

# MODERN ASPECTS OF THE FRIEDEL-CRAFTS REACTION

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## Introduction

THIS Review presents a picture of Friedel-Crafts reactions effected by aluminium chloride, especially those effecting acylation and alkylation of aromatic and aliphatic compounds, and surveys some of the peculiarities of this reagent in synthesis. It is the most versatile reagent (this is no commendation) and from time to time the innumerable reactions in which it plays a part have been described in book<sup>1</sup> and review. The present Review does not provide a literature summary or assign credit for each original observation and suggestion; reference is mainly confined to review articles and to papers in which the pertinent references have been assembled; work is included which has a bearing on the choice of practical procedure and on the more fundamental aspects of the subject.

Aluminium chloride has an ionic lattice with a heat of fusion of 17 kcal./mole and, as a consequence of its high lattice energy, the chloride has a low solubility in inert solvents, *e.g.*, carbon disulphide, light petroleum, benzene. The bromide is much more soluble; it has a molecular lattice with a heat of fusion of only 5.4 kcal./mole and, like gallium chloride, is particularly useful in those Friedel-Crafts reactions which are to be effected in homogeneous solution in inert solvents. In these the halides are present as  $Al_2X_6$ .

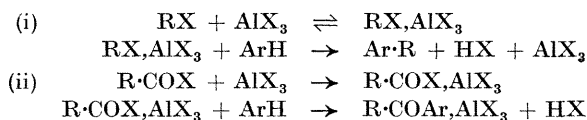
The chloride is readily soluble in compounds which contain a donor atom or group, *e.g.*, alcohols, ethers, ketones, acid chlorides, nitriles, and aromatic and aliphatic nitro-compounds, and the freezing-point method shows that in these the aluminium halides are present as  $AlX_3$ ; this is evidence that co-ordination complexes, solvent<sup>+</sup>- $AlX_3$ <sup>-</sup>, are formed. This ability to form complexes is explained on the basis that aluminium, in the monomer  $AlX_3$ , completes its group of eight electrons by attaching to itself a lone pair belonging to another atom. In many instances these addition compounds have been isolated as stable compounds under anhydrous conditions, *e.g.*,  $ROH, AlX_3$ ;  $R_2O, AlX_3$ ;  $R_2CO, AlX_3$ ;  $R \cdot COX, AlX_3$ ;  $RCN, AlX_3$ ;  $RNO_2, AlX_3$ ;  $C_5H_5N, AlX_3$ ; in others, they may exist only momentarily. This is the basis of its action in Friedel-Crafts reactions and loss of the original crystalline form of the catalyst is inherent in all but a few of these reactions; further, since aluminium halide is a polar catalyst, these reactions are of an ionic or polar type, *i.e.*, bonds are made and broken heterolytically.

Anhydrous aluminium chloride is often excessively active for the reaction

<sup>1</sup> C. A. Thomas, "Anhydrous Aluminium Chloride in Organic Chemistry", Reinhold, New York, 1942; B. T. Brooks, "The Chemistry of the Non-Benzenoid Hydrocarbons", Reinhold, New York, 1950.

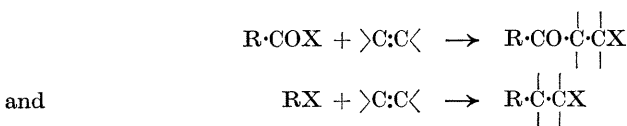
which is to be catalysed and provides undesirable side-reactions; these may be minimised by (a) working at low temperatures, (b) avoiding excessive quantities of the catalyst, (c) adding the reaction mixture to water as soon as the required reaction is essentially complete, (d) so modifying the catalyst, *e.g.*, by correct use of solvents, as to decrease its activity for the side-reactions without substantially affecting the main reaction, and (e) employing other catalysts.

The reactions of aromatic hydrocarbons (ArH) with (i) alkyl halide (RX) and (ii) acyl halide (R·COX), in the presence of aluminium halide, are generally believed to proceed by the mechanisms:



Although these offer a reasonable explanation of the function of the catalyst and are in accordance with the kinetic data, they have had to be modified and amplified. Section I below is concerned with the alkylation process and, since this involves systems containing aluminium halide, alkyl halide, aromatic hydrocarbon, and hydrogen halide, discussion is concerned with the various interactions of these components in so far as they indicate the mechanism or affect the course of the process. Section II is concerned with the acylation process and includes discussion of the reactions of aromatic ketones with excess of catalyst and of acylating agent since these add to the scope of the process and have a bearing on the choice of practical procedure.

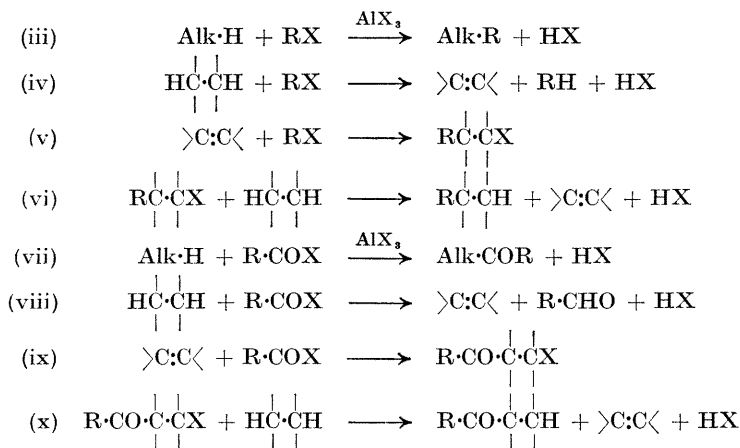
Within the last two decades, and perhaps as a consequence of the rise of the petroleum industry, increasing interest has been aroused in the application of the Friedel-Crafts reaction to aliphatic hydrocarbons. In simplest terms the reactions of olefins with acyl and alkyl halides are addition processes:



they are discussed in section III. In general, the former are fairly straightforward and readily afford  $\beta$ -halogeno-ketones or the  $\alpha\beta$ -unsaturated ketones obtained from them by loss of hydrogen halide. The latter are more complex: the product is an alkyl halide and, like the initial alkyl halide, may (a) combine with olefin, (b) isomerise, (c) dissociate into olefin and hydrogen halide or into olefin and alkyl halide, or (d) be reduced to saturated hydrocarbon.

Section III is also concerned with the reactions of acylating and alkylating agents with saturated hydrocarbons. Although the major products are sometimes compatible with the formulations (iii) and (vii), it is generally

believed that the reactions are initiated by transfer of hydrogen as in (iv) and (viii) and that the olefin thus produced participates in chain reactions (v—vi) and (ix—x). The alkylation process is the more beset by complications.



### I. Alkylation <sup>2</sup>

**Aromatic Hydrocarbon-Aluminium Halide.**—Aluminium chloride is only slightly soluble in aromatic hydrocarbons and does not combine with them. The bromide, on the other hand, dissolves readily to form coloured solutions of high polarity. Variation in vapour pressure of solutions of the bromide in benzene with composition of the solution indicates that the solid compound which separates is probably  $\text{Al}_2\text{Br}_6\cdot 2\text{C}_6\text{H}_6$ . H. C. Brown has suggested that these interactions afford  $\pi$ -complexes in which aluminium is attached to the ring as a whole. There is no evidence that they play any part in Friedel-Crafts reactions.

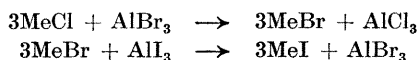
**Hydrogen Halide-Aluminium Halide.**—Although the combined action of these components on organic compounds provides many reactions, especially isomeric rearrangements, which are not effected by either halide alone, the belief that the two halides combine to provide a powerful acidic reagent  $\text{HALX}_4$  has not been substantiated. The solubility of hydrogen bromide in solutions of aluminium bromide in *n*-butane and *n*-hexane is not greater than that in these hydrocarbons; further, aluminium bromide is only slightly soluble in liquid hydrogen bromide and from vapour-pressure measurements appears to be in solution as  $\text{Al}_2\text{Br}_6$ . Absorption of hydrogen chloride by aluminium chloride under a wide variety of conditions has been sought in vain, nor is there evidence for complex formation in systems of gallium chloride-hydrogen chloride and of boron fluoride-hydrogen fluoride.

<sup>2</sup> (a) H. C. Brown, H. W. Pearsall, L. P. Eddy, W. J. Wallace, M. Grayson, and K. LeRoi Nelson, *Ind. Eng. Chem.*, 1953, **45**, 1462; (b) L. Schmerling, *ibid.*, p. 1447; (c) A. W. Francis, *Chem. Reviews*, 1948, **43**, 257; (d) C. C. Price, *Org. Reactions*, 1949, Vol. III, p. 1.

This compilation of negative evidence does not exclude the possibility that minute quantities of  $\text{HALX}_4$  or  $\text{HAL}_2\text{X}_7$  are formed and play a major role in Friedel-Crafts reactions. The application of isotopically marked halogen has enabled exchange of chlorine between hydrogen and aluminium chlorides to be demonstrated; <sup>3</sup> it is detectable at  $-80^\circ$ , rapid at  $100^\circ$ , and equilibrium at room temperature is established within five minutes. The corresponding bromides interact with comparable ease, while hydrogen chloride exchanges halogen readily at  $24^\circ$  with two-thirds of the bromine atoms in aluminium bromide; in this instance a mixed halide phase of composition  $\text{Al}_2\text{Br}_2\text{Cl}_4$  is formed <sup>4</sup> and it has been suggested that the two bromine atoms which are more resistant to replacement form the bridge of the dimeric molecule.

