The Friedel–Crafts Acylation of Alkenes

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1 Introduction

Friedel–Crafts acylation refers to that substitution of a hydrogen atom by an acyl group which occurs under the influence of certain strongly acidic catalysts.[1] The reaction has been applied to alkenes since 1892 and has been used in the synthesis of acyclic, cyclic, terpenic, steroidal, and aromatic ketones. Several general reviews[1,2] on Friedel–Crafts reactions have included a discussion of alkene acylations but, despite this, textbooks still imply that only aromatic substrates acylate satisfactorily.[3] Although the reactive intermediates in alkene acylations do permit a considerably greater variety of reactions than their aromatic counterparts, the careful observance of optimum reaction conditions allows reactions that are of considerable synthetic utility.[4]

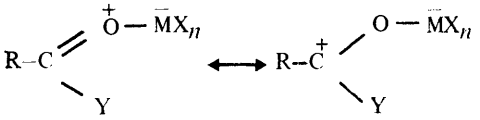
This review describes the interaction of non-functionally-substituted alkenes and Friedel–Crafts acylating agents. Although the products obtained may be rationalized in terms of normal carbonium ion processes, it will become clear that little is known concerning the detailed mechanism of even the simplest reaction steps. A discussion of side reactions is included in view of their significance in synthetic work. Finally, since many reactions herein contravene the definition of acylation as a substitution process, for the purpose of this review the term acylation is used in a broader sense to include reactions involving addition to the alkene bond.

2 The Acylating Species

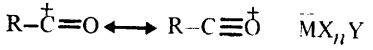
The directive effects of substituents at the alkene bond leave little doubt that Friedel–Crafts acylation involves electrophilic attack by the acylating agent upon the alkene. The means by which catalyst–acylating agent interactions produce an increased electrophilicity of the acylating agent are outlined below.

Acyl halides and Lewis acids form oxonium complexes (1), acylium salts (2), or mixtures of these species.[5] *X*-Ray studies of isolated oxonium complexes (1) confirm co-ordination *via* oxygen.[6] Weakening of the C=O bond is evident from

[1] G. A. Olah, 'Friedel–Crafts and Related Reactions', Wiley, New York, 1963.
[2] G. Baddeley, *Quart. Rev.*, 1954, **8**, 355; D. P. N. Satchell, *ibid.*, 1963, **17**, 160; P. F. G. Praill, 'Acylation Reactions', Pergamon Press, London, 1963.
[3] J. G. Sharefkin, *J. Chem. Educ.*, 1962, **39**, 206.
[4] H. O. House, 'Modern Synthetic Reactions', Benjamin, New York, 1965.
[5] H. H. Perkampus and W. Weiss, *Angew. Chem. Internat. Edn.*, 1968, **7**, 70.
[6] S. E. Rasmussen and N. C. Broch, *Chem. Comm.*, 1965, 289; W. Weiss and B. Chevrier, *ibid.*, 1967, 145.



(1)



(2)

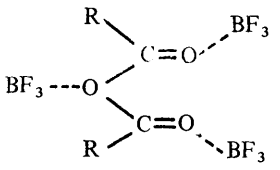
the increased bond length and from the decreased carbonyl stretching frequency in the i.r. spectrum.[7] In the n.m.r. spectra[8] the α-protons exhibit a downfield shift of τ *ca.* 0·5—1·0 as a result of such co-ordination, indicating the existence of a partial positive charge upon the carbonyl carbon. Although it seems highly likely that oxonium complexes are active acylating species it is difficult to provide indubitable evidence of this, since the molecular predominance of (1) in an acylating system does not preclude acylation *via* a small equilibrium concentration of acylium ions. Many acylium salts (2) have been isolated and all appear to be active in *C*-acylations.[9] The shortened C=O bond length[10] and the extent of increase in the carbonyl stretching frequency[11] indicate that the positive charge is localized principally upon the carbonyl carbon. This is supported by the large downfield shift (τ *ca.* 1·0—2·0) exhibited by the α-protons in the n.m.r. spectrum[12] and more directly by the marked deshielding of the carbonyl carbon in the ^{13}C n.m.r. spectrum.[13] Cryoscopic investigations[11,12] indicate that little or no ion separation occurs even in highly polar media, hence it is not acylium ions but (sterically more demanding) ion-pairs which probably effect acylation.

Aluminium chloride[14] and other strong Lewis acids react with carboxylic anhydrides to afford acyl halides:

$$(RCO)_2O + 2AlCl_3 \rightarrow RCOCl,AlCl_3 + RCO_2AlCl_2$$

[7] B. P. Susz and D. Cassimatis, *Helv. Chim. Acta*, 1961, **44**, 943.
[8] G. A. Olah, M. E. Moffat, S. J. Kuhn, and B. A. Hardie, *J. Amer. Chem. Soc.*, 1964, **86**, 2198.
[9] E. Lindner, *Angew. Chem. Internat. Edn.*, 1970, **9**, 114.
[10] J. M. LeCarpentier and R. Weiss, *Chem. Comm.*, 1968, 596; J. M. LeCarpentier, R. Weiss, and B. Chevrier, *Bull. Soc. Franc. Mineral. Crist.*, 1968, **91**, 544.
[11] B. P. Susz and J. J. Wuhrmann, *Helv. Chim. Acta*, 1957, **40**, 971; G. A. Olah, S. J. Kuhn, W. S. Tolgyesi, and E. B. Baker, *J. Amer. Chem. Soc.*, 1962, **84**, 2733; see also D. Cassimatis, J. P. Bonnin, and T. Theophanides, *Canad. J. Chem.*, 1970, **48**, 3860.
[12] G. A. Olah, S. J. Kuhn, S. H. Flood, and B. A. Hardie, *J. Amer. Chem. Soc.*, 1964, **86**, 2203; G. A. Olah and M. B. Comisarow, *ibid.*, 1966, **88**, 4442; G. A. Olah and A. M. White, *ibid.*, 1967, **89**, 7072.
[13] G. A. Olah, W. S. Tolgyesi, S. J. Kuhn, M. E. Moffat, I. J. Bastien, and E. B. Baker, *J. Amer. Chem. Soc.*, 1963, **85**, 1328.
[14] R. E. VanDyke and H. E. Crawford, *J. Amer. Chem. Soc.*, 1951, **73**, 2018; G. Baddeley and D. Voss, *J. Chem. Soc.*, 1954, 418.

