AN OUTLINE OF ACYLATION

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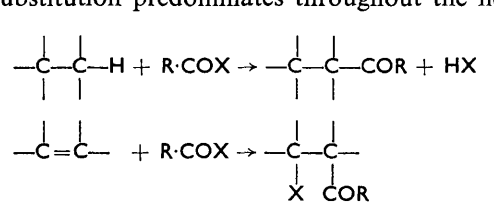
Introduction

We deal here with the most general features of acylation and both build round and illustrate these in subsequent sections.

1. The Nature of Acylation.—The essential feature of the process is the attachment to a substrate of a group R·C=O which is derived from an *acylating agent*. The latter usually has the form R·COX where X has a nature to be defined below. In this Review only those groups R which are joined to the carbonyl carbon atom directly through carbon are considered. This restriction eliminates acylating agents such as Cl·COX, NH_2·COX, Ph·NCO and others. However, no example embodying important principles is thereby lost.

The acylation of hydrocarbons being chosen as an illustration, two types of attachment process can be seen to be possible (*a*) substitution and (*b*) addition. Substitution predominates throughout the field.



The group R·CO may be derived from the acylating agent by either homolytic or heterolytic bond fission. We shall deal intentionally with heterolysis only, though the mechanisms of some types of acylation are still matters for conjecture. Attention will also largely be focussed on liquid systems. It is there that most acylations are carried out.

It appears that heterolysis of the C–X bond in R·COX, when it is at all easy, produces $R{\cdot}CO^+$ and X^- irrespective of the nature of X. That atom of the substrate which suffers acylation therefore always acts as a nucleophile. Structural features, and other circumstances, which in any way exaggerate the nucleophilicity of the substrate, or conversely the electrophilicity of the acylating agent, will usually favour reaction. These general considerations, when applied to particular cases, provide the basis for the understanding of both substituent effects and the roles played by catalysts. Catalysis of heterolytic reactions arises from the presence of additional electrophiles, or nucleophiles, which facilitate the overall process by modifying the reactants. In promoting acylation, catalysts function by

increasing either the electrophilicity of the acylating agent or the nucleophilic character of the substrate. These points are all illustrated in the text, where an attempt is made to outline the main types of acylation and the conditions which favour them. Acylation is a very widespread phenomenon, and there are a number of reactions (*e.g.* the preparation of acyl halides and the Haller–Bauer reaction) which, though not usually considered as such, may quite properly be so. Thus it has come about that while special aspects have been fully treated[1–6] no general survey of acylation processes exists. It is hoped that this Review will partly fill this gap, and in so doing, emphasise the features which unite the field as a whole. Thus, the Review is a constructive outline rather than a detailed critique. And the references, which are introductory rather than comprehensive, should be consulted for the finer structure of the subject. Discussion will be limited to acylation occurring at the following atoms:

F	O	N	C
Cl	S	P	Si
Br			
I			

2. Acylating Agents.—These may be divided into two classes. In the first, and larger, category are those compounds of the type R·COX in which X is an atom (*e.g.* Cl) or some quite familiar group (*e.g.* OH or $O{\cdot}SO_3H$). The other category contains "special" reagents, such as ketens and the esters of silicon. These reagents tend to be of limited application. They have been the subjects of little comparative work, and few generalisations about them are possible at present. Evidence has, however, accumulated about the relative reactivities of members of the first category.

(*a*) *The nature of the leaving group X.* The following rough order of reactivity obtains:

$$R{\cdot}COR' \sim R{\cdot}CHO < R{\cdot}CO{\cdot}NR'_2 < R{\cdot}CO_2R' < RCO{\cdot}O{\cdot}COR' < R{\cdot}COHal < RCO_2{\cdot}SO_3H < RCO_2{\cdot}ClO_3 \sim RCO^+\,BF_4^-.$$

Thus acylation by ketones is not often observed, whereas acyl tetrafluoroborates are very powerful reagents.[7] A reasonable generalisation is that the power of an acylating agent R·COX increases with the strength of the acid HX. The origin of the parallelism is clear: the separation of the anion X^- is involved in both phenomena. In R·COX the carbonyl group is always polarised, some net positive charge being located on the carbon atom.

[1] Baddeley, *Quart. Rev.*, 1954, **8**, 355; Gore, *Chem. Rev.*, 1955, **55**, 229.
[2] Thomas, "Anhydrous Aluminium Chloride in Organic Chemistry," Reinhold, 1942; Berliner, *Org. Reactions*, 1949, **5**, Ch. 5.
[3] Hauser and Hudson, *Org. Reactions*, 1942, **1**, Ch. 9; Hauser, Swamer, and Adams, *ibid.*, 1954, **8**, Ch. 3; Brandström, *Arkiv Kemi*, 1953, **6**, 155.
[4] Bender, *Chem. Rev.*, 1960, **60**, 53.
[5] Hamlin and Weston, *Org. Reactions*, 1957, **9**, Ch. 1.
[6] Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 686.
[7] Olah, Kuhn, Tolgyesi, and Baker, *J. Amer. Chem. Soc.*, 1962, **84**, 2733.

Groups X which attract electrons and possess some stability as X^- will exaggerate this positive charge, promote cleavage into $R{\cdot}CO^+$ and X^-, and thus aid reaction. Groups which repel electrons and provide anions of little stability will have the opposite effect. Examination of the rough reactivity series shows it to be consistent with the usual qualitative assignments of polar effects to groups.[8]

The same generalisation applies for subtler variation in the leaving group, achieved within a given type of reagent. Thus phenyl or cyanomethyl esters are more reactive than methyl derivatives,[9] and acyl bromides more reactive than the corresponding chlorides.[10]

(*b*) *The nature of R.* The effects on reactivity of changes in R are not as straightforward as for changes in X. Substituents which, by provision of electrons, favour the departure of X^- and stabilise the acylium ion* have the effect of reducing the charge on the carbonyl carbon atom in both the acylium ion and the polarised reagent. Electron-withdrawing substituents increase this charge but hinder ionisation. The effect of changes in R will depend, therefore, on whether the substrate reacts primarily with the ionised or with the un-ionised acylating agent, and, moreover, on which particular phase of the overall process is rate controlling. Similar effects are involved in other nucleophilic substitutions, and the factors concerned have often been more thoroughly discussed than is possible here.[4,8,10,11] Some of the points concerned are mentioned below. Steric effects of substituents will only be dealt with when they lead to changes in mechanism.

3. Mechanisms of Acylation.—As noted, with an acylating agent $R{\cdot}COX$, a substrate S may react with either the ionised or the polarised reagent.† On this basis, mechanisms of acylation, with the finer details of which this Review is not mainly concerned, may be divided into two types. These are represented below quite generally, without indication of the relative rates of the steps, which will depend on the system concerned.

$$\text{(I)} \quad R{\cdot}COX \underset{}{\overset{a}{\rightleftharpoons}} R{\cdot}CO^+ + X^- \text{ (or } R{\cdot}CO^+X^-) \xrightarrow[b]{S} \text{Products}$$

$$\text{(II)} \quad R{\cdot}COX + S \rightarrow \text{Products}$$

When step (*a*) alone is rate-determining in (I) and especially when other molecules of S apart from that which is actually acylated may assist

* Species $R{\cdot}CO^+$ may be called acylium ions. Other names are used less often.

† Supposing temporarily that one can always make a sharp distinction between these two species.

[8] Ingold, "Structure and Mechanism in Organic Chemistry," Bell and Sons, Ltd., London, 1953.

[9] *e.g.* Bodanszky, *Nature*, 1955, **175**, 685; Schwyzer, Feurer, and Iselin, *Helv. Chim. Acta*, 1955, **38**, 83.

[10] Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart, and Winston Inc., 1959; Streitweiser, *Chem. Rev.*, 1956, **56**, 571; Hine. "Physical Organic Chemistry," McGraw-Hill Book Co. Inc., 1962.

[11] Satchell, *J.*, 1961, 5404.

ionisation, then a rigid distinction between mechanisms (I) and (II) can only be made on the basis of particular definitions of molecularity and bonding change. "Borderline" controversies are really concerned only with definitions.[10,12] That mechanism (II) may sometimes show effects more or less characteristic of mechanism (I), depending on the relative importance of bond breaking or making in (II), has been a further fruitful source of confusion.

It is probable[4] that many examples of mechanism (II) occur *via* addition of the substrate to the carbonyl group, rather than *via* a direct synchronous displacement of X by S. For example, if the substrate is water we then have:

$$R{\cdot}COX + H_2O \rightleftharpoons R{\cdot}C(OH)_2X \rightarrow RCO_2H + HX$$

The individual steps of this scheme may be elaborated to suit a variety of contexts.[4] The postulation of such intermediates, which is largely based on the occurrence of oxygen exchange concurrent with acylation, has not, however, as yet proved essential in all cases—especially when acidic catalysis is involved.[13]

Reaction mechanisms for the " special " acylating agents have been little studied; and since the general reactions of ketens have been summarised only recently[14] a detailed consideration of these compounds will be excluded from this Review.

When dealing with acylation, it is important to remember that all processes may in principle be regarded as equilibria. An actual equilibrium position will depend on thermodynamic stabilities under the given experimental conditions. In preparative practice, as will be shown, equilibrium is often deliberately disturbed.

The following sections discuss systematically acylation, by a variety of appropriate reagents, at an halogen atom, at oxygen and sulphur, at nitrogen and phosphorus, and at carbon and silicon. Cross-links between the sections are noted and the emphasis within each is deliberately varied to display the several facets of the subject. Its important connections with biochemistry[4,15] have, however, been largely omitted.

Acylation at variously bound halogen atoms

Because of the relatively small number of mechanistic studies available which fall into this section, and because of the surprisingly patchy nature of the other work, we have given acylation at halogen a largely phenomenological approach. Moreover, organic chemists should note that we are

[12] Gold, *J.*, 1956, 4633; Bird, Hughes, and Ingold, *J.*, 1954, 634; Bateman, Church, Hughes, Ingold and Taher, *J.*, 1940, 979.

[13] Satchell, *J.*, 1963, 555.

[14] Quadbeck, *Angew. Chem.*, 1956, **68**, 361.

[15] (*a*) Albertson, *Org. Reactions*, 1962, **12**, Ch. 4; (*b*) Barnard, "General Cyto-Chemical Methods", Vol. 2, Academic Press, 1961; Davies and Green; *Adv. Enzymd.*, 1958, **20**, 283.

throughout more concerned with the possibility and ease of any particular acylation than with the extent to which it has actually been exploited.

1. Acylation of Hydrogen Halides.—The product, as in all examples of acylation at halogen, is an acyl halide.

(i) $$R{\cdot}COX + HHal \rightarrow R{\cdot}COHal + HX$$

(*a*) *Acylation of hydrogen halides with ketones, amides, and carboxylic acids.* Hydrogen halides are not normally acylated by such weak reagents. Little work concerning the pure, liquid halogen acids exists, except for hydrogen fluoride.[16] Carboxylic acids can be recovered in good yield after dissolution for long periods in this substance. This fact does not rule out the formation of small amounts of acyl fluoride, but the equilibrium position clearly lies well on the other side.

(ii) $$R{\cdot}CO_2H + HF \rightleftharpoons R{\cdot}COF + H_2O$$

Again, in common solvents, halogen acids protonate all three types of reagent (to some extent) primarily at the carbonylic oxygen atom, and in suitable solvents (*e.g.* water, ethanol) amides and carboxylic acids are thereafter solvolysed, but kinetic analysis does *not* require the presence of the acyl halide as an intermediate of low concentration.[17]

(*b*) *Acylation of hydrogen halides with anhydrides.*—While equilibrium (ii) lies far to the left, those like (iii) lie well to the right, at least for the

(iii) $$(R{\cdot}CO)_2O + H\,Hal \rightleftharpoons R{\cdot}CO_2H + R{\cdot}COHal$$

lower aliphatic anhydrides, even in the presence of excess of carboxylic acid. The reagents interact either alone or in solution in inert solvents.[18] For instance, with acetic anhydride and hydrogen bromide (or chloride) the equilibrium (iv) is rapidly set up. With hydrogen fluoride acetyl

(iv) $$(CH_3{\cdot}CO)_2O + HHal \rightleftharpoons CH_3{\cdot}COHal + CH_3{\cdot}CO_2H$$

fluoride is certainly formed, but the equilibrium appears to exhibit anomalies.[18,19] Further work is needed to verify that it is indeed as simple as for the chloride and bromide.

In *aqueous* solutions of hydrogen chloride on the other hand, acetic anhydride undergoes partial protonation and subsequent solvolysis, in which acetyl chloride is *not* an intermediate.[20a] The difference in behaviour shown by the aqueous and by the carboxylic acid solutions is probably due to the fact that in the latter the initial interaction between the, there undissociated,[21] halogen acid and the anhydride leads to an ion-pair;

[16] Simons, "Fluorine Chemistry," Academic Press, 1954.
[17] Long and Paul, *Chem. Rev.*, 1957, **57**, 935; Bunton, James, and Senior, *J.*, 1960, 3364.
[18] Satchell, *J.*, 1960, 1752.
[19] Olah and Kuhn, *J. Org. Chem.*, 1961, **26**, 237.
[20] (*a*) Gold and Hilton, *J.*, 1955, 838; (*b*) see, however, Koskikallio and Errasti, *Suomen Kemi*, 1962, **35***B*, 213.
[21] Kolthoff and Bruckenstein, *J. Amer. Chem. Soc.*, 1956, **78**, 1.

the halide ion thus remains easily available for attachment to the carbonyl carbon atom as in (v). However, the dissociation of ions in aqueous

(v) $$HCl + (R{\cdot}CO)_2O \rightleftharpoons [R{\cdot}CO(H^+){\cdot}O{\cdot}COR][Cl]^- \rightarrow R{\cdot}CO_2H + R{\cdot}COCl$$

solution permits the solvent to take the place of the halide ion [mechanism (vi)].

(vi) $$R{\cdot}CO(H^+){\cdot}O{\cdot}COR + H_2O \rightarrow R{\cdot}CO_2H + R{\cdot}CO_2H_2^+$$

Little is known in all these contexts of the behaviour of cyclic anhydrides.

(*c*) *Acylation of hydrogen halides with acyl halides.* The equilibrium

(vii) $$HHal^1 + R{\cdot}COHal^2 \rightleftharpoons HHal^2 + R{\cdot}COHal^1$$

(vii) involves halogen exchange. Two sorts are possible: isotopic or interhalogen (*e.g.* Cl for Br). The equilibrium constant for isotopic exchange will lie close to unity,[22] though this particular type of system does not seem to have been studied.

Most of the numerous existing experiments on halogen interchange unfortunately do not indicate which acyl halide is preferentially formed. This is because they have been of a preparative nature and have involved the use of excess of one reagent to ensure that equilibrium is forced to the desired side. Thus various acyl chlorides have been satisfactorily converted into fluorides, bromides, and iodides.[23] This is preparatively an important reaction. An inert solvent is sometimes used. A study[24] shows that in acetic acid the acyl fluoride is favoured thermodynamically over both the chloride and bromide, but that the bromide–chloride equilibrium lies on the acyl bromide side. However, because these equilibria involve also the hydrogen halides their positions are probably dependent on the solvent used.

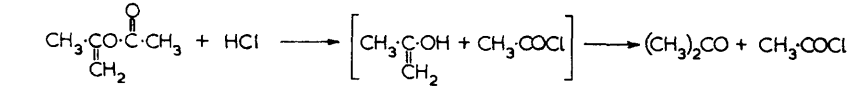
These reactions appear to be very fast.[24] Facts given below (p. 174) suggest that their mechanisms may often be of type (I).

(*d*) *Acylation of hydrogen halides with esters.* Esters in general should behave much as do the corresponding carboxylic acids. Usually little formation of acyl halide would be expected but there is scant evidence

(viii) $$R{\cdot}CO_2R' + HHal \rightleftharpoons R{\cdot}COHal + R'OH$$

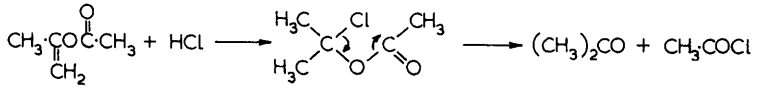
on this point.

In the special case when R′OH is an unstable enol which rapidly rearranges to a ketone, then, as would be expected, equilibrium (viii) is pulled well to the right. Thus, alone, or in inert solvents, isopropenyl acetate and hydrogen chloride give acetone and acetyl chloride.[25]



[22] Gold and Satchell, *Quart Rev.*, 1955, **9**, 51.
[23] Sonntag, *Chem. Rev.*, 1953, **52**, 237.
[24] Satchell, *J.*, 1963, 564.
[25] Hagermeyer and Hull, *Ind. Eng. Chem.*, 1949, **41**, 2920.

It is probable, however, that this acylation follows an unusual course, the hydrogen halide adding initially to the ethylenic (rather than to the carbonyl) group, this step being followed by halogen migration.[26]



In water-like solvents, in common with the behaviour of the structurally rather similar anhydrides, it is unlikely that the acyl halide is formed,[26] the solvent again taking the place of the halide ion (cf. p. 165).