**Alkyl Halide-Aluminium Halide.**—Aluminium chloride is only slightly soluble in methyl or ethyl chloride, and molecular-weight determinations demonstrate that it is present as  $\text{Al}_2\text{Cl}_6$  in solution; there is no evidence of complex formation, even at  $-31.3^\circ$ . On the other hand, the bromide is readily soluble in alkyl bromides and is present as  $\text{AlBr}_3$  in solution. Vapour-pressure measurements demonstrate the presence of a stable complex,  $\text{MeBr}\cdot\text{AlBr}_3$ , in solvent methyl bromide at  $0^\circ$  and a solid of this composition has been obtained by partial removal of solvent at  $-78^\circ$ ; gallium chloride in methyl chloride behaves similarly. Ethyl bromide forms a 1:1 complex with aluminium bromide but decomposition ensues and severely complicates physical measurements on this system. It is therefore unfortunate that up to the present solutions of aluminium bromide in ethyl bromide have been investigated in preference to those in methyl bromide. Addition of aluminium bromide effects a substantial increase in the apparent polarisation of ethyl bromide in *cyclohexane* solution; this is not a consequence of decomposition since the polarisation of the solution is constant for a short time before rising as decomposition occurs; it indicates that a polar complex is formed. These solutions conduct electricity, though feebly, and it has been suggested that they contain a small equilibrium concentration of free ions ( $\text{Et}^+ + \text{AlBr}_4^-$ ) and that, in view of the fairly low dielectric constant of the medium, there may be a greater concentration of ion-pairs.<sup>5</sup>

In many instances, exchange of halogen between alkyl and aluminium halides occurs readily; radioactive aluminium bromide rapidly exchanges all its bromine atoms with those of most aliphatic bromides, *e.g.*,  $\text{EtBr}$ ,  $\text{Bu}^t\text{Br}$ ,  $\text{CBr}_4$ , when the reactants are brought together at room temperature in carbon disulphide or in the absence of solvent, and the following reactions at  $0^\circ$  proceed essentially to completion in 24 hours:



These exchanges are probably effected by ionisation:  $\text{RX}\cdot\text{AlX}_3 \rightleftharpoons \overset{+}{\text{R}}\text{X} \cdot \overset{-}{\text{AlX}}_3$

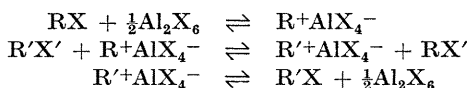
<sup>3</sup> M. Blau, W. T. Carnall, and J. E. Willard, *J. Amer. Chem. Soc.*, 1952, **74**, 5762.

<sup>4</sup> J. D. Corbett and N. W. Gregory, *ibid.*, 1953, **75**, 5238.

<sup>5</sup> F. Fairbrother, *Trans. Faraday Soc.*, 1941, **37**, 763; *J.*, 1945, 503; 1941, 293.

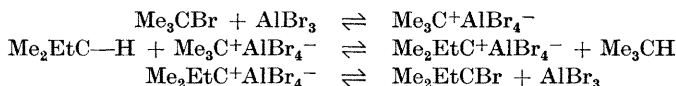
though bimolecular nucleophilic substitution may be involved especially when R is a *primary* alkyl group. Since exchange between methyl halide and dissolved metal halide is slow in comparison with the addition  $2\text{MeX} + \text{Al}_2\text{X}_6 \rightleftharpoons 2\text{MeX}, \text{AlX}_3$ , these addition compounds apparently involve a covalent carbon-halogen bond:  $\text{R}-\overset{+}{\text{X}}-\overset{-}{\text{AlX}}_3$ .

Aluminium halide may catalyse exchange of halogen between one alkyl halide and another; thus a mixture of carbon tetrachloride, ethyl iodide, and aluminium chloride affords carbon tetraiodide. Exchange between tertiary alkyl halides occurs very readily, *e.g.*, that between *tert.*-butyl chloride and *tert.*-amyl bromide in the presence of catalytic amounts of aluminium chloride is rapid at  $-35^\circ$  to  $-25^\circ$ . It probably involves transfer of halide ion from alkyl halide to alkyl cation:

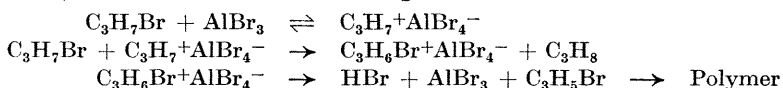


Primary alkyl halides participate much less readily in these exchanges.

Aluminium halide can also interchange halogen of an organic halide and hydrogen of a hydrocarbon; thus a mixture of *isopentane*, *tert.*-butyl bromide, and aluminium bromide rapidly affords *tert.*-pentyl bromide and *isobutane*; the reaction involves transfer of hydride ion:

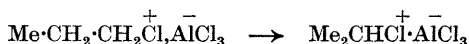


This interchange may occur also between one molecule of alkyl halide and another and be the cause of the decomposition of alkyl halides by aluminium halide; it is significant that *isopropyl* bromide with catalytic amounts of aluminium bromide evolves propane (0.5 mol.) and hydrogen bromide (0.5 mol.) in amounts which are compatible with the formulation:<sup>6</sup>



Other alkyl halides behave similarly though the rate of decomposition diminishes rapidly in the order: *tert.*-butyl > *isopropyl* > ethyl > methyl halide.<sup>7</sup>

The corresponding intramolecular transfer of hydride ion effects isomerisation of alkyl halides; in this way *n*-propyl chloride, for example, affords *isopropyl* chloride:



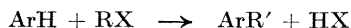
The possibility that this rearrangement involves elimination and subsequent addition of hydrogen chloride:



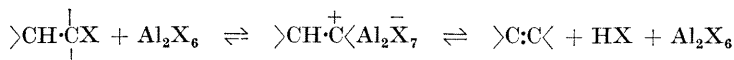
<sup>6</sup> G. Baddeley and W. Pickles, *J.*, 1953, 3726.

<sup>7</sup> P. Nield, W. Pickles, H. T. Taylor, S. Varma, R. Williamson, D. B. Wootton, and E. Wrench, unpublished work.

can be discounted: the transformation has been effected in an atmosphere of deuterium chloride without incurring exchange of hydrogen. Investigation of the isomerisation of alkyl halides by Friedel-Crafts catalysts is complicated by decomposition, and evidence for their occurrence is usually derived from change in configuration of alkyl group in the Friedel-Crafts alkylation process:



Although olefins are *evolved* by mixtures of alkyl and aluminium halides only at raised temperatures,<sup>8</sup> they are probably present in small amount in these mixtures at room temperature:



and catalysed interaction of olefin and alkyl halide, a reaction which is discussed in section III, may be another cause of the decomposition of these mixtures.

**Aromatic Hydrocarbon-Hydrogen Halide-Aluminium Halide.**—The three components readily combine to provide ternary complexes; these conduct electricity and, being highly polar, are not very soluble in hydrocarbons. Thus complexes of composition  $(\text{ArH})_n, \text{Al}_2\text{X}_6, \text{HX}$  or  $(\text{ArH})_n(\text{AlX}_3, \text{HX})_m$  are deposited when solutions or suspensions of aluminium halide in aromatic hydrocarbon have access to hydrogen halide. The ratio  $\text{HX} : \text{AlX}_3$  is a function of the basicity of the hydrocarbon, *i.e.*, of its ability to donate a pair of electrons, and of the pressure of the hydrogen halide. For example, the ratio  $\text{HBr} : \text{AlBr}_3$  in complexes which, at room temperature, are in equilibrium with hydrogen bromide at atmospheric pressure increases in the order: benzene (0.6) < toluene (0.8) < xylenes (1.0), and, as the pressure of hydrogen bromide is decreased, falls to zero if the hydrocarbon is benzene and to 0.5 if it is *m*- or *p*-xylene. Toluene, at  $-80^\circ$  and in the presence of hydrogen chloride, dissolves aluminium chloride to give a clear brilliant green solution in which the ratio  $\text{HCl} : \text{AlCl}_3$  is 1 : 1; this changes to 1 : 2 at  $-45^\circ$ . The reaction is reversible: removal of hydrogen chloride precipitates aluminium chloride and the toluene is recovered. The reactions of gallium chloride and hydrogen chloride with toluene and mesitylene are similar.

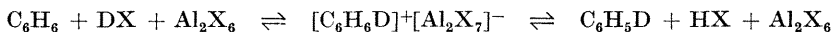
These results, in conjunction with the observation that solutions of boron fluoride in anhydrous hydrogen fluoride dissolve aromatic hydrocarbons until the ratio  $\text{ArH} : \text{BF}_3$  is 1 : 1, lead to the conclusion that salts of the type  $[\text{ArH}_2]^+[\text{MX}_4]^-$  are the basis of all these ternary complexes and that these should be formulated as  $[\text{ArH}_2, n\text{ArH}]^+[\text{AlX}_4, m\text{AlX}_3]^-$ , *i.e.*, the anion may combine with aluminium halide, and the cation with aromatic hydrocarbon. The colour which is a feature of many of these complexes is probably a consequence of the latter combination. Formation of these complexes can be used to separate aromatic from saturated hydrocarbons, and more basic from less basic aromatic hydrocarbons. In this respect, the basicity of benzene homologues is a function of the orientation as well

<sup>8</sup> C. Kerez, *Annalen*, 1885, **231**, 285; L. Meyer, *Ber.*, 1894, **27**, 2766.

as of the number of the alkyl groups attached to the benzene ring, *e.g.*, *meta*- is more basic than *para*-xylene, and the relative stabilities of the complexes are simply related to the relative rates of electrophilic substitution in the hydrocarbons. It follows that the stability of a complex is a measure of the ease of electron release by an individual carbon atom of the aromatic ring rather than of that by the ring as a whole, and that  $[\text{ArH}_2]^+$  is better represented by (I) than by the  $\pi$ -complex (II).

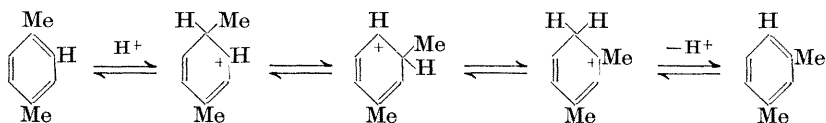


Addition of a proton at an unsubstituted position in the benzene ring may effect exchange of hydrogen; thus aluminium halide catalyses this exchange between benzene and deuterium halide:



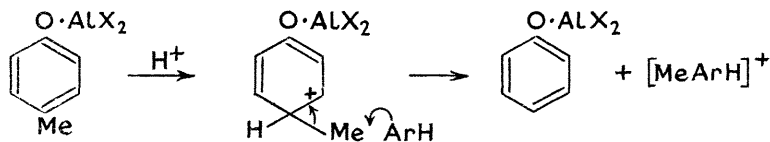
Addition at a position occupied by an alkyl group provides several possibilities including intra- and inter-molecular migration and isomerisation of the alkyl group. The relative importance of each is largely determined by the temperature of the reaction mixture, the structure of the alkyl group, and the number of alkyl groups attached to the benzene ring.