Milder Lewis acids result in adduct formation without decomposition but the resulting complexes have received little attention. Benzoic anhydride–boron trifluoride gives a 1 : 3 adduct, presumably (3).[15] Tin(IV) chloride affords 1 : 1 adducts[16] which exist predominantly in the *cis*-chelated form (4).



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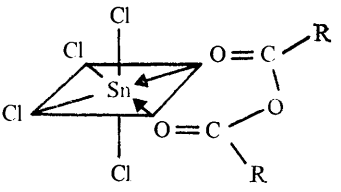

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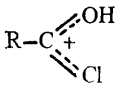

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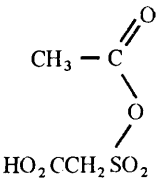


(6)

Lewis-acid-catalysed acylations using carboxylic acids most commonly employ zinc chloride–acetic acid–acetic anhydride as the catalyst–solvent system. Acylation *via* a mixed anhydride seems likely. Brönsted-acid-catalysed acylations using acid chlorides or anhydrides are not common. In sulphuric acid solution acyl halides react *via* haloacyloxonium ions (5)[17] whereas acetic anhydride is thought to react *via* the dissymmetric anhydride (6).[18] Trifluoracetic-anhydride-catalysed reactions of carboxylic acids similarly involve mixed anhydrides (RCO_2COCF_3).[19] Sulphuric-acid-catalysed intramolecular acylations of unsaturated carboxylic acids are frequently reported, and polyphosphoric acid (PPA) may be used in conjunction with carboxylic acids for both intra- and inter-molecular acylations.[20]

[15] D. Cook, *Canad. J. Chem.*, 1962, **40**, 445.
[16] P. Hunt and D. P. N. Satchell, *J. Chem. Soc.*, 1964, 5437.
[17] F. Carre and R. Corriu, *Bull. Soc. chim. France*, 1967, 2898; F. Carre, R. Corriu, and G. Dabosi, *ibid.*, 1967, 2905.
[18] A. Casaderval and A. Commeyras, *Bull. Soc. chim. France*, 1970, 1850, 1856; A. Casaderval, A. Commeyras, P. Paillous, and H. Collet, *ibid.*, 1970, 719; see also N. Bodor and M. J. S. Dewar, *Tetrahedron*, 1969, **25**, 5777.
[19] J. M. Tedder, *Chem. Rev.*, 1955, **55**, 787.
[20] S. B. Kulkarni and S. Dev, *Tetrahedron*, 1968, **24**, 553.

These reactions are usually represented as proceeding *via* acylium ion formation, such as is known to occur under more highly acidic conditions.[21]

3 Reactivities

The lack of kinetic studies in this field leads to the particularly unsatisfactory situation in which qualitative observations concerning reaction yields and velocities must be considered. Generally speaking, structural factors that enhance the nucleophilicity of the alkene or the electrophilicity of the acylating agent should favour reaction.

Selective alkene acylation in the presence of an aromatic substituent is generally possible[22] unless the alkene bears an electron-withdrawing group. In the acetylation of alkenes with zinc chloride–acetic anhydride, increasing alkene nucleophilicity is paralleled by an increase in yield:[23]

Alkene	$CH_2 = CH_2$	$n\text{-}C_5H_{11}CH = CH_2$	$MeCH = CHMe$
Yield(%)	0	2	7

Alkene	$Me_2C = CH_2$	$Me_2C = CMe_2$
Yield(%)	31	69

Reasonable yields (commonly 50% and frequently much higher) may be obtained from the less-branched alkenes by the use of a more reactive acylating system. Particularly nucleophilic alkenes, such as diphenylethylene, will react with the more electrophilic acyl halides (*e.g.*, RCOCl ; R = COCl, CO_2R^1, Ph, CCl_3) in the absence of added catalyst.[24]

A parallel generally exists between the reactivity of an acylating agent (RCOY) and the strength of the corresponding acid (HY). Acyl halides are more reactive than simple carboxylic anhydrides and the reactivity sequence RCOI > RCOBr > RCOCl > RCOF is frequently observed for *C*-acylations. Acetyl iodide is reported to acetylate cyclohexene in the absence of (added) catalyst.[25] The effect of the substituent (R) is less predictable since it may affect the reaction rate in two ways: (*i*) by altering the equilibria, producing acylating complexes and (*ii*) by altering the electrophilicity of the complexes so formed. Which of these opposing

[21] G. A. Olah, A. M. White, and D. H. O'Brien, *Chem. Rev.*, 1970, **70**, 561.
[22] E. Garbisch, *J. Org. Chem.*, 1962, **27**, 4243.
[23] A. P. Mesheryakov and L. V. Petrova, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 1950, 98.
[24] F. Bergmann and J. Klein, *J. Amer. Chem. Soc.*, 1952, **75**, 4333.
[25] P. G. Stevens, *J. Amer. Chem. Soc.*, 1934, **56**, 450.

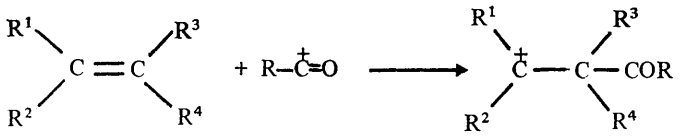
factors is dominant will depend upon the solvent, the catalyst, and the leaving group (Y).

The activity of Lewis acid catalysts will depend largely upon the extent to which they produce an electron-deficient carbonyl carbon at the acylating agent. No general sequence of catalyst activity is possible since Lewis acid strengths are strongly dependent upon the reference base (*e.g.* Y^- in acylium salts and C=O in oxonium complexes). Lewis acidity has recently been reviewed[26] and here it will suffice to say that of the commonly used catalysts aluminium and antimony halides are usually very active, tin(IV) chloride and boron trifluoride are of intermediate activity, whilst zinc chloride is rather mild. A slight molar excess of catalyst is usually employed since the ketone complexes with the catalyst, removing it from the sphere of reaction. The reported use of sub-stoicheiometric quantities of zinc chloride[27] and tin(IV) chloride[28] implies significant dissociation of the catalyst–ketone complexes.

