Acylation by Ketens and Isocyanates. A Mechanistic Comparison

By D. P. N. Satchell
DEPARTMENT OF CHEMISTRY, UNIVERSITY OF LONDON,
KING'S COLLEGE, STRAND, LONDON, WC2R 2LS

R. S. Satchell
DEPARTMENT OF CHEMISTRY, QUEEN ELIZABETH COLLEGE,
CAMPDEN HILL ROAD, LONDON, W8 7AH

1 Introduction

Ketens ($R_2C{=}C{=}O$) and isocyanates ($RN{=}C{=}O$) possess similar chemical structures and both types of compound have considerable industrial importance; usually, however, they feature only briefly, or not at all, in textbooks of organic chemistry. And although on occasion they crop up close together accidentally in chapters on molecular rearrangements, being produced respectively during the Wolff and Curtius rearrangements, their general preparation and, in particular, their reactions, are seldom compared. This general absence of what is really an obvious comparison is also noticeable in the research literature, and until very recently there had been virtually no cross-fertilization between researches with these two classes of compound. All this is now rapidly changing and the aim of this Review is to demonstrate how valuable such comparisons can be in the field of reaction mechanisms.

Ketens[1] and isocyanates [2,3] both undergo a variety of addition reactions to either single or double bonds in other compounds. Particularly characteristic are the additions to compounds HX and to molecules containing the $>C{=}C<$, $>C{=}N{-}$ and $>C{=}O$ groups, [equations (1)—(4)]; these are the reactions which have been most studied kinetically with a view to discovering their mechanisms. We shall concentrate particularly on reactions such as (1) and (2) and their catalysed counterparts. What is occurring here is, in effect, an acylation by the keten or isocyanate, the opening of the C=C, or N=C, double bond being the equivalent of leaving group departure in a more conventional acylation [*e.g.* equation (5)].[4] The most studied substrates HX have been alcohols, water, thiols, phenols, carboxylic acids, and amines. We deal with these in turn

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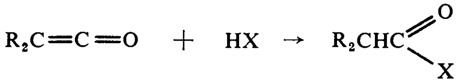
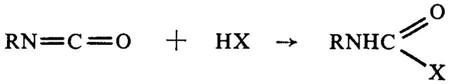
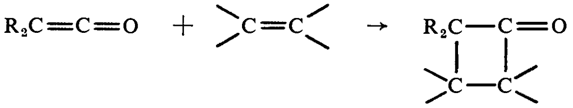
[1] R. N. Lacey, in 'The Chemistry of Alkenes', ed. S. Patai, Interscience, New York, 1964.
[2] A. Farkas and G. A. Mills, *Adv. Catalysis*, 1962, **13**, 393.
[3] S. Ozaki, *Chem. Rev.*, 1972, **72**, 457.
[4] D. P. N. Satchell, *Quart. Rev.*, 1963, **17**, 160.



$$\mathrm{R_2C{=}C{=}O + HX \rightarrow R_2CHC({=}O)X} \qquad (1)$$



$$\mathrm{RN{=}C{=}O + HX \rightarrow RNHC({=}O)X} \qquad (2)$$



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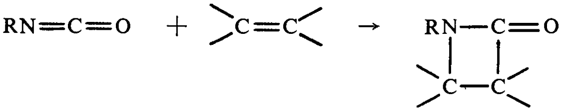
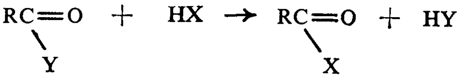


(4)

below, but first consider the general effects of changes in the groups R in the keten or isocyanate.



$$\mathrm{RC({=}O)Y + HX \rightarrow RC({=}O)X + HY} \qquad (5)$$

Virtually all the known reactions like (1) and (2) are heterolytic processes and, as we shall see, these mostly involve a kinetically dominant nucleophilic attack by X on the carbonyl carbon atom. In such circumstances it is natural to expect, as found experimentally, that electron withdrawal by R will facilitate reaction, the assumption being that this withdrawal will magnify the positive charge on the carbonyl carbon atom. However, the various theoretical calculations[5,6] on these unusual compounds with two perpendicular π-electron systems, although in very poor quantitative agreement, and even in places contradictory, do suggest, both for ketens and isocyanates, that changes in R have virtually no effect on the charge on the terminal oxygen atom, and that the charge on the carbonyl carbon atom is affected less than the charge on the isocyanate nitrogen atom (or the keten β-carbon atom). And, contrary to simple expectation, this latter charge can become more *negative* as electron withdrawal by R increases.[5] It is possible therefore that changes in R affect the overall velocity of reaction in the expected way mainly owing to their influence on the ease of proton transfer to the nitrogen and β-carbon atoms, processes which we shall find cannot, in fact, be kinetically

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[5] P. J. Lillford and D. P. N. Satchell, *J. Chem. Soc.* (*B*), 1970, 1016; A. C. Hopkinson, *J. C. S. Perkin II*, 1973, 795.

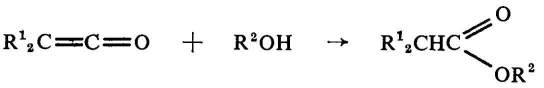
[6] B. M. Rode, W. Kosmus, and E. Nachbaur, *Chem. Phys. Letters*, 1972, **17**, 186; K. N. Houk, R. W. Strozier, and J. A. Hall, *Tetrahedron Letters*, 1974, 897; V. B. Zabrodin, *Russ. J. Phys. Chem.*, 1971, **45**, 376; S. P. Bondarenko, R. P. Tiger, E. V. Borisov, A. A. Bagaturyants, and S. G. Entelis, *Zhur. org. Khim*, 1974, **10**, 271.

ignored under the usual experimental conditions. Bulky R groups generally[1,2] hinder reactions (1) and (2) as they do also reactions (3) and (4). In any synchronous attack on the N=C or C=C bonds of the isocyanate or keten the substrate must approach from either above or below the molecular plane. This both minimizes steric effects and maximizes orbital overlap.

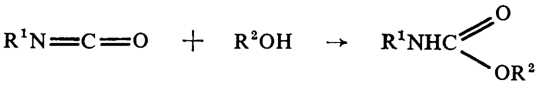
With some, although by no means all, substrates HX the reactions of most ketens and isocyanates with the pure liquid substrate is too fast for measurement by conventional techniques. It happens that in almost all kinetic studies to date an inert solvent has been used. The same is true of reactions like (3) and (4). The use of a solvent has the advantage that the reaction orders in both substrate and keten (or isocyanate) can be determined. Isocyanates appear stable in a variety of solvents, but ketens deteriorate rapidly in a surprising number of supposedly inert media owing to their ready polymerization and to their reactions with dissolved oxygen. It is found that ethers and aromatic hydrocarbons are the best solvents for kinetic work with ketens and it is fortunate for purposes of comparison that the bulk of the studies with isocyanates have also used such solvents. Only ketoketens ($R_2C{=}C{=}O$) have been successfully examined kinetically; aldoketens ($RHC{=}C{=}O$) are particularly susceptible to polymerization.[1] Isothiocyanates ($RN{=}C{=}S$) appear to behave mechanistically very much as do isocyanates.