Intramolecular migration of alkyl groups is most simply illustrated by the interconversion of *m*- and *p*-xylene in the presence of aluminium and hydrogen bromides at room temperature. The rate increases with the concentration of hydrogen bromide, and the position of equilibrium in the ternary complex, as distinct from that in the supernatant hydrocarbon which is present when insufficient quantities of the inorganic components are used, favours *m*-xylene, the more basic hydrocarbon. Separation of a crystalline complex allows the equilibrium to be displaced wholly to one side; thus *p*-xylene, after several days in the presence of the appropriate quantities of the inorganic components, affords a crystalline mass of composition  $(m\text{-Xylene})_3(\text{AlBr}_3, \text{HBr})_2$ . The absence of appreciable disproportionation, a reaction which occurs readily at  $100^\circ$  and affords toluene, mesitylene, and other hydrocarbons, shows the isomerisation to be an intramolecular rearrangement; it is best represented as involving a Wagner-Meerwein transformation:



The mechanism of intermolecular migration of methyl groups was made apparent by the observation that whereas phenol is not a product of the interaction of *p*-cresol and aluminium chloride at  $135^\circ$ , it is readily formed at this temperature if toluene is added to the reaction mixture; demethylation

is apparently effected by a bimolecular nucleophilic substitution by the hydrocarbon at the methyl group of the cresol :



Intermolecular migration of methyl groups in aromatic hydrocarbons is probably effected similarly, *e.g.*,  $C_6H_4Me_2 \xrightarrow{H^+} C_6H_5Me_2^+$ ;  $C_6H_5Me_2^+ + C_6H_4Me_2 \rightarrow C_6H_5Me + C_6H_4Me_3^+$ ;  $C_6H_4Me_3^+ \xrightarrow{-H^+} C_6H_3Me_3$ .

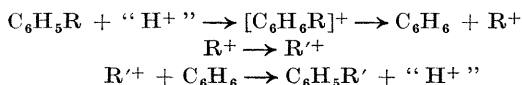
Relative to the methyl group, other alkyl groups are more susceptible to intermolecular migration; whereas toluene is quantitatively recovered after interaction with aluminium and hydrogen halides at room temperature, similar treatment of ethylbenzene and *n*-alkylbenzenes generally gives benzene and its di- and tri-alkyl derivatives. These disproportionations, even when effected at 100°, do not involve isomerisation of *n*-alkyl groups.<sup>9</sup> Since *n*-alkylbenzenes are the principal products of alkylation with *n*-alkyl halides and aluminium halide only in the cold, secondary alkylbenzenes being readily obtained at higher temperatures, these disproportionations do not seem to involve alkyl halide or alkyl cation. The mechanism assigned to the intermolecular transfer of methyl groups would satisfactorily account for these reactions if it were not incompatible with the order of mobility methyl < *n*-alkyl group: one expects bimolecular nucleophilic substitution to occur more readily at a methyl than at any other alkyl group.

The valuable work of MacCaulay and Lien has shown that these isomerisation and disproportionation reactions occur also when benzene homologues are dissolved in solutions of boron fluoride in anhydrous hydrogen fluoride, and has confirmed that the salts of *m*-xylene, mesitylene, and *isodurene* are more stable than those of the isomeric di-, tri-, and tetramethylbenzenes respectively. The rearrangements are made possible by the combination of proton and aromatic hydrocarbon, and predominantly *meta*-orientation of alkyl groups results.

The combined action of hydrogen and aluminium halides on *secondary* and *tertiary* alkylbenzenes may effect dealkylation by a process which is the reverse of the Friedel-Crafts reaction :



and it is clear that this process not only provides an alternative route for the migration of alkyl groups but may effect their isomerisation :

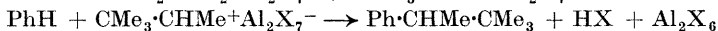
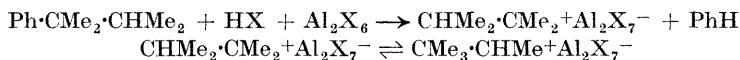


In fact, incursion of this phenomenon is usually accepted as evidence that

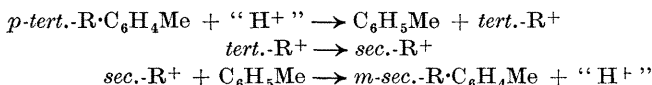
<sup>9</sup> G. Baddeley and J. Kenner, *J.*, 1935, 303; R. E. Kinney and L. A. Hamilton, *J. Amer. Chem. Soc.*, 1954, **76**, 786.



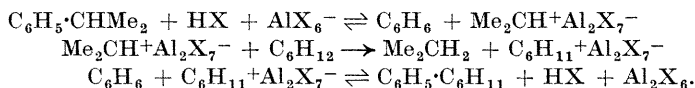
at some stage of the reaction the alkyl group is present as a cation. It is noteworthy that *tert.*-alkylbenzenes usually give *sec.*-alkylbenzenes by rearrangement; <sup>10</sup> thus 2 : 3-dimethyl-2-phenylbutane gives 2 : 2-dimethyl-3-phenylbutane :



and *p-tert.*-dodecyltoluene, the product of interaction of toluene and propylene tetramer in sulphuric acid, gives a *meta secondary* isomer :

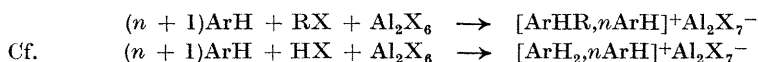


Evidence for the formation of alkyl cations by decomposition of *secondary* alkylbenzenes is afforded by the interesting observation that a mixture of *isopropylbenzene* and *cyclohexane* in the presence of aluminium halide gives *cyclohexylbenzene*; reaction evidently involves transfer of hydride ion from *cyclohexane* to *isopropyl* cation :



Primary alkyl cations have a comparatively large energy content, and fission of *primary* alkylbenzene into benzene and alkyl cation with consequent isomerisation of alkyl group does not occur even at 100°. However, *n*-propyl and *n*-butyl groups of more highly alkylated benzenes have been isomerised by reaction at 100°; thus 5-*sec.*-butyl-*m*-xylene has been obtained from 4-*n*-butyl-*m*-xylene.<sup>11</sup> Reaction at 20° gives the 5-*n*-butyl isomer.<sup>7</sup>

**Aromatic Hydrocarbon-Alkyl Halide-Aluminium Halide.**—The product of the initial reaction is a dense oil similar in composition to a tertiary complex of aromatic hydrocarbon, hydrogen halide, and aluminium halide :



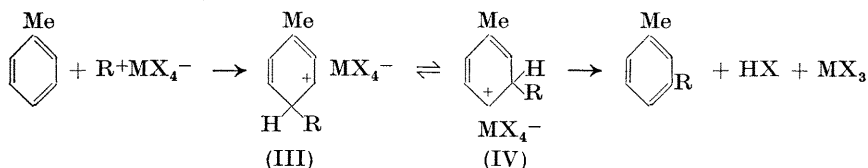
This oil, which increases in amount until the aluminium halide is present wholly in this form, plays an important part : (a) It is a catalyst for the reaction :  $\text{ArH} + \text{RX} \rightarrow \text{ArR} + \text{HX}$ , and only catalytic amounts of aluminium halide are therefore necessary. (b) It is a medium in which all the reactants are brought together and thus enabled to interact rapidly; it has been stated, but not proved, that the comparatively high polarity of the oil facilitates the reaction. (c) The oil contains uncombined hydrocarbon in only limited amount, and thus it favours polyalkylation. This adverse effect is largely overcome by vigorous stirring, or by replacing the aluminium halide by its solution in nitroparaffin and thus effecting homogeneous phase alkylation. (d) The hydrocarbons in the oil may

<sup>10</sup> L. Schmerling, "Catalytic Reactions of Hydrocarbons—Ionic Mechanisms", Symposium No. 24, Sept. 1952, New Jersey.

<sup>11</sup> Dorothy V. Nightingale and L. I. Smith, *J. Amer. Chem. Soc.*, 1939, **61**, 103.

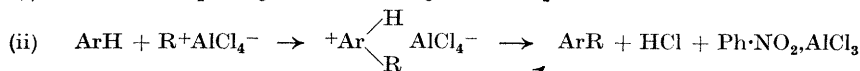
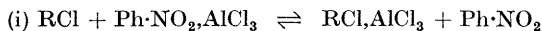
isomerise and disproportionate, and protracted experiments, especially at raised temperatures, afford hydrocarbon of equilibrium composition. Divergencies from this are usually on the side of directive influences and probably indicate incomplete redistribution.

It is often difficult to recognise which are the products of alkylation and which those of isomerisation. The two reactions have a common intermediate and isomerisation may be a part of, as well as a sequel to, the alkylation process; thus, should the life period of the cation (III) provide ample opportunity for the isomerisation (III  $\rightarrow$  IV), attack at the *para*-position of toluene would effect mainly *meta*-substitution. Further, since the life of (III) is related to the basic strength of the anion  $\text{MX}_4^-$ , the extent of *meta*-substitution would change when one metal halide is replaced by another. These speculations may explain the large yields of products of *meta*-alkylation even when the *para*-isomers do not readily rearrange, and the substantial difference incurred by replacing aluminium chloride by ferric chloride—these catalysts give mostly the *meta*- and the *para*-isomers respectively.

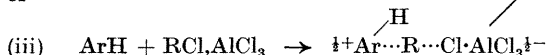


An alternative and more attractive explanation is obtained by recognising that alkylation involves a highly reactive electrophilic reagent,  $\text{RX}$ ,  $\text{AlX}_3$  or  $\text{R}^+\text{AlX}_4^-$ , of low selectivity and that in consequence the alkyl groups of benzene homologues have only little influence on the rate and site of further alkylation. For example, the rate of *isopropylation* of toluene is only twice that of benzene and the ratio of *para*- to *meta*-substitution is only 1.3.<sup>12</sup>

Kinetic studies of the reaction of 3:4-dichlorobenzyl chloride with several aromatic compounds in solvent nitrobenzene and with aluminium chloride in combination with nitrobenzene as catalyst have shown the reaction to be of the first order in respect of each component:  $\text{Rate} = k[\text{ArH}][\text{RCl}][\text{PhNO}_2, \text{AlCl}_3]$ , and the rate to be increased by increase in the basic, *i.e.*, nucleophilic, property of the aromatic compound. These relations are consistent with a mechanism involving a rate-determining nucleophilic attack by the aromatic compound on a product of interaction of the benzyl chloride and the catalyst:

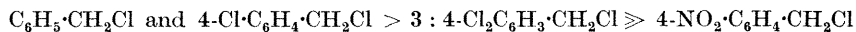


or



<sup>12</sup> H. C. Brown and K. LeRoi Nelson, *J. Amer. Chem. Soc.*, 1953, **75**, 6292.