Solvents of high dielectric constant usually facilitate high reaction rates, although this need not be so if the solvent is also capable of co-ordinating with the catalyst (*e.g.* nitro-compounds).[29]

4 Interaction of the Alkene and the Acylating Species

Electrophilic attack upon alkenes is frequently considered to involve formation of an intermediate π-complex in which the alkene π-electrons interact with the vacant orbitals of the electrophile. The extent to which such complexes actually participate in alkene reactions remains questionable[30] and pertinent data concerning acylations are unavailable. For the present purposes, reaction of the alkene and the acylating species may be considered to afford the cation (7), whatever its immediate progenitor, and it is the reactions of this ion with which the remainder of this review is primarily concerned.

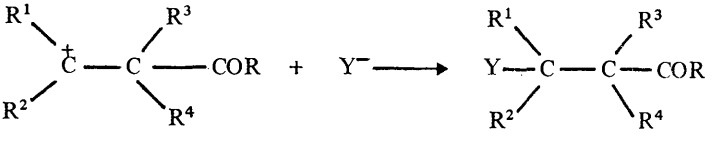


(7)

5 Anion Addition to the Intermediate Ion

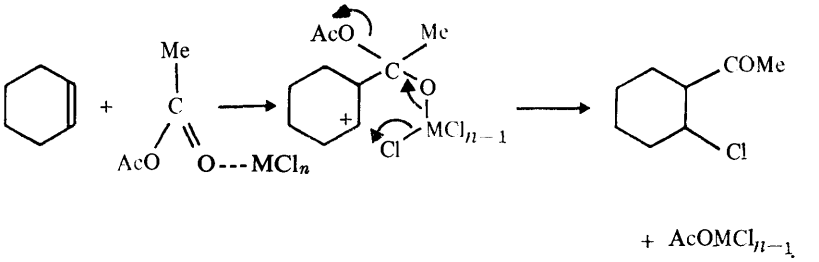
One manner in which the intermediate ion (7) may react is by attack upon an anion.

[26] D. P. N. Satchell and R. S. Satchell, *Chem. Rev.*, 1969, **69**, 251.
[27] M. Muhlstadt and P. Richter, *Chem. Ber.*, 1967, **100**, 1892.
[28] J. Colonge and K. Mostafavi, *Bull. Soc. chim. France*, 1939, **6**, 342.
[29] G. Hoonaert and P. J. Slootmaekers, *Bull. Soc. chim. belges*, 1969, **78**, 257.
[30] D. V. Banthorpe, *Chem. Rev.*, 1969, **69**.



(7)

When the acylating agent is an acid chloride, β-chloroketone is found in the reaction product.[31] Rather less anion addition is observed when acid anhydrides are used, particularly if the catalyst employed forms strong carboxylate ion complexes.[23] The generally lower extent of addition of carboxylate relative to halide has been attributed to the more complex nature of the counter ion involved,[32] but the failure to isolate keto-esters has, at least in part, resulted from the ease with which they decompose to unsaturated ketone. Detectable amounts of β-chloroketone are also formed in the zinc-chloride- and tin(IV)-chloride-catalysed acylations of alkenes using acid anhydrides, although acyl halide formation was not apparent. A cyclic transition state was invoked as an explanation (Scheme 1).



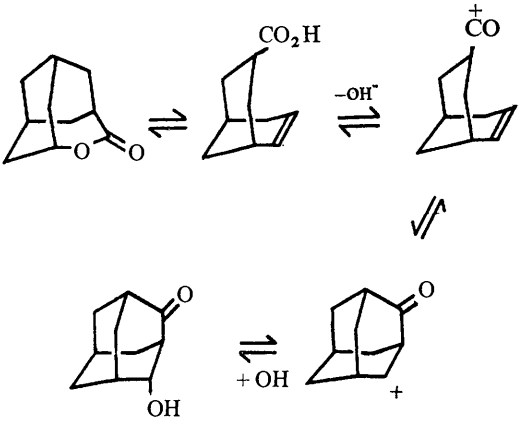
Scheme 1

The use of carboxylic acids may result in OH^- addition although this is usually only apparent if structural factors restrain unsaturated ketone formation. Such a case is the acid-catalysed equilibration of 4-oxohomoadamantan-5-one and 4-hydroxyadamantan-2-one (Scheme 2).[33]

Alkenes which afford a tertiary ion (7) tend to give less addition product. This is typical of carbonium ion reactions although the reasons are not precisely understood.[34]

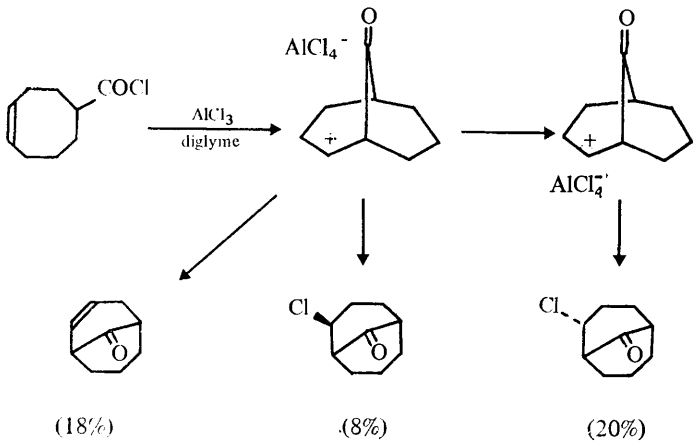
Determination of the stereochemistry of kinetically controlled addition products is fraught with difficulties. In the media employed the initial product may undergo re-ionization, enolization, elimination, or deacylation (see Section

[31] H. Wieland and L. Bettag, *Chem. Ber.*, 1922, **55**, 2246.
[32] D. P. N. Satchell and R. S. Satchell in 'The Chemistry of the Carbonyl Group', ed. S. Patai, J. Wiley, New York, 1966, p. 233.
[33] M. A. McKervey, D. Faulkner, and H. Hamill, *Tetrahedron Letters*, 1970, 1971.
[34] D. Bethell and V. Gold, 'Carbonium Ions', Academic Press, London, 1967, p. 197.