Because of these reactions of anhydrides and enol esters, hydrogen halide catalysed acylation of other substrates with them, in solvents which permit acyl halide formation, commonly proceeds *via* these latter species as intermediates,[18,27] e.g.,

(ix) $CH_3{\cdot}C(:CH_2){\cdot}O{\cdot}CO{\cdot}CH_3 + HHal \rightarrow (CH_3)_2\,CO + CH_3{\cdot}COHal$

(x) $CH_3{\cdot}COHal + ROH \rightarrow CH_3{\cdot}CO_2R + HHal$

Similar schemes obtain with other Brønsted acid catalysts (see p. 181). Such catalysed acylation is, in fact, widespread and preparatively important.

(*e*) *Acylation of hydrogen halides with ketens.* Ketens enter rapidly into addition reactions. Addition of a hydrogen halide produces an acyl halide.[28]

(xi) $R{\cdot}CH{=}C{=}O + HHal \rightleftharpoons R{\cdot}CH_2{\cdot}COHal$

Equilibria such as (xi) lie to the right.

2. Acylation of Halogen in Alkyl Halides.—Processes similar to (xii) appear to be rare. Judging from the behaviour of hydrogen halides just

(xii) $R'Hal + R{\cdot}COX \rightarrow R{\cdot}COHal + R'X$

discussed, rather powerful acylating agents should be necessary. Thus, alkyl halides which ionise readily exchange an anion with carboxylic acids rather than suffering halogen acylation[29] [reaction (xiii)].

(xiii) $R'Hal + R{\cdot}CO_2H \rightarrow R{\cdot}CO_2R' + HHal$

[Hydrogen halides (R′ = H) of course behave similarly, the process then also constituting hydrogen exchange.] Reaction with anhydrides [mechanism (xiv)] will provide the desired product and halogen exchange with acyl halides [equilibrium (xv)] will doubtless occur readily in many cases, but these processes have surprisingly received little deliberate study. Reaction (xiv) at least appears to be potentially useful synthetically.

[26] Wasserman and Wharton, *J. Amer. Chem. Soc.*, 1960, **82**, 661, 1411; Euranto and Kujanpaa, *Acta. Chem. Scand.*, 1961, **15**, 1209.
[27] Jeffery and Satchell, *J.*, 1962, 1876.
[28] Hagermeyer, *Ind. Eng. Chem.*, 1949, **41**, 765.
[29] *e.g.* Fainberg and Winstein, *J. Amer. Chem. Soc.*, 1956, **78**, 2770.

(xiv) $$R'Hal + (R{\cdot}CO)_2O \rightarrow R'O{\cdot}COR + R{\cdot}COHal$$

(xv) $$R'Hal^1 + R{\cdot}COHal^2 \rightleftharpoons R'Hal^2 + R{\cdot}COHal^1$$

3. Acylation of Acyl Halides.—Here acylation of halogen involves acyl exchange. This is clearly not likely to be prominent when R·COX is a weaker reagent than is R·COHal itself, for then the former will be the species most easily acylated. The following paragraphs illustrate this point.

(xvi) $$R'{\cdot}COHal + R{\cdot}COX \rightleftharpoons R{\cdot}COHal + R'{\cdot}COX$$

(*a*) *Reaction of acyl halides with amides.*—This may lead to a variety of products, though the amide is usually the species acylated especially when pyridine is present (p. 189). A few cases of acyl exchange (xvii) have actually been reported but these have not been clean.[23] This process should, however, be susceptible to acidic catalysis operating *via*

(xvii) $$R'{\cdot}COHal + R{\cdot}CO{\cdot}NHR'' \rightleftharpoons R{\cdot}COHal + R'{\cdot}CO{\cdot}NHR''$$

protonation of the amide.

(*b*) *Reaction of acyl halides with carboxylic acids.* This is a fairly

(xviii) $$R{\cdot}COHal + R'{\cdot}CO_2H \rightleftharpoons R'{\cdot}COHal + R{\cdot}CO_2H$$

well-known reaction. The dissolution of a deficit of an aliphatic, or aromatic, acyl halide in a carboxylic acid eventually results, provided that no halide is lost from solution, in the exchange of the acyl groups.[18] The reaction is faster the more reactive the original acyl halide. However, except perhaps when R′ is powerfully electron withdrawing the direct acylation (xviii) is obviously unlikely. The preferred path should involve the nucleophilic attack of carboxylic oxygen, a process which leads most easily to the anhydride [scheme (xix)]. In keeping with this, it is known that the reaction may be used to prepare anhydrides if the hydrogen halide

(xix) $$R{\cdot}COHal + R'{\cdot}CO_2H \rightarrow R{\cdot}C(Hal)(OH){\cdot}O{\cdot}COR' \rightarrow R{\cdot}CO{\cdot}O{\cdot}COR' + HHal$$

is efficiently removed.[30] If it is not, since the equilibrium positions for reactions like (xix) lies on the acyl halide side (p. 164) the following reactions will occur:

(xx) $$R{\cdot}CO{\cdot}O{\cdot}COR' + HHal \rightarrow R{\cdot}COHal + R'{\cdot}CO_2H$$

(xxi) $$R{\cdot}CO{\cdot}O{\cdot}COR' + HHal \rightarrow R'{\cdot}COHal + R{\cdot}CO_2H$$

The relative rates of schemes (xx) and (xxi) will depend on the natures of R and R′ (see p. 178) but with the acid $R'CO_2H$ in excess any R′·COHal formed will be effectively trapped, because subsequent reaction of R′·COHal with the medium will lead predominantly to $(R'{\cdot}CO)_2O$ and thus back again to R′·COHal. In this way R·COHal will eventually be converted into R′·COHal. When R′·COHal is low boiling compared with the other components the same effect may be produced by distilling

[30] *e.g.* Allen, Kibler, McLachlin and Wilson, *Org. Synth.*, 1946, **26**, 1.

it out of the mixture as it forms. Little hydrogen halide will be lost in this process during short periods because of its low equilibrium concentration. The high-boiling benzoyl chloride has been used in this way for the convenient preparation of other acyl chlorides directly from their parent acids.[31] It is emphasised, however, that these reactions in fact probably involve scheme (xix) followed by schemes (xx) and (xxi), rather than acylation of acyl halide by acid.

(*c*) *Reaction of acyl halides with esters.* Acyl exchange between esters and acyl halides may be written as in (xxii). The alternative interaction, not

(xxii) $$R{\cdot}COHal + R'{\cdot}CO_2R'' \rightleftharpoons R'{\cdot}COHal + R{\cdot}CO_2R''$$

involving acyl exchange, is (xxiii) [compare (xix)]. These processes have

(xxiii) $$R{\cdot}COHal + R'{\cdot}CO_2R'' \rightarrow R{\cdot}CO{\cdot}O{\cdot}COR' + R''Hal$$

been little studied. Benzoyl chloride and phenyl acetate, with catalysis by zinc chloride, do in fact yield phenyl benzoate and acetyl chloride[32] [reaction (xxiv)]. However, in view of the nature of the catalysis, and because acylation by R·COHal will also follow pathway (xxii), rather than (xxiii), when it is difficult for R″ to depart as a positive ion, it seems clear that the primary process here again is an attack on oxygen rather than on halogen.

(xxiv) $$Ph{\cdot}COCl + CH_3{\cdot}CO_2Ph \rightarrow CH_3{\cdot}COCl + Ph{\cdot}CO_2Ph$$

(*d*) *Reaction of acyl halides with anhydrides.* Benzoic anhydride has

(xxv) $$R{\cdot}COHal + (R'{\cdot}CO)_2O \rightleftharpoons R{\cdot}CO{\cdot}O{\cdot}COR' + R'{\cdot}COHal$$

been prepared from acetic anhydride *via* route (xxv),[33] but such processes have again been otherwise little studied; certainly not under rigorously controlled conditions. If the reagents were completely freed from moisture and other sources of free acid, the direct reaction might be possible, but HHal will obviously facilitate acyl exchange [(xxvi) and (xxvii)], and if a trace of free $R'CO_2H$ is initially present this alternative,

(xxvi) $$(R'{\cdot}CO)_2O + HHal \rightarrow R'{\cdot}CO_2H + R'{\cdot}COHal$$

(xxvii) $$R'{\cdot}CO_2H + R{\cdot}COHal \rightarrow R'{\cdot}CO{\cdot}O{\cdot}COR + HHal$$

and probably easier, route is again open. The details of these reactions will surely prove difficult to establish.

(*e*) *Reaction with other acyl halides.* Processes like (xxviii) are likely

(xxviii) $$R{\cdot}COHal^1 + R'{\cdot}COHal^2 \rightleftharpoons R'{\cdot}COHal^1 + R{\cdot}COHal^2$$

to be rapid but do not appear to have been deliberately studied.

(*f*) *Acylation of acyl halides with more powerful acylating agents.* As noted, the substances R·COX which are more powerful reagents than

[31] Brown, *J. Amer. Chem. Soc.*, 1938, **60**, 1325.
[32] Döbner, *Annalen*, 1881, **210**, 246.
[33] Zetzsche, Enderlin, Flütsch, and Menzi, *Helv. Chim. Acta*, 1926, **9**, 177.

acyl halides are those in which X^- is the anion of an inorganic acid stronger than the hydrogen halides (*e.g.* $X^- = HSO_4^-$, ClO_4^-, or BF_4^-). While acyl hydrogen sulphates, perchlorates, and tetrafluoroborates can be prepared, their great reactivity makes them difficult to isolate. These substances are therefore more often encountered as reaction intermediates in acid-catalysed acylation, than as reactants. In general in the text acylation by these substances will not be dealt with separately, but only when relevant to a discussion of acidic catalysis. Even with acyl halides as substrates it is clear that acylation of halogen [equilibrium (xxix)]

(xxix) $$R{\cdot}COHal + R'{\cdot}COX \rightleftharpoons R'{\cdot}COHal + R{\cdot}COX$$

will be rapid in the presence of such active species.

4. Acylation of Molecular Halogen.—Free halogen, especially in the presence of acidic or basic catalysts, tends to halogenate carbonyl compounds, rather than suffer acylation itself.[34] Thus, in the reaction between molecular halogen and an acylating agent R·COX it is very often a hydrogen atom in the group X, or R, which is replaced by a halogen atom, rather than the group X itself.[23,34]

Under suitable conditions acylation of the halogen may, however, be achieved with certain reagents. Thus the anhydrides (which, in fact, probably give some acyl halide under most conditions, especially with bromine and iodine) at low temperatures, in carbon tetrachloride solution and in the absence of light, react with chlorine at the carbonyl centre to give mainly acyl chlorides and hypochlorites.[35]

(xxx) $$(R{\cdot}CO)_2O + Cl_2 \xrightarrow{-15^\circ} R{\cdot}COCl + R{\cdot}CO_2Cl$$

Similar reactions, (xxxi) and (xxxii), occur with diacyl sulphides and disulphides.[35]

(xxxi) $$(R{\cdot}CO)_2S + Cl_2 \rightarrow R{\cdot}CO{\cdot}SCl + R{\cdot}COCl$$

(xxxii) $$(R{\cdot}CO)_2S_2 + Cl_2 \rightarrow R{\cdot}CO{\cdot}S_2Cl + R{\cdot}COCl$$

Since halogens are normally electro- rather than nucleo-philic reagents, primary attack on sulphur may be involved in these processes. A kinetic study of mechanism would be of value. This point is emphasised by the discussion which follows.

If anhydrides follow path (xxx) it is to be expected that acyl halides will interact with molecular halogen also. And they do.[23,36]

(xxxiii) $$R{\cdot}COHal^1 + (Hal^2)_2 \rightarrow R{\cdot}COHal^2 + Hal^1Hal^2$$

A kinetic study of the halogen exchange between acyl bromides and bromine, and between acyl iodides and iodine, has been made by tracer

[34] Bell, Gelles, and Möller, *Proc. Roy. Soc.*, 1949, *A*, **198**, 308.
[35] Böhme and Schmitz, *Ber.*, 1955, **88**, 354; Böhme and Clement, *Annalen*, 1952, **576**, 61.
[36] Goldman and Noyes, *J. Amer. Chem. Soc.*, 1957, **79**, 5370.

techniques.[36] Hexane and carbon tetrachloride were used as solvents. The iodide exchange is the faster. The reaction is definitely heterolytic. It appears that the transition state for the bimolecular reaction may approximate to the species $RCO^+ (Hal)_3^-$. A term involving two molecules of halogen also contributes—the second molecule perhaps acting as a specific solvating agent for the transition state in solvents of such low dielectric constant. The mechanism of this reaction may be viewed as an interesting example of an electrophilic substrate catalysing its own acylation. No doubt the reactions of hydrogen halides noted in paragraph 1 often involve such behaviour [*e.g.*, reaction (v)]. The phenomenon is quite general. For instance, the hydrogen-bonding properties of hydroxylic substrates provide similar effects (p. 174). The principles of catalysis are outlined on p. 173.

The function of iodine as a catalyst[37] in the reactions of acetyl chloride may be due to processes like (xxxiii), but the strong suspicion at present remains that much of any acyl iodide formation will result from adventitious traces of hydrogen iodide (see p. 165).

5. Acylation of Halogen Bonded to Miscellaneous Groups.—From the viewpoint of homogeneous acylation processes in general the most relevant examples of reaction at halogen atoms have been mentioned. However, for the experimental preparation of acyl halides rather different examples are of prime importance, at least for the chlorides. They all involve inorganic sources of halogen and some may be heterogeneous processes. Their mechanisms have been little studied.

(*a*) *Acylation of phosphorus halides.* Reaction (xxxiv) is conducted

(xxxiv) $$PCl_5 + R{\cdot}CO_2H \rightarrow POCl_3 + HCl + R{\cdot}COCl$$

(xxxv) $$PCl_3 + R{\cdot}CO_2H \rightarrow POCl + HCl + R{\cdot}COCl$$

with the free acid or its alkali-metal salt.[38] Choice between the tri- or penta-halide depends on the relative volatility of the products. It seems likely that the ester or the anhydride[39] will also react satisfactorily, though acetic anhydride is often used as a solvent for other transformations of phosphorus halides.[40]

Acyl fluorides, bromides, and iodides are usually prepared differently (see below).

(*b*) *Acylation of thionyl chloride.* Here again the free acid, or its

(xxxvi) $$SOCl_2 + R{\cdot}CO_2H \rightarrow R{\cdot}COCl + SO_2 + HCl$$

alkali-metal salt, acts as the usual source of acyl group.[38] Aspects of reac-

[37] Kosac and Hartough, U.S. Pat. 2,468,762/1949; *Idem*, *J. Amer. Chem. Soc.* 1946, **68**, 2639.
[38] Hickinbottom, " Reactions of Organic Compounds," Longmans, 1959.
[39] Schmidt, Blohm, and Jander, *Angew. Chem.*, 1947, *A*, **59**, 233.
[40] Kosolapoff, "Organophosphorus Compounds," Wiley and Sons, Inc., 1950.

tion mechanism with such sources of halogen have been discussed only in connection with syntheses of optically active *alkyl* halides.[41]

(*c*) *Acylation of saline halides.* Methods (*a*) and (*b*) above are the most important for acyl chlorides, though procedures based on acyl exchange (xvi) or reaction of hydrogen chloride with the anhydride (iii) are sometimes used.[31,42]

Acyl fluorides, bromides, and iodides are most often made by halogen exchange between the readily available acyl chlorides and either the hydrogen[43] (see p. 165) or a saline halide. Thus acyl chlorides heated with among other fluorides, those of sodium, potassium, ammonium, silver and zinc, yield corresponding acyl fluorides.[44] Iodides have been made from calcium and magnesium iodide.[45] Acyl fluorides and bromides are made less often from the anhydride and hydrogen halide.[19,46] Metallic halides may also replace the hydrogen halide in this reaction, though with less effect.[47]

(xxxvii) $CaF_2 + 2(CH_3{\cdot}CO)_2O \rightarrow Ca(O{\cdot}CO{\cdot}CH_3)_2 + 2CH_3{\cdot}COF$

Powerful Lewis acids also react,[39] but may retain the product (xxxviii).

(xxxviii) $AlCl_3 + (CH_3{\cdot}CO)_2O \rightarrow AlCl_2{\cdot}O{\cdot}CO{\cdot}CH_3 + CH_3{\cdot}CO{\cdot}Cl$

(xxxix) $AlCl_3 + CH_3{\cdot}COCl \rightarrow$ ionic complex.

(*d*) *Acylation of halogen bonded to sulphur.* A final example of halogen acylation concerns reaction of fluorosulphonic acid with carboxylic acids or their salts.[48]

(xl) $FHSO_3 + R{\cdot}CO_2H \rightarrow R{\cdot}COF + H_2SO_4$

Acylation of variously bound oxygen and sulphur atoms

Mechanistic studies of acylation at oxygen are plentiful, and in this section some emphasis is placed on the relationship between mechanism and catalysis. It is stressed that the principles illustrated here apply throughout the field.

1. Acylation of Water.—Acylation of the oxygen atom of water produces a carboxylic acid (xli); this process is commonly called hydrolysis.

