The weaker Grignard reagents, also, can be kept in ether for indefinite periods.

Anisole (111) and phenetole (54), probably because of their high boiling points as well as the activation imparted by a phenyl nucleus, are cleaved at high temperature by methyl- and ethyl-magnesium iodides. Benzyl ethyl ether (112) reacts with methylmagnesium iodide to form ethylbenzene.

Ethylene oxide represents a still more reactive type of ether which is cleaved readily by Grignard reagents. It can be cleaved also by the moderately active ethyl sodioisobutyrate (67), $(CH_3)_2C(Na)C(O)C_2H_5$.

Amines should be cleaved also, but with more difficulty than the ethers. When methylmagnesium iodide and dimethylaniline (65) interact together at 215°C. and the mixture is carbonated, a major product is *p*-dimethylaminophenylbenzoic acid, $(CH_3)_2NC_6H_4C_6H_4COOH$. One dimethylamino group has obviously been separated by cleavage. The steps in this process might be formulated as follows:

$$CH_3I + Mg \rightarrow CH_3MgI$$

$$CH_3MgI + C_6H_5N(CH_3)_2 \rightarrow CH_4 + —C_6H_4— + (CH_3)_2NMgI$$

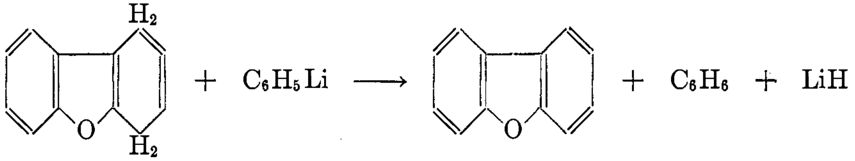
$$(CH_3)_2NMgI + C_6H_5N(CH_3)_2 \rightarrow (CH_3)_2NC_6H_4MgI + (CH_3)_2NH$$

$$(CH_3)_2NC_6H_4MgI + —C_6H_4— \rightarrow (CH_3)_2NC_6H_4C_6H_4MgI$$

Other miscellaneous cleavage reactions occur. Diphenylmercury, for example, is cleaved by butyllithium (25) with formation of phenyllithium. Phenyl selenide (25) is cleaved readily by butyl ether under conditions in which phenyl sulfide is partially cleaved and partially metalated, and diphenyl ether is not cleaved at all but is metalated. Formals (117) are cleaved by the Grignard reagent. Organolead and other related compounds are cleaved by lithium reagents (40).

D. Dehydrogenation

Phenyllithium converts 1,4-dihydrodibenzofuran (26) and 1,4-dihydrodibenzothiophene (31) to dibenzofuran and dibenzothiophene according to the equation



The reaction is not a general one for all hydroaromatic systems. The process is probably one of substitution, followed by elimination of lithium hydride, somewhat after the manner in which addition reactions, followed by elimination of an alkali hydride, occur (see Section VI C). The tendency for restoration of the conjugated cyclic structure plays a prominent rôle in such cases.

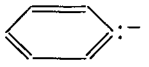
V. RESIDUAL POLARITY

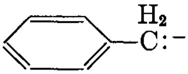
In agreement with the hypotheses set forth at the beginning of this paper, a salt derived from a base and an acid of unequal strengths will necessarily have a degree of reactivity related to the inequalities involved, and the stronger of the two ions will have an activity commensurate with its uncompensated strength. This unbalanced effect, since it emanates from the cation, must be of a positive nature and will, therefore, attract and disturb electrons in other bodies in the immediate vicinity, preferably in the anion to which it is attached by an electrostatic force, but also possibly in other substances with which it happens to be in contact. The result will be that the cation, without itself participating directly in a reaction, will nevertheless affect the reaction of the anion or other body. To consider otherwise is to state that an extremely strong polar force will, for no good reason at all, cease to act like a positive pole.

Such residual polarity can be shown with advantage in orientation studies. Three cases exist. In the first the expected ortho–para-orienting effect is completely set aside by the metal ion and the substituting group is caused to enter the meta position or another ring. In the second, the ortho–para-directing influence is largely or entirely preserved but substitution is made more difficult. In the third, but not decisive case, the conventional meta orientation caused by a carboxyl or carbonyl group is altered and ortho–para orientation results.

A. Meta-directing influence of alkali-metal cation

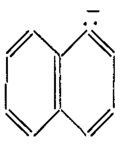
The phenyl and benzyl ions, shown below, might be expected to show an ortho–para-directive influence because the electrons no longer held by a covalence

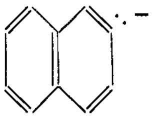




would be free to resonate with those in the ring and thus to increase the electron density in the aromatic nucleus. The results are quite contrary to such expectation. Metalation of phenylsodium and of benzylsodium takes place exclusively[4] in the meta position. The products obtained (88) by the action of amylsodium at 55–60°C. on these two salts are m-phenylenedisodium, m-$Na_2C_6H_4$, and m-homophenylenedisodium, m-$NaC_6H_4CH_2Na$.

So also in the case of the α- or β-naphthyl ions, the products expected from the anion acting alone would be the result of substitution, ortho or para to the α-

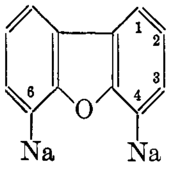


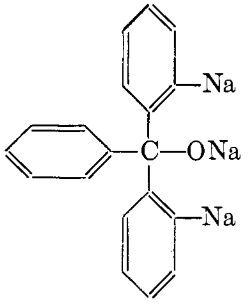


[4] This statement is true only if the stirring is adequate to secure thorough mixing of the reagents, both of which are insoluble. If the stirring is comparatively poor, a small amount of para substitution accompanies the meta substitution (85).

or β-position, respectively, because the electron density in the ring would be raised. The products actually present, prior to carbonation, are 1,3-naphthalenedisodium (83), the result of a meta-orienting influence, and 1,8- and 2,6-naphthalenedisodium, the result of inactivation (which is also the function of a meta-directing influence) of the first ring.

Other examples of inactivation of the ring to which the metal is attached are found in the formation of 4,6-dibenzofurandisodium (48) and 2,2′-triphenylcarbinoltrisodium (29).





In both instances the second sodium atom enters another rather than the same ring.

Substitution in the *m*-position implies a meta-directing influence. The principal meta-directing force already known in organic chemistry is a positive pole such as is found in anilinium salts or on the nitrogen atom of a nitro group. Now the only positive pole present in this reaction mixture is the sodium cation. Although bound to the anion by an electrostatic valence only, this ion cannot leave the vicinity of the anion because the operations are carried out either in petroleum ether, which is a non-dissolving solvent for the reagents (amylsodium with phenyl-, benzyl-, or naphthyl-sodium), or in ether, which is virtually a non-dissociating solvent for the metalation of the heterocyclic compound. Hence the cation remains adjacent to the anion and has the same effect as do all positive poles (69) which are attached to the nucleus. The result is a meta-directing influence (88).

A very simple explanation can be given for the fact that the position taken by the metalating group is meta to the directing ion. The positive pole attracts the electrons in the aromatic nucleus and thus reduces the availability in the ring as a whole of the said electrons to other groups or ions needing them in order to become attached to the ring. Now this influence of a positive pole attached to the ring, like the influence of any substituent, whether meta- or ortho–para-directing, will, according to the ordinary principle of conjugation, be greatest in the ortho and para and least in the meta position. Hence the sodium ion in amylsodium, seeking electrons, will have difficulty in acquiring them from phenylsodium but will find less difficulty in the meta position and will, therefore, enter meta to the first metal ion. In short, two strong electron-seeking ions or groups will have little or no tendency to take the conjugated ortho or para positions in an aromatic ring where their like influences would be in maximum competition with each other, but will take the meta position instead. The greater the positive polarity, the greater the percentage of meta substitution.

The only novelty in this meta-directive influence is that the force is attached by coulombic valence rather than by the covalence that exists in the anilinium ion or in nitrobenzene. That an electrostatic bond is no bar to an influence of the cation on the electrons of the anion is shown in inorganic chemistry by the fact that mercuric iodide is colored, although the dissociated iodide ion is colorless; and the color is explained by Fajans (21) as a result of the disturbance caused by the cation on the electrons of the anion. Pauling (100) has illustrated (figure 1) such an effect in a simple case such as that of mercuric iodide. Figure 2 shows the author's view of the effect of the adjacent sodium ion on the Pauling (100) formula for benzene.