Scheme 2

15). One investigation has avoided these difficulties by careful choice of the substrate and reaction conditions. The aluminium-chloride-catalysed cyclization of cyclo-oct-4-*cis*-ene-1-carboxylic acid chloride was shown to afford a mixture of stereoisomers in which the *trans* addition product predominated (Scheme 3).[35]



Scheme 3

Unfortunately, the rigid geometry which makes this system so amenable to meaningful stereochemical investigation also introduces factors which may make

[35] W. F. Erman and H. Kretschmar, *J. Org. Chem.*, 1968, **33**, 1545.

the results atypical. Reaction of cyclohexene with acetyl chloride–aluminium chloride affords *cis*- and *trans*-1-acetyl-2-chlorocyclohexane in *ca.* 3 : 1 ratio.[36] One may postulate that such *cis* addition arises from attack by the undissociated acylating complex followed by rapid collapse of the resulting ion pair.[37]

6 Tautomerism

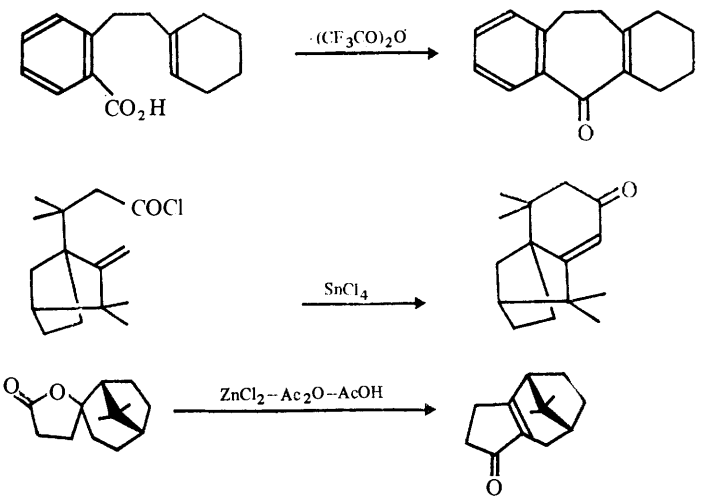
Before discussing the formation of unsaturated ketones it is necessary to draw attention to the acid- and base-catalysed prototropy of these compounds. Substituent effects upon these tautomeric equilibria have been investigated and the following generalisations have emerged:[38] (*i*) if the γ-positions are unsubstituted the equilibria between $\alpha\beta$- and $\beta\gamma$-unsaturated ketones will favour the conjugated isomer; (*ii*) introduction of alkyl substituents into the γ-position shifts the equilibrium towards the non-conjugated isomer; (*iii*) alkyl substitution at the α-position favours the conjugated isomer; (*iv*) alkyl substitution at the β-position has relatively little effect except in highly substituted systems when the non-conjugated isomer is frequently favoured. The effect of α- and γ-substituents are consistent with the hyperconjugative stabilization which they afford to the two tautomers. The effect of β-substitution in highly substituted systems probably arises as a consequence of steric compressions enforcing non-planar conformations of the conjugated enone system.[39] These generalizations account for the proportions of tautomers obtained from many acylations in which the product undergoes equilibration during or before isolation.

7 Formation of $\alpha\beta$-Unsaturated Ketone

$\alpha\beta$-Unsaturated ketones are undoubtedly the most frequently reported product of alkene acylations. Examples of some intramolecular reactions are shown below.[40–42]

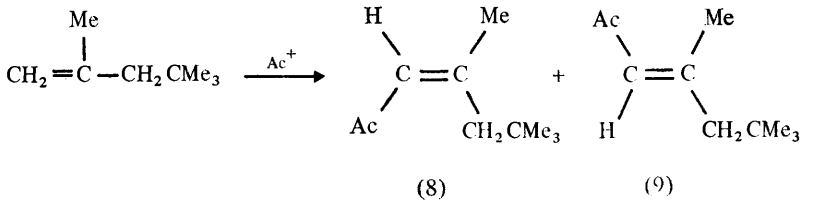
Isolation of conjugated ketone does not necessarily imply that it is a primary reaction product since it may also arise by an addition–elimination mechanism or *via* isomerization of non-conjugated ketone. If one considers proton ejection as involving attack by the cationic centre upon the electrons of a C—H σ-bond then the relatively low electron density at the C—H_α bond is unlikely to be conducive to α-proton loss. On the other hand, if C—H bond fission is well developed in the transition state leading to unsaturated ketone formation, then both the intrinsic acidity of H_α in the ion (7) and the developing conjugation in the $\alpha\beta$-unsaturated product should result in relatively ready transfer of H_α to an adjacent nucleophile or solvent molecule. Whilst several workers[1,2] admit tenta-

[36] L. Ötvös, H. Tüdos, and L. Radics, *Chem. and Ind.*, 1970, 597.
[37] P. B. D. De La Mare, *Sci. Progr.* (*Oxford*), 1968, **56**, 243; G. Hoonaert and H. Martens, *Tetrahedron Letters*, 1970, 1821.
[38] D. Cram, 'Fundamentals of Carbanion Chemistry', Academic Press, New York, 1965.
[39] J. K. Groves and N. Jones, *Tetrahedron*, 1969, **25**, 223.
[40] P. Dostert and E. Kyburz, *Helv. Chim. Acta*, 1970, **53**, 897.
[41] R. R. Sobli and S. Dev, *Tetrahedron*, 1970, **26**, 649.
[42] G. Büchi and W. D. Macleod, *J. Amer. Chem. Soc.*, 1962, **84**, 3205.



tive acceptance of the occurrence of direct α-proton loss, the importance of this mechanism as a general mode of conjugated ketone formation remains to be established conclusively.

Acylation of unsymmetrical alkenes may afford stereoisomeric conjugated ketones; thus 2,4,4-trimethylpent-1-ene yields (8) and (9).[43] Since kinetically-controlled acylation yields a βγ-unsaturated compound, the proportions of the stereoisomers obtained presumably reflect their relative thermodynamic stabilities.



