The Mechanism of Acylation*

By R. F. HUDSON, Geneva**

Zusammenfassung

Die Struktur des Grundzustandes eines Acylchloridmoleküls wird im Hinblick auf die beteiligten kanonischen Strukturen und auf neuere physikalische Messungen, einschließlich Bindungslängen und ^{35}Cl-Quadrupolkopplungskonstanten kurz diskutiert. Auf Grund dieser Strukturen und verfügbarer Reaktionsgeschwindigkeitsmessungen werden mögliche Reaktionsmechanismen der Hydrolyse von Acylchloriden, einer typischen Acylierungsreaktion, betrachtet. Beweise zugunsten zweier Mechanismen werden erbracht, von denen einer eine geschwindigkeitsbestimmende Bindungsbildung, der andere eine geschwindigkeitsbestimmende Ionisierung einschließt. Der erste Mechanismus, der durch elektronenanziehende Substituenten gefördert wird, geht wahrscheinlich über einen tetraedrischen sp^3-Zwischenzustand, wie der gleichzeitige ^{18}O-Austausch des Carbonylsauerstoffs und der geringe sterische Effekt zeigen. Der ionische Mechanismus wird durch elektronenabgebende Substituenten und durch stark polare Lösungsmittel gefördert und könnte die geschwindigkeitsbestimmende Bildung eines Acyliumions oder die Ionisierung des vorgebildeten Hydrates einschließen, um das Carboniumion $\mathrm{R\overset{+}{C}(OH)_2}$ zu bilden. Die Schwierigkeit, strukturelle Effekte zu deuten, wird kurz diskutiert im Hinblick auf die möglichen Elektronenstrukturen ($\mathrm{\overset{+}{R}{=}C{=}O}$ und $\mathrm{R{-}C{\equiv}\overset{+}{O}}$) des Acyliumions und auf die starke Konjugation im Grundzustand von Molekülen, in denen die Gruppe R ein freies Elektronenpaar besitzt.

The mechanism of nucleophilic substitution at a saturated carbon atom has been studied in considerable detail, and these studies have made a major contribution to theoretical organic chemistry. In particular the work of HUGHES and INGOLD has led to a broad classification of these reactions in terms of a rate determining ionisation mechanism (S_N1) and a direct displacement (S_N2) involving simultaneous bond making and bond breaking.

$$\mathrm{RX} \overset{\text{slow}}{\rightleftarrows} \mathrm{R^+ + X^-} \xrightarrow[\text{fast}]{Z^-} \mathrm{RZ + X^-} \qquad (S_N1)$$

$$\mathrm{Z^- + RX} \xrightarrow{\text{slow}} \mathrm{ZR + X^-} \qquad (S_N2)$$

Substitution at a carbonyl centre is more complex, owing to the presence of two electronegative centres, and to the influence of the π-bond of the carbonyl group. The detailed electronic distribution is therefore difficult to ascertain, and varies considerably with structure, as shown for example by the changes in infra-red stretching frequency of the carbonyl bond,[1] and the ionisation potential of the p π electrons of the oxygen atom.[2]

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* Lecture given to the Société Chimique de Genève.

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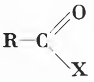
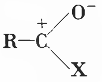
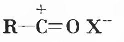
[1] LECOMTE, *Bull. Soc. Chim. France 1955*, 717; LORD and MILLER, *Appl. Spectroscopy 10* (1956) 115; KAGARISE, *J. Amer. Chem. Soc. 77* (1955) 1377.

[2] WALSH, *Trans. Faraday Soc. 42* (1946) 56.

In classical terms a carbonyl compound may be represented as a resonance hybrid of the canonical structures *I* to *V*.


I

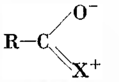

II


$R-\overset{+}{C}=O\ X^-$

III

$R-C\equiv O^+\ X^-$

IV


V

Structure II facilitates nucleophilic addition and consequently promotes a bimolecular displacement of X, which is repressed by structure V, whereas structures III and IV assist ionisation.