(xli) $R{\cdot}COX + H_2O \rightleftharpoons R{\cdot}CO_2H + HX$

[41] *e.g.* Bartlett and Herbrandson, *J. Amer. Chem. Soc.*, 1952, **74**, 5971; Lewis and Boozer, *ibid.*, 1953, **75**, 3182.
[42] Adams and Ulrich, *J. Amer. Chem. Soc.*, 1920, **42**, 599.
[43] Gustus and Stevens, *J. Amer. Chem. Soc.*, 1933, **55**, 374.
[44] Meslans and Girardet, *Compt. rend.*, 1896, **122**, 239; Mashentsev, *J. Appl. Chem., U.S.S.R.*, 1947, **20**, 854.
[45] Spindler, *Annalen*, 1855, **231**, 272.
[46] Colson, *Bull. Soc. chim. France*, 1897, **17**, 55.
[47] Mashentsev, *J. Gen. Chem. U.S.S.R.*, 1941, **11**, 1135.
[48] Traube and Krahmer, *Ber.*, 1919, **52**, 1293.

When X = OH it is called oxygen exchange. The hydrolyses of carboxylic amides, esters, anhydrides, and halides and their susceptibilities to acidic and basic catalysis, have been intensively studied (because of past concentration of interest on water as a solvent). Some aspects of the work have received specialised reviewing,[4,6,17] and quantitative treatments of substituent effects have also been based on it.[10,49] Here limitations of space will restrict our attention to its general and to its unique features.

For the most powerful acylating agents the equilibrium position of (xli) always lies well to the right, but for amides and esters it depends significantly on R and on the relative concentrations of the reactants. However, most kinetic studies of hydrolysis are made with a large excess of water, though this limits information obtainable about its molecularity in the reaction. Because of this limitation studies have sometimes been made with small concentrations of water in inert solvents.[50] It has been the accumulated work in this field (and in the related one of solvolysis by alcohols) which has been largely responsible, together with analogies drawn from solvolyses of *alkyl* halides,[10] for the description of the two general mechanisms for acylation already given (p. 162). Studies with hydroxylic compounds therefore in many ways constitute the kernel of mechanistic aspects of acylation.

In water ions are dissociated and step (I) (*b*) will usually be fast so that hydrolysis either involves a slow ionisation (I) (*a*) or a rate-influencing attack by the substrate oxygen atom (II). These possibilities exist for both spontaneous and catalysed hydrolyses. The ionisation route is favoured[8,10] by substituents R which either help to stabilise the acylium ion (*e.g.* *p*-methoxyphenyl) or hinder route (II) by blocking access to the unionised carbonyl carbon atom[51] (*e.g.* 2,6-xylyl). Mechanism (II) is usually favoured by substituents which withdraw electrons from the carbonyl carbon atom (see p. 162).

So far as the leaving group is concerned, in spontaneous hydrolysis most amides,[17] esters,[6,17] acids,[17,51] and anhydrides[52] will follow mechanism (II) while with acyl halides[53] mechanism (I) is often also found. As noted earlier this is comprehensible structurally.* Anhydrides and other less active reagents usually only exhibit mechanism (I) in the presence of catalysts, and then not often.[17,51,54] Brønsted-acid catalysts aid formation

* Esters may also, of course, be hydrolysed *via* alkyl–oxygen fission (xlii) but this process does not involve acylation.[6]

$$R{\cdot}CO_2{\vdots}R' + H_2{}^{18}O \rightarrow R{\cdot}CO_2H + R'{\cdot}{}^{18}OH$$

[49] Taft, "Steric Effects in Organic Chemistry," Wiley & Sons, Inc., 1956.

[50] *e.g.* Friedman and Elmore, *J. Amer. Chem. Soc.*, 1941, **63**, 864; Beretta and Jannelli, *Gazzetta*, 1953, **83**, 1009; Hudson and Stelzer, *Trans. Faraday Soc.*, 1958, **54**, 213.

[51] (*a*) Treffers and Hammett, *J. Amer. Chem. Soc.*, 1937, **59**, 1708; (*b*) Newman, *ibid.*, 1941, **63**, 2431; Jacobsen, *Ber.*, 1889, **22**, 1220.

[52] Gold, *Trans. Faraday Soc.*, 1948, **44**, 506.

[53] Archer, Hudson, and Wardill, *J.*, 1953, 888; Gold, Hilton, and Jefferson, *J.*, 1954, 2756; Crunden and Hudson, *J.*, 1956, 501; Ugi and Beck, *Ber*, 1961, **94**, 1839.

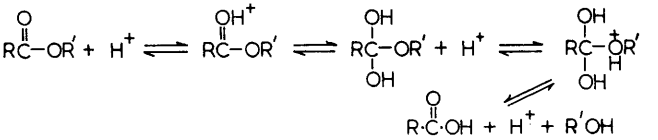
[54] Kuhn and Corwin, *J. Amer. Chem. Soc.*, 1948, **70**, 3370; Gillespie and Leisten, *Quart. Rev.*, 1954, **8**, 40; Leisten, *J.*, 1955, 298; Bunton and Perry, *J.*, 1960, 3070.

of acylium ions by protonating the reagent. The effective site (though not necessarily the most basic) must be the leaving group.[51,55a] There appears no escape from this conclusion even for those who might wish to escape it.[55b]

(xliii) $$R{\cdot}CO_2H + H^+ \rightarrow R{\cdot}CO_2H_2^+ \rightarrow R{\cdot}CO^+ + H_2O$$

(xliv) $$R{\cdot}CO{\cdot}NH_2 + H^+ \rightarrow R{\cdot}CO{\cdot}NH_3^+ \rightarrow R{\cdot}CO^+ + NH_3$$

In many acid-catalysed examples of mechanism(II)—though not necessarily in all[13]—two separate protonation steps may be involved (xlv), the more basic carbonyl site being also used.[56] Electrophilic catalysis

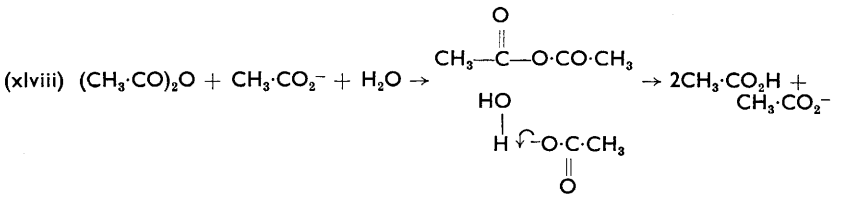
(xlv) 

by metal ions and by enzymes (topics with which we shall not deal) is also frequently considered to provide its crucial assistance at the leaving group.[57] It is interesting that acyl chlorides, bromides, and iodides do not exhibit acidic catalysis,[4,58a] presumably because in aqueous solution the leaving groups do not form a sufficiently stable unit with a proton.[13]

Basic catalysts either (*a*) temporarily take the place of the substrate (xlvi) or (*b*) increase its nucleophilicity [*e.g* (xlviii)].

(xlvi) $$(CH_3{\cdot}CO)_2O + H{\cdot}CO_2^- \rightleftharpoons CH_3{\cdot}CO{\cdot}O{\cdot}COH + CH_3{\cdot}CO_2^-$$

(xlvii) $$CH_3{\cdot}CO{\cdot}O{\cdot}COH + H_2O \rightarrow CH_3{\cdot}CO{\cdot}OH + H{\cdot}CO_2^-$$

(xlviii) 

These examples[4] are, of course, variations of mechanism (II). Pyridine catalysis [scheme (xlix)],[59] and that of other tertiary bases, operates by method (*a*). Base-catalysed examples of hydrolysis *via* mechanism (I) seem rare. This is because the base will need to be very weak (*e.g.* Cl^-) if

(xlix) $$(CH_3{\cdot}CO)_2O + NC_5H_5 \rightleftharpoons CH_3{\cdot}CO{\cdot}{}^+NC_5H_5 + CH_3{\cdot}CO_2^- \xrightarrow{H_2O} 2CH_3{\cdot}CO_2H + NC_5H_5$$

[55] (*a*) Duffy and Leisten, *J.*, 1960, 853; (*b*) Palmer, *Chem. and Ind.*, 1963, 589.
[56] Bunnett, *J. Amer. Chem. Soc.*, 1961, **83**, 4978; Hansen and Ney, *J. Org. Chem.*, 1962, **27**, 2059; Aksnes and Prue, *J.*, 1959, 103; Osborn and Whalley, *Trans. Faraday Soc.*, 1962, **58**, 2144; Martin, *J. Amer. Chem. Soc.*, 1962, **84**, 4130.
[57] *e.g.* Schwyzer and Hurlimann, *Helv. Chim. Acta*, 1954, **37**, 155.
[58] Gold and Hilton, *J.*, 1955, 3303; see, however, Hudson and Moss, *J.*, 1962, 5157.
[59] Gold and Jefferson, *J.*, 1953, 1416, 1409; Gold and Butler, *J.*, 1961, 4362; 1962, 589.

the intermediate acylating agent it produces is to have a chance of ionising. This very weakness precludes the formation of the intermediate.

In appropriate cases both acidic and basic catalysis may occur together.[60] And in suitable reactants acidic or basic groups neighbouring on the reaction centre may provide intramolecular catalysis.[4]

Many, perhaps most, spontaneous (*i.e.*, not deliberately catalysed) hydrolyses proceeding by mechanisms (I) and (II) will involve self-catalysis by other molecules of water acting as acids or bases.[61] This is the probable reason for the greater reactivity of associated, compared with monomeric, alcohol species in aprotic solvents.[50]

Reagents more powerful than acyl halides—*e.g.* acyl perchlorates and tetrafluoroborates—react very vigorously with water. This is one reason for its exclusion in Friedel–Crafts acylations. Being ionic already,[7,62] these compounds clearly react by mechanism (I). Lewis-acid catalysts are not often usable with water or alcohols because hydroxylic substrates either decompose them or form complexes with them.[63] This same phenomenon often leads to the protection of the OH group by the catalyst in Friedel–Crafts *C*-acylation of phenols.[11]

2. Acylation of Alcohols and Phenols.—Except that the product is an ester, the considerations here are much the same as for water. However, acylation with the alcohol acting also as solvent—usually called alcoholysis—will be generally less likely to exhibit mechanism (I). This is because the lower dielectric constant of alcohols will inhibit ionisation. The same remark applies for reactions between small concentrations of acylating agents and their substrates in inert solvents, for the dielectric constants of these are commonly low.[64] However, it does not always apply, for new opportunities for catalysis may arise. Thus, as noted, in aqueous solution the reaction of acetyl chloride is not acid-catalysed and is probably predominantly of type (II).[58] Yet in nitromethane[65] its reaction with 2-

(I) $$CH_3{\cdot}COCl + H_2O \rightarrow CH_3{\cdot}COOH + HCl$$

naphthol has significant acid-catalysed ionic components (Ii). This example shows how a reduction in the hydrogen-bonding power or in the

(Ii)
$$\begin{array}{ccccc} CH_3{\cdot}COCl + HCl & \rightleftharpoons & CH_3{\cdot}CO^+\,HCl_2^- & \rightleftharpoons & CH_3{\cdot}CO^+ + HCl_2^- \\ \downarrow \text{naphthol} & & \downarrow \text{naphthol} & & \downarrow \text{naphthol} \\ \text{Products} & & \text{Products} & & \text{Products} \end{array}$$ Fast / Slow

[60] *e.g.* Wyness, *J.*, 1958, 2934.

[61] Jencks and Carriuolo, *J. Amer. Chem. Soc.*, 1961, **83**, 1743; *idem.*, *ibid.*, 1960, **82**, 675; Berliner and Altschul, *ibid.*, 1952, **74**, 4110; Moelwyn-Hughes, *J.*, 1962, 4301.

[62] Susz and Wuhrmann, *Helv. Chim. Acta*, 1957, **40**, 971.

[63] *e.g.* Bradley, Caldwell, and Wardlaw, *J.*, 1957, 3039; de Maine, and Walsh, *J. Inorg. Nuclear Chem.*, 1961, **19**, 156; see, however, Sowa and Nieuwland, *J. Amer. Chem. Soc.*, 1933, **55**, 5052.

[64] Brown and Hudson, *J.*, 1953, 883.

[65] Satchell, *J.*, 1963, 558; see also Bender and Chen, *J. Amer. Chem. Soc.*, 1963, **85**, 30.

dielectric constant of the solvent (or both) can lead to new, or modified, catalytic routes arising from ionic association.

From the viewpoint of preparative acylation of alcohols, although even amides will often react,[38] the acylating agents which are usually chosen are those which are both relatively powerful and readily available. Thus the acid chloride or bromide, the anhydride and sometimes the carboxylic acid are used, together with appropriate catalysts where necessary. Reaction is usually conducted in the absence of any extra solvent. Most of the spontaneous reactions will be examples of mechanism (II). The most common[38] catalyst–reagent combinations are the acyl halide with pyridine or aqueous alkali, the anhydride with these catalysts or sodium acetate, sulphuric acid, perchloric acid, or boron trifluoride, and the carboxylic acid with sulphuric acid or boron trifluoride. Facts noted above lead us to suspect that catalysis by pyridine operates *via* route (xlix), that by alkali *via* route (xlviii), and that by sodium acetate perhaps *via* both. These processes are all elaborations of mechanism (II). With anhydrides, sulphuric and perchloric acid will probably also promote mechanism (II) by protonation as in (xlv), though in some recipes their (ionic) acyl derivatives may be formed[18,66] (see pp. 166, 179).

It seems probable that in all *preparative* acylations with boron trifluoride–anhydride combinations, sufficient hydrogen fluoride or suitable hydroxylic material is available to provide a strong Brønsted dual-acid (*e.g.* $HBF_3{\cdot}OR'$) and thus lead to the intermediate formation of some $RCO^+BF_4^-$ or $RCO^+\ BF_3{\cdot}OR'^-$. Hence the powerful nature of such mixtures and their use with otherwise resistant sterols.[67] Boron trifluoride–carboxylic acid mixtures (liii) may also sometimes acylate *via* mechanism

(liii) $$CH_3{\cdot}CO_2H + BF_3 \rightleftharpoons CH_3{\cdot}CO^+\ BF_3{\cdot}OH^- \xrightarrow{ROH} \text{Products}$$

(I),[68] though catalysis by sulphuric acid is here most likely to be *via* route (II) unless mechanism (I) is sterically favoured.[51]

With carboxylic acids, and under acidic catalysis, phenols, owing to their low nucleophilicity, are often acylated with difficulty.[38] The acylation of tertiary alcohols is also complicated under these conditions by their tendency to alkyl–oxygen fission.[69]

Ketens add both alcohols and water spontaneously, but this reaction is not widely used preparatively. The less reactive diketens generally behave (liii) as β-lactones[70] (cyclic esters) and therefore will not receive separate treatment.

(liiii) $$CH_2{=}\underset{\underset{O-CO}{|}}{C}{-}CH_2 + H_2O \longrightarrow CH_2{=}\underset{\underset{OH}{|}}{C}{\cdot}CH_2{\cdot}CO_2H \longrightarrow CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO_2H$$

[66] Jeffery and Satchell, *J.*, 1962, 1887.
[67] Topchieff, Zavgorodnii, and Paushkin, "Boron Fluoride and its Compounds as Catalysts in Organic Chemistry," Pergamon, 1959.
[68] Gold and Riley, *J.*, 1961, 1676.
[69] *e.g.* Hughes, Ingold, and Masterman, *J.*, 1939, 840.
[70] *e.g.* Turner and Harris, "Organic Chemistry," Longmans, 1952.

3. Acylation of Special Alcohols.—(*a*) *Sugars.* In their alcoholic roles these behave normally and may be acylated by the standard recipes already noted.[38]

(*b*) *Ortho-forms of aldehydes.* In aqueous solution aldehydes are in equilibrium with their ortho-form (liv).[71] Diacyl derivatives corresponding to this form can be prepared from the neat aldehyde, the anhydride,

(liv) $$CH_3{\cdot}CHO + H_2O \rightleftharpoons CH_3{\cdot}CH(OH)_2$$

and a *trace* of concentrated aqueous sulphuric acid.[72] However, the conditions of the preparation, [which involves overall addition of the anhydride to the double bond (lv)] make the intermediacy of the ortho-form

(lv) $$CH_3{\cdot}CHO + (CH_3{\cdot}CO)_2O \rightarrow CH_3{\cdot}CH(O{\cdot}CO{\cdot}CH_3)_2$$

unlikely. The catalyst will exist largely as acyl hydrogen sulphate.[66] Lewis acid catalysts may also be used.[72] Acylation is presumably involved at one stage. A study of the mechanism of this reaction would be welcome.

(*c*) *Enols.* Effective methods for the *O*-acylation of keto–enol systems which exist largely in the keto-form are important preparatively. Such methods require (i) the presence of a proton-transfer agent to maintain the equilibrium and (ii) an efficient acylating agent which consumes the small enol (or enolate) concentration thus provided without attacking the double bond.