(8) (9)

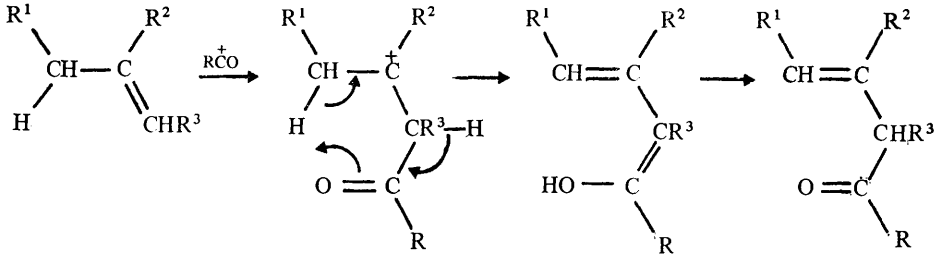
8 Formation of βγ-Unsaturated Ketones

In certain instances βγ-unsaturated ketones may, as a consequence of conformational factors, be the thermodynamically-controlled acylation product.[44] In many other cases βγ-unsaturated ketones are formed to the exclusion of thermodynamically more favourable conjugated isomers.[45] Diacylation studies also

[43] P. Arnaud, *Compt. rend.*, 1957, **244**, 1785.
[44] E. A. Braude and C. J. Timmons, *J. Chem. Soc.*, 1955, 3766.
[45] J. K. Groves and N. Jones, *J. Chem Soc.* (*C*), 1968, 2215; 1969, 609.

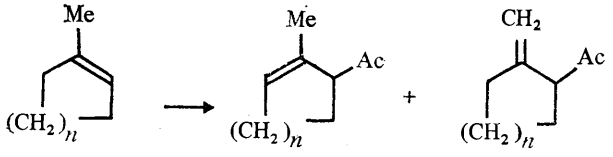
indicate that $\beta\gamma$-unsaturated ketones are frequently the kinetically controlled monoacylation product.[46]

Several mechanisms have been proposed to account for the formation of non-conjugated products, the most convincing of which involves transfer of a γ-proton to the carbonyl oxygen (10), a process which occurs extensively in the



(10)

chemistry of carbonyl compounds. This mechanism implies certain geometric limitations since it requires close proximity of the carbonyl oxygen and the γ-hydrogen. The acetylation of 1-methylcycloalkenes (11) can afford two $\beta\gamma$-unsaturated ketones and the observed effect of ring size upon the product distribution is perhaps related to the conformational preference of the acetyl group in the carbonium ions involved.[47] Studies upon conformationally more rigid systems could provide more conclusive evidence concerning the mechanism involved.

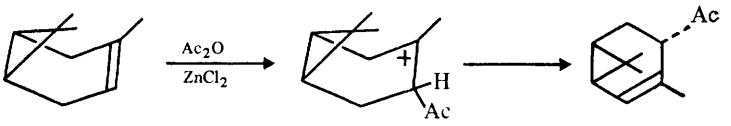


(11) (12) (13)

n	(12)	(13)
2	100%	0%.
3	64	36
4	17	67

[46] A. T. Balaban, W. Schroth, and G. Fischer, *Adv. Heterocyclic Chem.*, 1969, **10**, 241.
[47] J. K. Groves, Ph.D. Thesis, Lanchester Polytechnic, England, 1969; compare also J. A. Marshall, N. H. Anderson, and P. C. Johnson, *J. Org. Chem.*, 1970, **35**, 186.

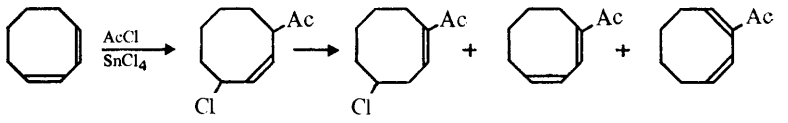
Acetylation of (+)-3-carene occurs *trans* to the cyclopropyl ring, probably as a consequence of the preferred conformation of this alkene. No evidence of cyclopropyl participation in the ion (14) was observed.[48]



(14)

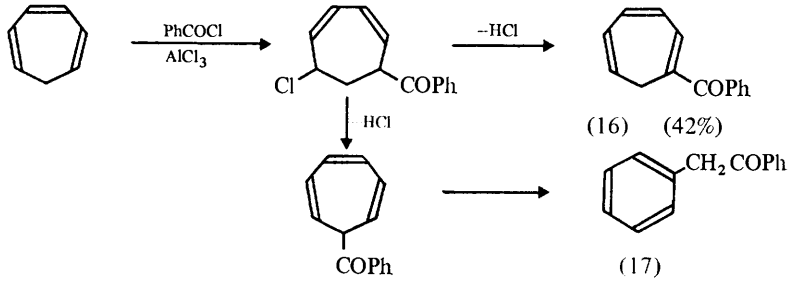
9 Interaction of the Intermediate Ion with a Further Unsaturated Centre

Acylation of 1,3-dienes should permit allylic rearrangements. 1,3-Cyclo-octadiene undergoes 1,4-addition of acetyl chloride but the resulting 3-acetyl-8-chlorocyclo-octene (15) undergoes ready isomerization and elimination.[49]



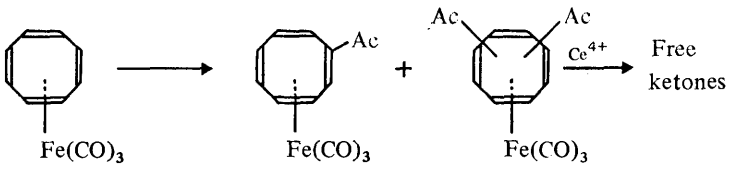
(15) (12%) (40%) (8%)

Similarly, cycloheptatriene undergoes 1,6-addition of benzoyl chloride.[50] Reaction at 0°C permits synthesis of 1-benzoylcycloheptatriene (16) whereas reaction at higher temperatures is accompanied by rearrangement to deoxy-benzoin (17). The extensive polymerization of cyclo-octatetraene which occurs upon attempted acylation of the free hydrocarbon can be circumvented by



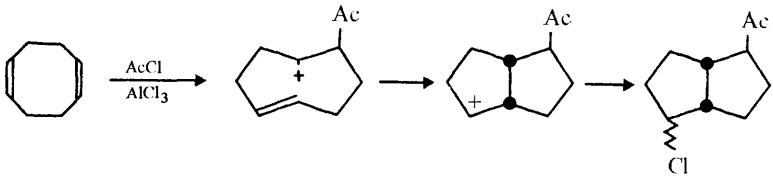
acylating cyclo-octatetraene iron tricarbonyl (18). Subsequent displacement of the iron tricarbonyl unit affords the free ketones.[51]

[48] P. J. Kropp, D. C. Heckert, and T. J. Flautt, *Tetrahedron*, 1968, **24**, 1385.
[49] T. S. Cantrell and B. L. Strasser, submitted to *J. Org. Chem.*, 1970.
[50] J. A. Blair and C. J. Tate, *Chem. Comm.*, 1969, 1506.
[51] B. F. G. Johnson, J. Lewis, A. W. Parkins, and G. L. P. Randall, *Chem. Comm.*, 1969, 595.