The order of decreasing reactivity of substituted benzyl chlorides is that of decreasing readiness of ionisation :



but, since the substituents will affect, not only the rate constant of reaction (ii) or (iii), but also the equilibrium constant of reaction (i), this does not prove that the corresponding cations are involved. Further, the observation that the use of mixed methylcyclohexane-nitrobenzene solvents containing 60% of the less polar component effects only a two-fold decrease in the rate does not identify the alkylating agent ; it indicates that the overall electrical charges of the reactants in the rate-determining process are commensurate with those in the transition state, and this relationship is not incompatible with either (ii) or (iii). Isomerisation of alkyl groups in the Friedel-Crafts reaction is evidence for the formation of alkyl cations as in (ii), and in the discussion which follows a fairly consistent interpretation of the data is obtained by application of the following considerations :

(a) Even with the least ionisable of alkyl halides, the primary alkyl halides, the alkylation reaction may involve ion-pairs, *e.g.*,  $\text{R}^+\text{AlX}_4^-$ , or solvated alkyl cations, *e.g.*,  $\text{MeNO}_2\cdots\text{R}^+$  in solvent nitromethane. (b) Alkyl cations readily rearrange in the direction of increasing stability : primary  $\rightarrow$  tertiary, primary  $\rightarrow$  secondary, and secondary  $\rightarrow$  tertiary, and reversal of these changes requires more drastic conditions. (c) The reactivity of alkyl cation in the alkylation process decreases in the order primary  $>$  secondary  $>$  tertiary. (d) The probability that the cation will rearrange before participating in the alkylation reaction is determined by the relative rates of the two processes.

The isomerisation of *n*-propyl and *n*-butyl cations is effected by transfer of hydride ion from secondary carbon atom to primary carbonium ion ( $-\text{CH}_2\cdot\text{CH}_2^+ \rightarrow -^+\text{CH}\cdot\text{CH}_3$ ) and, in the presence of benzene, does not occur sufficiently readily, apparently, to exclude the formation of *n*-alkyl benzene. It is more temperature-dependent than the primary alkylation of benzene, and is therefore less obtrusive at lower temperatures. Transfer of hydride ion from tertiary carbon atom ( $\text{>CH}\cdot\text{CH}_2^+ \rightarrow \text{>C}^+\cdot\text{CH}_3$ ) occurs more readily, and halides of the type  $\text{>CH}\cdot\text{CH}_2\text{X}$ , *e.g.*, *isobutyl* chloride and *isopentyl* bromide, do not give primary alkylbenzenes. *isoButyl* chloride, even at  $-18^\circ$ , gives *tert.*-butylbenzene while the pentylbenzene obtained from *isopentyl* bromide has the same composition as that from *tert.*-pentyl halide. Primary carbonium ion which is bonded to a quaternary carbon atom rearranges by transfer of an alkyl group ( $\text{R}_1\text{R}_2\text{R}_3\text{C}\cdot\text{CH}_2^+ \rightarrow \text{R}_1\text{R}_2\text{C}^+\cdot\text{CH}_2\text{R}_3$ ), tertiary carbonium ion is formed, and the product is the same as that when the corresponding tertiary alkyl halide is used. Thus *neopentyl* and *tert.*-pentyl chloride give the same alkylbenzenes.

*tert.*-Pentyl chloride at  $25-30^\circ$  affords a mixture of pentylbenzenes which contains less than 20% of *tert.*-pentylbenzene and, probably, is largely 2-methyl-3-phenylbutane :  $\text{Me}\cdot\text{CH}_2\cdot\text{CMe}_2\text{Cl} + \text{PhH} \rightarrow \text{Me}\cdot\text{CHPh}\cdot\text{CHMe}_2 + \text{Me}\cdot\text{CH}_2\cdot\text{CMe}_2\text{Ph}$ , while the hexylbenzene from 2-chloro-2 : 3-dimethylbutane is the secondary hexylbenzene, 2 : 2-dimethyl-3-phenylbutane, mixed

with about 10% of the tertiary isomer, 2 : 3-dimethyl-2-phenylbutane :  $\text{Me}_2\text{CH}\cdot\text{CMe}_2\text{Cl} + \text{PhH} \rightarrow \text{Me}_3\text{C}\cdot\text{CHMePh} + \text{Me}_2\text{CH}\cdot\text{CMe}_2\text{Ph}$ . Apparently, tertiary and secondary alkyl halides are interconvertible in the presence of aluminium chloride (the presence of zirconium chloride is also effective) and secondary alkylation predominates since it is the faster and less reversible reaction. Predominantly tertiary alkylation in the presence of aluminium chloride is peculiar to the *tert.*-butyl cation since its isomerisation, in contrast to that of any other tertiary alkyl cation, requires the difficult transition from tertiary to primary alkyl cation. Even that from tertiary to secondary does not occur when aluminium chloride is replaced by milder catalysts : as illustrated by the results shown in the Table, tertiary alkyl cation, whether obtained directly from tertiary alkyl halide or indirectly by isomerisation of primary and secondary alkyl cation, effects tertiary alkylation when ferric chloride or aluminium chloride in nitromethane is the catalyst.

*Products of alkylation of benzene*<sup>13</sup>

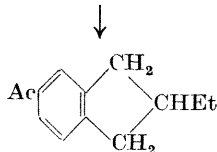
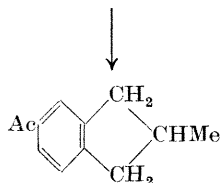
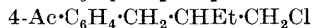
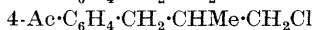
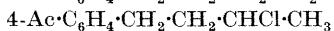
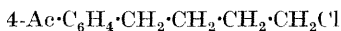
Alkyl halide	Catalyst	Product	Comment
$\text{Me}_3\text{CCl}$	$\text{AlCl}_3$ , $\text{FeCl}_3$ , or $\text{MeNO}_2\cdot\text{AlCl}_3$	$\text{Me}_3\text{CPh}$	
$\text{Me}\cdot\text{CH}_2\cdot\text{CMe}_2\text{Cl}$	$\text{AlCl}_3$	$\text{Me}\cdot\text{CHPh}\cdot\text{CHMe}_2$	Mainly
,,	$\text{FeCl}_3$ or $\text{MeNO}_2\cdot\text{AlCl}_3$	$\text{Me}\cdot\text{CH}_2\cdot\text{CMe}_2\text{Ph}$	Pure
$\text{Me}_2\text{CCl}\cdot\text{CHMe}_2$	$\text{AlCl}_3$ or $\text{ZrCl}_4$	$\text{Me}_3\text{C}\cdot\text{CHMePh}$	Mainly
,,	$\text{FeCl}_3$ or $\text{MeNO}_2\cdot\text{AlCl}_3$	$\text{Me}_2\text{CPh}\cdot\text{CHMe}_2$	Pure
$\text{Me}_3\text{C}\cdot\text{CH}_2\cdot\text{CH}_2\text{Cl}$	$\text{AlCl}_3$ , $\text{AlBr}_3$ , or $\text{ZrCl}_4$	$\text{Me}_3\text{C}\cdot\text{CHPh}\cdot\text{Me}$	Mainly
,,	$\text{FeCl}_3$ or $\text{MeNO}_2\cdot\text{AlCl}_3$	$\text{Me}_2\text{CPh}\cdot\text{CHMe}_2$	

The alkyl cations in the ion pairs  $\text{R}^+\text{AlX}_4^-$  and  $\text{R}^+\text{ZrX}_5^-$  are more reactive than those in  $\text{R}^+\text{FeX}_4^-$  or  $\text{MeNO}_2\cdot\text{R}^+$ , the alkylating agent in solvent nitromethane ; not only do the former isomerise more readily, especially in the direction tertiary  $\rightarrow$  secondary alkyl cation, and more readily alkylate aromatic compounds, but only they can abstract hydride ion from paraffin and *cycloparaffin* and thus initiate the isomerisation of these compounds at room temperature. In brief, and as must reasonably have been expected, the instability and reactivity of alkyl cation are determined, not only by its structure, but also by its environment.

Isomerisation of the alkylating agent is minimal when alkyl cation has ready access to the aromatic component and when this is a reactive nucleophilic reagent. In the following examples<sup>7</sup> readier access is illustrated by intramolecular alkylation ; whereas *n*-alkyl chlorides afford mixtures of primary and secondary alkylbenzenes, the  $\omega$ -chloroalkylbenzenes  $\text{Ph}\cdot[\text{CH}_2]_n\text{Cl}$ , where  $n = 3, 4$ , or  $5$ , readily cyclise in the presence of aluminium chloride to give the corresponding dicyclic hydrocarbons  $o\text{-C}_6\text{H}_4\langle[\text{CH}_2]_n$  (the report that  $\text{Ph}\cdot[\text{CH}_2]_5\text{Cl}$  gives *cyclopentylbenzene* was not justified and is incorrect). Further, the secondary and the tertiary aralkyl chlorides  $\text{Ph}\cdot[\text{CH}_2]_n\cdot\text{CHRCl}$  and  $\text{Ph}\cdot[\text{CH}_2]_n\cdot\text{CR}_2\text{Cl}$ , where  $n$  is 2 or 3 and R is alkyl, afford the corresponding dicyclic hydrocarbons. On the other hand, alkylation of less reactive aromatic compounds is more likely to involve

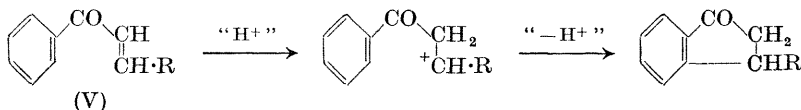
<sup>13</sup> L. Schmerling and J. P. West, *J. Amer. Chem. Soc.*, 1954, **76**, 1917.

isomerisation of the alkylating agent: rearrangement is a feature of the alkylation of acetophenone by *n*-propyl chloride, di-*n*-propyl ether, or *n*-propyl alcohol (*m*-isopropylacetophenone is obtained) and of the ring closure of chloroalkylacetophenones. Several of these compounds are listed below; the order indicates the probable course of isomerisation and 5-acetyl-2-alkylindane is the product in each instance.