FIG. 1. Normal and deformed ion as pictured by Pauling

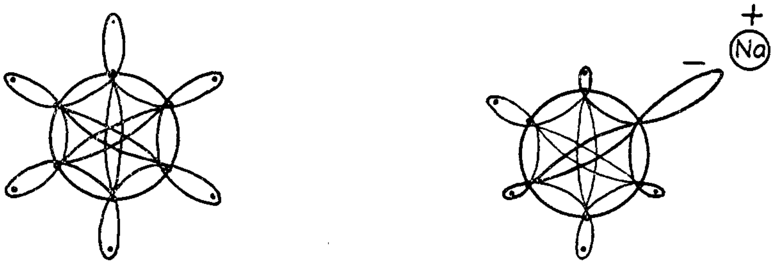


FIG. 2. On the left the benzene structure, as given by Pauling, is shown. On the right is a drawing which illustrates the possible changes caused by an adjacent sodium ion. Heavy lines to the ortho and para positions and restricted orbits at these points indicate major pulls on the electrons; lighter lines to the meta positions and moderately restricted orbits are meant to indicate minor attraction. A second sodium ion entering phenylsodium finds electrons more available in the meta than in the ortho or para position.

The strength of this meta-directing force of the sodium ion is attested by the fact that it is realized through the methylene group in benzylsodium (88). The product is exclusively meta.

$$C_6H_5CH_2Na + C_5H_{11}Na \rightarrow m\text{-}NaC_6H_4CH_2Na + C_5H_{12}$$

Only the strongest positive charges maintain a high degree of influence across a methylene group. Ingold and coworkers (4, 50, 51, 69) have shown that in nitration a single methylene group invariably reduces the percentage of meta nitration, the amount apparently depending on the strength of the positive pole. The effect of the strong trimethylammonium pole changes from 100 per cent meta to 88 per cent to 19 per cent as the pole is adjacent, one methylene group, and two methylene groups removed, respectively. The corresponding positions of the weaker nitro group cause 93, 48, and 13 per cent, respectively, of meta nitration.

B. Effect of cation in inhibiting substitution in the anion

In the second class of effects, the ortho–para-directing influence persists but the sodium ion makes metalation more difficult. The phenoxide ion, for example, contains one of the most readily substituted nuclei known, because the inductive (69, 70) and tautomeric (resonance) effects combine to favor substitution. In aqueous solution substitution occurs with extreme rapidity. In a non-aqueous and non-dissociating medium, however, substitution is retarded. The very reactive butylsodium (25), which will metalate benzene very readily, has no action on sodium phenoxide at room temperature even after 3 days' standing. With amylsodium at 55–60°C., substitution will occur in the ortho (87), and to some extent, in the diortho position.[5]

This persistence of the ortho–para-directing force of the oxygen atom, in spite of the positive polarity of the adjacent sodium ion, is not surprising, because the influence of the metal cation on the phenyl nucleus is counteracted by the resonance of the unbound oxygen electrons with those in the ring. The effect is akin to that which occurs in the case of chlorobenzene, where the inductive (70) effect of the halogen atom would normally cause meta substitution, but the tautomeric or resonance effect of the unbound electrons promotes an ortho–para effect. The latter prevails but substitution is more difficult.

If the sodium ion is removed a further distance from the aromatic nucleus, as in sodium benzoxide, $C_6H_5CH_2ONa$, its retardant effect should be even less. This material is, in fact, readily metalated by butyllithium (29) in ether solution, and the position taken by the entering group is ortho.

C. Effect of alkali-metal cation on carboxyl and carbonyl groups

Though not an example of residual polarity, the elimination of the common meta-directing influence of carboxyl and carbonyl groups is, nevertheless, an example of the conversion of such groups into anions by the presence of an alkali metal. Sodium benzoate, for example, is brominated or chlorinated (71) in the ortho position in aqueous solution, and is also metalated by amylsodium (85) in the ortho position in non-aqueous media, though the chief product in this last instance is triphenylcarbinol. In both cases the orienting influence in the anion is ortho. The effect of the sodium ion, adjacent to the anion but relatively far from the phenyl nucleus (and with its electron-attracting influence dampened by the large number of unbound electrons in the oxygen octet), is not sufficient to prevent the orientation which an anion should normally exhibit.

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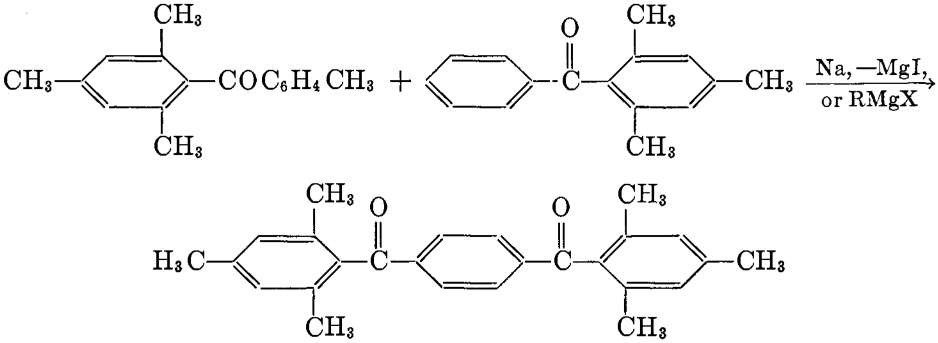
[5] Recent investigations have disclosed a fair amount of meta substitution also among the disubstituted product (87). The quantity is greater in potassium than in sodium phenoxide. A meta-directing influence is, therefore, not entirely muffled by the screening effect of unbound electrons in the oxygen octet.

Aroylation para to a carbonyl group (see the reaction below) is an example of the influence of an alkali metal in transforming the carbonyl group into a point of anionic activity. This reaction, discovered by Fuson (22) and coworkers, takes place under the influence of alkaline catalysts such as the Grignard reagent, sodium, and particularly, magnesious iodide. Addition of the metal to the oxygen end of a sterically hindered carbonyl group is not inhibited (76). Hence a salt is formed, the balance of the polarity in the carbonyl group (caused by comparative electron restraints (69, 70)) is changed, and the entering aroyl group is directed to the para position by an anionic directing influence.



VI. THE ION-PAIR AND DOMINANT CATION IN REACTIONS

Since organometallic salts are so reactive and the metal ion outweighs the anion in activity, the reactions in which the salt participates should be expressed, if possible, so as to show the rôle of the stronger ion. In brief, the reactions should be portrayed as the function of an electrophilic or electron-seeking reagent. Such behavior will be illustrated in the cases of nuclear metalation, side-chain metalation, certain so-called nucleophilic reactions (which, on this basis, are shown to be electrophilic in character), metal-halogen interchange, and disproportionation. The first four reactions concern aromatic systems; the last has to do with an aliphatic one.

A. Nuclear metalation

The action of an organoalkali reagent on an aromatic nucleus is that of a strong electron-attracting cation seeking attachment to the ring. The reaction is aided as much as possible by the anion which receives the displaced proton. This conclusion follows from the fact that the alkali-metal cation attacks the same position as do other electrophilic reagents, such as nitric and sulfuric acids, when it substitutes in a ring which already contains a directing influence, such as a methoxy group.

The number of illustrations where ortho- and para-directing groups cause metalation in the expected position is so large (see table 7) as to constitute conclusive evidence that the ordinary rules of orientation, as applied to the action of electrophilic reagents, hold also with reactive salts, such as the organoalkali reagents

TABLE 7

Substitution in aromatic nuclei containing ortho- and para-directing substituents

1. Directing influence of ethers

COMPOUND	REAGENT	PRODUCT*	REFERENCE
Anisole	Ethylmagnesium bromide	*o*-Anisylmagnesium bromide	(13)
Anisole	Propylmagnesium bromide	*o*-Anisylmagnesium bromide	(13)
Anisole	Phenyllithium	*o*-Lithioanisole	(126)
Anisole	Butyllithium	*o*-Methoxybenzoic acid	(25)
Anisole	Phenylsodium	*o*-Methoxybenzoic acid	(25)
Anisole	Amylsodium	*o*-Methoxybenzoic acid	(86)
Phenetole	2-Thienylmagnesium bromide	*o*-Phenetylmagnesium bromide	(13)
Phenyl ether	Butyllithium	*o*-Phenoxybenzoic acid	(25)
Phenyl ether	Ethylmagnesium bromide	*o*-Phenoxybenzoic acid	(112)
Phenyl ether	Phenylsodium	*o*-Phenylphenyl ether	(80)
Phenyl sulfide	Butyllithium	*o*-Phenylmercaptobenzoic acid	(25)
Phenyl sulfide	Phenylsodium	*o*-Phenylmercaptobenzoic acid	(25)
Benzyl methyl ether	Butyllithium	*o*-Carboxybenzyl methyl ether	(29)
p-Methoxytoluene	Amylsodium	*o*-Methoxy-*m*-toluic acid	(97)
p-Bromoanisole	*p*-Anisyllithium	5-Bromo-2-methoxybenzoic acid	(36)
p-Bromoanisole	Butyllithium	5-Bromo-2-methoxybenzoic acid	(36)
p-Bromoanisole	*p*-Anisyllithium	5-Bromo-2-lithioanisole	(126)
p-Bromoanisole	Phenyllithium	5-Bromo-2-lithioanisole	(126)
p-Bromodiphenyl ether	*p*-Lithiodiphenyl ether	5-Bromo-2-phenoxybenzoic acid	(36)
p-Bromodiphenyl ether	Butyllithium	5-Bromo-2-phenoxybenzoic acid	(36)