Table I: Bond lengths of alkyl and acyl chlorides

X	CH_2COX l_{C-X} Å	CH_3X l_{C-X} Å
F	1.37 ± 0.02^a	1.384^a
	1.41 ± 0.05^b	1.385^c
Cl	1.82 ± 0.02^a	1.779^a
	1.82 ± 0.01^d	1.786^e
Br	2.00 ± 0.04^a	1.936^a
	2.06 ± 0.08^d	1.939^f
I	2.21 ± 0.04^a	2.132^a
		2.144^e

(a) Allen and Sutton, *Trans. Faraday Soc. 47* (1951) 236.
(b) Skinner, quoted in ref. 1.
(c) Gilliam, Edwards and Gordy, *Physic. Rev. 75* (1949) 104.
(d) Dornte, quoted in ref. 1.
(e) Simmons, *Physic. Rev. 76* (1949) 686.
(f) Simmons and Swan, *Physic. Rev. 80* (1950) 289.

^{35}Cl Nuclear quadrupole resonance frequencies of halogen compounds

Compound	eq. *Q* (Mc *ps*)
Atomic ^{35}Cl	110.4^a
CH_3Cl	75.13^a
$C_2H_5O\cdot CO\cdot Cl$	33.858^b
$CCl_3\cdot COCl$	33.721^b
$(CH_3)_2N\cdot COCl$	31.8^b
$C_6H_5\cdot CO\cdot Cl$	29.93^b
$Cl\cdot C(O)(CH_2)_4\cdot CO\cdot Cl$	29.978^b
CH_3COCl	predicted at ca. 27.7^c
NaCl	$<1.^a$

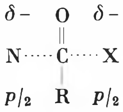
(a) Townes and Dailey, *J. Chem. Physics 17* (1949) 782.
(b) Bray, *J. Chem. Physics 23* (1955) 703.
(c) Bray, *J. Chem. Physics 22* (1954) 1787.

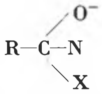
Recent measurements of bond lengths (Table I), molecular refraction, and nuclear quadrupole coupling constants of the ^{35}Cl atom (Table I), suggest that the charge density on the chlorine atom is greater than on the chlorine atom of the corresponding alkyl halide. This is surprising in view of the low electron density at the carbonyl carbon atom, and suggests that structure *IV* makes a significant contribution to the ground state.

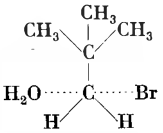
This structural evidence indicates that the C—Cl bond is readily ionised, in agreement with the relatively low dissociation energies of acyl halides.[3] On structural considerations alone therefore, we may conclude that the charge distribution represented by *II*, promotes bimolecular displacement through an addition intermediate, and the charge distribution represented by structure *IV*, which becomes more important in the transition state promotes a unimolecular ionisation mechanism.

The mechanism of bimolecular acylation

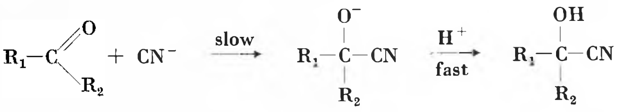
As pointed out by Ingold,[4] acylation may proceed through two alternative transition states, depending on the relative π-bond energy of the carbonyl bond, and the σ-bond energy of the bond formed. A planar transition state *VI* which is formed if the π-bond is retained[5] is electronically and sterically similar to an S_N2 transition state.


VI


VII


VIII

In the sp^3 hybridised structure *VII*, the N–C, σ-bond energy largely compensates for the loss of π-bond energy, as in the known stable compounds e.g. chloral hydrate[6] and trifluoro-acetone hydrate.[7] It is well known that carbonyl addition is a nucleophilic process and is promoted by electron withdrawing substituents, e.g. chloral hydrate is more stable than acetaldehyde hydrate.[8] Similarly, the classical work of Lapworth[9] established that the rate of cyanhydrin formation is controlled by nucleophilic addition,



In the hydrolysis of esters,[10] amides and acid chlorides,[11] tracer work has established the presence of symmetrical addition compounds. Thus, following earlier work on ^{18}O exchange between ketones and water, and carboxylic acids and water, Bender[10] showed that the

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[3] Carson and Skinner, *J. Chem. Soc. 1949*, 936, *1950*, 656.