Migration of halogen from one secondary carbon atom to another is a well-known phenomenon: reaction of 1-acetyl-2-chlorocyclohexane with benzene gives 1-acetyl-4-phenylcyclohexane, that of 1:2-dihalogenocyclohexane with benzene gives a mixture of 1:3- and 1:4-diphenylcyclohexane,<sup>14</sup> and *trans*-1:4-dibromocyclohexane has been obtained from the 1:2-isomer by the action of aluminium chloride in nitromethane.<sup>7</sup>

Alkylation of phenyl ketones requires vigorous alkylating agents, and tertiary alkyl cations are usually ineffective. On the other hand, ring closure of chloroalkyl phenyl ketones is comparatively easy; it can be effected by tertiary alkylation and is less likely to involve rearrangement. Thus the halogeno-ketones  $\text{Ph}\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\text{Br}$ ,  $\text{Ph}\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CHBr}\cdot\text{CH}_3$ , and  $\text{Ph}\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CMe}_2\text{Cl}$  afford the corresponding dicyclic ketones. The ease of intramolecular alkylation *ortho* to carbonyl group is further illustrated by the ready cyclisation of aryl vinyl ketones (V; R = H or alkyl) and  $\beta$ -arylacrylic acids (V; R =  $\text{CO}_2\text{H}$ ).<sup>15</sup>



Alkylation with olefin and aluminium halide requires the presence of hydrogen halide, or other source of proton, which reacts with the olefin to provide the alkylating agent:  $\text{>C:C<} + \text{HX} + \text{Al}_2\text{X}_6 \rightarrow \text{>CH}\cdot\text{C}^+ + \text{Al}_2\text{X}_7^-$ . It resembles alkylation with alkyl halide and is similarly affected by isomerisation. Alkylation with ethers and alcohols requires excess of aluminium halide and is probably effected by alkyl halide:  $\text{R}_2\text{O} + \text{AlX}_3 \rightarrow \text{R}_2\text{O}^+\text{AlX}_3^- \rightarrow \text{RO}\cdot\text{AlX}_2 + \text{RX}$  and  $\text{ROH} + \text{AlX}_3 \rightarrow \text{ROH}\cdot\text{AlX}_3 \rightarrow \text{HX} + \text{AlOX} + \text{RX}$ . A molecular proportion of aluminium halide (as  $\text{AlX}_3$ )

<sup>14</sup> C. D. Nenitzescu and I. G. Gavai, *Annalen*, 1935, **519**, 260; W. S. Johnson and R. D. Offenbauer, *J. Amer. Chem. Soc.*, 1945, **67**, 1045.

<sup>15</sup> G. Baddeley, G. Holt, and S. M. Makar, *J.*, 1952, 3289.

is consumed in this way and additional halide is therefore necessary to catalyse alkylation. Almost without exception, alkylation occurs only when the temperature is sufficiently high to ensure formation of alkyl halide. Isomerisation of the alkylating agent is as apparent in the alkylation of benzene with ethers as with the corresponding halides but may be a little less so with alcohols. The claim that *n*-propyl alcohol gave *n*-propylbenzene and no *isopropylbenzene* is not supported by our work. The small quantity of optically active *sec.*-butylbenzene which is formed in the reaction of benzene with active *sec.*-butyl alcohol has been offered as evidence for a typical bimolecular nucleophilic substitution:  $C_6H_6 + ROH, AlX_3 \rightarrow C_6H_6 \cdots R \cdots OH, AlX_3 \rightarrow C_6H_5 \cdot R + 2HX + AlOX$ ; it would be acceptable if optical purity were retained.

## II. Acylation of Aromatic Compounds

Interaction of benzene derivative (ArH), acyl halide (R·COX), and aluminium halide (formulated as  $AlX_3$ ) provides hydrogen halide and an oxonium complex of aromatic ketone and aluminium halide from which the ketone is obtained on addition to water:  $ArH + R \cdot COX + AlX_3 \rightarrow HX + Ar \cdot CRO, AlX_3 \xrightarrow{H_2O} Ar \cdot COR$ . Gradual addition of one component to a mixture of the other two, usually in a solvent, provides the three most popular methods. In general, preliminary mixing of benzene homologue and aluminium halide should be avoided since hydrogen halide will probably be present, and will most certainly be present after the first addition of acyl halide, and the benzene homologue may therefore isomerise or disproportionate. Thus gradual addition of propionyl chloride to a mixture of 3-phenylpentane and aluminium chloride in carbon disulphide gives propiophenone and a dipentylpropiophenone.<sup>16</sup>

Preliminary mixing of acyl and aluminium halides is often the best procedure. Like most organic compounds which have at least one oxygen atom, and, in contrast to alkyl and aryl halides generally, acyl halides combine exothermally with aluminium halides; the heats of complex formation indicate bonding of aluminium atom to oxygen atom, as in  $R \cdot CX : O^+, AlX_3^-$ .<sup>17</sup>

These complexes have been named as the effective electrophilic reagents in the Friedel-Crafts acylation reaction and this has been formulated as in (i) (p. 369). This formulation is compatible with the observation that ketones and aldehydes combine exothermally with aluminium halide to provide electrophilic reagents which can attack aromatic compounds.<sup>18</sup> Meerwein suggested the ionisation process (ii) and this has been substantiated by showing that halogen exchange occurs between acyl and aluminium halides.<sup>19</sup> The acyl cation obtained in this way may be the electrophilic

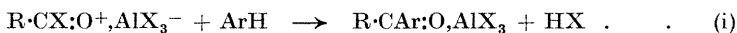
<sup>16</sup> Dorothy V. Nightingale, H. B. Huckler, and O. L. Wright, *J. Org. Chem.*, 1953, **18**, 244.

<sup>17</sup> M. H. Dilke, D. D. Eley, and Miss M. G. Sheppard, *Trans. Faraday Soc.*, 1950, **46**, 261.

<sup>18</sup> H. E. Ungnade and E. W. Crandall, *J. Amer. Chem. Soc.*, 1949, **71**, 2209.

<sup>19</sup> F. Fairbrother, *J.*, 1937, 503; G. Baddeley and D. Voss, *J.*, 1954, 418.

reagent of the Friedel-Crafts acylation process ;<sup>20</sup> this view requires that acyl halides which are sterically hindered in their reactions with nucleophilic reagents should not be so hindered in the Friedel-Crafts reaction. This is indeed the case : *e.g.*, 2 : 4 : 6-tribromobenzoyl halide, though sterically hindered in its reactions with water, alcohol, or alkali, readily exchanges halogen with aluminium halide and readily participates in the ketone synthesis. This acyl halide is quantitatively recovered when its addition compound with aluminium halide is decomposed with water ; the acyl cation shown in (ii) is therefore present only in traces and addition compounds of this type are to be represented by (iii). It is probable that, in general, acylation is effected both by the oxonium complex and by the acyl cation.



Whereas alkylation with alkyl halides requires only catalytic amounts of aluminium halide, acylation affords ketone in yields which are proportional to the amount of aluminium halide added, and it is complete when little more than a molecular proportion of reagent (as  $\text{AlX}_3$ ) is used. Ulich and Heyne<sup>21</sup> concluded that the reagent is firmly attached to the resulting ketone and no longer able to activate more acid halide ; this conclusion is not wholly true since halogen exchange between acid and aluminium halides continues in the presence of excess of ketone. Apparently, presence of ketone does not prevent formation of acyl cation, but lowers its efficacy as an acylating agent ; this deactivation is probably effected by association :  $\text{Ar}\cdot\text{CR}:\text{O} + \text{CR}:\text{O} \rightarrow [\text{Ar}\cdot\text{CR}:\text{O}\cdots\text{CR}:\text{O}]^+$ . Similarly, ability of solvents or added substances, *e.g.*, *m*-dinitrobenzene < acid halides, nitrobenzene, nitromethane < diethyl ether < benzophenone < *p*-methoxybenzophenone, to retard or even to suppress Friedel-Crafts reactions is related to their ability to solvate acyl cation and thus to reduce the electron demand and hence the activity for acylation purposes.

A further consequence of association of acylating agents with basic compounds—and acyl halide which is not in combination with aluminium halide is one such compound—is an increase in bulk of the agent and greater resistance to attack at the sterically more hindered positions of aromatic compounds. Thus acylation of chrysene and phenanthrene in nitrobenzene or in carbon disulphide occurs to a considerable extent in a side ring, while that of naphthalene leads to considerable reaction at the less reactive, but sterically less hindered,  $\beta$ -position. These two consequences of the presence of basic compounds—decrease in reactivity and increase in bulk of the acylating agent—are avoided by ensuring that these basic compounds are fully engaged by aluminium halide.<sup>22</sup>

<sup>20</sup> H. Burton and P. F. G. Prall, *Chem. and Ind.*, 1954, 75.

<sup>21</sup> Ulich and Heyne, *Z. Electrochem.*, 1935, **41**, 509.

<sup>22</sup> G. Baddeley, *J.*, 1949, 599 ; W. Carruthers, *J.*, 1953, 3486.