The sodium derivatives of potential enols often lead to *C*-acylation,[3] and the most usual base-catalysed reaction has involved the acyl halide with pyridine.[73] This method is satisfactory for β-diketones but can yield derivatives of the catalyst with simple ketones.[74] Recently acid-catalysed reactions with other enol-esters (*e.g.* isopropenyl acetate) or ketens as reagents, together with strong acid catalysts such as toluene-*p*-sulphonic have been used very successfully.[25,28] For enol-esters there is good evidence,[75] and for ketens it seems likely, that the acyl derivative of the catalyst is the active intermediate in these reactions. Mixtures of the same catalysts with the appropriate anhydrides would therefore also be predicted to be effective (see p. 166 and below). That they are[76] is gratifying. Brønsted-acid catalysed acylation by anhydrides and enol-esters in various contexts seems a fairly well-understood topic.

4. Acylation of Carboxylic Acids.—The product here is the anhydride, often an unsymmetrical anhydride.

(lvi) $$R'{\cdot}CO_2H + R{\cdot}COX \rightleftharpoons R'{\cdot}CO_2{\cdot}COR + HX$$

[71] Bell and McDougall, *Trans. Faraday Soc.*, 1960, **56**, 1281.
[72] *e.g.* Wegscheider and Späth, *Monatsh.*, 1909, **30**, 825; Ishikawa and Matsuo, *Repts. Sci. Res. Inst. Japan*, 1952, **28**, 307; Man, Sanderson, and Hauser, *J. Amer. Chem. Soc.*, 1950, **72**, 847.
[73] *e.g.* Claisen and Haase, *Ber.*, 1900, **33**, 3778.
[74] von Doering and McEwen, *J. Amer. Chem. Soc.*, 1951, **73**, 2104.
[75] Jeffery and Satchell, *J.*, 1962, 1906.
[76] Hartshorn and Wallis, *J.*, 1962, 3839.

(*a*) *Acylation of carboxylic acids with amides, esters, and other acids.*

(lvii) $$R{\cdot}CO_2H + R{\cdot}CO{\cdot}NH_2 \rightleftharpoons R{\cdot}CO{\cdot}O{\cdot}COR + NH_3$$

(lviii) $$R{\cdot}CO_2H + R{\cdot}CO_2R \rightleftharpoons R{\cdot}CO{\cdot}O{\cdot}COR + ROH$$

(lix) $$R{\cdot}CO_2H + R{\cdot}CO_2H \rightleftharpoons R{\cdot}CO{\cdot}O{\cdot}COR + H_2O$$

These equilibria normally lie well on the left; indeed (lvii) and (lviii) form the basis of preparations of esters and amides.[38] Nevertheless the existence of the equilibria permits acyl exchange between the reactants. If water is effectively removed scheme (lix) can be a feasible route to anhydrides.[77]

(*b*) *Reaction of carboxylic acids with anhydrides.* This is often used for the preparation of uncommon anhydrides from the free acid and the readily available acetic anhydride. The overall process observed, after distillation of the mixture, is (lx).[78] The equilibrium position depends on

(lx) $$2R{\cdot}CO_2H + (CH_3{\cdot}CO)_2O \rightleftharpoons (RCO)_2O + 2CH_3{\cdot}CO_2H$$

the reagents and their proportions, but is understandably more favourable to the new anhydride than are the positions of equilibria (lvii)–(lix). In preparative practice the relatively volatile acetic acid may often be distilled away as it forms. The probable mechanism is by stepwise exchange (lxi) of acyl groups. The intermediate, unsymmetrical anhydrides often

(lxi) $$R{\cdot}CO_2H + (CH_3{\cdot}CO)_2O \rightleftharpoons RCO_2{\cdot}CO{\cdot}CH_3 + CH_3{\cdot}CO_2H$$

(lxii) $$RCO_2H + RCO_2{\cdot}CO{\cdot}CH_3 \rightleftharpoons (RCO)_2O + CH_3{\cdot}CO_2H$$

disproportionate at usual distillation temperatures[79] (see below).

(*c*) *Acylation of carboxylic acids with acyl halides.* The equilibrium position will often be well to the left, but reaction (lxiii) may be used to

(lxiii) $$R{\cdot}CO_2H + R{\cdot}COHal \rightleftharpoons (R{\cdot}CO)_2O + HHal$$

prepare anhydrides if the hydrogen halide is efficiently removed (see p. 167). The reaction is therefore usually conducted in the presence of excess of pyridine or other tertiary base.[80] A common alternative procedure, which also combines the mechanistic device of basic catalysis with the preparative device of engagement of one of the products, is to start with the sodium, potassium, or silver salt of the acid. This has been perhaps the most used method for preparation of anhydrides.

Since such equilibria as (lxiii) are established much more rapidly than those like (lx), hydrogen halides will catalyse (lx), as, of course, will acids stronger than hydrogen halides.

(*d*) *Acylation of carboxylic acids with ketens.* This provides an im-

(lxiv) $$RCO_2H + CH_2{=}C{=}O \rightarrow RCO{\cdot}O{\cdot}CO{\cdot}CH_3$$

[77] Clark and Simons, *J. Amer. Chem. Soc.*, 1953, **75**, 6305.
[78] Clark and Rahrs, *Org. Syn. Coll. Vol.* 1, p. 91.
[79] Gold and Emery, *J.*, 1950, 1443.
[80] *e.g.* Kuhn and Löw, *Ber.*, 1944, **77**, 211.

portant commercial route to acetic anhydride and the best laboratory route to acetic carboxylic anhydrides.[79,81] No catalysis is necessary. Low-temperature purification is essential and some acyl exchange with unchanged acid is inevitable. Initial addition of a proton to the methylene group is the presumed mechanism.

5. Acylation of Carboxylic Anhydrides. Because of their symmetrical structure acylation of these substrates can only involve acyl exchange (lxv).

(lxv) $$(R\cdot CO)_2O + R'\cdot COX \rightleftharpoons R'\cdot CO\cdot O\cdot COR + R\cdot COX$$

Such reactions have been little studied. It is clear, however, that if X itself is not to be the substrate it will usually have to be either an anion of an inorganic acid or a group O·COR. We shall discuss only the latter case (lxvi).

(lxvi) $$(R\cdot CO)_2O + (R'\cdot CO)_2O \rightleftharpoons 2R'\cdot CO\cdot O\cdot COR$$

The equilibrium position depends markedly on the acyl groups involved. Thus the acetic–butyric system is more or less statistically controlled[82] whereas the acetic–trifluoroacetic system greatly favours the unsymmetrical anhydride.[83] High temperatures appear to favour the symmetrical anhydride. The direct bimolecular acylation of one anhydride by another may be involved in establishing these equilibria, but it seems more likely that routes involving traces of free carboxylic acid as impurity will be of prime importance.

Unsymmetrical carboxylic anhydrides, used under suitable conditions of temperature and solvent, are sometimes satisfactory as specific acylating agents.[84,15] More usually, however, both possible acyl derivatives are formed to significant extents. Their ratio appears to depend on both the nature of the solvent and the extent of catalysis, as well as on the relative polar and steric characteristics of the two halves of the anhydride molecule.[79,83] The nucleophilicity of the substrate is also a factor. A result of these circumstances is that halogenoacetic acetic anhydrides by no means always provide the halogenoacetyl derivative usually* expected on purely polar grounds, for reaction *via* mechanism (II), even though this mechanism usually operates. In the presence of strong acids and suitable solvents, anhydrides sometimes[54] react by mechanism (I) which, for an unsymmetrical anhydride, will preferentially provide the least active acylium ion. Many of the preparative products obtained with trifluoroacetic acetic anhydride may be rationalised[84] on this basis. However, the number of

* It is usually[79] considered that the main consideration is the relative polarities of the carbonyl carbon atoms. However, the nature of the leaving group is likely to be important also and this circumstance works in the opposite direction: the stronger acid component provides the more positive carbonyl carbon atom but also the more stable anion.

[81] Hurd and Dull, *J. Amer. Chem. Soc.*, 1932, **54**, 3427.

[82] Brown and Trotter, *J.*, 1951, 87.

[83] Bourne, Stacey, Tatlow, and Tedder, *J.*, 1949, 2976; 1951, 718; Bourne, Stacey, Tatlow, and Worrall, *J.*, 1958, 3268.

[84] Tedder, *Chem. Rev.*, 1955, 55, 787.

competing variables in all these systems makes it possible to explain many of the results in more than one way. Further work therefore appears necessary to realise anything approaching mechanistic certainty. Nevertheless, from the practical viewpoint it has proved very convenient that systems involving the trifluoroacetyl group usually yield mainly the other acyl derivative when the substrate is a carbon or an oxygen atom, and when free trifluoroacetic acid is present in the mixture. Thus esterification of alcohols by acids is simply effected by the addition of trifluoroacetic anhydride (lxvii). No solvent is used. This method appears especially useful for

(lxvii) $$R{\cdot}OH + R'{\cdot}CO_2H + (CF_3{\cdot}CO)_2O \rightarrow RO{\cdot}COR' + 2CF_3{\cdot}CO_2H$$

sugars. Examples of carbon acylation are given on p. 196.

Related structurally to unsymmetrical carboxylic anhydrides are the increasingly important[15,15a] acyl alkyl carbonates (R·CO·O·CO·OR'). These substances, which are readily made, usually cleave in the desired direction, though intramolecular acylation, *via* loss of carbon dioxide, can also occur. As expected they prove molder reagents than the acyl derivatives of most other common inorganic acids, whose description follows.

6. Acylation at Some OH Groups not attached to Carbon.—(*a*) *Anhydrous inorganic oxy-acids.* The best-studied are sulphuric, perchloric, phosphoric, and nitric acids.

Sulphuric acid. In the presence of this acid, such acylating agents as amides, carboxylic acids, and esters may react to some extent as follows:

(lxviii) $$2H_2SO_4 + R{\cdot}CO_2H \rightleftharpoons R{\cdot}CO_2{\cdot}SO_3H + H_3O^+HSO^-_4$$

(lxix) $$2H_2SO_4 + R{\cdot}CO_2R \rightleftharpoons RCO_2{\cdot}SO_3H + ROH_2^+\ HSO_4^-$$

(lxx) $$2H_2SO_4 + R{\cdot}CO{\cdot}NH_2 \rightleftharpoons RCO_2{\cdot}SO_3H + NH_4^+\ HSO_4^-$$

If the dielectric constant is high enough (*e.g.* if excess of sulphuric acid is used) all the species on the right hand side may be both ionised and dissociated.* The equilibrium position will, of course, also depend on R and in many systems reaction will not go appreciably beyond some protonation of the acylating agent.[55b]

With anhydrides the equilibrium will sometimes simplify to (lxxi) the known examples of which lie to the right.[54,66] There is some evidence that in

(lxxi) $$H_2SO_4 + (R{\cdot}CO)_2O \rightleftharpoons R{\cdot}CO_2{\cdot}SO_3H + R{\cdot}CO_2H$$

the presence of excess of anhydride, diacyl sulphates, formed in small concentration, can play a significant role as reaction intermediates in acylation of other substrates catalysed by sulphuric acid.[66]

There is little information about such equilibria as (lxxii). These would

(lxxii) $$H_2SO_4 + R{\cdot}COCl \rightleftharpoons R{\cdot}CO_2{\cdot}SO_3H + HCl$$

* The sulphuric acid anions then present may actually be more complex.[54]

be expected to be mobile. Many of these systems are unstable because of concurrent sulphonation in aromatic systems, or because aliphatic acyl sulphates can rearrange to sulpho-carboxylic acids,[85] perhaps *via* ketens (lxxiii) for ketens may add *anhydrous* sulphuric acid as HSO_3^+—OH^-.

(lxxiii) $$CH_3{\cdot}CO_2{\cdot}SO_3H \rightarrow CH_2{=}C{=}O + H_2SO_4 \rightarrow HSO_3{\cdot}CH_2{\cdot}CO_2H$$

Vinyl esters[27] are also sulphonated (compare p. 166). It is probable that a sample of free acyl sulphate has never been isolated, though the corresponding metal salts are known.[86] These too can act as acylating agents.

Perchloric, nitric, phosphoric, and nitrous acids. The reactions of these acids with acylating agents have been little studied. Acyl perchlorates, which are very reactive species, may be formed metathetically in a suitable solvent from acyl halides and silver perchlorate,[87] or in small concentration from perchloric acid and the carboxylic anhydride[18,88] or vinyl ester.[27] Perchloric is the best purely Brønsted acid catalyst for acylation by anhydrides or vinyl esters known.

Acyl nitrates are formed, among other species, from the anhydrides.[89] The equilibria (lxxiv) appear to lie to the right. However, it is interesting

(lxxiv) $$HNO_3 + (R{\cdot}CO)_2O \rightleftharpoons R{\cdot}CO_2{\cdot}NO_2 + R{\cdot}CO_2H$$

that while nitric acid–anhydride mixtures are often used for the nitration of substrates,[90] acylation by them has never been observed. Acyl nitrates must ionise preferentially to RCO_2^- and NO_2^+. In keeping with this acyloxylation by them has also been detected.[91]

Acyl phosphates are usually prepared from the sodium or silver salt and an acyl chloride. Both mono- (lxxv) and tri-acyl phosphates have been obtained in this way.[40] Mixtures of acyl derivatives are probably formed

(lxxv) $$AgO{\cdot}P(O)(OH)_2 + R{\cdot}COCl \rightarrow R{\cdot}CO_2{\cdot}P(O)(OH)_2 + AgCl$$

from anhydrides and phosphoric acid.[92] In contrast to the sulphuric acid system, monoacetyl phosphate is conveniently made from the strong aqueous acid and keten [reaction (lxxvi)].[81,93] As with all the other

(lxxvi) $$HO{\cdot}P(O)(OH)_2 + CH_2{=}C{=}O \rightarrow CH_3{\cdot}CO_2{\cdot}P(O)(OH)_2$$

oxy-acids dealt with here, isolation of the free acyl derivative is difficult and the corresponding sodium or barium salt is usually handled.

[85] Franchimont, *Rec. Trav. chim.*, 1888, **7**, 25; Jeffery and Satchell, *J.*, 1962, 1913.
[86] van Peski, *Rec. Trav. chim.*, 1921, **40**, 103; Kenner, *Chem. and Ind.*, 1951, 15.
[87] Burton and Praill, *J.*, 1950, 2034.
[88] Mackenzie and Winter, *Trans. Faraday Soc.*, 1948, **44**, 171, 243.
[89] Chédin and Fénéant, *Compt. rend.*, 1949, **229**, 115; Gold, Hughes, and Ingold, *J.*, 1950, 2467; Mal'kova, *J. Gen. Chem. U.S.S.R.*, 1954, **24**, 1151.
[90] *e.g.* Griffiths, Walkey, and Watson, *J.*, 1934, 631.
[91] Fischer, Packer, Vaughan, and Wright, *Proc. Chem. Soc.*, 1961, 369; Bordwell and Garbisch, *J. Amer. Chem. Soc.*, 1960, **82**, 3588.
[92] See, however, Bentley, *J. Amer. Chem. Soc.*, 1949, **71**, 2765.
[93] Bentley, *J. Amer. Chem. Soc.*, 1948, **70**, 2183.

Carboxylic anhydrides and nitrous acid probably form acyl nitrites.[94] Interestingly, the weak amide leads to free nitrogen[38] (lxxvii).

(lxxvii) $$HNO_2 + R{\cdot}CO{\cdot}NH_2 \rightarrow R{\cdot}CO_2H + N_2 + H_2O$$

The acyl derivates discussed above are, of course, often the reactive intermediates in acylation catalysed by the parent acids (see pp. 166, 199). Acyl phosphates are, in fact, rather inactive reagents[95] and catalysis by phosphoric acid is therefore comparatively seldom encountered. While phosphate systems are of great biological interest, their chemical complexity, together with the feebleness of acyl phosphates as acylating agents, has so far restricted their practical utility.[15,15a] Polyphosphoric acid, whose mode of action is not yet clear, has recently proved an effective catalyst in some contexts.[96]

(*b*) *Hydrogen peroxide and its derivatives.* Acylation of hydrogen peroxide provides either the peroxy-carboxylic acid or the diacyl peroxide (lxxviii). A stronger acid, a weaker base,[97] and therefore probably* a

(lxxviii) $$\underset{RCOX}{HO{\cdot}OH} \longrightarrow R{\cdot}CO{\cdot}O{\cdot}OH + HX \underset{R{\cdot}COX}{\longrightarrow} RCO{\cdot}O{\cdot}O{\cdot}COR + 2HX$$

weaker nucleophile than water, un-ionised hydrogen peroxide will be correspondingly more difficult to acylate. Reagents used commonly with phenols are usually applied, *i.e.* anhydride–sulphuric acid (lxxix) or acyl chloride–aqueous alkali (lxxx) mixtures. Less active reagents may, however,

(lxxix) $$HO{\cdot}OH + (CH_3{\cdot}CO)_2O \xrightarrow{H_2SO_4} CH_3{\cdot}CO{\cdot}O{\cdot}OH + CH_3{\cdot}CO_2H$$

(lxxx) $$HO{\cdot}OH + 2Ph{\cdot}COCl \xrightarrow{OH^-} Ph{\cdot}CO{\cdot}O{\cdot}O{\cdot}COPh + 2HCl$$

also be used.[38,98] (The comparison with water is actually complicated because the ion HOO^-—some of which will often be present—is a better nucleophile than is OH^-.[99])

Similar remarks apply to hydroperoxides $RR'R''C{\cdot}OOH$ which are more acidic than the corresponding alcohols. Catalytic acylation with acyl halides is successful and provides the peroxy-acid ester.[98]

(lxxxi) $$R_3C{\cdot}OOH + R'{\cdot}COHal \rightarrow R_3C{\cdot}O_2{\cdot}COR' + HHal$$

Diacyl peroxides—especially the aliphatic compounds and especially in the presence of bases—react with water or alcohols (lxxxii). An acylation

* Kinetic nucleophilicity and thermodynamic basicity do not invariably run parallel,[4] for polarisability is also a factor.