[4] Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell, 1953, p. 754.

[5] Dewar, *Electronic Theory of Organic Chemistry*, Oxford University Press, 1949.

[6] Davies, *Trans. Faraday Soc. 36* (1940) 333.

[7] Henne, Newman, Quill and Stainforth, *J. Amer. Chem. Soc. 69* (1947) 1819.

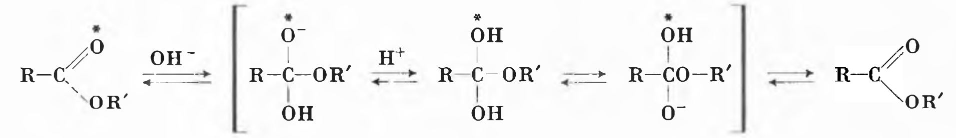
[8] Bell and Higginson, *Proc. Roy. Soc. A 197* (1949) 141.

[9] Lapworth and Manske, *J. Chem. Soc. 1928*, 2533.

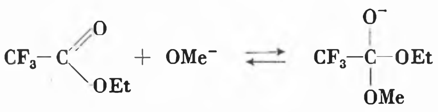
[10] Bender, *J. Amer. Chem. Soc. 73* (1951) 1626.

[11] Bunton, Lewis and Llewellyn, *Chem. Ind. 1954*, 1154.

carbonyl oxygen atom exchanges in the course of acid and alkaline hydrolysis of esters. This is interpreted by the following scheme for alkaline hydrolysis,



It was shown later[12] that the addition of sodium methoxide or ethoxide to ethyl trifluoroacetate in di n-butyl ether caused the carbonyl peak in the infra-red spectra to disappear. The reaction was reversible since the carbonyl peak reappeared on the addition of acid, in agreement with the following process,



The equilibrium constant decreases with the number of fluorine atoms in the alkyl chain (Table 2), following the decrease in the charge on the carbon atom.

This increase parallels the increase in rate of hydrolysis of the corresponding chloroacetates,[13] in agreement with a hydrolysis mechanism, proceeding through an intermediate.

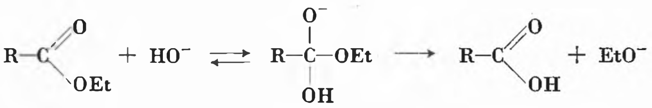


Table 2: The position of equilibrium for the addition reaction between esters and sodium methoxide in di-n-butyl ether

Esters	% addition
Ethyl acetate	0
Ethyl fluoroacetate	26
Ethyl difluoroacetate	77
Ethyl trifluoroacetate	96

These observations suggest strongly, but do not prove, that the transition state for bimolecular acylation assumes the tetrahedronal sp^3 hybridised structure of the addition intermediate. Further evidence in favour of this structure is provided by measurements of steric hindrance in hydrolysis and alcoholysis. Thus the substitution of alkyl groups in acetyl chloride has little effect on the reactivity,[14] as shown by the following data (Table 3).

On the other hand, β-substitution in alkyl halides produces large reductions in rate[15], e.g. the S_N2 hydrolysis of neopentyl bromide is at least 150 times slower than the hydrolysis of ethyl bromide, owing to steric compression in the transition state, *VIII*. The small differences in rate between acetyl chloride and trimethyl acetyl chloride show that the less strained transition state, *VII*, is formed.

Table 3: Comparison of the rate of hydrolysis of acyl[14] and alkyl chlorides[15]

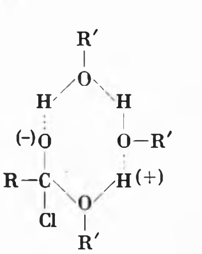
Compound	$10^4 K (s^{-1})$*	Compound	$10^6 K (s^{-1})$**
$CH_3 \cdot COCl$	8.9	C_2H_5Br	141
$C_2H_5 \cdot COCl$	9.87	$C_3H\text{-}Br$	80.3
$(CH_3)_2CH \cdot CO \cdot Cl$	8.2	$(CH_3)_2 \cdot CH \cdot CH_2Br$	11.3
$(CH_3)_3C \cdot COCl$	2.2	$(CH_3)_3C \cdot CH_2Br$	0.91***