Perrier<sup>23</sup> introduced the process of first forming the acid chloride-aluminium chloride complex. This procedure involves warming a mixture of the two chlorides, alone or in the presence of carbon disulphide, and though satisfactory with some acid chlorides, *e.g.*, benzoyl chloride, is unsatisfactory for general application: the aluminium chloride is covered by a protective layer of acid chloride-aluminium chloride complex and uncombined acid chloride remains. This difficulty is overcome by employing methylene or ethylene chloride in which homogeneous solutions are readily obtained at room temperature. Thus the acylating agent is often best and most readily obtained by adding acid halide or anhydride to a stirred suspension of an excess of aluminium chloride in methylene or ethylene chloride and decanting the solution of the acylating agent from undissolved aluminium chloride. The success of this method rests on the high solubility of the complex  $R\cdot COCl\cdot AlCl_3$  and the low solubility of aluminium chloride in these solvents; they enable the acylating agent to be readily obtained *in its most reactive form* and easily freed from excess of aluminium halide. An excess of this reagent is undesirable since it may effect isomerisation of the products of acylation. As an evident consequence of this possibility, attempts to improve the yield of ketone by making further additions of aluminium halide, warming the reaction mixture on the steam-bath, or keeping the mixture overnight are to be viewed with suspicion. The course of the acylation reaction can be followed by passing dry nitrogen through the mixture and titrimetrically estimating the displaced hydrogen halide. The temperature of the mixture should not be higher than is necessary for a convenient rate of reaction, and the mixture should be poured into dilute mineral acid as soon as the required reaction is essentially complete. The preparation of 2:5-diisopropylacetophenone is instructive: this compound is obtained by acetylation of *p*-diisopropylbenzene in carbon disulphide at temperatures below 5°; if, subsequently, the mixture is kept overnight at room temperature, the 3:5-isomer and much *m*-isopropylacetophenone are obtained; the 2:4-isomer is the product of acetylation at room temperature.<sup>24</sup>

Acid anhydrides combine with 2 mols. of aluminium halide to afford one of acylating agent:  $(R\cdot CO)_2O + 2AlX_3 \rightarrow R\cdot COX, AlX_3 + R\cdot CO\cdot O\cdot AlX_2$ . A consequence of the reverse reaction, interaction of acylating agent and acyloxyaluminium chloride, is illustrated by the formation of  $\alpha$ -tetralone when  $\gamma$ -phenylbutyric acid and acetyl chloride are brought together in the presence of aluminium chloride:  $CH_3\cdot COCl, AlCl_3 + Ph\cdot [CH_2]_3\cdot CO\cdot O\cdot AlCl_2 \rightleftharpoons Ph\cdot [CH_2]_3\cdot CO\cdot O\cdot CO\cdot CH_3, 2AlCl_3 \rightleftharpoons CH_3\cdot CO\cdot O\cdot AlCl_2 + Ph\cdot [CH_2]_3\cdot COCl, AlCl_3 \rightarrow \alpha\text{-tetralone}$ . To effect intermolecular acylation of this and similar acids it is therefore necessary to protect the carboxyl group by esterification and to employ 2 mols. of aluminium halide: one to engage the ester and the other to provide the acylating agent:  $Ph\cdot [CH_2]_3\cdot CO_2Et, AlX_3 + R\cdot COX, AlX_3 \rightarrow p\text{-}R\cdot CO\cdot C_6H_4\cdot [CH_2]_3\cdot CO_2Et$ .

The rate and the site of substitution by the acylating agent from mono-

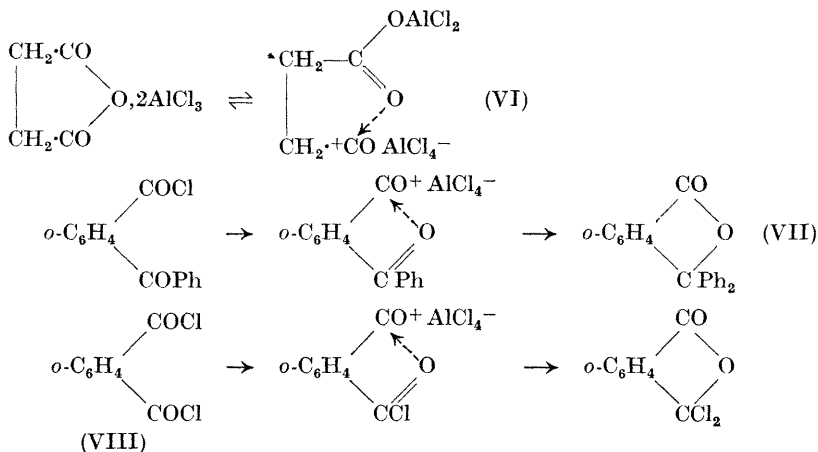
<sup>23</sup> Perrier, *Bull. Soc. chim.*, 1903, **31**, 859.

<sup>24</sup> G. Baddeley, G. Holt, and W. Pickles, *J.*, 1952, 4162.



basic acid anhydride are essentially the same as those by the corresponding acid chloride-aluminium chloride complex. On the other hand, dibasic acid anhydrides, even in the presence of an excess of aluminium halide, afford comparatively bulky acylating agents of low reactivity; <sup>25</sup> *i.e.*, they behave as do acid halide-aluminium halide complexes in nitromethane or nitrobenzene. The cause of this behaviour probably originates with intramolecular association of acyloxyaluminium chloride group and acylating agent; *e.g.*, the acylating agent derived from succinic anhydride may be represented by (VI).

Interaction of acyl cation and oxygen atom of a neighbouring group is illustrated by the formation of diphenylphthalide (VII) from *o*-benzoylbenzoyl chloride and benzene, and by the isomerisation of phthaloyl chloride (VIII).



Preliminary mixing of acyl and aluminium halides must, of course, be avoided when it effects undesirable reactions. These may arise in at least two ways: (a) The acid chloride may contain a group, *e.g.*, an aryl or olefinic group not attached to carbonyl or other deactivating group, which will react either intra- or inter-molecularly with the acylating agent. (b) The acyl cation may decompose with evolution of carbon monoxide and formation of alkyl cation:  $\text{R} \cdot \text{COCl}, \text{AlCl}_3 \rightarrow \text{R} \cdot \text{CO}^+ \text{AlCl}_4^- \rightarrow \text{R}^+ \text{AlCl}_4^- + \text{CO}$ .

Decarbonylation occurs the more readily the greater the stability of the resulting alkyl cation, and is a feature of tertiary and  $\alpha$ -phenylacetyl halides. Thus pivaloyl chloride may effect tertiary butylation, while diphenylacetyl,  $\alpha$ -phenylpropionyl, and  $\alpha$ -methyl- $\alpha$ -phenylpropionyl chloride may effect aralkylation.

Decomposition of pivaloyl and other tertiary acid halides by aluminium halide in the presence of aromatic compounds has been extensively investigated by Rothstein and Saville.<sup>26</sup> The following results demonstrate that

<sup>25</sup> E. Berliner, *Org. Reactions*, Vol. V, p. 229.

<sup>26</sup> E. Rothstein and R. W. Saville, *J.*, 1949, 1946 *et seq.*; S. Archer and M. Jackman, *Chem. and Ind.*, 1954, 784.

evolution of carbon monoxide is minimised, acylation being dominant, when acyl cation has ready access to the aromatic component and when this is a reactive nucleophilic reagent: (a) The yields of carbon monoxide in the reaction of pivaloyl chloride with aluminium chloride in benzene (87%), toluene (53%), and anisole (7%) decrease with increase in the nucleophilic reactivity of the medium. (b) Dilution of these reaction mixtures with carbon disulphide decreases the frequency with which acyl cation encounters the aromatic components, and the yields of carbon monoxide are thereby increased. (c) The acyl cations from the acid chlorides  $\text{Ph} \cdot [\text{CH}_2]_n \cdot \text{CMe}_2 \cdot \text{COCl}$ , where  $n = 1$  or 2, have ready intramolecular access to the benzene ring and cyclisation is effected without decomposition. (d) This ready accessibility no longer obtains when  $n = 3$ , carbon monoxide is evolved, and intramolecular alkylation gives 1:2:3:4-tetrahydro-1:1-dimethylnaphthalene: (e) Both intramolecular acylation and intramolecular alkylation occur with difficulty when the phenyl group of  $\text{Ph} \cdot [\text{CH}_2]_n \cdot \text{CMe}_2 \cdot \text{COCl}$  is replaced by *p*-acetylphenyl, and not only is carbon monoxide evolved, but also the tertiary alkyl cation isomerises; 7-acetyl-1:2:3:4-tetrahydro-2-methylnaphthalene is obtained.

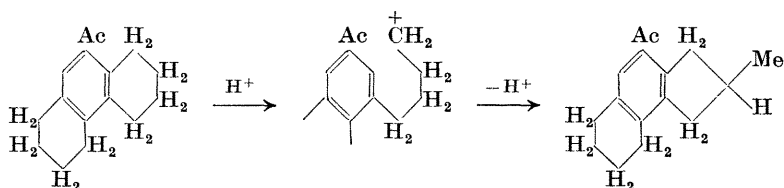
Methylene and ethylene chloride are not suitable solvents in which to effect comparatively slow acylations; chloromethylation and chloroethylation interfere. For example, they should not be used as diluents in the cyclisation of  $\omega$ -phenylalkanoyl chlorides by the high-dilution technique; carbon disulphide is suitable:<sup>27</sup> a very dilute solution of acid chloride is very slowly added to a suspension of aluminium chloride in boiling carbon disulphide. Cyclisation of the compounds  $\text{Ph} \cdot [\text{CH}_2]_n \cdot \text{COCl}$  occurs at the *ortho*-position when  $1 < n \leq 5$ , and at the *para*-position when  $n \geq 8$ ; it is not effected when  $n = 6$  or 7.

**Isomerisation of Aromatic Ketones.**<sup>28, 7</sup>—Many 2-alkylaryl ketones, including *o*-alkylaryl and *o*-hydroxyaryl ketones, are unstable in the presence of hydrogen halide and excess of aluminium halide, especially at raised temperatures, and undergo a variety of *irreversible* changes which have been classified and illustrated as follows: (i) The ketone may suffer fission into aromatic hydrocarbon and acyl cation which recombine to provide an isomeric ketone: 2-methyl- and 4-hydroxy-2-methyl-acetophenone afford 4-methyl- and 2-hydroxy-4-methyl-acetophenone respectively;  $\alpha$ -naphthyl ketones behave similarly, thus affording the  $\beta$ -isomers. (ii) The 2-alkyl group may migrate intramolecularly to the adjacent *m*-position: 2:5-dimethyl- and 2:5-diethyl-acetophenone and their 6-hydroxy-derivatives rearrange to the corresponding 3:5-isomers. (iii) In 2:6-dialkylaryl ketones, both these alkyl groups may migrate to the corresponding *m*-positions: isomerisation of 2:4:6-trimethylacetophenone at 100° and 125° gives the 2:4:5- and the 3:4:5-isomer respectively. Migration of 2- and 6-alkyl groups provides ready access to those 3:5-dialkyl- and 3:4:5-trialkyl-phenyl ketones in which the alkyl groups are methyl, ethyl, or *n*-propyl. The method is not applicable with secondary or tertiary alkyl

<sup>27</sup> R. Huisgen, W. Rapp, I. Ugi, H. Walz, and I. Glogger, *Annalen*, 1954, **586**, 52.