2. Directing influence of amines

COMPOUND	REAGENT	PRODUCT	REFERENCE
Aniline	Butyllithium	Anthranilic acid	(29)
Aniline	Amylsodium	Anthranilic acid	(87)
N-Butylaniline	Butyllithium	*N*-Butylanthranilic acid	(29)
Dimethylaniline	Amylsodium	*N*,*N*-Dimethylanthranilic acid	(25, 86)
Dimethylaniline	Methylmagnesium iodide	*p*-Dimethylaminobenzoic acid	(65)
Dimethylaniline	Ethylmagnesium bromide	*N*,*N*-Dimethylanthranilic acid	(13)
Diphenylamine	Butylsodium	*N*-Phenylanthranilic acid	(29)

3. Directing influence of hydrocarbons

COMPOUND	REAGENT	PRODUCT	REFERENCE
Isopropylbenzene	Amylsodium	*p*-Isopropylbenzoic acid	(89)
Biphenyl	Butyllithium	*p*-Phenylbenzoic acid	(25)
Biphenyl	Butylsodium	*p*-Phenylbenzoic acid	(25)
Biphenyl	Amylsodium	*p*-Phenylbenzoic acid	(94)

TABLE 7—*Concluded*

4. Directing influence of alcohols and phenols (as the sodium salt)

COMPOUND	REAGENT	PRODUCT	REFERENCE
Benzyl alcohol	Butyllithium	*o*-Carboxybenzyl alcohol	(29)
Benzohydrol	Butyllithium	*o*-Carboxybenzohydrol	(29)
Triphenylcarbinol	Butyllithium	Triphenylcarbinol-2,2′-carboxylic acid	(29)
Phenol	Amylsodium	Salicylic acid and 2-hydroxyisophthalic acid	(65)

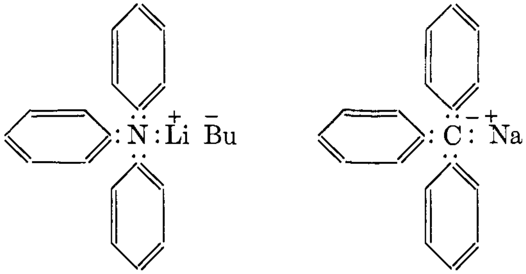
5. Directing influence when the orienting group is in the ring

COMPOUND	REAGENT	PRODUCT	REFERENCE
Furan	Phenyllithium	2-Furoic acid	(25, 27)
Furan	Methyllithium	2-Furoic acid	(25, 27)
Furan	Amylsodium	2-Furoic acid and 2,5-furandicarboxylic acid	(91)
2-Methylfuran	Butyllithium	5-Methyl-2-furoic acid	(25)
2-Methylfuran	Phenyllithium	5-Methyl-2-furoic acid	(25)
Thiophene	Ethylsodium	2-Thiophenecarboxylic acid	(107)
Thionaphthene	Sodium amide	2-Thionaphthenecarboxylic acid	(122)
Thionaphthene	Ethylmagnesium bromide	2-Thionaphthenecarboxylic acid	(122)
Dibenzofuran	Butylsodium	4,6-Disodiodibenzofuran	(48)
Dibenzothiophene	Butyllithium	4-Dibenzothiophenecarboxylic acid	(25)
Dibenzothiophene	Amylsodium	4-Dibenzothiophenecarboxylic acid	(25)
Dibenzothiophene	Phenylsodium	4-Dibenzothiophenecarboxylic acid	(25)
Carbazole	Butyllithium	Carbazole-4-carboxylic acid	(34)
N-Ethylcarbazole	Butyllithium	5-Ethylcarbazole-4-carboxylic acid	(34)
N-Phenylcarbazole	Butyllithium	9-(2′,6′-Dicarboxyphenyl)carbazole	(44)

* The product is listed as the acid when the organometallic compound was carbonated, and as the organometallic compound when otherwise treated.

and the Grignard reagent. Methoxy and dimethylamino groups direct the metal exclusively to the ortho position, while alkyl and aryl groups direct largely to the para position.

Only a few exceptions to the influence of ortho- and para-directing groups in metalation are known. Butyllithium, for example, metalates triphenylamine (28) and triphenylarsine (43) in the meta rather than the ortho or para position, in spite of the ortho-directing influence of an amino or arseno group. In view of (*1*) the much slower rate of, and general resistance to, meta substitution and (*2*) the fact that when an ortho- and a meta-directing influence are operating against each other, the ortho outranks the meta, it is logical to suppose that some action has taken place at the nitrogen atom which has extinguished its ortho-directing influence and replaced it by one which permits only the more difficult meta substitution. The only positive pole present in the reaction mixture is the lithium ion in butyllithium. Should it form a complex with triphenylamine—and metal ions in the related Grignard reagent are often regarded as being solvated by the ether and amines used as solvents—a structure like that shown below and resembling somewhat that of triphenylmethylsodium, might be formed. The unbound electrons of the nitrogen atom, which normally would resonate with those in the ring and induce ortho–para substitution, would be restrained by the residual polarity of the lithium ion. The similarity to triphenylmethylsodium suggests that the three phenyl groups, which confer such marked acidity upon the hydrogen attached to the central carbon atom, have also conferred on the central nitrogen (or arsenic also) atom an unusual capacity toward forming a comparatively stable salt-like complex with butyllithium, which is sufficiently effective to permit the residual polarity (Section V A) of the lithium ion to act as a meta-directing force.



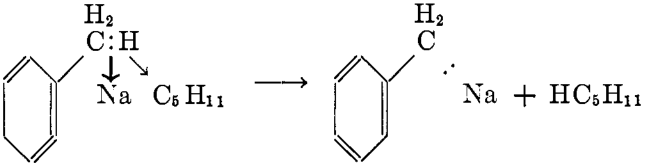
Phenylcalcium iodide (32) metalates dibenzothiophene in the 3-position, which is meta to the thioether directing group, although phenyllithium (31) and phenylpotassium metalate the same compound in the normal or 4-position. Benzylpotassium (39) fails to metalate dibenzofuran under conditions which are successful for benzylsodium. Both of these results (from phenylcalcium iodide and from benzylpotassium) suggest that a metal ion has become attached in some manner to the compound about to be metalated in such a way as to obliterate the expected ortho substutition and to cause meta substitution, or to inactivate the system so that no metalation occurs. Complex formation is frequently related to the size of the ions involved as well as to their comparative strengths. The particular combinations that would be stable enough to permit such effective control of orientation would not be expected in the usual reactions in which ethers, thioethers, and amines are involved.

Another possible abnormal metalation might be mentioned. When thionaphthene (122) is dimetalated by sodium amide in hot xylene, some of the product is a 2,3-disodio derivative. Substitution ortho to the sulfur atom would be expected. Entrance of the second metal in the 3-position is unexpected unless one regards that position as activated by an adjacent benz nucleus.

B. Side-chain metalation

Metalation in the side chain can be pictured as an electrophilic (88) process, although in this case there is no orienting influence which makes a comparison with other electrophilic reagents possible. The merit of the electrophilic picture as contrasted with the nucleophilic one can be shown best by stating each in detail.

According to the electrophilic picture, the alkali-metal cation must play the leading rôle, aided as far as possible by the anion, which takes a minor but important part. When, therefore, a toluene molecule collides with the ion pair, the residual polarity in the metal cation attracts the electrons of the carbon–hydrogen covalency in the side chain. The proton is thus loosened by the cation and then taken by the anion. The suggested process is illustrated below with heavy and light arrows indicating major and minor forces:



This picture has the advantage of conforming to other evidences of the electrophilic character of organoalkali reagents. It agrees with the evidence for residual polarity in the alkali-metal cation, which in this case should be capable of exerting upon the molecule with which it collides the same type of influence which any positive pole permanently attached to the molecule can effect (compare, e.g., the increased acidity of *o*- and *p*-nitrotoluenes) and therefore, at that moment, to labilize the proton by attracting its binding electrons so that formation of a new salt is facilitated. Finally, a joint action of the ion-pair is provided for; and such dual participation, as in the Walden inversion, should proceed with greater ease than would a process which places all of the work on a single ion.