* IN H_2O in dioxan, 25° ** 50% aqueous ethanol, 95°
*** S_N1 reaction

Little is known of the lifetime of the addition intermediate *VII*, although the ^{18}O exchange experiments[11] show that the life is sufficiently long for the appropriate proton transfer to occur. The elegant work of **Eigen**[16] has shown that protons and hydroxyl ions combine almost instantaneously ($K_2 \approx 1 \, . \, mole^{-1} s^{-1}$), even when the ions are separated by two water molecules. The proton transfer producing ^{18}O exchange could therefore occur in intermediate *VII* in a time comparable to the lifetime of a transition state.

We have shown,[17] by studying the alcoholysis of acetyl chloride in dilute solutions of alcohols in non-polar solvents, that the rate of reaction is proportional to the concentration of alcohol *in the associated state* over a wide concentration range. This suggests that the transition state is associated with a discrete number of alcohol molecules to give a non-polar assembly *IX*, which collapses to give the reaction products.

$$(R'OH)_n + R \cdot COCl \rightleftharpoons RCOCl(R'OH)_n \rightarrow RCOOH + HCl(ROH)_n$$



IX

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[12] **Bender**, *J. Amer. Chem. Soc. 75* (1953) 5986.

[13] **Flom**, quoted by **Bender**, ref. 12.

[14] **Weller**, Ph. D. Thesis, London 1955.

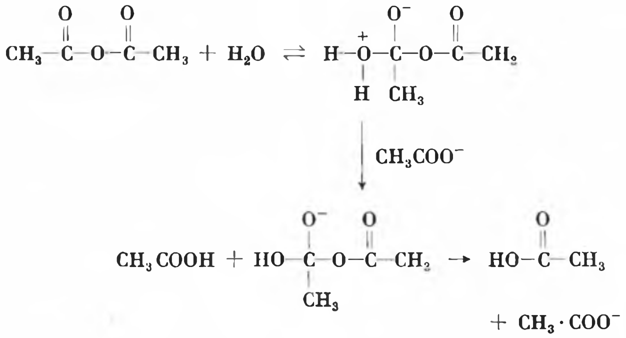
[15] **Dostrovsky** and **Hughes**, *J. Chem. Soc. 1946*, 171.

[16] **Eigen**, *Disc. Faraday Soc. 17* (1954) 194.

[17] **Hudson** and **Saville**, *J. Chem. Soc. 1955*, 4114; **Hudson** and **Stelzer**, *Trans. Faraday Soc. 54* (1958) 213.

Similar hydrogen bonded complexes have been detected kinetically in ester hydrolysis.[18]

In some cases, general base catalysis in the BRÖNSTED sense has been observed. For example the hydrolysis of acetic anhydride[19] is catalysed by acetate ions, which may be represented by the following reaction scheme.



The reaction of amines with esters[20] is catalysed by bases showing that an essentially similar reaction occurs, although various modified reaction schemes have been suggested, involving steps such that the proton transfer is not rate determining.

The duality of mechanism

Early measurements have established that electron withdrawing substituents increase the reactivity of acyl halides and esters, e.g. as shown by the following rate order for the alcoholysis.[21]

$$CCl_3 \cdot COCl > CHCl_2 \cdot COCl > CH_2ClCOCl > CH_3COCl$$

Similarly, many measurements of the rate of alcoholysis[21, 22] and aminolysis of substituted benzoyl chlorides,[23] and of the alkaline hydrolysis of the corresponding esters[24] and amides, showed that electron attracting groups in the *p*-position increase the reactivity (Table 4).