[94] Saville and Lees, *J.*, 1958, 2262.

[95] Koshland, *J. Amer. Chem. Soc.*, 1952, **74**, 2286; Di Sabato and Jencks, *J. Amer. Chem. Soc.*, 1961, **83**, 4393.

[96] Popp and McEwan, *Chem. Rev.*, 1958, **58**, 321.

[97] Sidgwick, "Chemical Elements and their Compounds," Vol. 11, Oxford, 1951; Mitchell and Wynne-Jones, *Trans. Faraday Soc.*, 1956, **52**, 824.

[98] Davies, "Organic Peroxides," Butterworth, 1961.

[99] Pearson and Edgington, *J. Amer. Chem. Soc.*, 1962, **84**, 4607.

is involved and the O–O bond remains intact.[100] Acylation by peracid esters occurs similarly. Solvolysis by water is faster than for the corresponding non-peroxy-compounds[98]—a result in keeping with the greater acidic strength of hydroperoxides compared with alcohols (compare p. 161). There is every reason to suppose the mechanisms of the reactions described here to be heterolytic.[98] Peroxide homolysis occurs in other contexts.

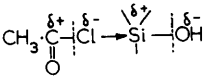
(lxxxii) $$(R{\cdot}CO)_2O_2 + R'{\cdot}OH \rightarrow R{\cdot}CO_2R' + R{\cdot}CO{\cdot}O{\cdot}OH$$

(*c*) *Organosilanols.* These compounds have been treated with acid chlorides and anhydrides. With the chlorides, trialkylsilanols yield the corresponding trialkylsilyl halide[101] (lxxxiii). Thus the oxygen atom is

(lxxxiii) $$R_3Si{\cdot}OH + R{\cdot}COCl \rightarrow R_3Si{\cdot}Cl + R{\cdot}CO_2H$$

acylated, but it is not certain that an Si–O–C bond is involved at any stage. The reaction could be a straightforward anionic replacement followed by acylation of the freed hydroxyl ion. The same type of process may obtain in the reaction (lxxxv) with anhydrides[102] but seems unlikely. However,

(lxxxiv)



(lxxxv) $$R_3Si{\cdot}OH + (CH_3{\cdot}CO)_2O \rightarrow R_3Si{\cdot}O{\cdot}CO{\cdot}CH_3 + CH_3{\cdot}CO_2H$$

acylation of oxygen attached to silicon must be involved in reaction (lxxxvi).[103]

(lxxxvi) $$R_3Si{\cdot}ONa + CH_3{\cdot}COCl \rightarrow R_3Si{\cdot}O{\cdot}CO{\cdot}CH_3 + NaCl$$

Silanediols are dehydrated by acyl halides by unknown routes.[104]

7. Acylation at Sulphur.—Data concerning sulphur compounds are still relatively sparse.[105] Nevertheless the facts which are known, when compared with those established for oxygen compounds, provide further examples of the principles governing acylation outlined in the Introduction. Thus, because sulphur is more electropositive than oxygen, the sulphur atoms in hydrogen sulphide, thiols (R·SH) and thio-acids (R·CO·SH) carry relatively more positive charge and are therefore less nucleophilic than are the corresponding oxygen atoms in the oxygen analogues. Furthermore, thio-acids and thiols are usually more acidic than the corresponding oxygen compounds. It is to be expected therefore that the thiols will undergo acylation less readily than alcohols and that thio-acids will be more

[100] Baeyer and Villiger, *Ber.*, 1900, **33**, 1569; Bunton, Lewis, and Llewellyn, *J.*, 1956, 1226.
[101] Martin and Kipping, *J.* 1909, **95**, 302.
[102] Nebergall and Johnson, *J. Amer. Chem. Soc.*, 1949, **71**, 4022.
[103] Nametkin, Topchiev, and Machus, *Doklady Akad. Nauk. S.S.S.R.*, 1952, **87**, 233.
[104] Kipping, *J.*, 1912, **101**, 2125.
[105] Reid, "Organic Chemistry of Bivalent Sulphur," Vol. IV, Chemical Publishing Co., 1962.

powerful acylating agents than are carboxylic acids. The following sections show that these expectations may be generally realised. However, an unambiguous comparison between thiols and alcohols is not always easy to achieve because RS^- will always be more likely to be present than RO^-, and such ions are very powerful nucleophiles compared with the un-ionised substrates. The same difficulty arises in comparisons of the acylatabilities of hydroperoxides and alcohols (see p. 181).

(*a*) *Acylation of hydrogen sulphide.* Acylation produces a thiocarboxylic acid (lxxxvii). Even such powerful reagents as acyl halides provide better

(lxxxvii) $$H_2S + R{\cdot}COX \rightleftharpoons R{\cdot}CO{\cdot}SH + HX$$

yields in the presence of catalysts,[106,107] especially bases which remove free hydrogen halide. It is probable that equilibria like (lxxxviii) do not lie so

(lxxxviii) $$H_2S + R{\cdot}COCl \rightleftharpoons R{\cdot}CO{\cdot}SH + HCl$$

far to the right as do the corresponding oxygen systems[108] (p. 172). Fairly drastic basic catalysis appears usual with less-powerful reagents. Thus esters are generally used with the metal salt[109] (lxxxix) and anhydrides

(lxxxix) $$NaSH + CH_3{\cdot}CO_2Ph \rightarrow CH_3{\cdot}CO{\cdot}SNa + PhOH$$

either with the salt or with pyridine catalysis.[110] Keten adds hydrogen sulphide in characteristic fashion[111] (xc).

(xc) $$H_2S + CH_2{=}C{=}O \rightarrow CH_3{\cdot}CO{\cdot}SH$$

(*b*) *Acylation of thiols.*—The product is a thiol ester [scheme (xci)].

(xci) $$RSH + R'{\cdot}COX \rightleftharpoons R'{\cdot}CO{\cdot}SR + HX$$

A study[112] of such equilibria as (xcii) shows that they lie notably further

(xcii) $$C_2H_5{\cdot}SH + R{\cdot}CO_2H \rightleftharpoons RCO{\cdot}S{\cdot}C_2H_5 + H_2O$$

towards the free-acid side than do the corresponding systems not involving sulphur. For preparative purposes therefore the carboxylic acids are little used.

As with hydrogen sulphide, phenyl esters are satisfactory when added to the sodium salt (xciii). Carboxylic anhydrides and acid chlorides are also

(xciii) $$NaSR + CH_3{\cdot}CO_2Ph \rightarrow CH_3{\cdot}CO{\cdot}SR + PhONa$$

often used with basic catalysts[110,113] though it is probable that these are not always necessary.[106,114] However, it seems clear that somewhat

[106] Arndt and Bekir, *Ber.*, 1930, **63**, 2390.
[107] Sunner and Nilson, *Svensk Kem. Tidskr.*, 1942, **54**, 163.
[108] Klatt, *Z. anorg. Chem.*, 1937, **232**, 404.
[109] Auger and Billy, *Compt. rend.*, 1901, **136**, 555.
[110] Houben-Weyl, "Methoden der Organischen Chemie," Verlag, 1955, Vol. 9.
[111] Holmberg and Schjanberg, *Arkiv Kemi, Min., Geol.*, 1940, **14**, *A*, 22.
[112] Faber and Reid, *J. Amer. Chem. Soc.*, 1917, **39**, 1930.
[113] Hepworth and Clapham, *J.*, 1921, **119**, 1188; Wenzel and Reid, *J. Amer. Chem. Soc.*, 1937, **59**, 1089.
[114] Whitaker, *J. Amer. Chem. Soc.*, 1962, **84**, 1900.

more drastic conditions are required to acylate thiols than those which suffice for alcohols and phenols. Keten acylates mercaptans in good yield.[115]

(*c*) *Acylation of thio-acids.* The product is a diacyl sulphide (xciv). As with the oxygen analogues only the symmetrical compounds are stable.

(xciv) $$R{\cdot}CO{\cdot}SH + R'{\cdot}COX \rightleftharpoons R'{\cdot}CO{\cdot}S{\cdot}COR + HX$$

Good yields of sulphides are obtainable from the low-pressure distillation of the thio-acid with the corresponding acyl chloride (xcv).[116]

(xcv) $$CH_3{\cdot}CO{\cdot}SH + CH_3{\cdot}COCl \rightleftharpoons (CH_3{\cdot}CO)_2S + HCl$$

The use of other acylating agents has been little studied.

(*d*) *Thio-derivatives as acylating agents.* Thiol esters, thio-acids, and thio-anhydrides (diacyl sulphides) are not considered as acylating agents throughout the text generally, because they have not been much used as such. It seems, however, that sulphur derivatives can, in the main, display as wide a range of behaviour as their oxygen analogues.[105] Thus thio-acids acylate isothiocyanates[117] (compare p. 188) and thiol esters exhibit self-condensation[105] (compare p. 194). Phenyl thiol-esters do not, however, undergo the Fries rearrangement[118] (compare p. 200).

As noted above, thio-acids might theoretically be expected to be more powerful reagents than their oxygen analogues, and the same considerations should apply to thiol-esters and thio-anhydrides. There is little unambiguous information on this point, except perhaps for thio-acids.* These compounds are indeed reported to acylate anilines more rapidly than do the corresponding carboxylic acids.[105] Thiol-esters are useful for the acylation of amines.[15a,119] However, their catalysed reactions with water appear sometimes faster, but at others slower, than those of the oxygen analogues.[120] The reactivity of diacyl monosulphides has not received much attention. Thus the expected general superiority of the sulphur over the corresponding oxygen compounds remains unestablished. Further work in this field will be welcome.

Acetyl-co-enzyme A—a biological source of active acyl groups—contains[121] the unit $CH_3{\cdot}CO{\cdot}S$.

8. Acylation at Oxygen and Sulphur not Bound to Hydrogen.—In the presence of Lewis acids, ethers, particularly aliphatic ethers, react with acyl halides, anhydrides, and sometimes even with carboxylic acids.[122]

* See, however, p. 164.

[115] Hurd and Williams, *J. Amer. Chem. Soc.*, 1936, **58**, 962.
[116] Bonner, *J. Amer. Chem. Soc.*, 1950, **72**, 4270.
[117] Johnson, *J. Amer. Chem. Soc.*, 1906, **28**, 1454.
[118] Tarbell and Herz, *J. Amer. Chem. Soc.*, 1953, **75**, 1668.
[119] King, Stewart, and Cheldelin, *Science*, 1953, **117**, 439.
[120] Rylander and Tarbell, *J. Amer. Chem. Soc.*, 1950, **72**, 3021.
[121] Lynen and Reichert, *Angew. Chem.*, 1951, **63**, 47.
[122] Burwell, *Chem. Rev.*, 1954, **54**, 615.

The product is an ester. Since the alkoxyl group is a very poor leaving group, although Lewis acids provide very active acylating agents from the carbonyl component (xcvi), the fact that they also form complexes with ethers, occasionally cleaving them (xcvii), makes the course of the overall process (xcviii) uncertain.

(xcvi) $$R{\cdot}COCl + FeCl_3 \rightleftharpoons R{\cdot}CO^+FeCl_4^-$$

(xcvii) $$ROR' + FeCl_3 \rightleftharpoons R'_2O{\rightarrow}FeCl_3 \rightarrow R'Cl + R'OFeCl_2$$

(xcviii) $$R'OR' + R{\cdot}COCl \rightarrow RCO_2R' + R'Cl$$

Boron trifluoride is a particularly good catalyst in this reaction,[123] which is of preparative importance.

Acyl bromides and iodides are reported[122] to cleave ethers in the absence of catalysts, but some free hydrogen bromide and iodide will doubtless be present in such systems, and will provide the following route:

(xcix) $$ROR + HBr \rightarrow ROH + RBr$$

(c) $$ROH + CH_3{\cdot}COBr \rightarrow RO{\cdot}CO{\cdot}CH_3 + HBr$$

Sulphides are also cleaved in similar circumstances.

Aryl ethers will usually undergo preferential ring acylation.[2]

Acylation at variously bound nitrogen and phosphorus atoms

Amines are more basic than alcohols and their nitrogen atoms tend to attack carbonyl carbon atoms, and so become acylated, correspondingly more readily. Indeed many acylations at nitrogen, even by esters, proceed satisfactorily without catalysts and, except in circumstances which greatly favour ionisation of the acylating agent, they would all seem likely to follow mechanism (II). Available evidence, which is scanty, supports this view.[10,15,124] Basic catalysis will perhaps operate mainly *via* route (xlviii). Acid catalysis is not common because any free acid catalyst is inactivated by (and also inactivates) some of the amine to be acylated. Thus anhydrous phosphoric acid, which is sometimes used as a catalyst for the direct acylation of weakly basic amines by carboxylic acids, is much less effective with more basic amines.[125] Acid catalysts (*e.g.* sulphuric acid) are often effective in combination with anhydrides because then the catalyst itself is largely acylated.

It follows from the ease with which some esters react that, were it not for salt formation, carboxylic acids would probably spontaneously acylate amines more readily, with the removal of the water formed being of less importance (see below).

The generally facile nature of acylation at nitrogen has been responsible for the use of a number of unusual acylating agents with such systems. Some of these are mentioned.

[123] Smorgonskii, *Zhur. obshchei Khim.*, 1947, **17**, 416.
[124] Williams and Hinshelwood, *J.*, 1934, 1079; Bender and Jones, *J. Org. Chem.*, 1962, **27**, 3771.
[125] Snyder and Elston, *J. Amer. Chem. Soc.*, 1954, **76**, 3039.

1. Acylation of Ammonia.—This provides the simple amide [route (ci)]. Ammonia probably reacts spontaneously with all reagents of type

(ci) $$NH_3 + R{\cdot}COX \rightleftharpoons R{\cdot}CO{\cdot}NH_2 + HX$$

RCOX except ketones (even amides probably give some nitrogen exchange[126]). It can be used either as the liquid, dissolved in an inert solvent, or often simply as its concentrated aqueous solution.[38] In the last case some accompanying base-catalysed hydrolysis of the acylating agent is inevitable. That the method is feasible demonstrates the powerful nucleophilic character of ammonia.

(*a*) *Acylation of ammonia with esters.* Aqueous ammonia is often

(cii) $$NH_3 + R{\cdot}CO_2R' \rightleftharpoons R{\cdot}CO{\cdot}NH_2 + R'OH$$

used at room temperature.[38] For weakly electrophilic or sterically hindered esters, basic catalysis in alcohol solution is used. The active nucleophile is then probably NH_2^-. Equilibria such as (cii) generally lie to the right.

(*b*) *Acylation of ammonia with carboxylic acids.* Here the observed sequence is as in[38] (ciii). The mechanism of the overall reaction is not clear.

(ciii) $$NH_3 + R{\cdot}CO_2H \rightleftharpoons RCO_2^-\ NH_4^+ \xrightarrow[\text{heat}]{} R{\cdot}CO{\cdot}NH_2 + H_2O$$

The reactants may be ammonia and the free acid present in small equilibrium amounts. The system is complicated by its often heterogeneous nature and by the hydration of the salt. Excess of acid and removal of the water are usually necessary for preparative purposes. The method is nevertheless frequently used.[127]

(*c*) *Acylation of ammonia with anhydrides and acyl halides.* These

(civ) $$2NH_3 + R{\cdot}COHal \rightarrow R{\cdot}CO{\cdot}NH_2 + NH_4^+\ Hal^-$$

(cv) $$NH_3 + (R{\cdot}CO)_2O \rightleftharpoons R{\cdot}CO{\cdot}NH_2 + R{\cdot}CO_2H$$

reactions proceed readily in aqueous, alcoholic, or aprotic solvents.[128] The equilibria lie well to the right (see p. 177).

(*d*) *Acylation of ammonia with ketones.* Non-enolisable,* but otherwise normal, simple ketones such as benzophenone or di-t-butyl ketone are cleaved by sodamide at high temperature giving acylation at nitrogen (Haller–Bauer reaction[5]). This reaction (cvi) is interesting theoretically

(cvi) $$NaNH_2 + (Me_3C)_2CO \rightarrow Me_3C{\cdot}CO{\cdot}NH_2 + Me_3CNa$$
$$\rightarrow Me_3C{\cdot}CO{\cdot}NHNa + Me_3CH$$

because it can be viewed as the powerful basic catalysis of the acylation of ammonia by a ketone, and so shows that only very forcing conditions are effective with so feeble an acylating agent even for reaction at nitrogen.

* Enolisable ketones suffer self-condensation in the presence of bases.

[126] *e.g.* Hurd, Dull, and Martin, *J. Amer. Chem. Soc.*, 1932, **54**, 1974.