The nucleophilic picture requires that the anion play the leading rôle. The initial and only necessary phase would be:

$$C_6H_5CH_3 + C_5H_{11}^- \rightarrow C_6H_5CH_2^- + C_5H_{12}$$

The merit of this view is simplicity; a proton is abstracted, and a new ion is formed. The difficulty is that the picture violates a sense of proportion in that the weaker partner of an ion-pair takes the leading rôle, while the stronger one remains adjacent but idle. In view of the fact that the sodium ion is capable of rendering the electrons in the phenyl and benzyl ions so unavailable that meta substitution results (see Section V A), it would appear unlikely that the sodium ion in amylsodium would release its attraction for the electrons of the amyl ion, and thus permit it to react singly, until a more suitable point for the attractive force of the cation had been found.

Metalation in the side chain rather than the nucleus accords with the expectation that, in general, the product of a substitution will be a salt of the strongest pseudo acid possible (Section IV A). The margin between nuclear and side-chain metalation may, however, be very slight. Had substitution in the nucleus occurred, the cation would have entered the para position under the directive influence of the alkyl radical (Section VI A). According to the principle that the effect of groups in the acidity of hydrocarbo acids is, in general, in the same direction as that in ammono and carboxylic acids (Section III C), the acidity of $C_6H_5CH_2$—H (K_A for phenylacetic acid is 5.4×10^{-5}) will be higher than that for p-$CH_3C_6H_4$—H (K_A for p-toluic acid is 4.5×10^{-5}). The greater stability of the benzylsodium salt over the isomeric p-tolylsodium is reflected also by the fact that the sodium and potassium salts prepared from p-chlorotoluene rearrange (41) readily, when heated, to the benzylmetal salt. The corresponding lithium salt does not change under the same condition.

The possibility of ortho metalation as well as para has not been considered in this discussion, partly because it occurs either not at all or to a slight extent only (89), and partly because a comparison of the hydrocarbo acid, o-$CH_3C_6H_4$—H, with o-toluic acid ($K_A = 1.25 \times 10^{-4}$) does not provide a fair judgment since, according to Dippy (18), the value for o-toluic acid is abnormally high because of a "limited formation of hydrogen bond."

The chance of side chain *vs.* nuclear metalation is affected greatly by alkyl groups. The isopropyl (89) group causes the metal to enter the para position and the butyl radical appears also to favor that position, judged by the absence of further side-chain alkylation in the dialkylation of toluene by propyl chloride in the presence of sodium (88, 96).

$$C_6H_5CH_3 + Na + C_3H_7Cl \longrightarrow C_6H_5CH_2C_3H_7 \xrightarrow{Na + C_3H_7Cl} p\text{-}C_3H_7C_6H_4CH_2C_3H_7$$

C. The so-called nucleophilic reactions

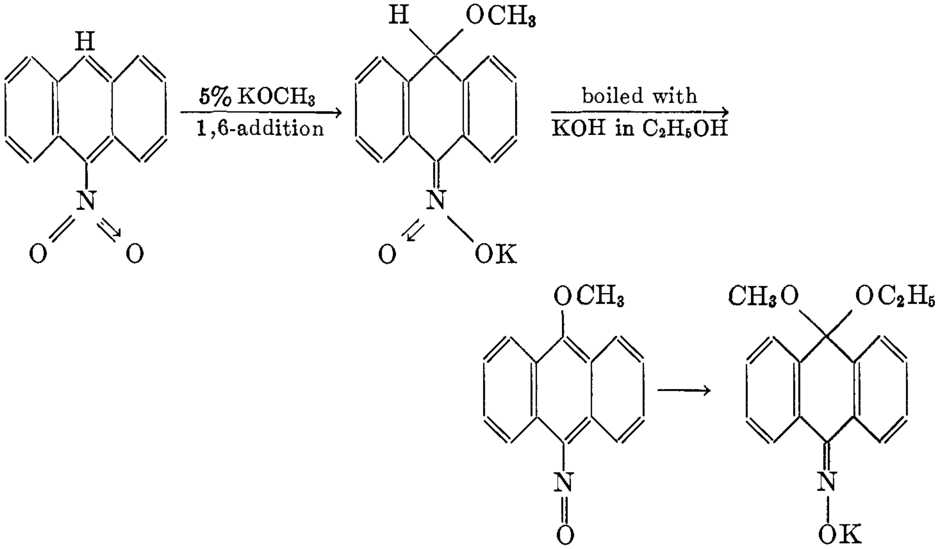
A nucleophilic reagent (70, 121) is ordinarily understood to be one which reacts in a manner opposite to that of an electrophilic one, i.e., by introducing an electron-donating rather than an electron-attracting group. Hence meta-directing groups—for example, nitro—will cause such reagents to substitute in the ortho or para position, as indicated below:

$$C_6H_5NO_2 + KOH \xrightarrow{O} o\text{-}HOC_6H_4NO_2$$

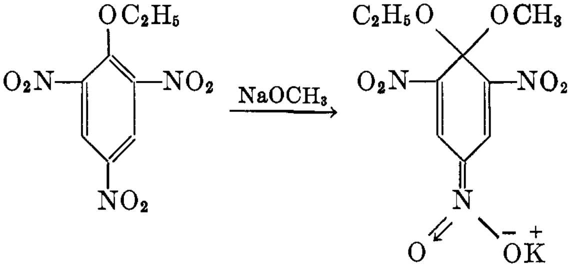
That nucleophilic reagents, the opposite of electrophilic reagents, should exist, is eminently reasonable. That the above and similar reactions are good examples of the action of nucleophilic reagents is questioned. Potassium hydroxide or methoxide is the salt of a very weak acid and an active alkali metal. According to the arguments presented in this paper, such reagents are by nature electrophilic. Unless the environment favors dissociation—and many of these reactions are carried out in non-aqueous solvents or at high concentration—or other factors intervene to insure the reaction of the hydroxide or alkoxide ion only, the cation should play the leading role.

The electrophilic character of this reaction does, indeed, appear most reasonable. The first step consists of a 1,4-addition—a process which is merely one of the common reactions of salts (see Section IV B)—in which the cation seeks the position of maximum electron density, and does so the more readily as the cation becomes stronger (KOH > NaOH). The second phase is restoration of the conjugated ring system by an elimination (loss of alkali hydride) or oxidation process.

The additive character of the reaction has long been recognized. In 1902, Meisenheimer (82) observed that potassium methoxide in 5 per cent methanol (approximately 0.7 normal) added to 9-nitroanthracene. The addition product, when boiled with ethyl alcoholic potassium hydroxide, was converted to the oxime of an acetal, by steps which are pictured below.