Table 4: Relative rates of solvolysis of *p*-substituted benzoyl chlorides

Solvent	Reactant	NO_2	Br	Cl	CH_3	CH_3O
1. Benzene	aniline	8.5	–	1.5	0.56	–
2. Ether	ethanol (40 %)	32.5	2.5	2.9	0.47	0.25
3. Ethanol	ethanol	21.6	2.1	1.9	0.78	0.81
4. Acetone	water (5 %)	35	3.2	–	0.55	0.60
5. Acetone	water (50 %)	11.5	0.92	0.85	2.9	30
6. Formic acid	water (1 %)	~0	0.086	–	6.6	v. fast

In solvents of high polarity (e.g. water and formic acid), electron releasing substituents increase the reactivity, such that the rate order is completely reversed[25] (Table 4), suggesting that the mechanism changes completely from the bimolecular mechanism to a mechanism involving a rate determing ionisation.

Moreover, in formic acid, the rate of reaction of *p*-nitrobenzoyl chloride is proportional to the concentration of water[25] showing the reaction to be bimolecular (Table 5). In addition, the rate is increased by the addition of formate ions.

Table 5: The effect of water concentration on the rate of hydrolysis of benzoyl chloride and p-nitrobenzoyl chloride[25] in formic acid

Benzoyl chloride, 9°		*p*-nitrobenzoyl-chloride 20°	
H_2O (vol-%)	$10^4 K_1 (s^{-1})$	H_2O (vol-%)	$10^5 K_1 (s^{-1})$
1.0	34.4	1.6	1.8
1.6	36.8	2.7	3.2
2.7	38.0	4.6	4.8
4.6	39.2	5.8	7.8

The rates solvolysis of benzoyl chloride and toluoyl chloride are however almost independent of the water and formate ion concentrations, suggesting that the reaction proceeds by a rate determining ionisation.

As shown by the rate data, 4 and 5, of Table 4, an increase in the water content of the medium influences the rate of the various chlorides to very different extents. This is shown clearly by the comparison (Fig. 1) of the rates of solvolysis of *p*-nitro-and *p*-methoxy benzoyl chlorides, in acetone-water mixtures.[26]

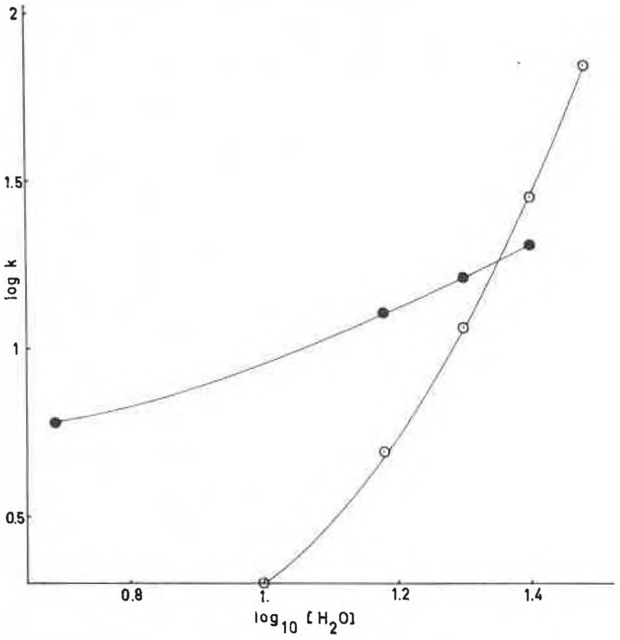


Fig. 1. The change in the rate of solvolysis of *p*-nitrobenzoyl chloride –●– and *p*-methoxybenzoyl chloride –○– in acetone-water mixtures with change in water concentration

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[18] ASKNESS, *Acta Chem. Scand. 1960*, 1475, 1526.

[19] KILPATRICK, *J. Amer. Chem. Soc. 50* (1928) 2891; BUTLER and GOLD, *Proc. Chem. Soc. 1960*, 15.

[20] BUNNETT and DAVIS, *J. Amer. Chem. Soc. 82* (1960) 665; JENCKS and CARRIUOLO, *ibid.* 675.

[21] BRANCH and NIXON, *J. Amer. Chem. Soc. 58* (1936) 2499.

[22] NORRIS, FASCE and STAUD, *J. Amer. Chem. Soc. 57* (1935) 1415; NORRIS and GREGORY, *J. Amer. Chem. Soc. 50* (1928) 1813.