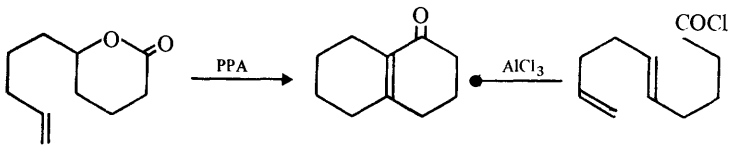
(18)

1,5-Dienes afford an intermediate ion in which the remaining alkene bond is suitably situated to permit nucleophilic attack upon the ionic centre with consequent formation of a new σ-bond. 1,5-Cyclo-octadiene affords 2-acetyl-6-chlorobicyclo[3,3,0]octane (19) as a mixture of *exo*- and *endo*-isomers.[52]



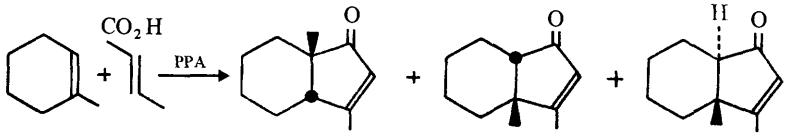
(19) (48%)

Similar cyclizations of acyclic dienoic acid derivatives are also known, *e.g.* formation of (20).[53]



(20)

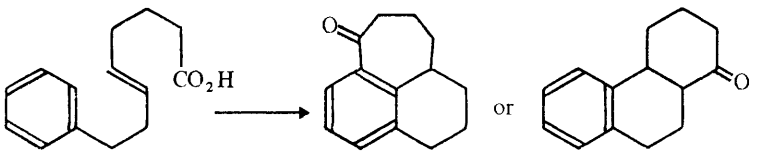
Reaction of 1-methylcyclohexene with crotonic acid affords the normal acylation–alkylation products (22) and (23), together with a small amount of a product (21) derived either by anti-Markovnikov addition of the acylating agent or by an alkylation–acylation mechanism.[54] According to the conditions employed,



(21) (5%) (22) (15%) (23) (25%)

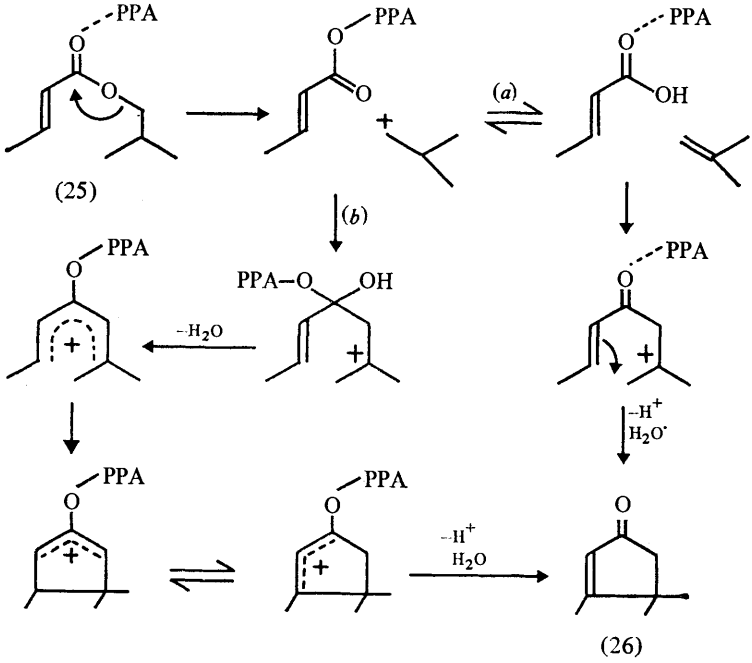
[52] T. S. Cantrell, *J. Org. Chem.*, 1967, **32**, 1667.
[53] M. F. Ansell and M. H. Palmer, *J. Chem. Soc.*, 1960, 5219.
[54] S. B. Kulkarni and S. Dev, *Tetrahedron*, 1968, **24**, 545.

trans-8-phenyl-5-octenoic acid (24) can be made to undergo alkylation–acylation or acylation–alkylation.[55]



(24)

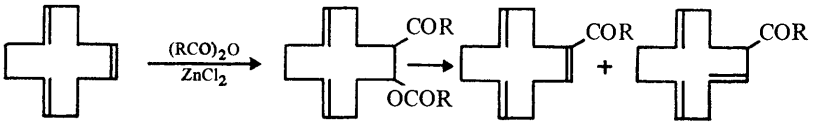
An interesting new synthesis of cyclopentenones involves the treatment of $\alpha\beta$-unsaturated esters [*e.g.* (25)] with polyphosphoric acid. Alkyl–oxygen heterolysis is followed either by (*a*) alkene formation and subsequent acylation or by (*b*) nucleophilic attack by the transient alkyl cation upon the carbonyl carbon (Scheme 4). Cyclization of the intermediate ion yields the five-membered ring ketone (26).[56]



Scheme 4

[55] M. F. Ansell and S. S. Brown, *J. Chem. Soc.*, 1958, 3956.
[56] J. M. Conia and M. L. Levirend, *Bull. Soc. chim. France*, 1970, 2981, 2992.

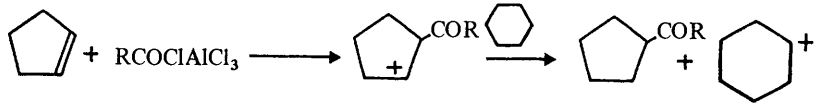
The failure of cyclododeca-1-*cis*-5-*trans*-9-*trans*-triene (27) to undergo intramolecular cyclization is probably a consequence of rapid and essentially irreversible anion addition.[57]



(27)

10 Intermolecular Hydride Transfer

Nenitzescu and co-workers have shown that the use of a saturated hydrocarbon solvent for alkene acylations can provide a convenient synthesis of saturated ketones (Scheme 5).[58] Hydrogenation results from hydride abstraction from the solvent by the intermediate cation.* The ion formed by the solvent undergoes dehydrogenation and polymerization.