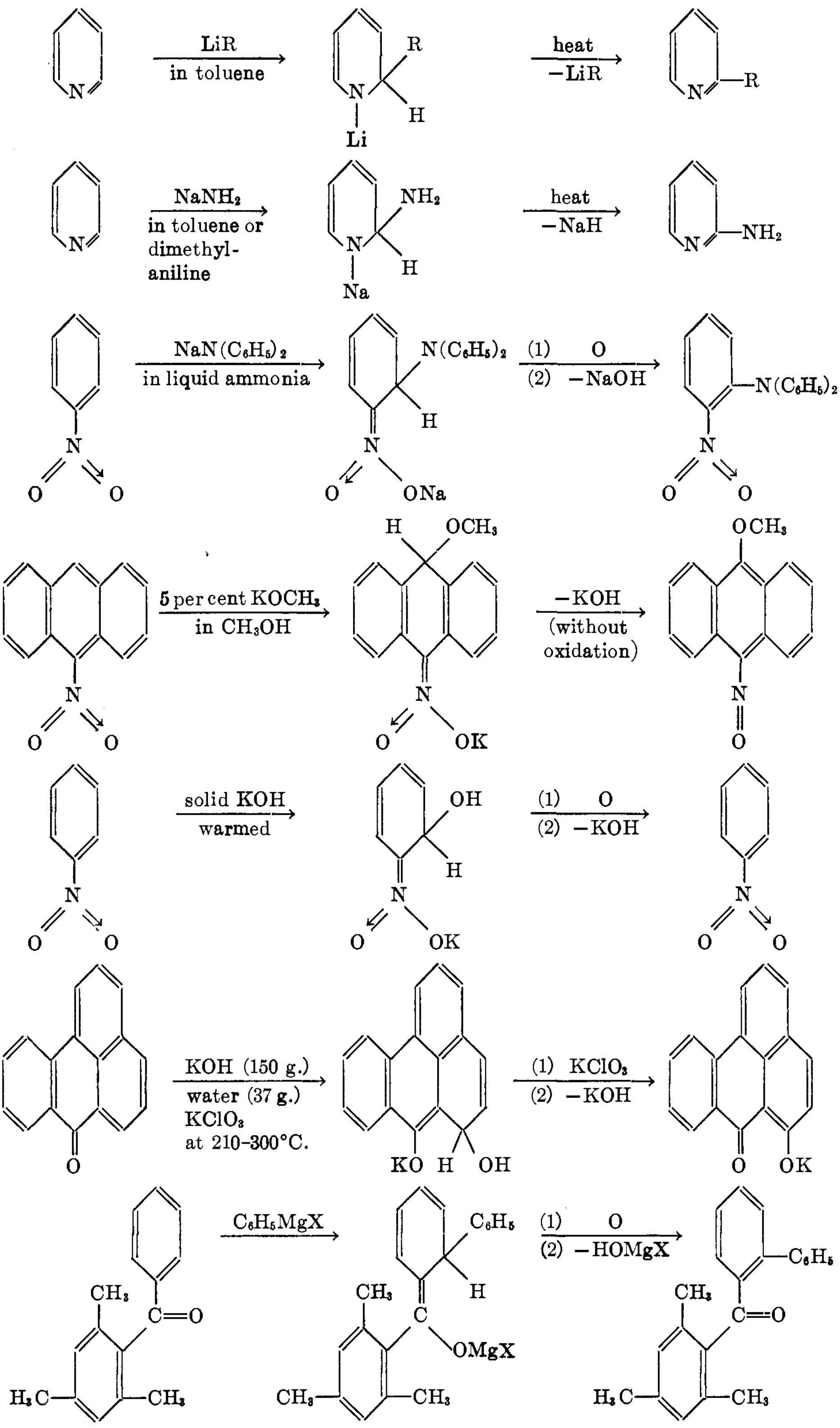
The addition of sodium methoxide to trinitrophenetole has also been regarded (82) as an addition process.



The relation which these additive processes have to other similar additive processes (6, 75) is clearly shown in table 8. The first two examples show the addition of alkyllithiums (138) and sodium amide (118) to the C=N bond in

TABLE 8

Typical additions of active salts to ring and conjugated systems

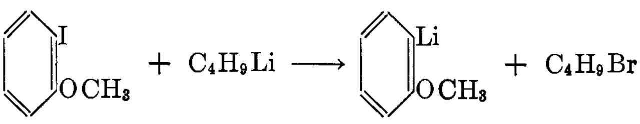


pyridine. At higher temperatures lithium hydride and sodium hydride are split off, so that the net result is the alkylation and amination of pyridine. In the third example, sodium diphenylamide (7) undergoes 1,4-addition with nitrobenzene in liquid ammonia. The dihydro product then either eliminates sodium hydride or loses hydrogen by oxidation with excess nitrobenzene. The net result of the process is an amination—substitution of diphenylamine in this instance—of nitrobenzene. In the fourth example, a step in the reactions observed by Meisenheimer (82) is shown, the addition being across the 1,6-positions, and the process being completed by thermal elimination of potassium hydroxide. The fifth example is the reaction of powdered potassium hydroxide with nitrobenzene (127). The conjugated ring system is restored by oxidation by air or nitrobenzene. The net result is hydroxylation. Similarly, mesobenzanthrone reacts with potassium hydroxide and aqueous potassium chlorate at 210–310°C. to give 4- and 2-hydroxymesobenzanthrones (9) by steps similar to those of the other reactions. Finally, phenylmagnesium bromide adds in the 1,4-positions to benzoylmesitylene (23), because the normal addition across the carbonyl group is impeded by steric hindrance. Oxidation of the enol addition product by air restores the aromatic system.

These reactions are essentially the same with respect to the first step. The reactive salts show an electrophilic character. The dominant and electron-seeking cations attach themselves at the position of greatest electron density in the molecule; the alkyl, amino, alkoxy, and hydroxy groups take the 2-, 4-, or 6-position remote from the position of the metal ion; and the net result—after thermal decomposition, or oxidation by air, nitrobenene, or perchlorate—is alkylation, amination, alkoxylation, or hydroxylation of the nucleus. Representation of such processes as nucleophilic gives a wrong impression, for the term "nucleophilic reagent" implies the opposite of an electrophilic reagent. In reality, the nature of the reagent has not changed; only the manner in which the reagent reacts is different. The dominance of the cation, so clearly evident in other reactions, is not extinguished merely because the reaction is an addition, rather than a substitution, process.

D. Metal–halogen interchange and related effects

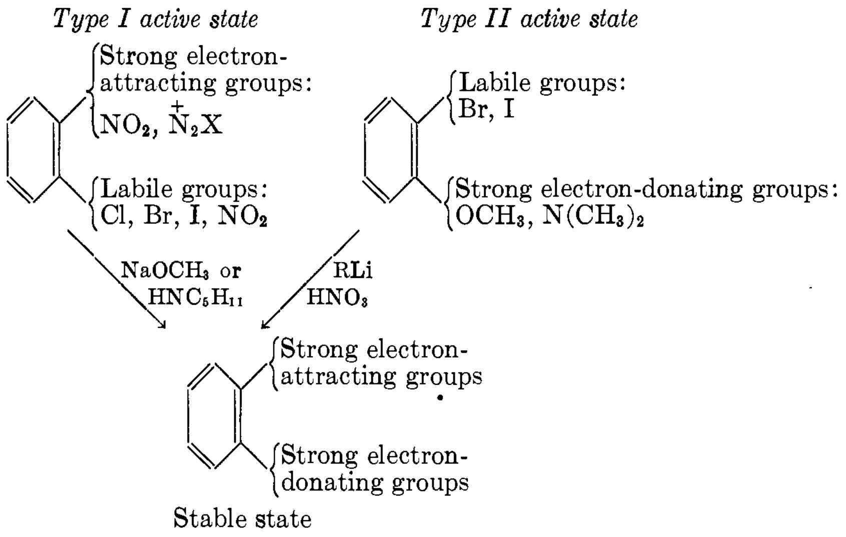
The interchange of metal and halogen arouses more than ordinary interest



because the reaction normally expected would lead to a Wurtz product and sodium halide. The interchange has been observed a few times (33, 101, 104, 131) with aliphatic compounds and has been found to be reversible (33) in some cases. The chief interest, however, has been in the aromatic series (37, 126). In general, an interchange occurs readily with iodides, to some extent with bromides, and little, if any, with chlorides (79, 84).

Although the reason for an interchange rather than a Wurtz reaction cannot be specified, the effect in the aromatic series can be related to the activating influence of the groups involved. According to such a plan, the alkali-metal cation will play the same rôle as does any strong electron-attracting group. In order to appreciate this rôle, it is necessary to present a brief discussion of the general phenomena involved and then to show the way in which the metal cation fulfills expectations.

Strong electron-attracting groups, such as nitro, diazonium, and alkyl-substituted ammonium, have long been recognized as promoting the replacement of an ortho or para halogen atom by a strong electron-donating group such as methoxy, phenoxy, hydroxy, amino, and the like. This type of activity will be designated as type I. The converse of this rule (type II activity) is that strong electron-donating groups, such as methoxy or dimethylamino, will promote the replacement of an ortho or para halogen atom by a strong electron-attracting group, such as nitro or an alkali-metal ion. These rules are represented graphically below:



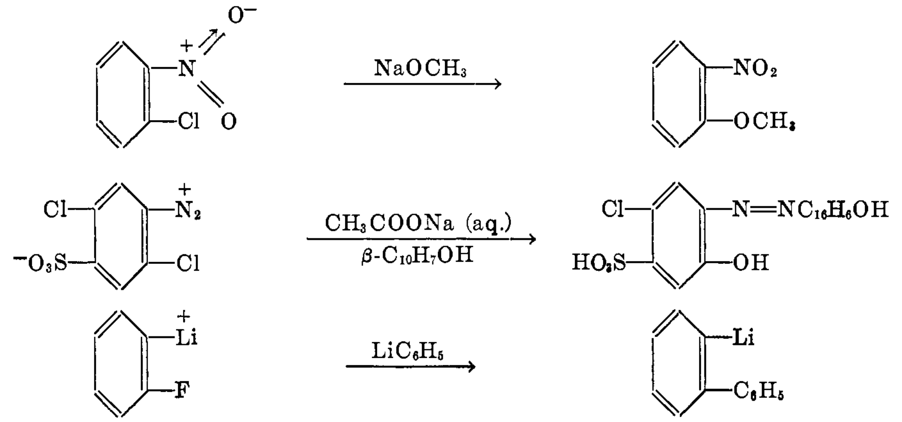
These statements accord with the general view (10) that nitro and methoxy groups have opposite activating effects when substituted in the aromatic nucleus. The halogen atoms are between the two extremes. With appropriate reagents the halogen atom can sometimes be removed and replaced by a group which will neutralize the effect of the one already in the nucleus. Other active groups besides the halogen, such as a nitro group adjacent to a nitro group, are replaced by a methoxy or an electron-donating group. In any event, the system progresses toward the stable state of two highly activating groups of opposite kind, neutralizing the effect of each other. The reaction is obviously best realized in the ortho and para positions where the groups are in a vinylogous relation, and of these two positions the ortho is frequently the most reactive, possibly because the distance between activator and activated is less than in the para position.