2 Reaction with Alcohols

Reactions (6) and (7), whose equilibrium positions lie far to the right, lead to an ester and a urethane, respectively. In synthetic work a catalyst is normally added



$$R^1_2C{=}C{=}O + R^2OH \rightarrow R^1_2CHC(=O)OR^2 \qquad (6)$$



$$R^1N{=}C{=}O + R^2OH \rightarrow R^1NHC(=O)OR^2 \qquad (7)$$

since otherwise the reactions can be quite slow. Process (7) is of particular industrial importance because the reactions of di-isocyanates with glycols lead to the valuable polyurethanes.[7] Probably owing to this commercial interest the literature concerning reaction (7) is voluminous and includes the majority of the kinetic studies with isocyanates.[2,8] Much of this work is, however, of only marginal interest mechanistically, having been conducted under unsatisfactory conditions and/or having received incorrect interpretation. Moreover, kinetic

[7] J. H. Saunders and K. C. Frisch, 'Polyurethanes, Chemistry and Technology', Interscience, New York, 1962.

[8] S. G. Entelis and O. V. Nesterov, *Russ. Chem. Rev.*, 1966, **35**, 917; A. Petrus, *Internat. Chem. Eng.*, 1971, **11**, 314.

studies with di-isocyanates have only recently begun to use correct algebraic analyses.[9]

Compared with isocyanates there have been few kinetic studies of any sort with ketens, but of these the largest group again concerns alcoholysis. The results, put alongside the picture emerging for isocyanates, provide an interesting parallel.

A. Isocyanates.—(i) *The spontaneous reaction.* Kinetic studies with isocyanates got off to an unfortunate start,[10,11] and the influence of this has been long-lasting both procedurally and interpretively. Thus even today most studies still use Baker's conditions (employing roughly equal concentrations of isocyanate and alcohol and determining the apparent second-order rate constant), and Baker's mechanism for the spontaneous alcoholysis[11] is still sometimes alluded to as if it were a real possibility, whereas it has been evident for some years that it is not.[2,12] The difficulty in determining the second-order constant arises from the facts, now known, that the reaction proceeds largely (or even entirely) *via* certain alcohol polymers, and that the concentrations of these relative both to monomers and to each other must normally change as alcohol is consumed during the reaction. The observed second-order constant is therefore rarely properly constant even within a single kinetic run, and almost invariably depends upon the initial stoicheiometric alcohol concentration—as discovered by Baker and many others.[2,8] The situation is further complicated by the circumstance that apparently good second-order behaviour can sometimes be found, over a limited concentration range, owing either to the insensitivity of second-order plots or to the alcohol being present largely in one polymeric form. These various complications have led to much confused rationalization from which the field has been slow to emerge. By far the best way to examine these, and indeed most, systems is to use pseudo-first order conditions; in the present context this means keeping the alcohol in a ten (or more) fold excess over the isocyanate. Unfortunately this approach has been adopted only recently and by only a few workers.

Ephraim, Woodward, and Mesrobian,[13] followed by Oberth and Bruenner,[14] were among the earliest to suggest that both the kinetic complexities, and the fact that alcoholysis is almost invariably fastest in non-co-ordinating solvents,[2] can be explained by the participation of polymeric alcohol. But their treatments were rather elaborate and based on conjectures about the polymer concentrations, and their ideas were largely disregarded. It is now evident, however, that the

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[9] L. I. Sarynina, V. V. Evreinov, E. K. Khodzhasva, and S. G. Entelis, *Kinetika i Kataliz*, 1972, **13**, 314; G. Borkent and J. J. Van Aartsen, *Rec. Trav. chim.*, 1972, **91**, 1079.

[10] J. W. Baker and J. B. Holdsworth, *J. Chem. Soc.*, 1947, 713.

[11] J. W. Baker and J. Gaunt, *J. Chem. Soc.*, 1949, 9.

[12] W. G. P. Robertson and J. E. Stutchbury, *J. Chem. Soc.*, 1964, 4000.

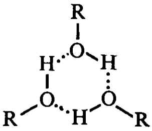
[13] S. Ephraim, A. E. Woodward, and R. B. Mesrobian, *J. Amer. Chem. Soc.*, 1958, **80**, 1326.

[14] A. E. Oberth and R. S. Bruenner, *J. Phys. Chem.*, 1968, **72**, 845.

contribution of polymeric alcohol is of paramount importance.[15-17] One analysis,[15] using diethyl ether as solvent, shows that towards *p*-chlorophenyl isocyanate the reactivity sequence is tetramer ≈ trimer ≫ dimer ≫ monomer. In this solvent the monomer (which contributes negligibly) and dimer are hydrogen-bonded to solvent molecules, (1), whereas the higher polymers are cyclic, [*e.g.* (2)]. In non-co-ordinating solvents all the alcohol species will be

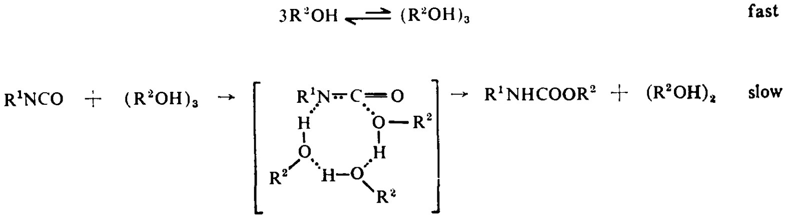
$ROH \cdots\cdots OEt_2$

(1)



(2)

solvent-free; in such systems the importance of polymer is again evident, but it seems that the monomers can also contribute significantly.[16] The reason[15] that the most reactive species are the polymers (and in co-ordinating solvents the solvent-free, cyclic polymers) is that the transition states in these isocyanate additions are probably cyclic. If it were just a matter of nucleophilic attack on carbon, species (1) should be as effective as species (2), if not more effective. The cumulative evidence for the involvement of cyclic transition states in the majority of the reactions we shall be considering is formidable. For RNCO systems, independent experimental work [18] suggests that the proton can be expected to be transferred directly to the nitrogen atom, as in species (3), rather than to the oxygen atom. This is in keeping, as noted above, with the effects observed on changing R in RNCO and also avoids the necessity of postulating a subsequent rapid prototropic rearrangement.



(3)

Scheme 1

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[15] S. A. Lammiman and R. S. Satchell, *J. C. S. Perkin II*, 1972, 2300.

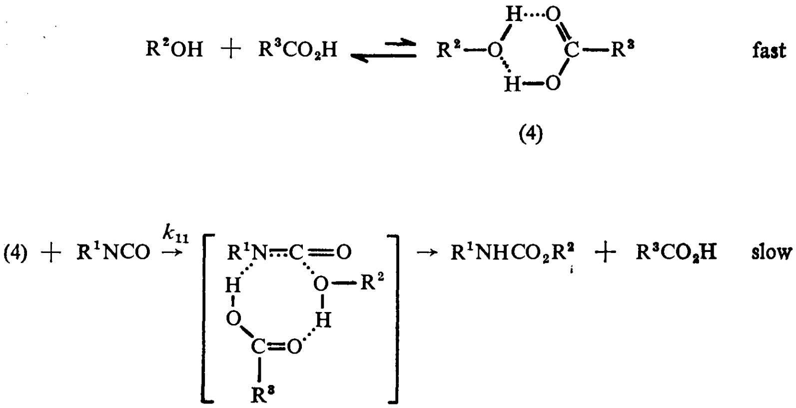
[16] R. P. Tiger, L. S. Bekhli, S. P. Bondarenko, and S. G. Entelis, *Zhur. org. Khim.*, 1973, 9, 1563.