[127] *e.g.* Coleman and Alvarado, *Org. Syn. Coll. Vol.* 1, p. 3.

[128] *e.g.* Aschan, *Ber.*, 1898, **31**, 2344; Philbrook, *J. Org. Chem.*, 1954, **19**, 623.

2. Acylation of Primary and Secondary Alkyl and Arylamines. (*a*) *General.* These reactions are very similar to those outlined for ammonia and the same comments apply. Acylation can be represented generally as (cvii) where R′ and R″ = alkyl, aryl, or H. Some amines, particularly

(cvii) $$R'R''NH + R{\cdot}COX \rightleftharpoons R{\cdot}CO{\cdot}NR'R'' + HX$$

negatively substituted arylamines, are so much less nucleophilic than ammonia that catalysis is needed. This is especially so, of course, with the less-active acylating agents. Common catalytic procedures involve alkoxide with esters,[129] sulphuric or phosphoric acid with anhydrides[130] and carboxylic acids,[125] and aqueous alkali with aroyl halides (the well-known Schotten–Baumann reaction[131]). Some of these systems are usually heterogeneous. The reaction, nevertheless, probably takes place in solution.

(*b*) *Acylation with ketens.* Combination as in scheme (cviii) is rapid

(cviii) $$R'NH_2 + R{\cdot}CH{=}C{=}O \rightarrow R{\cdot}CH_2{\cdot}CO{\cdot}NHR'$$

and usually conducted in an inert medium.

(*c*) *Acylation with other special reagents.* The paragraphs which follow deal with reagents which have so far been used mainly for acylation of amines.

Thio-acids and thiol esters. Thioacetic acid reacts more readily than does acetic acid itself.[105,132] This is reasonable (p. 182) though in view of the complexity of the reaction with amines [see route (ciii)] it is not necessarily a clear pointer to the mechanism. Thus, formation of the volatile hydrogen sulphide (rather than of water) may be significant.

(cix) $$RNH_2 + R'{\cdot}CO{\cdot}SH \rightleftharpoons R'{\cdot}CO{\cdot}NHR + H_2S$$

Thiol esters actually appear generally more useful than the free acids for acylating amines.[15] As noted, they sometimes have advantages over their oxygen analogues.

Silicon tetraesters. Arylamines heated in benzene with compounds like silicon tetra-acetate [scheme (cx)] yield acyl derivatives.[133] The reaction mechanism is not known.

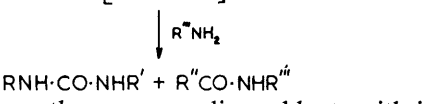
(cx) $$PhNH_2 + Si(O{\cdot}CO{\cdot}CH_3)_4 \rightarrow PhNH{\cdot}CO{\cdot}CH_3 + Si(O{\cdot}CO{\cdot}CH_3)_3{\cdot}OH$$

1:1 *Adducts of carboxylic acids with carbodi-imides and keten imines.* These adducts[134,135] are structurally similar to enol-esters (p. 165) and even

[129] Russell, *J. Amer. Chem. Soc.*, 1950, **72**, 1853.
[130] Smith and Orton, *J.*, 1908, **93**, 1242.
[131] Schotten, *Ber.*, 1888, **21**, 2235; Baumann, *Ber.*, 1886, **19**, 3218.
[132] Pawlewski, *Ber.*, 1902, **35**, 110.
[133] Malatesta, *Gazzetta*, 1948, **78**, 753; Yur'ev, Belyakavo, Kostetskii, and Prokof'ev, *Zhur. obshchei Khim.*, 1959, **29**, 2594.
[134] Khorana, *Chem. Rev.*, 1953, **53**, 145.
[135] *e.g.* Stevens, and Munk, *J. Amer. Chem. Soc.*, 1958, **80**, 4065.

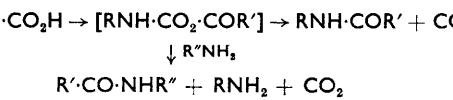
more reactive. They are usually unstable except at low temperatures and provide both inter- and intra-molecular acylation (cxi).

(cxi)



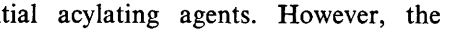
Acyl carbamates. These are the corresponding adducts with isocyanic esters. They also provide both inter- and intra-molecular acylation.[136,137]

(cxii)

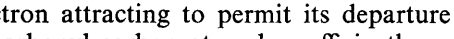


Trihalogeno-ketones and -aldehydes. Aldehydes and ketones are not usually considered potential acylating agents. However, the group $C(Hal)_3$ is sufficiently electron attracting to permit its departure as an anion after attack at the carbonyl carbon atom by sufficiently powerful nucleophiles.[138]

(cxiii)

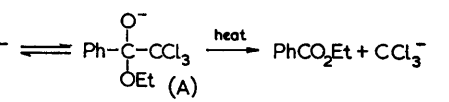


(cxiv)

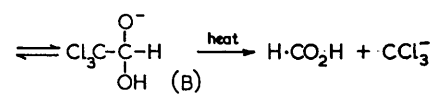


It is clear that OH^- or $OAlk^-$ could also act as the nucleophile; processes (cxiii) and (cxiv) are then seen to be extensions of the final stage of the haloform reaction.[70]

(cxv)



(cxvi)



Both reactions (cxv) and (cxvi) constitute acylation. From the viewpoint of preparative *O*-acylation this aspect of the reaction is rather unimportant and was consequently not mentioned in that context. However, the addition intermediates (A) and (B) that would normally be postulated for such cases of mechanism (II) are seen to be the anions of the familiar

* The behaviour of chloral hydrate is of particular significance for two further points of mechanistic detail. Its failure to yield chloroform in acidic media (it undergoes dehydration if anything) demonstrates both the necessity of a leaving group capable of accepting a proton for the operation of acid-catalysed solvolysis, and the importance of $HO{\cdot}CRX{\cdot}O^-$ and even of $CRX(O^-)_2$ [compared with $(HO)_2CRX$] as the reactive intermediate in basic catalysis.]

[136] Naegeli and Tyabji, *Helv. Chim. Acta*, 1935, **18**, 142; Kopple and Thursack, *J.*, 1962, 2065.

[137] Sidgwick, "Organic Chemistry of Nitrogen," Oxford, 1945.

[138] Atherton, Openshaw, and Todd, *J.*, 1945, 660; Blicke and Lu, *J. Amer. Chem. Soc.*, 1952, **74**, 3933.

(and stable) chloral hydrate and of a hemiacetal. This direct, logical connection with the acetals is good support for the ubiquity of carbonyl addition in base-catalysed acylation generally.* Most hemiacetals (and therefore the corresponding ketones) do not provide acylation because neither alkyl group can easily depart as an anion. However, β-diketones acylate in a reaction (cxvii) which is the reverse of the Claisen condensation[139] (see p. 194). Here the departing group $R{\cdot}CO{\cdot}CH^-_2$ is stabilised by

$$H_2O + RCO{\cdot}CH_2{\cdot}COR' \overset{OH^-}{\rightleftharpoons} R'{\cdot}CO_2H + R{\cdot}CO{\cdot}CH_3 \quad \text{(cxvii)}$$

its potentially enolic character. Some other ketones with powerful electron-withdrawing substitutes can also be solvolysed.[139] Amines could also be used as substrates.

3. Acylation of Primary and Secondary Amides. In these compounds NH adjacent to a carbonyl group undergoes acylation (cxviii). Such reactions have been comparatively little studied as have the positions of the

$$R{\cdot}CO{\cdot}NHR' + R''{\cdot}COX \rightleftharpoons R{\cdot}CO{\cdot}NR'{\cdot}COR'' + HX \quad \text{(cxviii)}$$

equilibria involved. *ortho*-Substituents appear to affect the stability of diacyl anilides.[140] The ability of the diacylamine products to acylate other compounds has also received little attention.[141] Just as diacylamines are more difficult to prepare than the corresponding acylamines, because of the extra electron drain on the attacking nitrogen atom, so for the same reason they might be expected to be more powerful acylating agents.

(*a*) *Acylation with other amides.* Acylation by such weak reagents is unusual. Powerful basic catalysis, provided by sodium, is used in condensing acetamide (cxix)[142]

$$CH_3{\cdot}CO{\cdot}NHNa + CH_3{\cdot}CO{\cdot}NH_2 \rightarrow CH_3CO{\cdot}N(Na){\cdot}CO{\cdot}CH_3 + NH_3 \quad \text{(cxix)}$$

(*b*) *Acylation of amides with anhydrides.* Reaction (cxx) is general

$$R{\cdot}CO{\cdot}NH_2 + (R'{\cdot}CO)_2O \rightleftharpoons R{\cdot}CO{\cdot}NH{\cdot}COR' + R'{\cdot}CO_2H \quad \text{(cxx)}$$

and occurs more readily on heating or in the presence of suitable basic catalysts[137,140] (*e.g.* pyridine).

(*c*) *Acylation of amides with acyl halides.* As expected acylation appears most ready in these cases, often occurring on mixing the reagents in an inert solvent.[137]

$$R{\cdot}CO{\cdot}NH_2 + R'{\cdot}COCl \rightleftharpoons R{\cdot}CO{\cdot}NH{\cdot}COR' + HCl \quad \text{(cxxi)}$$

All these processes are probably (though there is little definite evidence) examples of mechanism (II): bimolecular reactions between acylating

[139] Pearson and Mayerle, *J. Amer. Chem. Soc.*, 1951, **73**, 926; Gustafsson and Johanson, *Acta. Chem. Scand.*, 1948, **2**, 42.
[140] *e.g.* Wilkinson and Finar, *J.*, 1946, 115; Sudborough, *J.*, 1901, **79**, 533.
[141] Dippy and Moss, *J.*, 1952, 2205.
[142] Rakshit, *J.*, 1913, **103**, 1559.

agent and substrate or the modified forms of these species produced by the catalyst.

4. Acylation of Isocyanic Esters.—These compounds contain the reactive grouping NCO, and can themselves act as acylating agents, introducing the group RNH·CO. Indeed, the course of their reactions with alcohols and with amines[38] is consistent with the fact that carboxylic acids first suffer acylation at oxygen [see scheme (cxii))]. The acyl carbamate subsequently rearranges to produce a final acylation at nitrogen. With anhydrides[137] diacylation at nitrogen occurs [scheme (cxxii)]. Carbodiimides and keten imines are acylated by routes involving similar rearrangements (p. 187). The mechanisms of these reactions need further investigation.

(cxxii) $$RNCO + (R'CO)_2O \rightarrow RN(COR')_2 + CO_2$$

5. Acylation of Tertiary Amines and Amides.—In these compounds there is no replaceable hydrogen on the nitrogen atom. Any acylation at nitrogen therefore involves its quadrivalent state. Sufficiently basic tertiary amines and amides combine with the more reactive acylating agents to produce ionic compounds very susceptible to further reaction.[143] Such compounds doubtless occur as intermediates in many acylations catalysed by tertiary amines.[59,143] Examples have already been given. Compound

(cxxiii) $$R_3N + (R'\cdot CO)_2O \rightleftharpoons [R_3N\cdot COR']^+[R'\cdot CO_2]^-$$

(cxxiv) $$C_5H_5N + R\cdot COCl \rightleftharpoons [C_5H_5N\cdot COR]^+[Cl]^-$$

formation is sometimes prevented by steric hindrance.[59]

Pyridines, like deactivated aromatic compounds, are resistant to *C*-acylation. Hence their great utility as catalysts. However, their use is not always trouble-free[74] (p. 176).

6. Acylation at Nitrogen attached to Atoms other than Carbon.—(*a*) *Acylation of hydrazines and hydroxylamines.* The reactions of these compounds are similar to those of ammonia: the products, hydrazides [reaction (cxxv)] and hydroxamic acids [reaction (cxxvi)], correspond to amides. Reaction occurs readily with esters and even with amides[38] [reaction (cxxvii)], if the evolved ammonia is removed.

(cxxv) $$NH_2\cdot NH_2 + R\cdot COX \rightleftharpoons R\cdot CO\cdot NH\cdot NH_2 + HX$$

(cxxvi) $$NH_2\cdot OH + R\cdot COX \rightleftharpoons R\cdot CO\cdot NH\cdot OH + HX$$

(cxxvii) $$NH_2\cdot NH_2 + Ph\cdot CO\cdot {}^{15}NH_2 \rightleftharpoons Ph\cdot CO\cdot NH\cdot NH_2 + {}^{15}NH_3$$

The further acylation of the products in these reactions will not be dealt with. It appears to contain no special interest from the present viewpoint.

[143] *e.g.* Freudenberg and Peters, *Ber.*, 1919, **52**, 1463; Adkins and Thompson, *J. Amer. Chem. Soc.*, 1949, **71**, 2242; Hall, *ibid.*, 1956, **78**, 2717.

(*b*) *Acylation of azide salts.* The thermal instability of azides usually precludes their distillation. In preparing acyl azides use is made of their insolubility in water. Addition of an aroyl chloride to a solution of sodium azide in aqueous acetone leads to the azide.[38] The reaction is effectively a

(cxxviii) $$NaN_3 + Ph{\cdot}COCl \rightarrow Ph{\cdot}CON_3 + NaCl$$

base-catalysed acylation of hydrazoic acid. Anhydrides, which are less-readily hydrolysed than acyl halides, might sometimes replace the latter in this reaction.

Acyl azides themselves acylate water slowly and amines reasonably rapidly.[144] Their mildness as reagents has been extensively utilised for the synthesis of peptides and polypeptides from amino-acids,[145] though the use of other acylating agents for this purpose is now becoming more common.[15,15a]

(*c*) *Acylation at* N–P *and* N–Si *bonds.* The mechanism and scope of reaction (cxxix) is not known but it can prove more successful than

(cxxix) $$RN{=}P{\cdot}NHR + 2R'{\cdot}CO_2H \rightarrow 2R'{\cdot}CO{\cdot}NHR + HPO_2$$

conventional acylations.[146] The process illustrates the potentialities of compounds outside the carbon field. The substance $P(NMePh)_3$ has also been used in a similar context,[147] and compounds with N–P linkages seem generally useful for the production of amides directly from the carboxylic acid.[15a]

It appears usual also for N–Si bonds in amino-organosilanes to cleave in the presence of acylating agents[148] [reaction (cxxx)]. It is conceivable

(cxxx) $$(C_2H_5)_3Si{\cdot}NH_2 + (CH_3{\cdot}CO)_2O \rightarrow CH_3{\cdot}CO{\cdot}NH_2 + (C_2H_5)_3Si{\cdot}O{\cdot}CO{\cdot}CH_3$$

that eventually some such reaction may prove a useful general method of acylation at nitrogen.

7. Acylation at Phosphorus.—The organic chemistry of phosphorus differs more from that of nitrogen than does that of sulphur from that of oxygen. This generalisation is certainly reflected in acylation. Nitrogen is the most-easily acylated element in the First Period but very few acyl derivatives of phosphorus have been reported and some of these are unstable.[40] The low electronegativity of phosphorus means that a particularly polar carbonyl carbon atom is required to give a stable acyl derivative. Thus phosphine reacts with trichloroacetyl chloride [reaction (cxxxi)] and chloroacetyl chloride to give a stable and an unstable solid respectively.[149,40]

[144] Curtius, *J. prakt. Chem.*, 1917, **95**, 327.
[145] Fruton, *Advances in Protein Chem.*, 1954, **5**, 1.
[146] Grimmel, Guenther, and Morgan, *J. Amer. Chem. Soc.*, 1946, **68**, 539.
[147] Abramovitch, Hey, and Long, *J.*, 1957, 1781.
[148] Eaborn, "Organosilicon Compounds," Butterworths, 1960.
[149] Steiner, *Ber.*, 1875, **8**, 1177.

(cxxxi) $$CCl_3{\cdot}COCl + PH_3 \rightarrow CCl_3{\cdot}CO{\cdot}PH_2 + HCl$$

Hydroxyderivatives of primary (RPH_2) and secondary (R_2PH) phosphines tend to undergo-*O*- rather than *P*-acylation.[40] Few, if any, *P*-acyl derivatives of primary and secondary phosphines have been reported. Tertiary phosphines generally form quaternary complexes somewhat in the manner of tertiary amines, but with reagents like anhydrides or acyl chlorides this does not usually appear to lead to quaternary acyl complexes.[40] However, with acetic anhydride, trialkyl phosphites[150] provide a pentavalent acylated phosphorus atom, perhaps *via* a phosphonium intermediate (cxxxii). A similar reaction occurs with acyl halides.[151]

(cxxxii) $$(RO)_3P + (CH_3{\cdot}CO)_2O \rightarrow [(RO)_3P{\cdot}CO{\cdot}CH_3]^+[O{\cdot}CO{\cdot}CH_3]^- \rightarrow RO{\cdot}CO{\cdot}CH_3 + (RO)_2P(O){\cdot}CO{\cdot}CH_3$$

As noted on p. 170, phosphorus halides are frequently heated with potential acylating agents (*e.g.* carboxylic acids and anhydrides) in order to prepare acyl halides. Some of these processes are complex, but no concurrent acylation of phosphorus seems to occur.[40]

Acylation at variously bound carbon and silicon atoms

The saturated, and even the unsaturated, carbon atom is a much less nucleophilic entity than are the corresponding nitrogen or oxygen atoms. Powerful catalysis is usually necessary to achieve acylation at carbon even with such reagents as acyl halides. Thus, acidic catalysts more powerful than the hydrogen halides are often required. The stronger Lewis acids, and perchloric or sulphuric acid are therefore the most useful. The use of sulphuric acid is restricted to systems it does not attack in other ways. Anhydrous hydrogen fluoride is sometimes employed owing to its ability to form polymeric anions of great stability and consequent low basicity.[152] The use of alkoxides or the formation of metal derivatives are the forms most often taken by basic catalysis.