Examples in the type I class are very numerous. The activation of a halogen atom ortho to a nitro group has long been known and has been studied (16) extensively. Sodium hydroxide, sodium alkoxides, sodium phenoxides, piperidine, and the like can be used for the reaction. The lability of a halogen atom ortho to a diazonium group (98, 108) is also common. The number of examples of these types of activation which could be listed are too numerous to tabulate in this paper. It is sufficient to state that the reactions are well known and to give an example in table 9 for the sake of comparison. Similar statements can be made with respect to the activation of a nitro group ortho or para to another nitro group (16) or a diazonium (5) ion. The nitrile (63) group also causes an ortho, nitro, or halogen atom to be replaceable.

The comparable case with the organoalkali compounds would be that of a halogen activated by a metal cation in the ortho position, for if such a juxtaposition of halogen and cation could be realized, the strong electron attraction of the latter should permit easy replacement of the halogen by a group which would be more suitable than the halogen. The situation is, of course, rare, because of the difficulty of introducing a metal ortho to a halogen without metathesis. Yet one well-defined case is known.

TABLE 9

Examples of activation of a halogen atom ortho to a positive pole



Wittig (125) and coworkers have found that the reaction of phenyllithium with the four monohalobenzenes gives 8, 10, 8, and 70 per cent yields of biphenyl from the iodo, bromo, chloro, and fluoro compounds, respectively. The high yield with the fluoro compound is interpreted as meaning that metalation of fluorobenzene first occurs. The fluorine atom is made active by the adjacent

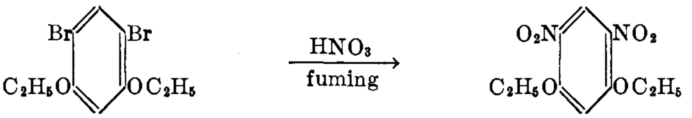
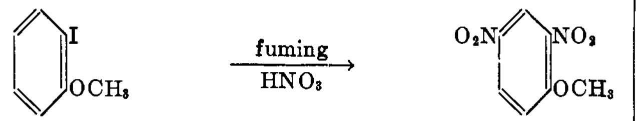
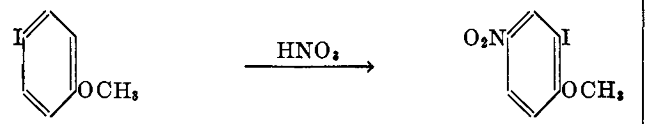
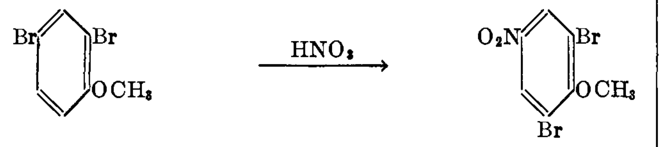
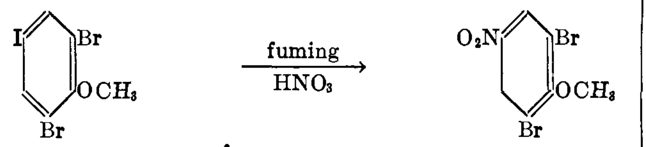
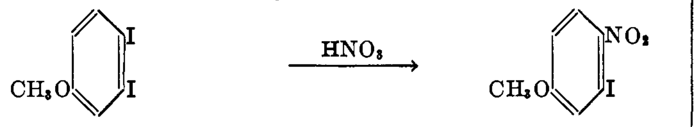
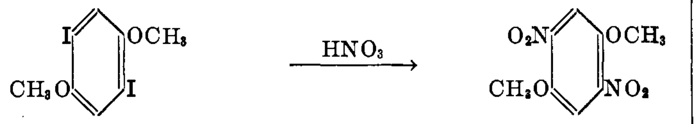
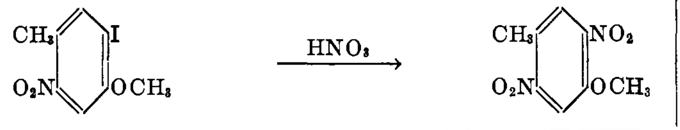
$$FC_6H_5 + LiC_6H_5 \rightarrow o\text{-}FC_6H_4Li + C_6H_6$$

lithium ion so that it reacts readily with more phenyllithium. Proof of

$$o\text{-}FC_6H_4Li + C_6H_5Li \rightarrow o\text{-}LiC_6H_4C_6H_5 + LiF$$

TABLE 10

Examples of nitro-halogen interchange

NITRO-HALOGEN INTERCHANGE	REFERENCE
 $\xrightarrow[\text{fuming}]{HNO_3}$	(73)
 $\xrightarrow[HNO_3]{\text{fuming}}$	(74)
 $\xrightarrow{HNO_3}$	(102)
 $\xrightarrow{HNO_3}$	(8)
 $\xrightarrow[HNO_3]{\text{fuming}}$	(62)
 $\xrightarrow{HNO_3}$	(103)
 $\xrightarrow{HNO_3}$	(103)
 $\xrightarrow{HNO_3}$	(103)

the formation of a lithiofluorobenzene is furnished by decomposing the reaction product (fluorobiphenyl) with benzophenone instead of with water. *o*-Phenyltriphenylcarbinol is formed.

$$o\text{-}LiC_6H_4C_6H_5 + (C_6H_5)_2CO \rightarrow o\text{-}C_6H_5C_6H_4C(OH)(C_6H_5)_2$$

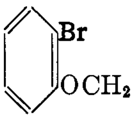
No evidence could be found that amylsodium causes a similar metalation of chlorobenzene, for the products of carbonation contained no trace of *o*-chloro-benzoic acid (90). It is clear, however, from Wittig's work that a metalation is possible in reactions of organoalkali compounds with aromatic halogen compounds, and that the halogen atom in the ring is activated by an adjacent cation.

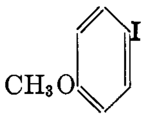
Activity in the type II class will be illustrated by reactions which are the exact opposite of two of the three typical examples shown in table 9 for type I activity. These examples will show nitro–halogen and metal–halogen interchange. An exact opposite of the diazonium-activating influence cannot be given, for the obvious reason that there is no reagent for introducing the diazonium ion directly into the nucleus.

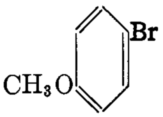
Nitro–halogen interchange, that is, replacement of a halogen atom ortho or para to a methoxy group by a nitro group, occurs frequently enough to warrant the conclusion that the reaction is a characteristic phenomenon. The process is all the more remarkable because it often occurs in spite of the tendency for nitration in some other position. Some examples of nitro–halogen interchange are shown in table 10.

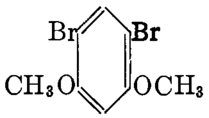
The ease of the reaction of the diethyl ether of dibromoresorcinol with fuming nitric acid is in contrast to the lack of reactivity with a reagent which would introduce another ethoxy group. Heating in a sealed tube to 100°C. with sodium methoxide and to 230°C. with sodium phenoxide effects no replacement of halogen. In some of the other illustrations the halogen halide eliminated caused substitution in another position in the ring under the oxidizing influence of nitric acid. Nitro–halogen interchange is seen to be comparatively common and the iodine atoms appears to be more reactive than the bromine.

In a similar way, metal–halogen interchange neutralizes the effect of an electron-donating group by an electron-attracting group, usually in the ortho and para positions. Some compounds which undergo this interchange of lithium for a halogen when allowed to react with butyllithium are shown below. The halogen atom replaced by metal is shown in heavy type.