[17] O. I. Kolodyazhnyi and L. I. Samarai, *Ukrain. khim. Zhur.*, 1973, 39, 1260.

[18] G. A. Olah, J. Nishimura, and P. Kreienbuehl, *J. Amer. Chem. Soc.*, 1973, 95, 7672.

The dependence of overall alcohol reactivity on the group R in ROH is complex and indicates competing steric, electronic, and possibly other factors.[2,8,15] This complexity, the moderate hydrogen isotope effect[9,17] ($k_H/k_D \approx 1.7$), the large negative value[8] of $\Delta S^{\ddagger}$ (*ca.* − 40 cal degree^{-1} mol^{-1}) and the small value[8] of $\Delta H^{\ddagger}$ (*ca.* 8 kcal mol^{-1}) are all compatible with a transition state such as (3). The small value of $\Delta H^{\ddagger}$ probably arises from the opposing effects of temperature on pairs of reactions such as those in Scheme 1. The fact that phenols, and alcohols carrying electron-withdrawing substituents, react relatively slowly[8] suggests that the nucleophilic attack on carbon is the dominant factor in fixing the energy of the transition states. It is no surprise that thiols, which are poor nucleophiles and form polymers with reluctance, react negligibly slowly with isocyanates in the absence of catalysts.[19]

(ii) *The carboxylic acid catalysed reaction.*[20] Relatively low concentrations of carboxylic acids catalyse the alcoholysis of isocyanates but their catalytic efficiency is inversely related to their acid strength. In ethereal solvents, in concentration regions where the acids are largely monomeric, the catalysed route displays a simple kinetic form, being first order in each reactant, *i.e.*, $d[\text{product}]/dt = k[\text{isocyanate}]\,[\text{alcohol}]_{\text{stoich}}[\text{acid}]$. It has been shown, using ethanol, *p*-chlorophenylisocyanate, and a series of acids, that reaction proceeds *via* a 1:1-alcohol–catalyst adduct whose concentration, although proportional to the product $[\text{alcohol}]_{\text{stoich}} \times [\text{acid}]$, depends little on acid strength. This, and other evidence, suggests that the adduct is cyclic. Scheme (2), in which the acid acts as a bifunctional catalyst, and assumes the role of the extra alcohol molecules



(4)

(5)

Scheme 2

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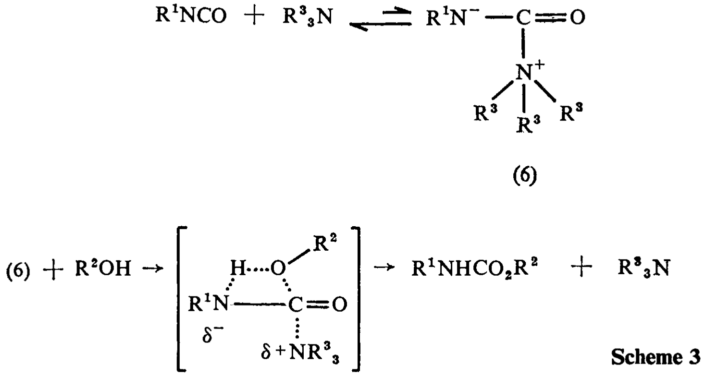
[19] J. Hetfleys, P. Svoboda, M. Jakcubkova, and V. Chvalovsky, *Coll. Czech. Chem. Comm.*, 1973, **38**, 717.

[20] S. A. Lammiman and R. S. Satchell, *J. C. S. Perkin II*, 1974, 877.

in the spontaneous reaction, is compatible with all the facts. The magnitude of k_{11} is inversely dependent on acid strength and this suggests that the acid's role in increasing the nucleophilicity of the alcohol is more important than its role in proton transfer.

(iii) ***The tertiary amine catalysed reaction.*** A good deal of attention has been paid to this type of catalysis[2,8] which (probably) most often obeys the simple kinetic form $d[\text{product}]/dt = k[\text{isocyanate}]\,[\text{alcohol}]_{\text{stoich}}[\text{amine}]$. Baker and co-workers[10] found that normally the strongest bases were the best catalysts, but that sterically hindered bases were comparatively inactive. This has been largely confirmed by later work.[8] Two mechanisms (Schemes 3 and 4) are compatible with these and other facts and it is difficult as yet to choose definitely between them. Baker, using methanol and working under unfavourable kinetic conditions, supported a scheme like Scheme 3 in view of the observed steric effects.[10]



fast

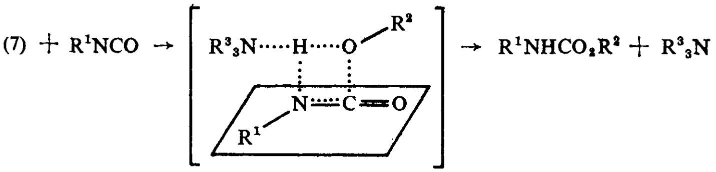
slow

Scheme 3

However, with thiols, phenols, and other acidic alcohols[19,21] polar complexes like (7) are certainly formed with tertiary bases in the usual solvents, and steric effects seem less important. Hence for these alcohols Scheme 4 is probably

$$R^2OH + R^3{}_3N \rightleftharpoons R^3{}_3N\cdots\cdots HOR^2 \text{ (or } R^3{}_3N^+H\cdots\cdots\bar{O}R^2) \qquad \text{fast}$$

(7)



slow

(8)

Scheme 4

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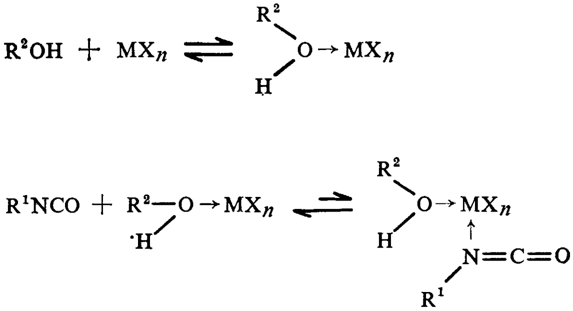
[21] A. Farkas and P. F. Strohm, *Ind. and Eng. Chem. (Fundamentals)*, 1965, **4**, 32; A. Farkas and K. G. Flynn, *J. Amer. Chem. Soc.*, 1960, **82**, 642; J. Burkus, *J. Org. Chem.*, 1962, **27**, 474; E. Dyer, J. F. Glenn, and E. G. Lendrat, *ibid.* 1961, **26**, 2919; A. K. Zhitinkina and M. V. Shoshtaeva, *Sin. Fiz. khim. Polim.*, 1968, 117.

followed. The parallel work with ketens also argues strongly in favour of this scheme for all alcohols (see below) but it may be that in the isocyanate reaction there is a transition from the mechanism of Scheme 3 to that of Scheme 4 as the interaction between catalyst and alcohol becomes stronger. Certainly complexes like (6) seem possible, if only because the dimerization of isocyanates can be catalysed by tertiary bases.[22] However, for isocyanates, unlike ketens, there has been no comparison of the effects of tertiary bases on the dimerization and on the alcoholysis. More work is needed here. Because the spontaneous reactions of phenols and thiols are so slow, the effect of tertiary base catalysis is especially marked for these substrates.