Because of the great disparity between the reactivities of water and hydrocarbons towards acylating agents, good yields in *C*-acylation are often only obtainable under anhydrous conditions. Moreover, the presence of water must reduce any Brønsted acidity and, as mentioned on p. 174, is liable to lead to decomposition of Lewis acids. Friedel–Crafts acylation, a reaction which falls mainly within the present section, is well known to require anhydrous conditions for greatest success.

Work on most aspects of *C*-acylation, although very voluminous because of preparative activity, has yet to rise above a very qualitative level. Here the main emphasis is therefore placed simply on the *nature* of the necessary catalysis.

[150] Cadogan, *Quart. Rev.*, 1962, **16**, 208.
[151] Kabachnik and Rossiyskaya, *Izvest. Akad. Nauk S.S.S.R.*, 1945, 364.
[152] Bell and McCoubrey, *Proc. Roy. Soc.*, 1956, *A*, **234**, 192.

1. Acylation at C–H Bonds in Aliphatic Hydrocarbons.—These com-

(cxxxiii) $$RH + R'\cdot COX \rightarrow R'\cdot COR + HX$$

pounds are particularly resistant to acylation. Some reaction results with acyl chlorides in the presence of aluminium chloride, but it is accompanied by isomerisation and dehydrogenation.[153] The latter processes are common for saturated hydrocarbons in the presence of aluminium chloride[154] and while the mechanism of acylation is mysterious, it seems more likely to involve the addition of R'·COCl to an olefin intermediate, followed by reduction, than a nucleophilic attack of RH on R'·COCl. These reactions comprise one of the least understood aspects of heterolytic acylation.

2. Acylation at C–Metal Bonds in Derivatives of Aliphatic Hydrocarbons.—Typical reactions, which are usually conducted in inert media of low dielectric constant, such as ether or benzene, are given below. They may be considered examples of basic catalysis,* though the metal

(cxxxiv) $$RNa + R'\cdot COCl \rightarrow R'\cdot COR + NaCl$$

(cxxxv) $$RZnBr + R'\cdot COBr \rightarrow R'\cdot COR + ZnBr_2$$

(cxxxvi) $$RMgBr + R'\cdot CO_2Et \rightarrow R'\cdot COR + MgBr\cdot OEt$$

(cxxxvii) $$R_2Cd + 2R'\cdot COCl \rightarrow 2R'\cdot COR + CdCl_2$$

derivative is pre-formed from a suitable alkyl halide.[38]

Most organometallic compounds tend to react further than shown above. They add to the carbonyl group of the ketone. Thus the product of the reaction between Grignard reagents and acyl derivatives is usually the tertiary alcohol.[70] By conducting the reaction at low temperature and in the presence of excess of acylating agent, the ketone may, however, be isolated.[155] Some metal derivatives (*e.g.* those of cadmium) show little tendency to attack the ketone.[155] While all the above reactions are formally similar, and probably all involve eventual heterolysis of the metal–carbon bond, their mechanistic details seem likely to be rather different. They will certainly involve different degrees of free carbonium ion character for the alkyl group, and in some cases an additional molecule of organometallic compound may activate the acylating agent by weak Lewis-acid catalysis.[10] Moreover, the nature of Grignard reagents is complex.[156] However, each reaction probably represents only a particular catalysed elaboration of mechanism (II). The intermediates usually written[70] for Grignard reactions in which the organometallic compound has added to the carbonyl double bond, are in line with this, though the behaviour of cadmium alkyls appears

* The juxtaposition of the very electropositive metal producing a sufficiently nucleophilic carbon atom.

[153] *e.g.* Hopff, *Ber.*, 1931, **64**, 2739; Hopff, Nenitzescu, Isacescu, and Cantuniari, *Ber.*, 1936, **69**, 2244.

[154] *e.g.* Ipatieff and Grosse, *Ind. Eng. Chem.*, 1936, **28**, 1461.

[155] Shirley, *Org. Reactions*, 1954, **8**, Ch. 2.

[156] Schlenk and Schlenk, *Ber.*, 1929, **62**, 920; Ashby and Becker, *J. Amer. Chem. Soc.*, 1963, **85**, 118.

to be more complicated.[155] The finer details of these preparatively important processes await further study of organometallic compounds—especially kinetic study.

3. Acylation at "Active" C–H Bonds.—For aliphatic compounds containing electron-attracting groups (such as C=O or C≡N) adjacent to a C–H bond, the carbanion or sodio-derivative can usually be produced directly by addition of sodium alkoxide, sodium amide, or similar strong base.* Benzene or ether is often used as solvent. The presence of a suitable acylating agent results in *C*-acylation.[3] The nature of the catalysis usually

(cxxxviii) $$R{\cdot}CH_2{\cdot}CN + R'{\cdot}COX \underset{NaOEt}{\rightleftharpoons} R'{\cdot}CO{\cdot}CH(CN)R + HX$$

restricts choice of acylating agent to an ester. Similarly esters, ketones, and nitriles are the common substrates. Typical and important examples for the organic chemist are the acetoacetic ester (cxxxix) and Claisen (cxl) condensations. The Dieckmann reaction is another variation.[3] To what

(cxxxix) $$2CH_3{\cdot}CO_2Et \rightleftharpoons CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO_2Et + EtOH$$

(cxl) $$CH_3{\cdot}CO_2Et + (CH_3)_2CO \rightleftharpoons CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}CH_3 + EtOH$$

extent reaction (cxxxix) is involved when reaction (cxl) proceeds is not clear, though the ketone does provide the more reactive carbanion. These equilibria would probably all lie very largely to the left were not the diketo-products stabilised to some extent as the cyclic hydrogen-bonded enols.[3] In preparative practice the alcohol is often removed to reduce back reaction (see p. 189). The processes are again seemingly all straightforward examples of nucleophilic attack at the carbonyl carbon atom. Intramolecular variations (leading to ring formation) are known, for example the Kostanecki reaction.

This acylation by esters is usually more satisfactory than the reaction of acyl halide or anhydride with the pre-formed (*i.e.* free from alkoxide, etc.) sodio-derivative. The latter reaction,[3] though only slightly reversible, is not straightforward and often provides *O*- as well as *C*-acylation (cxli) or even diacylation at the active methylene group. The products depend

(cxli) $$NaCHR{\cdot}COR + 2R'{\cdot}COCl \rightarrow R'{\cdot}CO{\cdot}CR{=}CR{\cdot}O{\cdot}COR' + HCl + NaCl$$

markedly on the solvent used.

Brønsted-acid catalysis in potentially enolic systems normally results in *O*-acylation (p. 176). However, boron trifluoride,[3] and recently aluminium trichloride,[157] have been shown to provide fair yields of β-keto-derivatives. Discussion of these reactions is conveniently left until the end of the next section.

It would appear that the factors which control the competition between

* With ketones pyridine often favours enol formation and hence *O*-acylation (p. 176).

[157] Kaneyuki, *Bull. Chem. Soc. Japan*, 1962, **35**, 519.

C- and *O*- acylation generally are poorly understood. More work on this interesting and difficult problem is needed.

4. Acylation at Olefinic and Acetylenic Carbon.—Acetylenes are notable for the ease with which they form metal derivatives with loss of hydrogen. These derivatives, analogous to those discussed under para. (2) above, react similarly[158] with acylating agents. Carboxylic halides and anhydrides are the usual reagents but less-active species may be effective.

(cxlii) $RC{\equiv}CNa + R'{\cdot}COCl \rightarrow R'{\cdot}CO{\cdot}C{\equiv}CR + NaCl$

(cxliii) $RC{\equiv}CMgBr + (R'{\cdot}CO)_2O \rightarrow R'{\cdot}CO{\cdot}C{\equiv}CR + MgBr{\cdot}O{\cdot}COR'$

Under Lewis-acid catalysis acetylenes and olefins *add* acyl halides giving β-halogeno-ketones [reaction (cxliv)]. With some compounds, and especially when inert solvents are used, rather than the undiluted

(cxliv) $CH_2{=}CH_2 + R{\cdot}COCl \rightarrow R{\cdot}CO{\cdot}CH_2{\cdot}CH_2Cl$

acyl halide, loss of hydrogen halide occurs to give apparent or indirect substitution[159a] (cxlv). Olefins also add anhydrides (cxlvi) in the presence

(cxlv) $CH_2{=}CHCl + CH_3{\cdot}COCl \rightarrow CH_3{\cdot}CO{\cdot}CH_2{\cdot}CHCl_2 \rightarrow CH_3{\cdot}CO{\cdot}CH{=}CHCl + HCl$

of suitable* Lewis acids. Again substitution often results.[67,159b] Carboxylic acids usually add in the sense H^+ and RCO_2^- and therefore do not provide acylation (see however below).

(cxlvi) $CHR{=}CHR + (R'{\cdot}CO)_2O \rightarrow R'{\cdot}CO{\cdot}CHR{\cdot}CHR{\cdot}O{\cdot}COR' \rightarrow R'{\cdot}CO{\cdot}CR{=}CHR + R'{\cdot}CO_2H$

These Lewis-acid catalysed reactions, like other typical Friedel–Crafts processes (p. 198) in solutions of fairly low dielectric constant, probably initially involve nucleophilic attack by the olefin (or acetylene) on polar complexes, examples of which we will write provisionally as in reactions (cxlvii) and (cxlviii). The final stage could be either the addition of the anion to the substrate (A) or the abstraction of a proton (B). There are two facts which point to route (B), which represents a *direct* substitution, as having some importance in such reactions. First, as noted, an environment

(cxlvii) $CH_2{=}CH_2 + [CH_3{\cdot}CO]^+[SnCl_5]^- \rightarrow [SnCl_5]^-[CH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_3]^+$

(cxlviii) $CH_2{=}CH_2 + (RCO)_2\overset{\delta+}{O}{\rightarrow}\overset{\delta-}{Z}nCl_2 \rightarrow [RCO{\cdot}CH_2{\cdot}CH_2]^+[ZnCl_2{\cdot}O{\cdot}COR]^-$

of undiluted acyl halide favours β-halogeno-derivatives.[159a] This could be due to the greater opportunity for such reactions as (cli). Secondly,

(cxlix) $[CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_2]^+[SnCl_5]^- \overset{A}{\searrow} CH_3{\cdot}CO{\cdot}CH_2CH_2Cl + SnCl_4$; $\overset{B}{\searrow} CH_3{\cdot}CO{\cdot}CH{=}CH_2 + HCl + SnCl_4$

* Lewis acids which do not undergo halogen acylation (see p. 171).

[158] *e.g.* Nightingale and Wadsworth, *J. Amer. Chem. Soc.*, 1945, **67**, 416; Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 39.

[159] (*a*) Catch, Elliott, Hey, and Jones, *J.*, 1948, 278; Jones and Taylor, *J.*, 1961, 1345. (*b*) Meshcheryakov and Petrova, *Izvest. Akad. Nauk. S.S.S.R.*, 1951, **5**, 576.

(cl) $[R{\cdot}CO{\cdot}CH_2{\cdot}CH_2]^+[ZnCl_2{\cdot}O{\cdot}COR]^- \overset{A}{\underset{B}{\rightleftharpoons}} R{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}COR + ZnCl_2$ / $R{\cdot}CO{\cdot}CH{=}CH_2 + HZnCl_2{\cdot}O{\cdot}CO{\cdot}R$

(cli) $[CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_2]^+[SnCl_5]^- + CH_3{\cdot}COCl \rightarrow CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_2Cl + [CH_3{\cdot}CO]^+[SnCl_5]^-$

those Lewis acids which form the strongest complexes with carboxylic acids and their anions, give rise to the least-addition product.[159b] However, substitution *via* addition can definitely also occur;[159a] perhaps *via* reversal of (A) followed by (B). The relative importance of these steps will naturally depend on the particular system concerned.

Olefins and acetylenes are acylated by carboxylic acids in the presence of trifluoroacetic anhydride.[160] The reactive species is, of course, the unsymmetrical anhydride (p. 178) which, in this instance, is sufficiently reactive alone* to give with olefins an unstable addition intermediate [reaction (cliii)]. This intermediate (like many of those discussed above) then loses a molecule of acid. Suitable olefinic acids can be cyclised by this

(clii) $RCO_2H + (CF_3{\cdot}CO)_2O \rightleftharpoons R{\cdot}CO_2{\cdot}CO{\cdot}CF_3 + CF_3CO_2H$

(cliii) $CHR'{=}CHR' + R{\cdot}CO_2{\cdot}CO{\cdot}CF_3 \rightarrow R{\cdot}CO{\cdot}CHR'{\cdot}CHR'{\cdot}O{\cdot}CO{\cdot}CF_3 \rightarrow R{\cdot}CO{\cdot}CR'{=}CHR' + CF_3{\cdot}CO_2H$

route. With acetylenes the intermediate is a stable enol trifluoroacetate (C). There seems no reason why other Brønsted-acid catalysed routes to β-unsaturated ketones *via* anhydrides should not be developed.

$$R{\cdot}CO{\cdot}CR{=}CR'{\cdot}O{\cdot}CO{\cdot}CF_3 \quad (C)$$

The reactive C–C double bonds in quinones tend to be preferentially acyloxylated by anhydrides: only their oxygen atoms are easily acylated. The mechanism of this type of reaction needs clarification.[88]

Like other acid-catalysed acylation at apparently saturated C–H bonds (see p. 193) there action with saturated aliphatic ketones[3] (which gives β-diketones) catalysed by boron trifluoride probably involves attack at an olefinic carbon atom, *i.e.* preliminary enolisation is involved. In all real Lewis-acid systems some Brønsted acid will also exist (if only in traces) and this provides the rapid route to enolisation (cliv). Electrophilic attack by the acylating agent on the olefinic carbon follows, and is the probable reason why methylene rather than methyl derivatives are most easily formed from unsymmetrical ketones. Base-catalysed acylation of ketones (p. 194) leads to methyl derivatives because a methyl proton is most easily abstracted. Of the two possible enols, however, that to the methylene group provides the most nucleophilic carbon atom.†

The diketone is isolated as the stable boron complex (Y) which perhaps provides a clue to the superiority of boron trifluoride as a catalyst for *C*-

* Or perhaps because of the concomitant presence of trifluoroacetic acid (p. 179).

† Steric hindrance may sometimes interfere with this generalisation.[3,67]

[160] Henne and Tedder, *J.*, 1953, 3628; Royals and Hendy, *J. Org. Chem.*, 1950, **15**, 1147.

(cliv) $CH_3{\cdot}CO{\cdot}CH_2R + BF_3 + HF \rightleftharpoons CH_3{\cdot}\underset{\underset{HO\rightarrow BF_3}{|}}{C}{=}CHR + HF$

(clv) $(R'CO)_2O + BF_3 \rightleftharpoons [R'CO]^+[BF_3{\cdot}O{\cdot}COR']^-$

(clvi) $CH_3{\cdot}\underset{\underset{F_3B\leftarrow OH}{|}}{C}{=}CHR + [R'CO]^+[BF_3{\cdot}O{\cdot}COR']^- \longrightarrow CH_3{\cdot}\underset{\underset{F_3B\leftarrow O}{|}}{C}{=}\underset{\underset{H}{|}}{CR}\underset{\underset{COR'}{|}}{} + R'{\cdot}\underset{\underset{OH}{|}}{CO}\rightarrow BF_3$

$\downarrow$

(Y) $CH_3{\cdot}\underset{\underset{O}{|}}{C}{=}CR{-}\underset{\underset{O}{\|}}{C}R'$ (O–BF_2) + HF

rather than *O*-acylation. As with other acid catalysts *O*-acylation probably occurs (to an extent dependent on the availability of boron trifluoride to protect the enolic oxygen atom—compare p. 174) but in this case the resulting enol ester [reaction (clvii)] will also yield the diketone complex [reaction (clviii)].

(clvii) $CH_3{\cdot}CO{\cdot}CH_3 + (CH_3CO)_2O \overset{BF_3}{\rightleftharpoons} CH_3{\cdot}\underset{\underset{O{\cdot}CO{\cdot}CH_3}{|}}{C}{=}CH_2 + CH_3{\cdot}CO_2H$

(clviii) $CH_3{\cdot}\underset{\underset{O{\cdot}CO{\cdot}CH_3}{|}}{C}{=}CH_2 + 2BF_3 + (CH_3{\cdot}CO)_2O \longrightarrow \left[CH_3{\cdot}\underset{\underset{O}{\|}}{C}{-}CH_2{-}\underset{\underset{O{\cdot}CO{\cdot}CH_3}{|}}{C}{\cdot}CH_3\right]^+[BF_3{\cdot}O{\cdot}CO{\cdot}CH_3]^-$ (F_3B)

$\downarrow$

$CH_3{\cdot}\underset{\underset{O}{\|}}{C}{-}CH{=}\underset{\underset{O}{|}}{C}{\cdot}CH_3 + CH_3{\cdot}COF + CH_3\underset{\underset{OH}{|}}{CO}\rightarrow BF_3$ (O–BF_2)

A detailed study of the mechanisms of these, and of the perhaps similar processes involving aluminium chloride, would be most valuable. (See comments on p. 194).