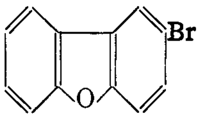


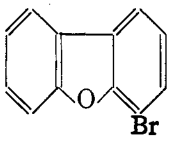


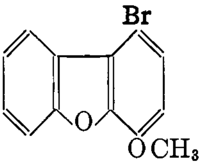




Reference.........(36) (37) (37) (126)



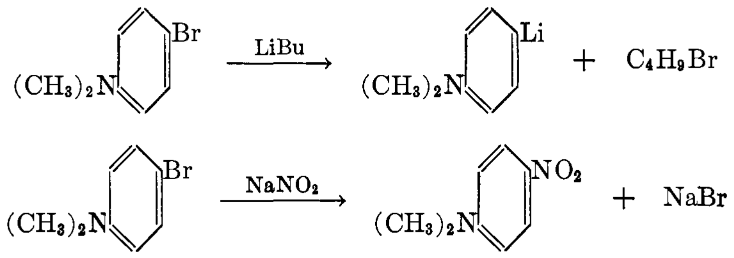




Reference...........(47) (47) (45)

3-Bromobenzofuran also undergoes the metal–halogen interchange with butyllithium. This reaction is unusual because the halogen is meta to the activating linkage. The tendency for the electron-attracting group to occupy a position where it will be better able to neutralize the electron-donating group is shown, however, by the fact that, after carbonation, the products are found to be 3- and 4-carboxydibenzofurans (47).

As might be expected, interchange takes place also when the dimethylamino group is present. Either a metal ion (24) or a nitro group (130) will replace bromine.



Replacement of a halogen atom by a metal cation has been observed also in the reaction of *p*-iodotoluene (33) with phenyllithium and of α-bromonaphthalene with a number of alkyllithium compounds. *m*-Bromodimethylaniline (38) also undergoes some replacement. The most characteristic cases, however, are those in which a methoxy or ether linkage activates the halogen in the ortho or para position.

The activation by a methoxy or dimethylamino group must not be confused with those reactions in which a hydroxy, amino, or other group with a replaceable hydrogen causes a replacement. The process with these latter groups appears to operate by an initial substitution of the hydrogen of the hydroxy or amino group and then by a rearrangement (17) to force a replacement of the nuclear atom. A large number of such indirect substitution reactions are known.

E. Disproportionation

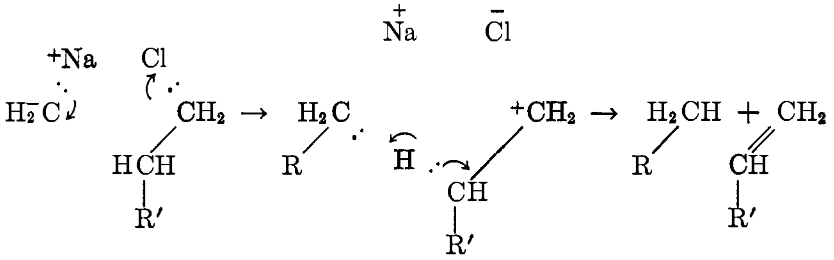
When an organoalkali compound reacts with an organic halide, cleavage takes place and coupling and disproportionation occur. In disproportionation the saturated product comes from the organometallic compound; the unsaturated one or its equivalent from the halide. Representative equations are:

$$C_5H_{11}Na + C_4H_2Cl \longrightarrow C_5H_{12} + C_4H_6 + NaCl$$

$$C_3H_7Na + (CH_3)_3CCH_2Cl \longrightarrow C_3H_2 + (CH_3)_2\overline{C\text{—}CH_2\text{—}C}H_2$$

Proof of this statement rests on two independent studies: one an analysis (84) of the products from the reaction of amylsodium and octylsodium with ethyl, propyl, butyl, and hexyl chlorides, bromides, and iodides and the other a study (124) of the reaction of ethylsodium with hexyl chloride and of propylsodium with neopentyl chloride. Except for some metal–halogen interchange (84) that occurs, the products are in accordance with the above rule.

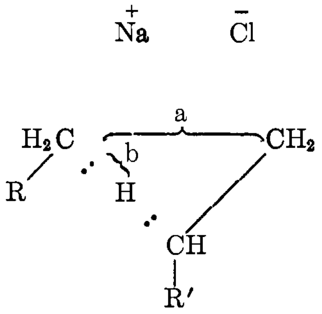
The explanation of disproportionation from the viewpoint that the organosodium compound is an electrophilic reagent is that the metal cation seeks the point of highest electron density in the alkyl halide—namely, the halide atom. In the ensuing system of sextets and open octets, the space relationships are such that the hydrogen on the β-carbon atom of the alkyl halide (or the hydrogen atom of the γ-carbon atom if none is available in the β-position) shifts to the ion originally attached to the metal cation. This sequence of changes may well be so near to each other as to be practically simultaneous. Possible steps are shown below:



The process is an interesting one because free-energy data (99), given below,

	FREE ENERGY
Ethylene	+12,300
Ethane	−10,700
Butane	−6,200
Trimethylethylene	+13,700
Pentane	−8,600
Decane	−2,900

suggest the unlikelihood (93) of a disproportioning as compared with a coupling reaction. Experimental facts show that disproportionation is usually the common reaction. The discrepancy is reconciled by the mechanism pictured. In the formula below, the distance, a, required to be bridged for the coupling

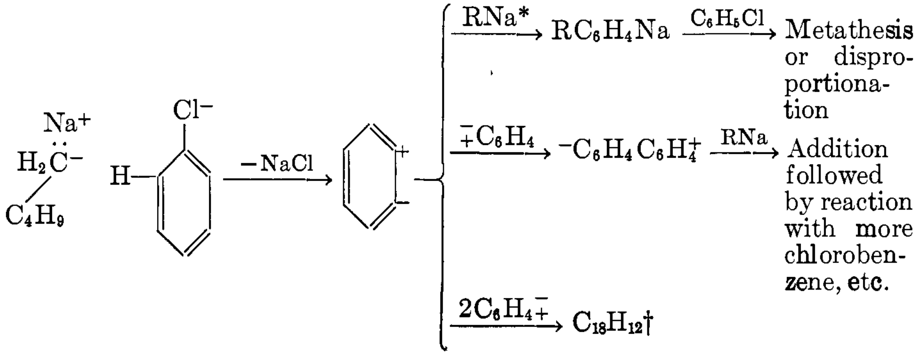


process, is greater than the distance, b, over which the hydrogen atom must travel to effect disproportionation. The force tending toward coupling is therefore disadvantageously disposed, as compared with that for disproportionation.

When disproportionation (84) occurs between an arylsodium and an alkyl chloride, the aromatic hydrocarbon and an olefin are formed. The rapidity with which the olefin is formed reduces the chances of higher degrees of polymerization. When disproportionation occurs between an alkylsodium and an aryl

$$C_6H_5Na + C_5H_{11}Cl \rightarrow C_6H_6 + C_5H_{10} + NaCl$$

chloride, the unsaturated product is *o*-phenylene, which cannot undergo intramolecular stabilization and therefore adds alkylsodium or undergoes polymerization with another molecule of *o*-phenylene. Polymers and all higher molecular weight compounds will be exclusively aromatic or composed of more aromatic than aliphatic radicals. Ortho products predominate in the numerous combinations possible.



$*R = C_5H_{11}$ † Triphenylene

The process of disproportionation bears some similarity (123, 124) to the elimination reaction in that an alkyl halide is converted to an olefin. The common interpretation (68) of the latter process is that proton elimination is the first step in the reaction, and chloride-ion elimination is the second. The explanation of the process which the organoalkali (88) reagent induces is that the steps may well be simultaneous but if there is any order, chlorine elimination precedes rather than follows proton transfer. The contrasting features in the interpretations are illustrated below (equations 1 and 2) in the formation of pentene from amyl chloride:

$$(1) \quad C_3H_5CH_2{-}CH_2Cl \xrightarrow[\text{proton abstraction}]{C_2H_5O^-}$$

$$C_3H_5\underset{\cdot\cdot}{C}H{-}CH_2Cl \xrightarrow[\text{chlorine elimination}]{-Cl^-} C_3H_5CH{=}CH_2$$

$$(2) \quad C_3H_5CH_2{-}CH_2Cl \xrightarrow[\text{chlorine elimination}]{NaR}$$

$$C_3H_5CH_2{-}CH_2^- \xrightarrow[\text{proton removal}]{-H} C_3H_5CH{=}CH_2$$

The condition of the reagent that causes elimination can be markedly different in the two processes. In the former, the ions are dissociated in alcohol or aqueous alcohol so that the reaction can be that of the individual ions. The anion, as a base, takes a proton. Chlorine is eliminated as an ion. In the latter, the solvent is non-dissociating and in some cases non-dissolving. The ions of the organometallic reagent are therefore adjacent. In such a condition, the sodium ion exerts a powerful attraction for the electrons of the anion. In the absence of a solvating agent, which would offer a multitude of electrons for the cation, it is unreasonable to suppose that this ion will release its attraction and permit the alkyl anion to acquire a proton, before it has found other electrons which satisfy better its attractive force.