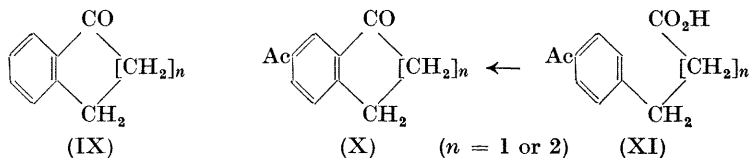
<sup>28</sup> G. Baddeley and A. G. Pendleton, *J.*, 1952, 807.

groups as these are replaced by hydrogen or methyl under the conditions required for the isomerisation.<sup>7</sup> The 2-alkyl group may migrate to the neighbouring *meta*-position when this is already occupied by an alkyl group; the more mobile group will then migrate to the *p*-position. (iv) The 2-alkyl group may be eliminated if it is *n*-propyl or a larger *n*-alkyl group: 2:5-di-*n*-propylacetophenone gives a mixture of the 3:5-isomer and 3-*n*-propylacetophenone. Secondary alkyl groups are still more readily displaced: *m*-isopropyl- and 3:5-diisopropyl-acetophenone are obtained in yields of 65% and 24% respectively from the 2:5-isomer and excess of aluminium chloride in ethylene chloride at room temperature. (v) Dealkylation of the ketone, as in (iv), is followed by alkylation only when this is effected intramolecularly. Thus 9-acetyl-1:2:3:4:5:6:7:8-octahydrophenanthrene affords 7-acetyl-2-methyl-4:5-cyclohexenoidane in excellent yield:



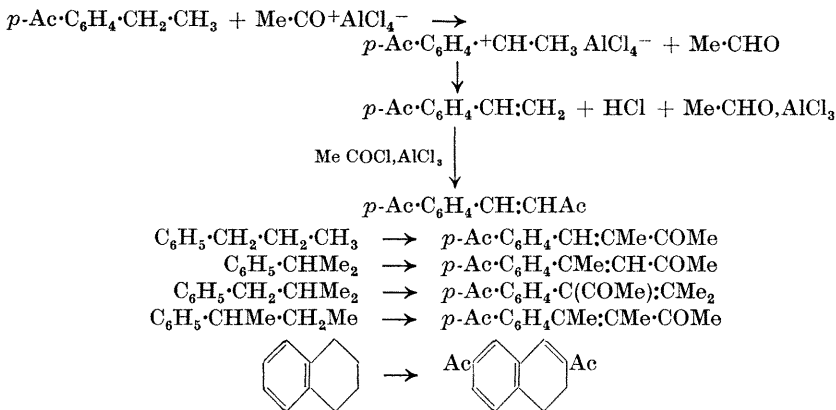
All these reactions are determined by steric interaction and provide ketones in which the carbonyl group is less encumbered by vicinal groups.<sup>29</sup>

**Dehydrogenation by the Acylating Agent.**—Acylation of monoalkylbenzenes affords only monoacyl and mainly the 4-acyl derivatives. On the other hand, more reactive benzene derivatives, *e.g.*, *p*-cresol, mesitylene, and durene, can be diacylated. *m*-Xylene is a borderline case: its 4:6-diacetyl derivative has been recently obtained in low yield by the Friedel-Crafts method. Intramolecular acylation of aromatic ketones is comparatively easy; thus the ketones (IX) cannot be acetylated whereas the diketones (X) are readily obtained from the keto-acids (XI) by fusion with aluminium chloride.<sup>7</sup> Similarly, *o*-aryl-benzoic acids afford anthraquinones.



When Friedel-Crafts acylation is hindered by the presence of a deactivating group in the nucleophilic component, reaction may involve transfer of hydride ions from an aromatic side-chain to the acyl cation and, as illustrated by the interaction of *p*-ethylacetophenone with an excess of acetylating agent, culminate in the formation of an olefinic diketone. Other examples are listed.<sup>7</sup>

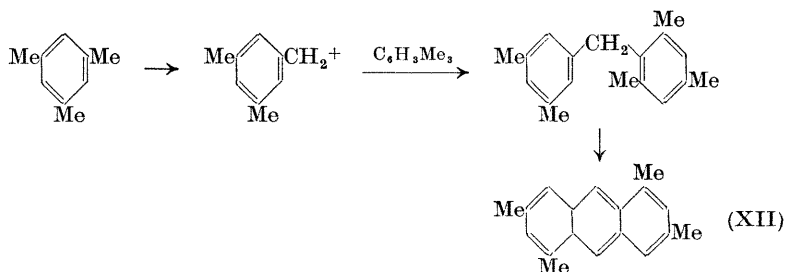
<sup>29</sup> G. Baddeley, *J.*, 1944, 232.



Loss of hydride ion to acyl cation occurs at a carbon atom adjacent to the benzene ring since, in this way, resonance stabilisation of the resulting carbonium ion is best effected. This stabilising effect requires release of electrons from the benzene ring, and the methylene or methine group is therefore more readily attacked when in the *meta*-position to the acyl group. Thus tetralin affords 3 : 6-diacetyl-1 : 2-dihydronaphthalene.<sup>30</sup>

Dehydrogenation of a side chain of an aromatic ketone proceeds at a convenient rate only at raised temperatures, usually at 70—100°, and aliphatic acid halides are unstable under these conditions. The reactions formulated are therefore accompanied by decomposition of acetyl chloride and formation of acetylacetone and other compounds.

When the alkyl group is methyl, the benzyl cation obtained by loss of hydride ion may effect benzylation; this possibility is realised in the reactions of mesitylene, durene, and *isodurene* severally with pivaloyl chloride. Acylation *ortho* to alkyl group, especially by the bulky pivaloyl cation, is sterically hindered and comparatively slow and the alternative reaction, transfer of hydride ion, accompanies the acylation and decarbonylation processes; it culminates in the formation of anthracene homologues. Thus tetramethylantracene, probably (XII), was obtained from mesitylene, and hexamethylantracene from durene and *isodurene*:<sup>31</sup>



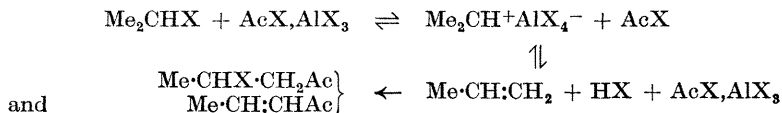
<sup>30</sup> G. Baddeley, E. Wrench, and R. Williamson, *J.*, 1953, 2110.

<sup>31</sup> Dorothy V. Nightingale, R. L. Sublett, R. A. Carpenter, and H. D. Radford, *J. Org. Chem.*, 1951, 16, 655.

### III. Acylating Agent and Aliphatic Hydrocarbons

Reaction of acid halide with olefin does not proceed as smoothly as with aromatic hydrocarbon, and yields of definite compounds can be low. It is most conveniently effected by addition of olefin to a solution of acyl halide-aluminium halide complex in methylene or ethylene chloride, though acyl halide itself and nitromethane have been successfully used as solvent.<sup>32</sup> Acyl cation combines with that carbon atom of the ethylenic group which holds the smaller number of alkyl groups and the resulting cation may (a) combine with chloride ion affording  $\beta$ -chloro-ketone, (b) isomerise by transfer of hydride ion and subsequently combine with chloride ion, and (c) afford unsaturated ketone by loss of a proton. All these processes participate in the reaction of *cyclohexene* with acetyl chloride in the presence of aluminium chloride; the products are (a) 2-chloro*cyclohexyl* methyl ketone, (b) the 3- and the 4-chloro-isomer which, unlike the 2-isomer, are not readily dehydrohalogenated by distillation from sodium carbonate or tertiary amine, and (c) 1-*cyclohexenyl* methyl ketone. Process (a) is favoured by a decrease in temperature whereas a higher temperature and a larger amount of catalyst assist process (c). Cleaner products and more reproducible results are obtained when acyl halide is replaced by the anhydride of a monocarboxylic acid, and stannic chloride has been successfully used as catalyst.<sup>33</sup> Anhydrides of dicarboxylic acids do not readily react with olefins, and yields of definite compounds from them are regularly low.<sup>7</sup>

When milder catalysts, *e.g.*, zinc chloride or stannic chloride, are used, the alkyl or *cycloalkyl* chloride obtained by addition of hydrogen chloride to olefin, *e.g.*,  $\text{>C:C<} + \text{HCl} + \text{ZnCl}_2 \rightarrow \text{>CH-}\overset{\text{Cl}}{\underset{\text{ZnCl}_2}{\text{C}}}$ , can be an important by-product. This addition process is readily reversible in the presence of aluminium halide, and alkyl halide in the presence of this catalyst may therefore be used as a convenient source of olefin;<sup>7</sup> *e.g.*, addition of *isopropyl* bromide to acetyl chloride-aluminium chloride in methylene chloride affords pent-3-en-2-one and 4-chloropentan-2-one:



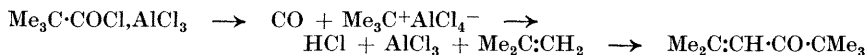
As expected, the ease with which alkyl halides participate in these reactions decreases in the order tertiary > secondary > primary alkyl, and iodide > bromide > chloride.

An interesting ramification of this reaction is afforded by the decomposition of tertiary acid halides in the presence of aluminium halide; tertiary

<sup>32</sup> G. Baddeley, H. T. Taylor, and W. Pickles, *J.*, 1953, 124; J. R. Catch, D. F. Elliott, D. H. Hey, and E. R. H. Jones, *J.*, 1948, 278.

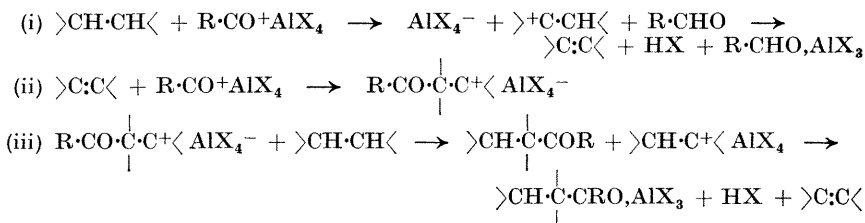
<sup>33</sup> E. E. Royals and C. M. Hendry, *J. Org. Chem.*, 1950, 15, 1149.

alkyl cation is formed and in the absence of aromatic hydrocarbon or other nucleophilic reagent provides olefin which combines with the acylating agent; the decomposition of pivaloyl chloride exemplifies the process:



Preparation of an olefin from an alkyl halide in the presence of an acylating agent involves the alkyl cation as intermediate and may therefore incur isomerisation; e.g., addition of *cyclohexyl* chloride or bromide to acetyl chloride-aluminium chloride in methylene chloride gives methyl 2-methyl-1-*cyclopentenyl* ketone, and addition of *n*-butyl iodide gives 3-methylpent-3-en-2-one. Rearrangement of the carbon skeleton in reactions of this type can be prevented by addition of nitromethane, nitrobenzene, acyl halide, or other suitably basic compound which, while not preventing reaction, will assist removal of proton from the alkyl cation, and thus enable the formation of olefin to forestall isomerisation; thus interaction of *cyclohexyl* halide and acetylating agent in the presence of a nitro-compound gives *cyclohex-1-enyl* methyl ketone.