Scheme 5

In the absence of large steric requirements the rate of such hydride transfer processes is a direct function of the relative stabilities of the incipient and disappearing cations[59] and hence should be most rapid with branched hydrocarbon solvents. In fact, cycloalkanes also appear capable of hydride donation at a practicable rate. Alkenes themselves are efficient hydride donors since they afford allylic cations but they are normally precluded from fulfilling this role by an adverse concentration factor.

In certain instances the stereochemistry of products resulting from hydride abstraction have been established, for example, the 1-acetyl-2-methylcyclopentane formed by the dehydrogenation–acetylation of cyclohexane is predominantly the more stable *trans*-isomer.[36,60] Delivery of hydride to the less hindered face of the intermediate ion (7) might be expected,[61] but since the necessary excess of highly active catalyst provides conditions conducive to

*Previous authors have suggested that reduction proceeds *via* chloroketone or unsaturated ketone. Recent ^{14}C-labelling experiments show that reduction of the intermediate cation is considerably faster than that of either of these postulated intermediates. Personal communication, L. Ötvös, H. Tudos, and A. Szabolcs, 1971.

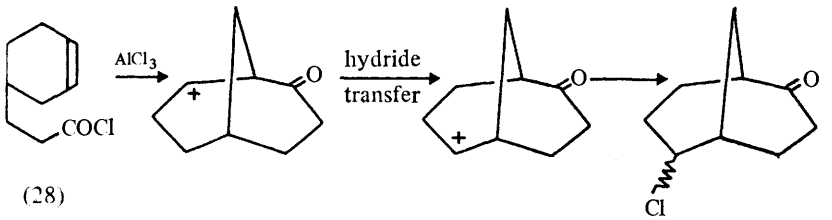
[57] J. Graefe, M. Muhlstadt, and D. M. Muller, *Tetrahedron*, 1970, **26**, 2677.
[58] C. D. Nenitzescu and E. Cioranescu, *Chem. Ber.*, 1936, **69**, 1820.
[59] N. C. Deno, G. Saines, and M. Spangler, *J. Amer. Chem. Soc.*, 1962, **84**, 3295.
[60] H. Pines and N. E. Hoffman, *J. Amer. Chem. Soc.*, 1954, **76**, 4417.
[61] R. M. Carlson and R. K. Hill, *J. Org. Chem.*, 1969, **34**, 4178.

enolate formation,[62] reliable data concerning the stereochemistry of kinetically-controlled acylation products are difficult to obtain.

11 Intramolecular Hydride Transfer

The intermediate ion (7) is destabilized by the electron-withdrawing effect of the adjacent carbonyl group. Accommodation of the positive charge at a position more remote from the carbonyl group by one or more hydride shifts is one manner in which the ion may increase its stability. The activation energy for 1,2-shifts is minimal when the vacant *p*-orbital at the cationic centre and the C—H bond of the migrating hydrogen are coplanar. It is also expected to decrease with increase in the positive charge at the migration terminus.[63]

Under certain conditions cyclopentene is reported to afford 86% γ-chloroketone, presumably derived from a 1,2-hydride shift. In view of the inductive effect of the carbonyl group the hydride transfer process may continue beyond the γ-carbon; thus 4% of 1-benzoyl-4-chlorocyclohexane is obtained as a by-product from the benzoylation of cyclohexene.[64] Similarly, cyclization of 3-(cyclohex-3-en-1-yl)propionyl chloride (28) may afford the intramolecular hydride transfer product (29).[65]



(28) (29)

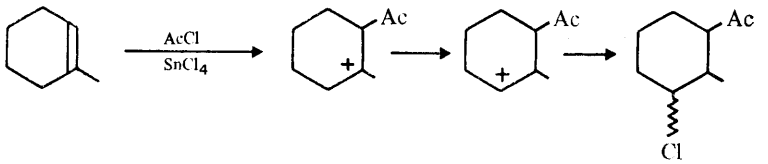
Nenitzescu has shown that for acyclic systems the hydride shift process may continue until the positive charge reaches the most remote secondary, but not primary, carbon atom.[1] Treatment of the resulting chloroketone with benzene results in alkylation of the aromatic compound in preparative yield: *e.g.* (30).[66]

$$C_4H_9CH{=}CH_2 + PhCOCl \xrightarrow[\text{ii PhH}]{\text{i } AlCl_3} Ph(Me)CH(CH_2)_4COPh$$

(30)

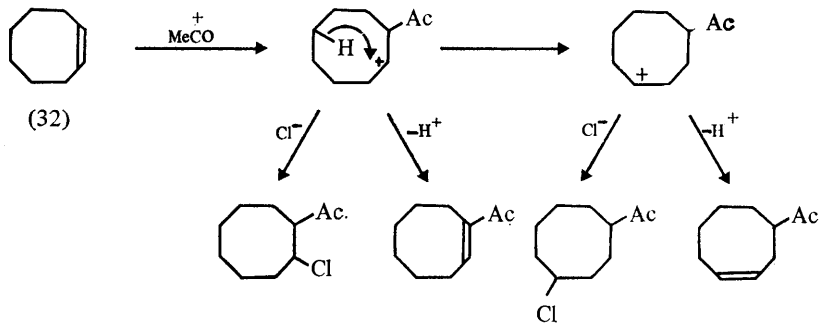
[62] H. O. House, V. Paragamian, R. S. Ro, and D. J. Wluka, *J. Amer. Chem. Soc.*, 1960, **82**, 1457.
[63] J. L. Fry and G. J. Karabastos in 'Carbonium Ions', ed. G. A. Olah and P. von R. Schleyer, J. Wiley, New York, 1968, Vol. 2, p. 526.
[64] C. L. Stevens and E. Farkas, *J. Amer. Chem. Soc.*, 1953, **75**, 3306.
[65] E. Marvell, R. S. Knutson, T. McEwen, D. Sturmer, W. Ferderici, and K. Salisbury *J. Org. Chem.*, 1970, **35**, 391.
[66] A. D. Grebenyuk and N. F. Zaitseva, *Zhur. org. Khim.*, 1968 **4**, 302 (*Chem. Abs.*, 1968, **68**, 95449).