VII. ELIMINATION OF THE METAL-ION INFLUENCE

Dissociation of the ions is, obviously, one of the principal factors which can have a bearing on whether the alkaline salt acts as an ion-pair or as individual ions. In the former state the reagent should, by the interpretation used in this paper, serve as an electrophilic reagent. In the latter state, it could function as a nucleophilic one.

TABLE 11

Comparison of conductivities of salts in ether, pyridine, and water

SALT	SOLVENT	DIELECTRIC CONSTANT	DILUTION VOLUME L	EQUIVALENT CONDUCTANCE
Triphenylmethylsodium	Ether	4.7	13.9 381.	0.073 0.0053
Triphenylmethylsodium	Pyridine	12.5	3900.	19.2
Triphenylmethylpotassium	Pyridine		2400. 6020.	19.2 19.4
Lithium iodide	Ether	4.7	437.	0.042
Lithium iodide	Water	81.1	1024.	110.3

When the salt is insoluble, as in the case of amylsodium in petroleum ether, the ions must be adjacent to each other and not dissociated. The reactions would preferably be those of an ion-pair. Neither is there much likelihood that soluble compounds, such as butyllithium, will dissociate in petroleum solvents, because of the extremely low dielectric constant of this medium.

When the reagent is dissolved in ethyl ether the possibility of the dissociated ions, instead of the ion-pair, effecting the reaction must be considered, because solutions in this solvent often conduct the electric current. Nevertheless good reasons can be advanced for favoring the ion-pair behavior: (*1*) the dissociation must be very slight because the conductance is so low, and (*2*) the potassium salt of triphenylmethyl reacts many times faster than the sodium salt.

The degree of dissociation of salts in ether as compared with other solvents can be judged from the data in table 11, recorded by Ziegler and Wollschitt (137).

The data in table 11 show that the difference between the conductance of lithium iodide in ether, where the ions are partially dissociated, and that in water, where they are completely dissociated, is approximately 2500 fold. The conductance of triphenylmethylsodium is of the same general order of magnitude as is that of lithium iodide, but shows the abnormal behavior of having a maximum conductance before infinite dilution is reached. If these values are regarded as furnishing a fair basis for a rough approximation of the proportions of ion-pairs and dissociated ions, the conclusion would be drawn that the latter may be present to the extent of a little less than 0.05 per cent of the total amount of organoalkali compound present. If the adjacent cation causes the ion-pair to have a reactivity different from that of the dissociated ion, the latter would have to be approximately 2600 times as reactive in order to have an equal share in the reaction and even more reactive if largely responsible. If the behavior of the anion is unaffected by the adjacent cation, these differences would, of course, have no significance for the problem at hand, except in so far as the probability of contact is affected.

That the rôle of cation in ether solution need not be that of an inert partner, even in salt–acid interchange, is indicated by the fact that Conant and Wheland (15) found that α-naphthyldiphenylmethylsodium required about a month in order to reach equilibrium with diphenylbiphenylmethane in ether, whereas the potassium salt needed but a few hours. They noticed that an abnormal decoloration, which took place instantaneously when α-naphthyldiphenylmethylpotassium reacted with triphenylmethane, required a few minutes to several months when the corresponding sodium salt was used. These results, together with the evidences of residual polarity and the satisfactory explanation offered for reactions of organoalkali compounds, are consistent with the view that a strong cation can create a disturbance in the electrons of the anion so that, in effect, it plays a definite part in the reactions which involve anions. Certainly, no serious error in proper representation of the processes in ether would appear to be made if the reactions were always expressed as the work of an ion-pair rather than that of the anion only.

Attention has been called (table 11) to the fact that the conductivity in ether solution is higher in concentrated than in dilute solution. This result might be interpreted as indicating complex ions. The equation below represents the complex ion in its simplest form and the solvated cation.

$$(C_6H_5)_3CNa + (C_6H_5)_3CNa + (C_2H_5)_2O \rightarrow [(C_6H_5)_3CNa(C_6H_5)_3C]^- + [Na\!:\!O(C_2H_5)_2]^+$$

If such a condition exists there might be some question as to whether the complex anion so formed would be appreciably more reactive than the ion-pair from which it is produced; but should it be more reactive there would appear to be good reason for doubting that it is over 2000 times more reactive.

It is true that there are some instances where reactions (40) have been shown to be somewhat faster in the slightly dissociating solvent, ether, than in the non-dissociating one, petroleum ether. Isobutyllithium and butyllithium (39) are relatively weak metalating agents in petroleum ether but are effective in diethyl ether. Diphenyl ether with butyllithium (25) gave only a 7 per cent yield of the

2-lithio product in petroleum ether but a 54–60 per cent yield in ethyl ether. These differences cannot at present be credited with certainty to the slight amount of ionization that is present in ether as compared with none in petroleum ether. Variations in boiling points of the reaction mixtures, in concentrations of reagents, or degrees of association may equally be responsible for all such effects. Two different ethers may, in fact, show an equally large variation. Butyllithium (39), for example, metalates dibenzofuran better in dibutyl ether than in ethyl ether.

In alcohol and acetone solutions the salts are dissociated, more so than in pyridine, in which, according to table 11, triphenylmethylsodium is somewhat dissociated, i.e., about one-fifth the maximum possible. Reactions in such solvents may, therefore, be the work of individual ions rather than ion-pairs.

In such media, the reagent may be regarded either as nucleophilic or electrophilic, according to the character of the other reactant, the comparative activity of the undissociated salt and the dissociated ion, or probably the concentration of the reagents.

VIII. CONCLUSION

At the beginning of this paper the current opinion, that organoalkali compounds are salts, was made the basis for a series of premises for connecting *(1)* the chemical behavior of these compounds with that of the chemistry of salts in general and *(2)* the activity of the cation with that of strong electron-attracting groups. Enough illustrations have been given to show that the behavior of these and related compounds can be interpreted from these viewpoints. The field is very broad. Space does not permit inclusion of many other examples that are compatible with these ideas.

An alternative view that the strong cation confers high reactivity upon the anion, which in turn acts as the principal reagent in the reaction, could have been developed. This paper must not be construed as denying such a possibility. Something might, in fact, be said in favor of the view that a hydrocarbo ion, which could attain a stable state by acquiring a proton and thus changing to a hydrocarbon, would act as a strong driving force in any reaction. Yet such a view involves an indirect rather than a direct approach to the problem. The cation activates the anion; the anion then effects the reaction. No account is taken of the fact that in metalations, for example, the strong tendency of the anion to acquire a proton can be realized only by severance of a proton from another hydrocarbon; and consideration of the net energy change in such a process might go far toward dispelling the illusion created by viewing only the affinity of a hydrocarbo base for a proton. Nor is any explanation readily apparent as to how a cation can be active enough to create or maintain an unusually reactive anion, and at the same time be so inactive as to fail to have an effect upon the compound with which the anion or salt is reacting. The capacity of a cation of such activity to pick out or create positions of maximum electron density in any system with which the ion-pair is in contact, and thus to stimulate formation of a new salt, is overlooked.

This review has not considered also the possibility that the organoalkali compounds are partly covalent in character. This supposition has much to recommend it. The lithium compounds have many properties that indicate that the bond between the metal and the organic radical is covalent. But presentation of the subject under the supposition that covalency plays a fractional part in the reactions of all organoalkali compounds involves more difficulties than the view that electrovalency and covalency are merely two extremes of binding (21), differing in degree, not in kind. On the other hand, correlation of the chemistry of the distinctly polar organosodium compounds with that of the chemistry of such organic compounds as nitrobenzene and anilinium salts (*cf.* orienting influence) covers all intermediate cases such as may exist with the lithium compound.

In any event, there are well-defined cases such as the orienting influence of the sodium ion, the directive influence of ortho–para-directing groups on metalation, and the interchange reactions, where the behavior is explicable on the same grounds which have long been conventional in organic chemistry. In order to make this correlation, the simple concept of an ion-pair and of a dominant cation, which serves as does an active substituent, fits admirably. As long as the physical conditions under which the reagents operate keep the members of the ion-pair together, the distinction between electrovalence and covalence has no great significance in a large number of cases. Only when solvation, dilution, or some other factor permits the ions to fall apart does the difference between the two types of valence become meaningful. Interpretations on the basis of the simple premises set up at the beginning of this paper—namely, that the organoalkali compounds are salts, whose activities are proportioned to the differences in strengths of the acid components and metal from which the salt is theoretically derived, and whose reactions are characterized by the degree of dominance of the cation—are, therefore, adequate for all known facts related to the organoalkali compounds.

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