(iv) *Catalysis by metal derivatives.*[8] By far the most effective catalysts, and therefore the most interesting to industry, are various metal derivatives, notably metal acetylacetonates; alkyl-, alkoxy-, and halogeno-tin and lead compounds (such as dibutyltin dilaurate); and a variety of other, broadly similar species.[2,8] With weakly acidic alcohols these catalysts have activities a million, or more, times greater than tertiary amines, although with phenols they are less effective than are the amines. The metal-based catalysts are normally liquids or contain groups which render them soluble in organic solvents. At present there exists little understanding either of their sometimes great efficiency or of its dependence on structure. In essence they appear to be Lewis acid catalysts co-ordinating to either (or both) the alcohol and the isocyanate. Studies exist which favour all these possibilities.[23] A co-ordinated alcohol molecule would be rendered a much more powerful hydrogen acid and would perhaps readily protonate a free, or better, an adjacently bound isocyanate species, so leading to an ion-pair which could subsequently provide the products; Scheme 5 illustrates such a process.



(9)

$$(9) \rightarrow R^1NHC^+{=}O\,[R^2OMX_n]^- \rightarrow R^1NHCOOR^2 + MX_n$$

Scheme 5

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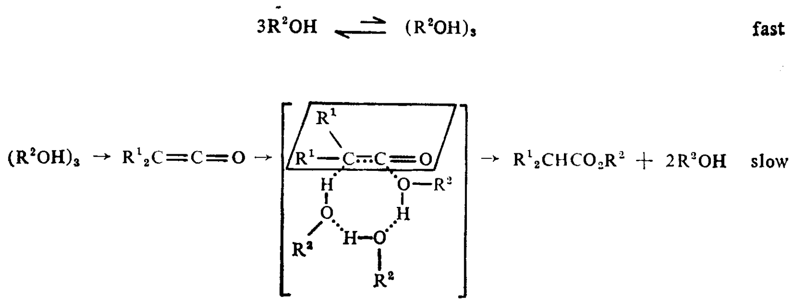
[22] K. G. Flynn and D. R. Nenortus, *J. Org. Chem.*, 1963, **28**, 3527.

[23] A. E. Oberth and R. S. Bruenner, *Ind. and Eng. Chem.* (*Funamentals*), 1969, **8**, 383; V. B. Zabrodin, O. V. Nesterov, and S. G. Entelis, *Kinetika i Kataliz*, 1969, **10**, 663; T. E. Lipatova, L. A. Bakalo, and L. V. Racheva, *Sin. Fiz. khim. Polim.*, 1973, 80.

Such a scheme could perhaps account qualitatively for all the facts. It involves an intramolecular electrophilic addition; this could be fast.

B. Ketens.—(i) *The spontaneous and carboxylic acid catalysed reactions.* Kinetic studies of these systems reveal in all essentials the pattern described above for isocyanates. For the spontaneous reaction[24] there is as yet no hard evidence for the participation of alcohol monomers, although they may be involved with sterically hindered alcohols which polymerize with difficulty.[25] The predominant route for various alcohols and dimethylketen in diethyl ether solution[24] is shown in Scheme 6 (*cf.* Scheme 1).



Scheme 6

For the carboxylic acid catalysis in ethereal solvents it is found,[24] as for isocyanates, that the catalytic efficiency falls as the acid strength rises and that the rate equation is $d[\text{products}]/dt = k[\text{keten}]\,[\text{alcohol}]_{\text{stoich}}[\text{acid}]$. A mechanism similar to Scheme 2 is highly probable.

As with isocyanates, thiols react very slowly with ketens in the absence of catalysts. There is good evidence that the spontaneous addition of alkyl thiols is predominantly a radical reaction.[26] However, in the presence of carboxylic acids[26] a powerful catalysis results whose mechanism is again probably analogous to Scheme 2.

(ii) *The tertiary amine catalysed reaction.* In an important series of studies, principally using toluene as solvent, Pracejus and co-workers[27] have shown that low concentrations of tertiary amines catalyse not only the reaction of ketens with alcohols, but also the dimerization of the keten. And although sterically hindered bases are less effective in both reactions, the dimerization is particularly dependent upon an unencumbered nitrogen atom. Since the catalysed dimerization presumably proceeds *via* an outline scheme such as Scheme 7, it seems unlikely

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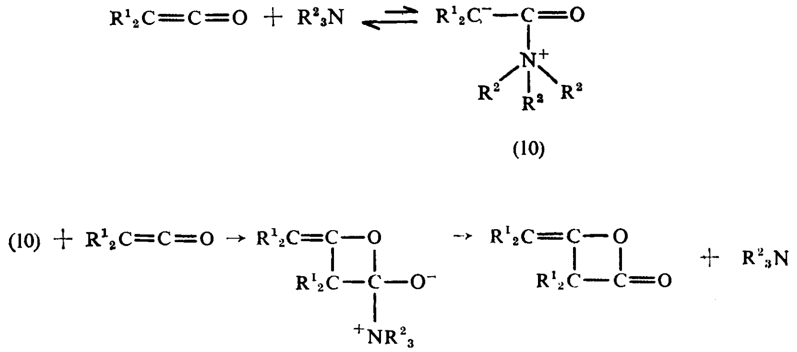
[24] P. J. Lillford and D. P. N. Satchell, *J. Chem. Soc.* (*B*), 1968, 889.
[25] W. T. Brady, W. L. Vaughn, and E. F. Hoff, *J. Org. Chem.*, 1969, **34**, 843.
[26] P. J. Lillford and D. P. N. Satchell, *J. Chem. Soc.* (*B*), 1970, 1303.
[27] A. Tille and H. Pracejus, *Chem. Ber.*, 1967, **100**, 196; R. Samtleben, *J. prakt. Chem.*, 1972, **314**, 157.



Scheme 7

that the alcoholysis can employ a mechanism in which the catalyst plays a similar (nucleophilic) role. Two other facts in strong support of a mechanism like Scheme 4, rather than one like Scheme 3, for the alcoholysis of ketens are (i), that alcohol–tertiary base equilibria are known in toluene, and (ii), that with the *strongest* bases, the rate equation $d[\text{products}]/dt = k[\text{keten}]\,[\text{alcohol}]_{\text{stoich}}\,[\text{base}]$ observed at the higher temperatures reduces at low temperatures to $d[\text{product}]/dt = k'[\text{keten}]\,[\text{base}]$.[27] This can be accounted for by pre-equilibrium of Scheme 4 shifting well to the right under the latter conditions. A mechanism like Scheme 3 cannot account for this kinetic effect. Other factors also point to the correctness of a scheme analogous to Scheme 4, and moderate steric effects would be expected in forming a transition state like (8), unless the groups R^1 and R^3 are quite small. The rather complete work with ketens therefore supports the suggestion of Farkas and Strohm[21] concerning isocyanates.