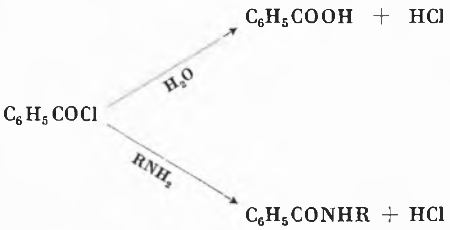
[23] WILLIAMS and HINSHELWOOD, *J. Chem. Soc. 1934*, 1079.

[24] HAMMETT, *Physical Organic Chemistry*, McGraw Hill, 1940, p. 189.

[25] CRUNDEN and HUDSON, *J. Chem. Soc. 1956*, 501.

The sensitivity of the rate to an increase in polarity of the solvent (ionising power) is a measure of the polarity of the transition state.[26, 27] The greater sensitivity of *p*-methoxybenzoyl chloride shows that the transition state is highly polar, in agreement with the tendency to undergo an ionisation reaction.

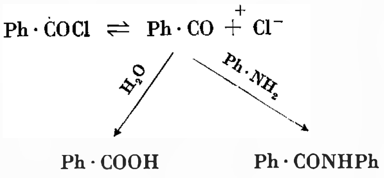
The prediction of a change in mechanism with increase in water concentration was supported by **Gold, Hilton** and **Jefferson**[28] by studying the effect of added amine on the rate of reaction of benzoyl chloride in aqueous acetone. By comparing the rate constants K_1 and K_0 for the reaction of benzoyl chloride in the presence and absence of *p*-chloroaniline,



with the product compositions, it was shown that the concentration of anilide formed is greater than that predicted from the bimolecular rate constant for the reaction between aniline and benzoyl chloride. Thus if both reactions proceed by bimolecular mechanisms,

$$\frac{[\text{anilide}]}{[\text{benzoic acid}]} = \frac{K_1 - K_0}{K_0}.$$

This agreement was obtained from measurements in 80% acetone —20% water. In 50% aqueous acetone however, the product ratio was considerably greater than the rate ratio showing that ca. 40% of the anilide was produced in a non-rate determining stage, in agreement with the mechanism,



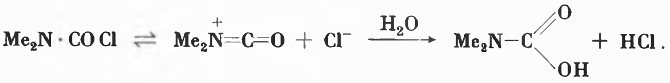
By comparing solvolysis rates in formic acid and in aqueous acetone, **Hudson** and **Crunden**[25] obtained a value of 40% S_N1 participation in 65% aqueous acetone, in good agreement with the above value. They obtained estimates of the contribution of the ionisation mechanism to the solvolysis of some substituted benzoyl chlorides (Table 6), by assuming that the rates of ionisation were equal in the two solvents, in which the S_N1 reaction of alkyl halides proceed at the same rate (solvents of equal ionising power[29]). The increase in rate in the aqueous solvent was then attributed to the bimolecular reaction, thus enabling the proportion of the reaction proceeding by each mechanism to be established.

Table 6

Compound	65% aq. acetone	Formic acid (1% water)	% S_N1
p-$CH_3\cdot C_6H_4\cdot COCl$	$28 \times 10^{-3}\ s^{-1}$	$19 \times 10^{-3}\ s^{-1}$	70
$C_6H_5\cdot COCl$	8.9×10^{-3}	3.5×10^{-3}	40
p-$Br{-}C_6H_4\ COCl$	2.2×10^{-3}	2.4×10^{-4}	10
p-$NO_2{-}C_6H_4\ COCl$	3.0×10^{-3}	1.0×10^{-6}	— 0

The nature of the ionisation reaction

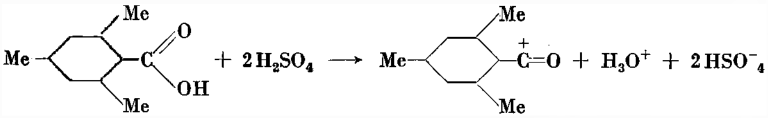
Strong evidence for an ionisation, S_N1 mechanism, for the hydrolysis of carbamyl chlorides has been presented by **Hall.**[30] Hydroxide ions have no effect on the rate of reaction of dimethyl carbamyl chloride, which is greatly reduced by chloride ions. Evidence for the existence of an intermediate was obtained by the isolation of dimethyl 3.3 tetramethylene urea, on the addition of pyrrolidine to the aqueous reaction mixture. These observations were interpreted by the following reaction mechanism,