Alkyl and *cyclo*alkyl cations, and therefrom olefins and their products of reaction with acylating agent, can also be obtained from paraffins and naphthenes by transfer of hydride ion to the acyl cation [reaction (i) below]. Should isomerisation occur, it cannot be prevented by addition of a nitro-compound or similar reagents since these, when present, prevent all reaction from occurring. Nenitzescu and Cantuniari<sup>34</sup> were the first to show that a saturated hydrocarbon can hydrogenate the products of reaction of an olefin with an acylating agent [reaction (iii)]; they obtained *cyclohexyl* methyl ketone in good yield by addition of *cyclohexane* to the reaction mixture afforded by the acetylation of *cyclohexene*; consequently, reaction (i) initiates the chain reaction (ii)-(iii), and the overall reaction affords ketone which is saturated and free from halogen:

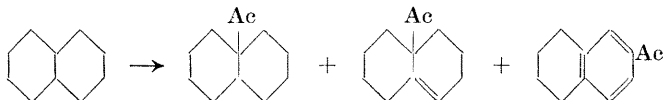


The preparation of 3 : 4-dimethylpentan-2-one ( $\text{Me}\cdot[\text{CH}_2]_3\cdot\text{Me} \rightarrow \text{CMe}_2:\text{CHMe} \rightarrow \text{CHMe}_2\cdot\text{CHMe}\cdot\text{COMe}$ ) and methyl 2-methyl*cyclopentyl* ketone by reaction of acetylating agent with *n*-pentane and *cyclohexane* respectively exemplifies the process.

Loss of hydride ion by a saturated hydrocarbon occurs most readily

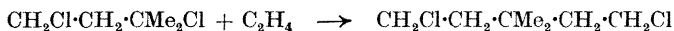
<sup>34</sup> C. D. Nenitzescu and I. P. Cantuniari, *Annalen*, 1934, **510**, 269.

at a tertiary carbon atom ; thus decalin reacts more readily with acetylating agent than does *cyclohexane* ; a mixture of ketones is obtained : <sup>7</sup>

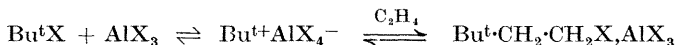


The reactions illustrated in this section involve, among other reagents, alkyl cation and olefin, and interaction of these two may afford the major by-product.

**Alkylating Agent and Aliphatic Hydrocarbon.**<sup>10, 35</sup>—Alkyl halides containing at least three carbon atoms can combine with olefins in the presence of catalysts of the Friedel-Crafts type to yield halogenoalkanes of higher molecular weight. The primary reaction is addition of alkyl halide to the double bond of the olefin :  $\text{>C:C<} + \text{RX, AlX}_3 \rightarrow \text{>CR}\cdot\text{CX, AlX}_3$ , the alkyl cation adding to the carbon atom that holds the smaller number of alkyl groups. In general, the products of addition are obtained most readily with tertiary alkyl halides and least readily with the primary isomers ; thus *tert.*-butyl chloride adds more readily to ethylene than does *isopropyl* chloride, and the reaction of isoprene dihydrochloride with ethylene in the presence of aluminium chloride at  $-12^\circ$  provides 1 : 5-dichloro-3 : 3-dimethylpentane :



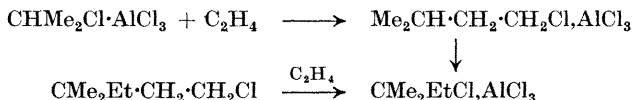
Interaction of ethylene with *tert.*-butyl chloride and bromide in the presence of aluminium bromide and chloride respectively at  $-40^\circ$  to  $-50^\circ$  gives a hexyl halide in which the halogen of the *tert.*-butyl halide predominates ; this indicates that addition occurs, not only in the manner :



but also by the chain-carrying exchange reaction :



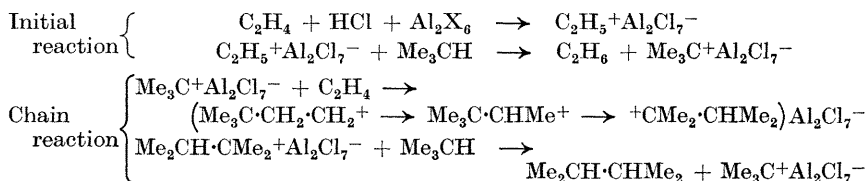
Isomerisation of alkyl halide may precede or follow the addition reaction ; for example, reaction of *neopentyl* chloride with ethylene at  $-20^\circ$  to  $-40^\circ$  in the presence of aluminium chloride affords 1-chloro-3 : 3-dimethylpentane, the product of interaction of ethylene and *tert.*-pentyl chloride :  $\text{Me}_3\text{C}\cdot\text{CH}_2\text{Cl} \rightarrow \text{CMe}_2\text{EtCl} \rightarrow \text{CMe}_2\text{Et}\cdot\text{CH}_2\cdot\text{CH}_2\text{Cl}$ , and the same product is afforded by the interaction of *isopropyl* chloride and ethylene since 1-chloro-3-methylbutane, the product of the primary reaction, gives *tert.*-pentyl chloride by rearrangement and this halide adds more rapidly to olefin than does secondary halide :



*cyclo*Hexyl chloride reacts similarly : it combines with two mols. of ethylene to give 1-2'-chloroethyl-1-ethyl*cyclo*hexane.

<sup>35</sup> G. Egloff and G. Hulla, *Chem. Reviews*, 1945, **37**, 323.

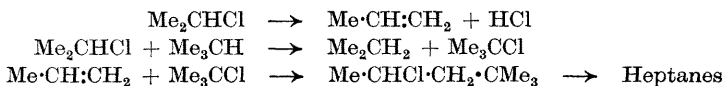
Loss of hydride ion by a saturated hydrocarbon can be a convenient source of alkyl cation for addition to olefin, and the catalytic interaction of olefin and paraffin, especially *isoparaffin*, has been studied extensively since the reaction was discovered by Ipatieff and Pines in 1935. The chain-reaction scheme proposed by Schmerling provides a logical and plausible explanation and is conveniently illustrated by the interaction of *isobutane* and ethylene in the presence of hydrogen and aluminium chlorides :



Reaction is initiated by transfer of hydride ion from the paraffin to the alkyl cation afforded by addition of proton to olefin ; and the chain reaction, which involves isomerisation of alkyl cations, is maintained by transfer of hydride ion from the paraffin to the product of addition of alkylating agent to olefin.

In these reaction mixtures the alkyl cation may isomerise, combine with olefin to provide a larger cation, or, conversely, dissociate into olefin and a smaller cation, abstract hydride ion, or lose a proton to afford olefin ; complications are therefore readily envisaged. An obvious one is illustrated by the interaction of propylene and *isobutane* ; the net effect is one of hydrogen transfer with resultant conversion of propylene into propane and of *isobutane* into octane :  $\text{C}_4\text{H}_{10} + \text{C}_3\text{H}_6 \rightarrow \text{C}_8\text{H}_{18} + \text{C}_3\text{H}_8$  ; octanes are among the products of all interactions of *isobutane* with olefins and alkyl halides and undoubtedly the reaction occurred largely as follows :  $\text{C}_3\text{H}_6 + \text{HCl} \rightarrow \text{CHMe}_2\text{Cl}$  ;  $\text{CHMe}_2\text{Cl} + \text{CHMe}_3 \rightarrow \text{C}_3\text{H}_8 + \text{CMe}_3\text{Cl}$  ;  $\text{CMe}_3\text{Cl} \rightarrow \text{CMe}_2\cdot\text{CH}_2 + \text{HCl}$  ;  $\text{CMe}_3\text{Cl} + \text{CMe}_2\cdot\text{CH}_2 \rightarrow \text{C}_8\text{H}_{17}\text{Cl}$  ;  $\text{C}_8\text{H}_{17}\text{Cl} + \text{CHMe}_3 \rightarrow \text{C}_8\text{H}_{18} + \text{CMe}_3\text{Cl}$ . Other complications include (a) isomerisation of saturated hydrocarbon :  $\text{Alkyl}_1 - \text{H} + \text{R}^+ \rightarrow \text{Alkyl}_1^+ + \text{RH}$ ,  $\text{Alkyl}_1^+ \rightarrow \text{Alkyl}_2^+$ ,  $\text{Alkyl}_2^+ + \text{Alkyl}_1 - \text{H} \rightarrow \text{Alkyl}_2 - \text{H} + \text{Alkyl}_1^+$ , and (b) abstraction of hydride ion from the allylic position of olefin :  $\text{>C} \begin{array}{c} | \\ \text{C} \\ | \\ \text{CH} \end{array} + \text{Alkyl}^+ \rightarrow \text{>C} \begin{array}{c} | \\ \text{C} \\ | \\ \text{C} \end{array} + \text{Alkyl-H}$ .

The relative importance of the several types of reaction varies with change of experimental conditions ; for example, dissociation of alkyl cation into olefin is given added weight by the presence of a suitable proton acceptor. This effect is clearly illustrated by the influence of nitromethane on the catalysed interaction of *isobutane* and *isopropyl chloride*. This reaction may give as much as 90% of the propane available by reduction of the chloride, but when nitromethane is present heptanes are obtained as a consequence of dehydrochlorination of *isopropyl chloride* :





The reader will have noticed that the Friedel-Crafts reaction is concerned largely with interactions of two types: those in which a carbonium ion combines with an unsaturated carbon atom and those in which it abstracts a hydride ion from a saturated carbon atom. He will therefore recognise some of the limitations of the reaction; for example, it will be clear that whereas unsaturated acid chlorides may be cyclised (*e.g.*, citronellic acid chloride affords pulegone) and alkanes  $\text{RH}$  may afford ketones  $\text{R}\cdot\text{CO}\cdot\text{R}'$ , attempts to cyclise saturated acid halides must be fruitless. Much exploratory work remains to be done before the potentialities of the reaction in aliphatic and alicyclic chemistry can be fully appreciated.