(iii) *Catalysis by acid amides.*[28] As we have seen, in the spontaneous and the carboxylic acid-catalysed reactions, alcoholysis is facilitated by species which effect a cyclic proton transfer to the β-carbon atom. It is no surprise to find therefore that acid amides, which can act as bifunctional catalysts [*e.g.* (12)], accelerate the alcoholysis. The rate equation is $d[\text{product}]/dt = [\text{keten}]\,[\text{amide}]\,[\text{alcohol}]_{\text{stoich}}$; the mechanism is doubtless Scheme 8. A similar route probably underlies the auto-catalysis by urethane[2] sometimes observed in the isocyanate reaction.

(iv) *Catalysis by metal derivatives.* One of the few groups to notice the similarity between keten and isocyanate reactions, Pracejus and co-workers,[29] have tested the effects of metal derivatives on keten alcoholysis. Surprisingly they drew a blank: only one compound (copper acetylacetonate) provided powerful catalysis. The significance of this result is not yet understood.

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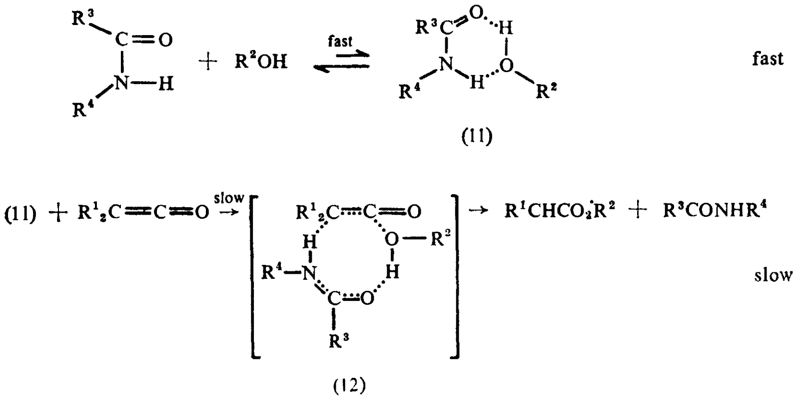
[28] H. Pracejus and R. Samtleben, *Tetrahedron Letters*, 1970, 2189.

[29] H. Pracejus and R. Samtleben, *Z. Chem.*, 1972, **12**, 153.



Scheme 8

3 Reaction with Water

The acylations (8) and (9) lead to substituted acetic and carbamic acids, respectively. Under appropriate conditions further reaction is possible in both

$$R_2C{=}C{=}O + H_2O \rightarrow R_2CHCO_2H \tag{8}$$

$$RN{=}C{=}O + H_2O \rightarrow RNHCO_2H \tag{9}$$

cases.[1,2] An excess of keten gives the anhydride (10), but with an excess of water little anhydride results, carboxylic acids mostly being less reactive than water towards ketens. Similar considerations probably also apply for isocyanates but

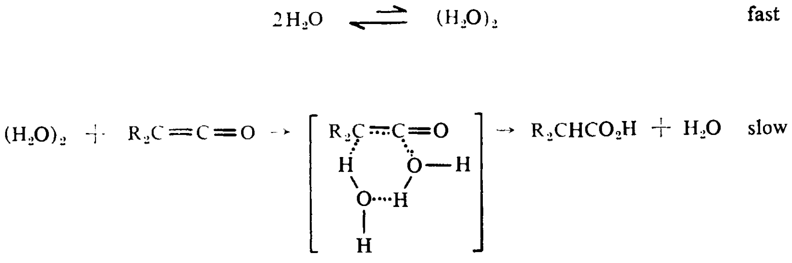
$$R_2CHCO_2H + R_2C{=}C{=}O \rightarrow (R_2CHCO)_2O \tag{10}$$

with the added complication that carbamic acids and their anhydrides lose carbon dioxide readily. An excess of isocyanate will eventually result in formation of the urea [equations (11) and (12)]. This release of carbon dioxide is the basis of the production of polyurethane foams.[7]

$$RNHCO_2H \xrightarrow{-CO_2} RNH_2 \xrightarrow{RNCO} (RNH)_2CO \tag{11}$$

$$RNHCO_2H \xrightarrow{RNCO} (RNHCO)_2O \xrightarrow{-CO_2} (RNH)_2CO \tag{12}$$

A. Ketens.[24]—The spontaneous reaction of ketens with water is auto-catalytic. This is expected in view of the catalysis of alcoholysis by carboxylic acids (p. 239). For dimethylketen in diethyl ether at water concentrations $\lesssim$ 0.3M, the spontaneous and acid-catalysed routes have the rate equations $d[\text{product}]/dt = k[\text{keten}][\text{water}]^2$ and $d[\text{product}]/dt = k[\text{keten}][\text{water}][\text{acid}]$, respectively. When $[H_2O] < 0.3$M little polymeric water exists in ether at ordinary temperatures, but significant amounts of polymer form at higher concentrations. In this region the reaction order in water rises above 2 in the spontaneous hydrolysis. With $[H_2O] \lesssim 0.3$M, the mechanism of Scheme 9 is probable for the spontaneous reaction. The involvement of polymeric water is supported by the increase in order in this species at high concentrations. Other polymers will then doubtless coexist with the dimer and more than one route will be viable. Polymeric water is clearly much more reactive than the monomer for whose participation there is no evidence. The parallel with alcoholysis is striking (p. 239).



(13)

Scheme 9

In the product-catalysed reaction the acid presumably takes over the role of the second water molecule in (13) in a mechanism analogous to Scheme 2. In non-co-ordinating solvents different reactions orders may prevail owing to the greater extent of hydrogen-bonding.

No studies exist of catalysis by tertiary bases.

B. Isocyanates.—The hydrolysis of isocyanates has not yet been studied under satisfactory conditions. However, it is evidently catalysed by tertiary bases,[2] and, as for ketens, the spontaneous reaction shows every sign of involving polymeric water. Thus the order in water is greater than unity,[30] and the reaction is faster in benzene than in dioxan.[2] The latter type of finding is common to all the spontaneous reactions with which we are dealing. It arises not because the monomeric substrate is deactivated in the co-ordinating solvent by hydrogen-bonding to the solvent, as has often been suggested—quite the reverse, such solvents

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[30] R. P. Tiger, L. S. Bekhli, and S. G. Entelis, *Kinetika i Kataliz*, 1971, **12**, 318.

act as feeble base catalysts—but because polymeric substrate is more abundant in non-co-ordinating solvents and this is the dominant factor in fixing reactivity.