5. Acylation at Aromatic Carbon.—Aromatic compounds with electron-withdrawing substituents undergo acylation with difficulty even in the presence of the most powerful catalysts: nitrobenzene has often been used as an inert solvent. On the other hand, the most reactive aromatic compounds can sometimes be acylated in the apparent absence of catalysts.

Base-catalysed aromatic acylation is restricted to reactions which involve an aryl-metal derivative.[161] The principles involved are the same as for the aliphatic organometallic compounds. With the acid-catalysed synthesis of aromatic ketones we reach one of the great division of Friedel

[161] *e.g.* Gilman and Nelson, *Rec. Trav. chim.*, 1936, **55**, 518; Cason, *J. Amer. Chem. Soc.*, 1946, **68**, 2078; Latpin and Lyubimova, *Zhur. obshchei Khim.*, 1949, **19**, 707.

–Crafts processes;[1,2] one whose examples far exceed those of the analogous reactions at olefinic carbon already noted. Moreover, besides Lewis acids, strong Brønsted acids such as perchloric, sulphuric, and anhydrous hydrofluoric are often used as catalysts.

(*a*) *Acylation of aromatic compounds with acyl halides.*—We invert

(clix) $$ArH + R{\cdot}COHal \rightarrow Ar{\cdot}COR + HHal$$

our usual order in this instance and deal with acyl halides first because, for aromatic systems they provide the simplest behaviour. The typical Friedel–Crafts reaction involves the acyl chloride with aluminium chloride as catalyst.[2] A variety of other metal halides are effective,[1] though a really quantitative comparison of their activities has still to be made. Some of them participate as dimers[162] (*e.g.* Al_2Cl_6) and others may be involved in solvation of the intermediate complexes (p. 196) as well as in producing them. Likewise, complexes with more than one molecule of acyl halide per molecule of catalysts may exist.[11] Catalyst is also engaged by the products and for this reason more than one molecular equivalent is often required.[1,2] Kinetically therefore, Friedel–Crafts reactions are usually complicated.[11,162] In preparative practice they are also often heterogeneous.

The nature of the predominant complex between the acyl and metal halides depends on the system,[7,55b,163] but probably some of each of (A) and (B) is always formed. However, acylation may always occur entirely

(A) $[R{\cdot}CO]^+[M(Hal)_{x+1}]^-$; (B) $Hal{\cdot}CR{=}\overset{\delta+}{O}{\rightarrow}\overset{\delta-}{M}(Hal)_x$

through (A), *i.e. via* mechanism (I). The additional participation of (B) —the so-called "duality of mechanism"—although reasonable has yet to be convincingly demonstrated in spite of much tentative argumentation. The importance of (A) is indicated by the fact that acyl fluorides, chlorides, and bromides tend to be most powerfully catalysed by metal fluorides, chlorides, and bromides, respectively[123] (*e.g.*, $RCOF,BF_3$ is a better combination than $RCOCl,BF_3$). Furthermore, a molecule of catalyst is required to accept the leaving group (Hal) and this provides an extra complication for acylation *via* (B). Schemes like the following also have the advantage of being analogous to other typical electrophilic aromatic substitutions.[88*]

(clx) $$[R{\cdot}CO]^+[BF_4]^- + C_6H_6 \longrightarrow \left[\begin{array}{c} H \quad COR \\ \bigcirc \end{array}\right]^+ [BF_4]^- \longrightarrow R{\cdot}CO{\cdot}C_6H_5 + BF_3 + HF$$

It should be noted that in all Friedel–Crafts contexts, acyl chlorides and bromides, as well as fluorides, suffer catalysis with Lewis acids, whereas

* In some media (*e.g.* nitrobenzene) the ionic complexes will be dissociated, and in others they will be solvated: both factors may effect reactivity.

[162] Jensen and Brown, *J. Amer. Chem. Soc.*, 1958, **80**, 2291, 3039.

[163] Cooke, Susz, and Herschmann, *Helv. Chim. Acta*, 1954, **37**, 1280.

acylation by the former is not catalysed by the hydrogen ion in aqueous solution (p. 195). The transition between these two extremes of behaviour is provided by systems favourable to bonding between a Brønsted-acid catalyst and chloride or bromide. One such system (li) involves hydrogen halide catalysis in nitromethane, where HCl_2^- ions are stable. It may be seen therefore that there is no sharp distinction between Brønsted- and Lewis-acid catalysis of acylation: a requirement always involved is the ability to form a sufficiently stable unit with the leaving group in the environment concerned (compare p. 174). The use[164] of anhydrous hydrogen fluoride with acyl chlorides* for aromatic acylation provides another example standing between the protonation processes usually typical of Brønsted-acid catalysis and the acceptor behaviour often considered possible only for Lewis acids (clxi). Protonation itself is only one

(clxi) $$ArH + RCO^+ HF_2^- \rightarrow Ar{\cdot}COR + 2HF$$

extreme of acceptor behaviour: in catalysis, therefore, as elsewhere, the Lewis definition of acids—as electrophiles—proves the most embracing.

Some high-temperature, apparently uncatalysed, acylations by acyl halides[165] may, in fact, involve catalysis by adventitious hydrogen halide.

(*b*) *Acylation of aromatics with anhydrides.* These reactions probably take one of two courses, depending on the nature of the catalyst. In the first, the catalyst is decomposed by the anhydride to give an acyl halide (clxii) which then reacts as described above.[42] This is hardly a catalysed

(clxii) $$(R{\cdot}CO)_2O + AlCl_3 \rightarrow R{\cdot}COCl + AlCl_2{\cdot}O{\cdot}COR$$

acylation by an anhydride: the "catalyst" is not necessarily regenerated. The second type of behaviour, which is a catalysed acylation, seems likely both in catalysis by Brønsted acids such as perchloric, sulphuric, or $H_2SnCl_4(OAc)_2$[18,88,166] and also in catalysis by the less-easily decomposed Lewis acids like boron trifluoride or stannic chloride.[167] It involves (see also p. 166) formation of an active acyl derivative of the catalyst [scheme (clxiii)]. The active species are thus probably essentially similar to those

(clxiii) $$(CH_3{\cdot}CO)_2O + HClO_4 \rightleftharpoons CH_3{\cdot}CO^+ClO^-_4 + CH_3{\cdot}CO_2H$$

(clxiv) $$(CH_3{\cdot}CO)_2O + SnCl_4 \rightleftharpoons \overset{\delta+}{[CH_3{\cdot}CO]^+}\overset{\delta-}{[SnCl_4{\cdot}O{\cdot}CO{\cdot}CH_3]^-}$$
$$(\text{or } (CH_3{\cdot}CO)_2O \rightarrow SnCl_4)$$

involved for acyl halides, though details concerning the complexes between Lewis acids and anhydrides are still sparse.

On most preparative occasions sufficient free carboxylic acid (or other

* Probably actually the fluorides (see p. 171).

[164] Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1939, **61**, 1272; see also Kopple and Katz, *ibid.*, 1956, **78**, 6199; Johnson, *Org. Reactions*, 1944, **2**, Ch. 4.

[165] *e.g.* Lockett and Short, *J.*, 1939, 787.

[166] Satchell, *J.*, 1962, 1894; Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1937, **59**, 1028.

[167] Satchell, *J.*, 1962, 1899; Burton and Praill, *J.*, 1951, 726; *idem*, *Chem. and Ind.*, 1954, 90.

hydroxylic material) will be present to convert some, or all, of any Lewis acid catalyst into a Brønsted dual-acid.[168] Thus with stannic chloride the catalyst may often really be $H_2SnCl_4(O{\cdot}CO{\cdot}R)_2$ and the intermediate complex[166] $[RCO]^+[HSnCl_4(O{\cdot}CO{\cdot}R)_2]^-$ rather than $[R{\cdot}CO]^+[SnCl_4{\cdot}O{\cdot}CO{\cdot}R]^-$ (see p. 175).

(*c*) *Acylation of aromatics with carboxylic esters, amides and acids.* Such unreactive acylating agents can often be used with aromatic compounds in the presence of suitable catalysts.[1,2,84,169] However, the active intermediates formed in these reactions are not known with much certainty.

It is to be remembered that for acid-catalysed *C*-acylation an intermediate of approaching acylium-ion character will usually be required. With easily decomposed Lewis acids like aluminium chloride, processes similar to (cxlv) probably occur[2,169] These provide acyl halides. Genuinely

(clxv) $$R{\cdot}CO_2Et + AlCl_3 \rightarrow R{\cdot}COCl + AlCl_2{\cdot}OEt$$

catalysed acylation is probably restricted to the presence of species like HF, H_2SO_4, $HBF_3{\cdot}O{\cdot}CO{\cdot}CH_3$, BF_3, and perhaps occasionally $SnCl_4$, or $ZnCl_2$. In the presence of strong Brønsted acid *some* ionisation probably occurs (p. 179) with all carboxylic acids or esters—especially if the dielectric constant is favourable (clxvi). This may be sufficient to provide reaction.

(clxvi) $$R{\cdot}CO_2H + 2H_2SO_4 \rightleftharpoons R{\cdot}CO^+ + 2HSO_4^- + H_3O^+$$

Alternatively, in liquid hydrogen fluoride, although carboxylic acids can be essentially completely recovered, some little acyl fluoride may be formed (p. 164). If so this will lead to $RCO^+HF_2^-$ and hence to acylation. In many systems, and certainly when the carboxylic acid is the reagent, Lewis acid catalysts will be more or less converted into powerful Brønsted acids (see above). Catalysis may then again be *via* some proton-stimulated heterolysis. Equilibria like (clxvii) may also exist (compare p. 175). Even in the absence of these effects, Lewis acids will doubtless co-ordinate with esters or amides, producing a polarised, and even occasionally an ionised, reagent. However, while it is easy to speculate about them—and perhaps

(clxvii) $$R{\cdot}CO_2H_2^+\ BF_3{\cdot}O{\cdot}COR^- \rightleftharpoons R{\cdot}CO^+BF_3OH^- + R{\cdot}CO_2H$$

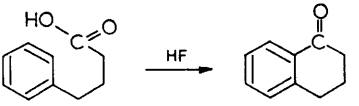
correctly—the details of acid-catalysed *C*-acylation by such mild reagents as those considered here, remain largely unexamined experimentally. Thus the mechanism of catalysis in the Fries rearrangement[170] (which appears essentially an intermolecular acylation among the molecules of a phenyl ester) is still little understood.

It is noteworthy that *intra*molecular *C*-acylation is, in general, surprisingly easy compared with the intermolecular reaction. The use of the

[168] Bethell, Gold and Satchell, *J.*, 1958, 1918; Satchell, *J.*, 1958, 3910.
[169] Dippy and Wood, *J.*, 1949, 2719.
[170] Blatt, *Org. Reactions*, 1942, **1**, Ch. 11.

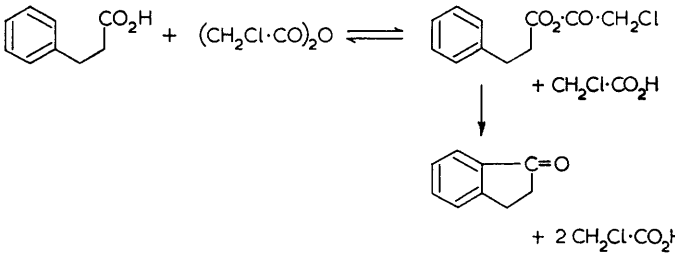
carboxylic acid, with hydrogen fluoride as catalyst, is common in this context.[164] Unsymmetrical carboxylic anhydrides alone seem occasionally

(clxviii)



sufficiently reactive[84,171] [scheme (clxix)], although catalysis by the free acid usually also present in such systems is probably involved (compare p. 179).

(clxix)



Polyphosphoric acid has recently become a popular catalyst for intramolecular acylation, though its mode of action remains obscure.[96]

6. Acylation at Carbon Attached to a Heteroatom.—*C*-Acylation in unsaturated heterocyclic compounds, which usually leads to substitution in the 2-position, will not be discussed here. It has not yet been so intensively investigated as the homocyclic field, but appears to involve no new principles.[2] Ring opening does not seem usual, though mild catalysts which do not themselves cleave the substrate are desirable. Unreactive compounds like pyridine usually acylate at the heteroatom only, if at all (p. 190).

The smaller, strained and saturated ring systems, like 1,2-epoxides and sulphides, usually do cleave, the positive fragment of the reagent attaching itself to the heteroatom.[105,172] As described on p. 184 open-chain aliphatic ethers and sulphides also undergo acylation at the heteroatom rather than at carbon.

A special example of acylation at carbon attached to a "heteroatom" concerns hydrogen cyanide[28,173] [reaction (clxx)]. Acyl cyanides are satisfactory reagents for the acylation of amines.[173]

(clxx) $$HCN + CH_2{=}C{=}O \rightarrow CH_3{\cdot}CO{\cdot}CN$$

7. Acylation at Carbon by Replacement of Atoms other than Hydrogen or Metal.—Examples of such processes appear rare, for in most instances (*e.g.* alcohols or amines) the other atom, being more electronegative, is

[171] Unger, *Annalen*, 1933, **504**, 267.
[172] Davies and Savige, *J.*, 1951, 774.
[173] Dornow and Theidel, *Angew. Chem.*, 1954, **66**, 605.

preferentially acylated. An unusual case is diazomethane[174] which can add ketones with loss of nitrogen [reaction (clxxi)]. This, however, is hardly

(clxxi) $$CH_2N_2 + R_2CO \rightarrow R{\cdot}CO{\cdot}CH_2R + N_2$$

a typical acylation. With acyl halides,[175] hydrogen replacement occurs (clxxii).

(clxxii) $$CH_2N_2 + R{\cdot}COCl \rightarrow RCO{\cdot}CHN_2 + HCl$$

8. Acylation at Silicon.—Examples are even more scanty than for phosphorus.[148] In attacking silicon bonds acylating agents usually acylate the attached atom or yield the carboxylate. The reason for this is that silicon is much more electropositive than are the atoms commonly attached to it (*e.g.* carbon, oxygen, halogen). Even Si–H bonds are polarised[148] in the sense Si^+—H^-. Nucleophilic attack by silicon is therefore rare and $\equiv Si{\cdot}CO-$ structures whenever they do form are usually unstable. This is especially so in the presence of bases, for these easily attack the silicon atom.[148] Silicon thus provides an even more difficult problem than the direct acylation at aliphatic carbon. The most powerful catalytic methods are necessary and the reaction of metal derivatives with acyl halides is therefore employed[176] (clxxiii).

(clxxiii) $$Ph_3SiK + Ph{\cdot}COCl \rightarrow Ph_3Si{\cdot}COPh + KCl$$

Conclusion

Since these Reviews are intended for the general reader, specialist terminology—rife in the fields of catalysis and nucleophilic substitution—has been deliberately omitted. Shorthand terms like S_N1 and general acid catalysis frustrate the uninitiated and often limit and confuse the expert. Their inclusion and detailed illustration would, in any case, add little of moment to the type of data we have marshalled. In this context we note with regret the cumbersome obscurity of some current "shorthand" usages.

In a short review of a large subject an author is tempted to generalise: indeed it should be part of his aim. Most generalisations, however, admit exceptions, and many readers will be aware of significant points we have omitted. We know some of these ourselves, yet feel we have legitimately demonstrated that seen broadly, in terms of ease of reaction and nature of mechanism, acylation processes at the various environmentally different sites, present a discernible and chemically sensible pattern. In a given environment, of those elements discussed, the heavier members of any group tend to be the less readily acylated. Relative electronegativities go far in explaining this effect. The variations in susceptibility to attack on

[174] Gutsche, *Org. Reactions*, 1954, **8**, Ch. 8.
[175] *e.g.* Bradley and Schwarzenbach, *J.*, 1928, 2907.
[176] Brook, *J. Amer. Chem. Soc.*, 1957, **79**, 4373; Wittenberg, Aoki, and Gilman, *ibid.*, 1958, **80**, 5933.

passing from group to group cannot always be rationalised so simply. Here, because of differences in valency, environmentally exact comparisons cannot be made, and a variety of effects contribute to reactivity. However, as will have been seen, the observed behaviour seems in keeping with general chemical expectation.

The subject's least satisfactory general feature is the comparative absence of kinetic studies of mechanism. As a result, the details of many of the schemes quoted for *C*-, *Halogen*-, and *N*-acylation remain very uncertain. To fill in our present outline of knowledge the most pressing need is for effort in this area. Mechanisms deduced only from reaction products and the gentle arts of "electron-pushing" should not continue to satisfy the self-respecting chemist.