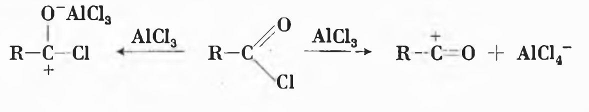
$$\mathrm{Me_2N\cdot CO\,Cl} \rightleftharpoons \mathrm{Me_2\overset{+}{N}{=}C{=}O} + \mathrm{Cl^-} \xrightarrow{\mathrm{H_2O}} \mathrm{Me_2N{-}C}\begin{smallmatrix}{/\!\!/}\mathrm{O}\\ \backslash\mathrm{OH}\end{smallmatrix} + \mathrm{HCl}.$$

originally postulated for the ionisation reaction of benzoyl chloride and mesitoyl chloride.[25, 31]

The high reactivity of mesitoyl chloride,[31] and the sensitivity to solvent changes[26] and electrophilic catalysis,[17] have been interpreted[31] by the S_N1 mechanism, since the acylium ion can be readily produced by electrophilic action. Thus the van t'Hoff factor of 4.0 observed[32] for mesitoic acid in sulphuric acid is readily interpreted by the reaction



More recently **Susz** and co-workers[33] have shown that Lewis acids and acyl chlorides give two kinds of complexes in non-aqueous solution, the one involving interaction at the carbonyl group, and the other interaction at the chlorine atom to give an acylium ion recognised by the infra red vibration frequency in the 2,000 to 2,2000 cm⁻¹ range.



$$X \qquad \mathrm{R{-}\overset{\overset{\displaystyle O^-AlCl_3}{|}}{\underset{+}{C}}{-}Cl} \xleftarrow{\mathrm{AlCl_3}} \mathrm{R{-}C}\begin{smallmatrix}{/\!\!/}\mathrm{O}\\ \backslash\mathrm{Cl}\end{smallmatrix} \xrightarrow{\mathrm{AlCl_3}} \mathrm{R{-}\overset{+}{C}{=}O} + \mathrm{AlCl_4^-} \qquad XI$$

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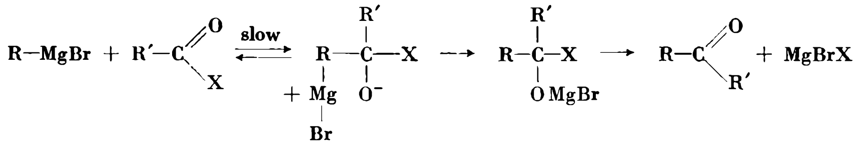
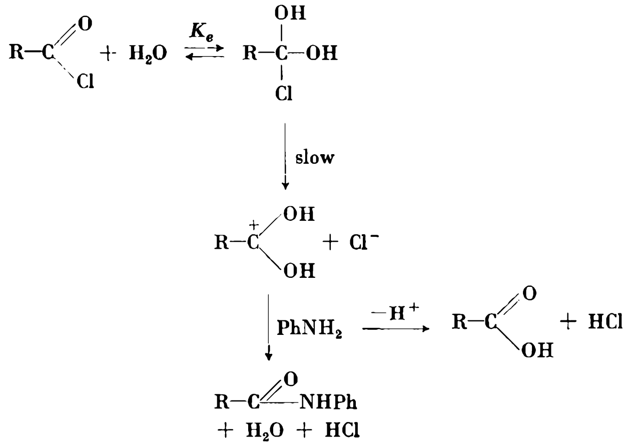
[26] **Brown** and **Hudson**, *J. Chem. Soc. 1953*, 3352.
[27] Reference 4, p. 345.
[28] **Gold, Hilton** and **Jefferson**, *J. Chem. Soc. 1954*, 2756.
[29] **Grunwald** and **Winstein**, *J. Amer. Chem. Soc. 70* (1948) 846.
[30] **Hall**, *J. Amer. Chem. Soc. 77* (1955) 5993.
[31] **Hudson** and **Wardill**, *J. Chem. Soc. 1950*, 1729.
[32] **Treffers** and **Hammett**, *J. Amer. Chem. Soc. 59* (1937) 1708.
[33] **Susz** and **Cassimatis**, *Helv. Chim. Acta 44* (1961) 395.