4 Reaction with Carboxylic Acids

For both ketens and isocyanates the initial product here is an anhydride, usually an unsymmetrical anhydride. In the presence of an excess of acid the initial product tends to react further, as shown in (13) and (14). The particular product mixture depends upon the contact time and the other conditions.[31] Reaction (13) is used industrially to manufacture acetic anhydride and in the laboratory for preparation of unsymmetrical carboxylic anhydrides.

$$\begin{array}{lcl} R^1{}_2C{=}C{=}O \;+\; R^2CO_2H \;\rightarrow & R^1{}_2CHCOO{\cdot}COR^2 & \qquad (13) \\ & \downarrow R^2CO_2H & \\ & (R^2CO)_2O + R^1{}_2CHCO_2H & \\ & \downarrow & \\ & \mathit{etc} & \end{array}$$

$$\begin{array}{lcl} R^1N{=}C{=}O \;+\; R^2CO_2H \;\rightarrow & R^1NHCOO{\cdot}COR^2 & \qquad (14 \\ & \downarrow R^2CO_2H & \\ & (R^2CO)_2O + R^1NHCO_2H & \\ & \downarrow & \\ & R^1NH_2 + CO_2 & \end{array}$$

All but the strongest carboxylic acids react relatively slowly at ordinary temperatures so that in most cases where other keten and isocyanate additions are catalysed by carboxylic acids little of the catalyst is consumed.

A. Ketens.[32]—Kinetic studies of the first step of equation (13), using a series of substituted acetic acids with diphenylketen in dichlorobenzene and with dimethylketen in diethyl ether solution, show that for acids weaker than monochloroacetic acid the rate of spontaneous addition is inversely related to acid strength. On the other hand the strongest acids, dichloro- and especially trifluoro-acetic acid, add relatively rapidly. The rate equation is normally $d[\text{product}]/dt = k[\text{keten}]\,[\text{acid}]_{\text{stoich}}$. At the concentrations used the acids are largely monomeric in ether and dimeric in dichlorobenzene. For the weaker acids, whose nucleophilicity is evidently more important than their acidity, the

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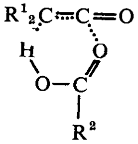
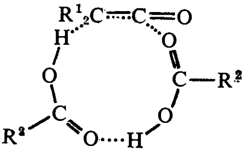
[31] W. D'Olieslager and I. De Aguirre, *Bull. Soc. chim. France*, 1967, 179; M. L. P. De Troparevsky, A. E. A. Mitta, and A. Troparevsky, *Anales Asoc. quim. argentina*, 1973, **61**, 227.

[32] J. M. Briody, P. J. Lillford, and D. P. N. Satchell, *J. Chem. Soc.* (*B*), 1968, 885.

transition states (14) and (15) are probable. With a bifunctional substrate the polymer is clearly of no great advantage, but happens to be the predominant form in dichlorobenzene.



(14)



(15)

In the vapour phase[33] the reaction of keten with acetic acid also involves just the monomer and the appropriate transition state is (14; $R^1 = H$, $R^2 = Me$) which, sensibly enough, and as pointed out by Blake and Davies, is the same as that proposed for the thermal decomposition of acetic anhydride. Indeed it is important to realize that the mechanisms of all the various additions we are considering have implications for the transition states of the corresponding eliminations (which in most cases have not yet been studied).

The predominantly electrophilic mechanism involved for addition of the strongest acids is discussed below.

B. Isocyanates.—Little clear-cut kinetic work exists here. What is known[34] is strikingly similar to the findings with ketens. Again there is an evident change in mechanism from predominantly nucleophilic to predominantly electrophilic addition at an acid strength about that of monochloroacetic. The nucleophilic route can be catalysed by tertiary amines, the electrophilic route by boron fluoride.

5 Reaction with Amines

With ketens primary and secondary amines lead to amides and with isocyanates to ureas [equations (15) and (16) respectively]. Normally the equilibrium positions of processes (15) and (16) lie far to the right[1,2] but for isothiocyanates a

$$R^1_2C{=}C{=}O + R^2NH_2 \rightleftharpoons R^1_2CHCONHR^2 \qquad (15)$$

$$R^1N{=}C{=}O + R^2NH_2 \rightleftharpoons R^1NHCONHR^2 \qquad (16)$$

more evenly balanced position can be obtained;[35] in this case primary amines lead to ureas which can cleave in two directions [equation (17)].

$$R^1NCS + R^2NH_2 \rightleftharpoons R^1NHCSNHR^2 \rightleftharpoons R^2NCS + R^1NH_2 \qquad (17)$$

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[33] P. G. Blake and H. H. Davies, *J. Chem. Soc.* (*B*), 1971, 1727.

[34] S. Ozaki and S. Shimada, *Nippon Kagaku Zasshi*, 1959, **80**, 430.

[35] W. Vanasshe and G. Hoornaert, *Bull. Soc. chim. belges*, 1971, **80**, 505.

A. Isocyanates.—(i) *The spontaneous reaction.* It is now widely[36] agreed that the general kinetic form of the spontaneous reaction is d[product]/dt = $\{k_1$[amine] + k_2[amine]^2 + k_3[amine] [urea product]$\}$ [isocyanate]. Clearly the monomer can react, but the relative importance of each of the terms for any given system depends upon the amine, the solvent and the relative concentrations of amine and isocyanate. With an excess of amine the auto-catalytic term is of little importance. As the dielectric constant of the medium is raised the overall velocity rises but, for any fixed value of [amine]$_{\text{stoich}}$, the ratio k_1[amine]/k_2[amine]^2 falls as the hydrogen-bonding capacity of the solvent, and therefore the ratio [monomer]/[dimer], decreases. Bulky substituents in either the isocyanate or the amine slow the reaction down, but otherwise an increase in amine basicity leads to a faster rate. The same kinetic pattern is found for the forward steps of the isothiocyanate equilibria.[35]

(ii) *Catalysis by tertiary nitrogen bases.* Catalysis has been observed[2] but it is relatively feeble on a pK_a basis: for a tertiary base of the same pK_a as the amine undergoing acylation the kinetic term representing self-catalysis (*i.e.* k_2[amine]^2) is normally much more important than that for catalysis by the tertiary base in spite of the fact that steric effects seem small in the latter catalysis.[37] In general therefore the presence of a tertiary base appears to add a small extra term to the rate equation, but the exact kinetic form of this catalysis is still uncertain.[2,37,38]

(iii) *Catalysis by bifunctional catalysts such as amides, ureas, and carboxylic acids.* Such catalysts are relatively very effective compared with tertiary amines.[37] As for the addition of *O*-nucleophiles to isocyanates, the efficiency of carboxylic acids varies inversely with their acid strength. This fact, and the great efficiency of bifunctional catalysts generally, points strongly to the occurrence of cyclic transition states in their reactions [*e.g.* (18)]. The same type of cycle cannot be written for tertiary bases which may assist here *via* transition states like (16) in which the base plays two contradictory roles; the net effect is slight catalysis because in all the cycles it is nucleophilic attack on the carbonyl carbon atom which is the dominant feature. Overleaf are illustrated the likely transition states (16)—(19) for the various catalytic paths to aminolysis. These routes almost certainly involve a rapid, prior association of amine with catalyst, followed by a rate-determining attack on the isocyanate, *e.g.* Scheme 10. If the pre-equilibrium lies well to the left this scheme leads to the correct kinetic form; the scheme is also compatible with the moderate primary hydrogen isotope effects[35,37] and with the usual values of $\Delta S^{\ddagger}$ (*ca.* -40 cal deg^{-1} mol^{-1}) and of $\Delta H^{\ddagger}$ (*ca.* 6 kcal mol^{-1}) for the various catalysed routes.[38,39] The low value of $\Delta H^{\ddagger}$ is again expected (see p. 236) from the opposing effects of temperature on the processes of Scheme 10.

All these conclusions are strongly supported by related work[39,40] on the

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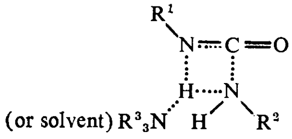
[36] I. De Aguirre and J. C. Jungers, *Bull. Soc. chim. France*, 1965, 1316; N. K. Vorob'ev and O. K. Shebanova, *Izvest. V.U.Z. Khim. i. khim. Teknol.*, 1974, **17**, 688.

[37] J. M. Briody and D. Narinesingh, *Tetrahedron Letters*, 1971, 4143.

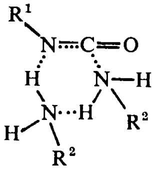
[38] N. K. Vorob'ev, E. A. Chizhova, G. E. Titova, and O. K. Shebanova, *Izvest. V.U.Z. Khim. i khim. Teknol.*, 1972, **15**, 700.

[39] A. P. Grekov and V. V. Shevchenko, *Reakts. spos. org. Soedinenii*, 1968, **5**, 47.

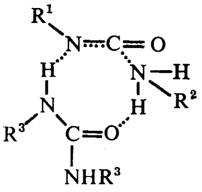
[40] A. P. Grekov and G. V. Ostrosko, *Zhur. org. Khim.*, 1974, **10**, 530.



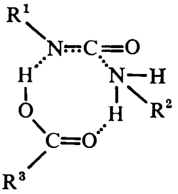
(16)



(17)



(18)



(19)

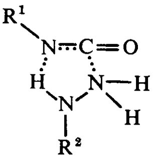
$$2R^2NH_2 \rightleftharpoons (R^2NH_2)_2 \qquad \text{fast}$$

$$(R^2NH_2)_2 + R^1NCO \longrightarrow [(17)] \longrightarrow R^1NHCONHR^2 + R^2NH_2 \qquad \text{slow}$$

Scheme 10

acylation of hydrazides in benzene solution [reaction (18)]. Here the spontaneous reaction probably has no important kinetic terms in $[R^2NR^3NH_2]^2$ when $R^3 = H$. This is sensible since the hydrazide itself can then act as a bifunctional reagent, as in (20).

$$R^1NCO + R^2NR^3NH_2 \rightarrow R^1NHCONHNR^2R^3 \qquad (18)$$



(20)

B. Ketens.[41,42]—The information available for ketens again bears a striking similarity to that outlined for isocyanates. Thus the rate equation for the spontaneous reaction has the form $d[\text{product}]/dt = \{k_1[\text{amine}] + k_2[\text{amine}]^2\}$

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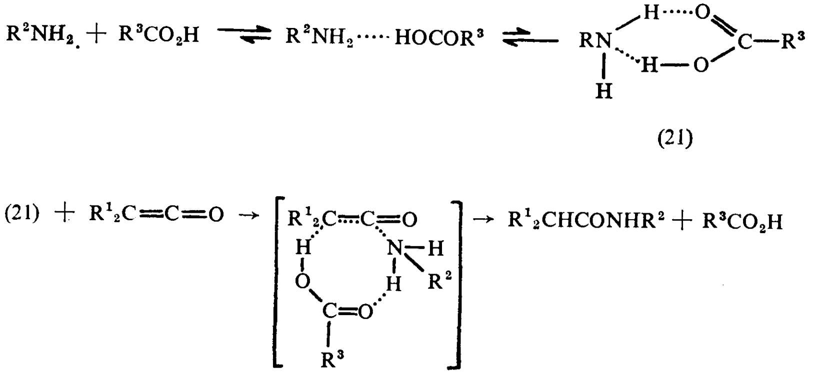
[41] P. J. Lillford and D. P. N. Satchell, *J. Chem. Soc.* (*B*), 1967, 360.

[42] J. M. Briody and D. P. N. Satchell, *Tetrahedron*, 1966, **22**, 2649; P. J. Lillford and D. P. N. Satchell, *J. Chem. Soc.* (*B*), 1968, 54.

[keten] in both ether and benzene solutions. In both solvents, in the absence of steric hindrance, both k_1 and k_2 are directly related to the strength of the base. Auto-catalysis by the amide product has not been observed, probably because the experimental conditions involved use of an excess of amine. Minor catalysis by tertiary amines and major catalysis by carboxylic acids are again found and their kinetic forms have been more clearly established than for the isocyanate reactions. With carboxylic acids the inverse dependence on acid strength appears yet again, and in diethyl ether where the acids exist as monomers, the observed rate equation is $d[\text{product}]/dt = k[\text{amine}]\,[\text{keten}]\,[\text{acid}]_{\text{stoich}}$. Scheme 11,

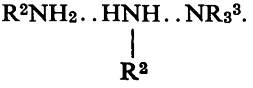

(21)

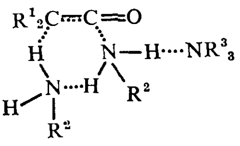
(22)

Scheme 11

analogous to Scheme 2, is strongly suggested. An amine-catalysed addition of the acid, followed by acylation of amine by the anhydride formed, plays a negligible part in these reactions.

In catalysis by tertiary amines the rate equation for the spontaneous reaction is augmented to $d[\text{product}]/dt = \{(k_1 + k'_1[\text{tertiary amine}])\,[\text{amine}] + (k_2 + k'_2[\text{tertiary amine}])\,[\text{amine}]^2\}\,[\text{keten}]$. Hence the tertiary amine can evidently assist both the monomer and dimer routes. The transition state for the path controlled by k'_2 is presumably (23), and could be formed from keten and the species


$$R^2NH_2..\underset{\substack{|\\ R^2}}{HNH}..NR_3^3.$$


(23)

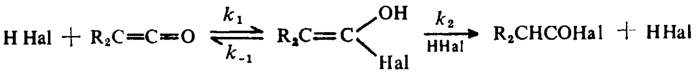
6 Reaction with Strong Hydrogen Acids

As mentioned above, carboxylic acids which are stronger than monochloroacetic acid undergo electrophilic addition to both ketens and isocyanates. Other classes of powerful hydrogen acids have been little studied with isocyanates, but with ketens the hydrogen halides also display electrophilic addition[43] to give finally acyl halides, as in equation (19). These hydrogen halide additions, like

$$\mathrm{R_2C{=}C{=}O + HHal \rightarrow R_2CHCOHal} \qquad (19)$$

that of trifluoroacetic acid, are very fast compared to the other types of addition so far considered; the catalysis of reactions of ketens[44] (and probably of isocyanates) by hydrogen halides and other mineral acids arises from their preliminary conversion into the acyl halide, acyl hydrogen sulphate, *etc.* The widespread belief, often voiced in textbooks,[45] that ketens are more reactive species than the corresponding acyl halides is mistaken. It arose because ketens are often used in the presence of sulphuric acid as catalyst, when the observed reactivity is probably that of the acyl hydrogen sulphate, which is indeed greater than that of the acyl halide.[46] In the absence of catalysts ketens have reactivities lying between those of the corresponding acyl halides and anhydrides.[41]