Both kinds of complexes would explain the enhanced acetylating properties produced by electrophilic agents. In this connection it is noted that the Grignard reaction may proceed via an intermediate, similar to structure *X*, the rate order[34] R-COF > R-COCl > R-COBr showing that it is formed by nucleophilic action of the incipient carbanion,

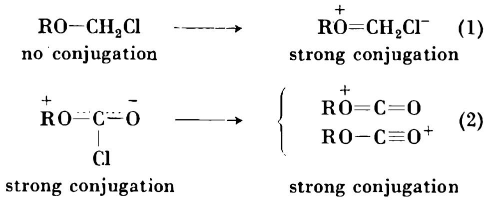


In aqueous solution however, pre-hydration must be considered, and in view of the ^{18}O exchange observed in the hydrolysis of benzoyl chlorides,[11] an alternative ionisation mechanism has been proposed, viz.



This mechanism, advanced by HALL[30] to explain the low reactivity of ethyl chloroformate compared with that of benzoyl chloride in highly aqueous solution, also explains the detection of a reactive intermediate[28] on the addition of aniline (p. 398).

According to HALL, the S_N1 reactivity of ethyl chloroformate should be greater than the S_N1 reactivity of benzoyl chloride, in view of the greater ease of electron release from the alkoxy-group. Thus α-chloromethyl ether is considerably more reactive ($\sim 10^{10}$ times) than benzyl chloride in ionising solvents. The analogy between alkyl and acyl chlorides is however unjustified, since the latter may be strongly conjugated in the ground state. This is illustrated as follows,



$$RO{-}CH_2Cl \longrightarrow \overset{+}{R}O{=}CH_2Cl^- \quad (1)$$

no conjugation — strong conjugation

$$\overset{+}{R}O{\cdots}\underset{\displaystyle Cl}{\underset{|}{C}}{\cdots}\overset{-}{O} \longrightarrow \left\{\begin{array}{l}\overset{+}{R}O{=}C{=}O\\ RO{-}C{\equiv}O^+\end{array}\right. \quad (2)$$

strong conjugation — strong conjugation

According to simple molecular orbital theory, reaction 2 leads to no increase in conjugation energy, but if allowance is made for electronic repulsions, an increase in conjugation energy, considerably less however than in process (1), is predicted.

Since the transition state lies between the initial and final structures, the change in conjugation energy may be small, and of the same order as changes in the energy of the σ-bonds (inductive effects). It is therefore difficult to predict the relative energies of the initial and transition states. It should also be noted that the acylium ion can adopt alternative structures analogous to allene and acetylene, which also complicates the interpretation.

It is possible therefore that the rate sequence discussed by HALL, e.g. which is found in highly aqueous media.

$$CH_3\text{-}COCl > Ph\text{-}COCl > EtO\text{-}COCl > Me_2N\text{-}COCl$$

in terms of an S_N2 mechanism for the first two and an S_N1 mechanism for the last one, may be the rate sequence for S_N1 ionisation. In this connection it is interesting to note that the ^{35}Cl nuclear quadrupole frequencies (Table 1) show that the ionic character of the C–Cl bonds increases in the same direction as the reactivity.

It is obvious that the differention between a direct ionisation mechanism (S_N1) in water and an ionisation mechanism preceeded by hydration is particularly difficult, and further measurements of the extent of ^{18}O exchange under conditions where rate determining ionisations have been postulated, must be made.

The brief discussion in this lecture has shown the multiplicity of reactions which are possible for acylation, and the progress which has been made in the past decade in unravelling the mechanisms.

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[34] FIESER and FIESER, *Organic Chemistry*, Reinhold, New York 1956, p. 183.