The kinetics of addition of hydrogen halides and of trifluoroacetic acid to ketens in ethereal solvents exhibit[43] a rate equation of the form d[product]/dt = a[hydrogen halide]^2 [keten]/(1 + b[hydrogen halide]). One explanation is mechanism (20), since application of the steady-state approximation leads to:



$$\mathrm{HHal + R_2C{=}C{=}O \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R_2C{=}C\begin{matrix}\diagup OH\\ \diagdown Hal\end{matrix} \xrightarrow[\mathrm{HHal}]{k_2} R_2CHCOHal + HHal} \qquad (20)$$

d[product]/dt = k_1k_2[HHal]^2 [keten]/(k_{-1} + k_2[HHal]). In this mechanism the prototropic second step thus becomes rate-determining at small values of [HHal]. Observed isotope effects and relative reactivities are also compatible with this mechanism which constitutes the only substantial evidence for an initial *O*-protonation of ketens throughout the field. Everywhere else the facts point to the direct, usually synchronous, transfer to the β-carbon atom.[5,43] The general findings for isocyanates are, of course, similar and it will be interesting to learn whether the addition of strong acids to isocyanates does in fact continue the parallelism.

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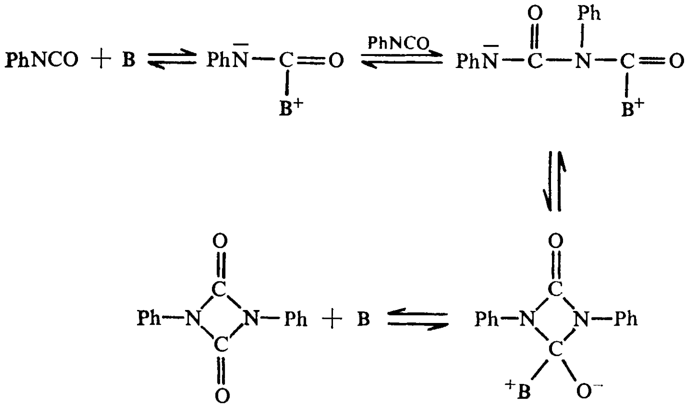
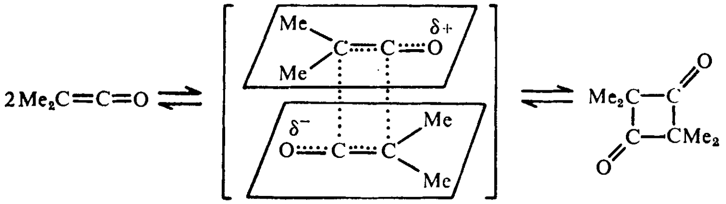
[43] P. J. Lillford and D. P. N. Satchell, *J. Chem. Soc.* (*B*), 1968, 897.
[44] D. P. N. Satchell, *Chem. and Ind.*, 1974, 683.
[45] N. L. Allinger, M. P. Cava, D. C. De Jough, C. R. Johnson, N. A. Lebel, and C. L. Stevens, 'Organic Chemistry', Worth Publications Inc., New York, 1971.
[46] E. A. Jeffrey and D. P. N. Satchell, *J. Chem. Soc.*, 1962, 1887.

7 Addition to Compounds Containing Double-bonds

This is another type of reaction in which the behaviour of ketens and isocyanates is evidently very similar. Briefly it can be said that two heterolytic mechanisms have been identified: a zwitterionic, step-wise scheme and a simple four-centre addition. The step-wise scheme is found in the tertiary base-catalysed dimerization of both ketens, (Scheme 7), and isocyanates,[47] (Scheme 12), and the straightforward four-centre route (which is believed to involve a weakly polar and slightly distorted transition state) in the uncatalysed dimerization of ketens,[48] (Scheme 13), and in many additions of ketens and isocyanates to olefins.[49] On the other hand, addition of isocyanates to C=N bonds is normally step-wise,[50] while both routes occur simultaneously in particularly favourable circumstances.[51] The balance



Scheme 12



Scheme 13

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[47] R. E. Buckles and L. A. McGrew, *J. Amer. Chem. Soc.*, 1966, **88**, 3582.
[48] R. Huisgen and P. Otto, *J. Amer. Chem. Soc.*, 1968, **90**, 5342.
[49] J. E. Baldwin and J. A. Kapecki, *J. Amer. Chem. Soc.*, 1970, **92**, 4868; F. Effenberger, G. Prossel, and P. Fischer, *Chem. Ber.*, 1971, **104**, 2002.
[50] H. Ulrich, *Accounts Chem. Res.*, 1969, **2**, 186.
[51] R. Huisgen and P. Otto, *J. Amer. Chem. Soc.*, 1969, **91**, 5922.

between these heterolytic routes depends upon solvent polarity and other factors as yet unelucidated. The myth that electrocyclic reactions proceed *via* mechanisms which are neither heterolytic nor homolytic has fortunately not yet affected discussion in this part of the electrocyclic field.

8 Conclusions

The remarkable similarity between the results obtained with isocyanates and with ketens hardly needs further emphasis. What is particularly impressive is the virtual identity of the respective rate equations and the close parallelism in substrate reactivity towards both classes of compound *i.e.*, amines $\gg$ alcohols $\simeq$ water $\gg$ thiols $<$ carboxylic acids $\ll$ trihaloacetic acids and hydrogen halides. For both classes there exist also both a nucleophilic and an electrophilic route to addition, with the changeover point in mechanism occurring in each case at species HX of pK_a close to that of chloroacetic acid.

Cyclic transition states are, of course, to be expected for reactions like (3) and (4), but the widespread occurrence of cyclic transition states during the addition of species HX in non-hydroxylic solvents, is also now hardly to be doubted. As explained in the Introduction such addition is equivalent to the acylation of HX and the frequently proposed synchronous transfer of a proton to the nitrogen or β-carbon atoms is equivalent[44] to acid-catalysed assistance of leaving-group departure in more conventional acylations, *e.g.* (5). In conventional acylations in hydroxylic media this catalysis is effected by solvent molecules (or by deliberately added acid) and is always available. It is most significant therefore that in non-hydroxylic media, where solvent hydrogen-bonding is *not* available, the mechanisms of conventional acylations are invariably observed to change towards routes involving cyclic transition states, closely resembling those considered in this Review, in which extra substrate or catalyst molecules effect the cyclic transfer of protons from substrate to leaving group.[43,44] These cycles not only provide catalysis of leaving group departure, they supply too a simultaneous base-catalysis of proton removal from the substrate and also help to minimize charge separation. Acylation by ketens and isocyanates therefore fits nicely into the current overall picture of acylation in non-hydroxylic solvents.