Nenitzescu has also shown that a tertiary carbon does not necessarily prevent hydride migrations which locate the charge in a position more remote from a carbonyl group. Such is the case in the formation of (31) from the acetylation of 1-methylcyclohexene.[67]



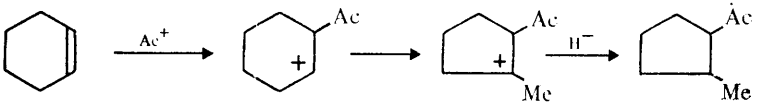
(31)

In medium ring systems the favourable geometric arrangement of non-contiguous carbon atoms facilitates higher-order hydride shifts. *cis*-Cyclo-octene (32) has been shown to afford products in which 1,5- or 1,3-hydride shifts constitute the major reaction pathway.[68]



12 More Complex Rearrangements

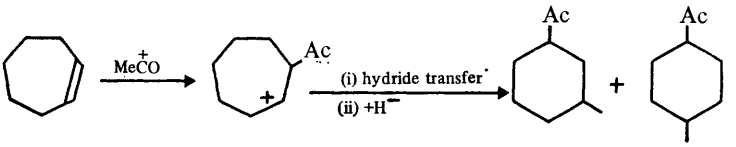
The skeletal rearrangements that occur in alkene acylations may generally be represented as involving attack by the cationic centre upon the electrons of a C—C σ-bond with subsequent or concurrent hydride migration. Unfortunately, the detailed mechanism of the ring-contraction reactions, which so commonly occur, remain a matter for conjecture.



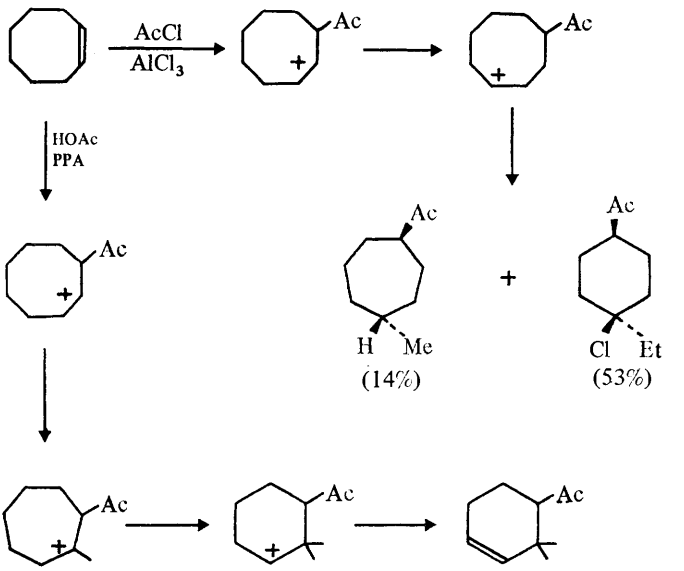
(33)

[67] N. Dufort and J. Lafontaine *Canad. J. Chem.*, 1968, **46**, 1065; N. Dufort and J. Allard, *ibid.*, 1969, **47**, 2403.
[68] J. K. Groves and N. Jones, *J. Chem. Soc.* (*C*), 1969, 1718.

The acetylcyclohexylium ion readily rearranges to the tertiary ion (33).[69] Acylation of cycloheptene can result in similar ring-contraction products[70] but in certain circumstances hydride migration may precede ring contraction.[71]



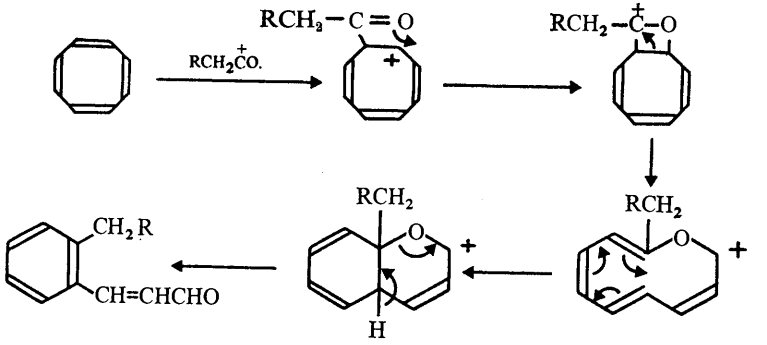
Complex rearrangements in the acetylcyclo-octylium ion have also been reported (Scheme 6).[52,72]



Scheme 6

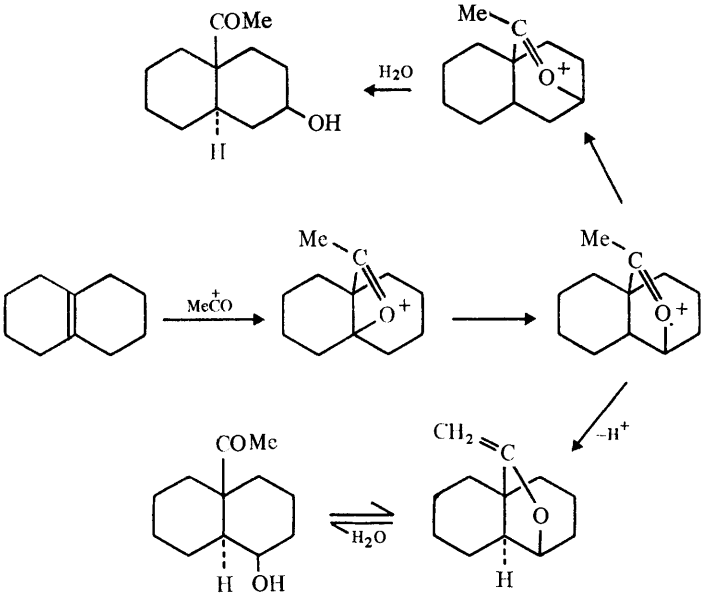
In order to explain the formation of the aldehydes (34) as low-yield products from the acetylation and propionylation of cyclo-octatetrene, Cope suggested participation of the carbonyl oxygen.[73] More convincing evidence of such par-

[69] L. Ötvös and H. Tudos, *Chem. and Ind.*, 1969, 1140.
[70] L. Rand and R. J. Dolinski, *J. Org. Chem.*, 1966, **31**, 3063.
[71] S. L. Friess and R. Pinson, *J. Amer. Chem. Soc.*, 1951, **73**, 3512.
[72] L. Rand and R. J. Dolinski, *J. Org. Chem.*, 1966, **31**, 4061.
[73] A. C. Cope, T. A. Liss, and D. S. Smith, *J. Amer. Chem. Soc.*, 1957, **79**, 240.



(34)

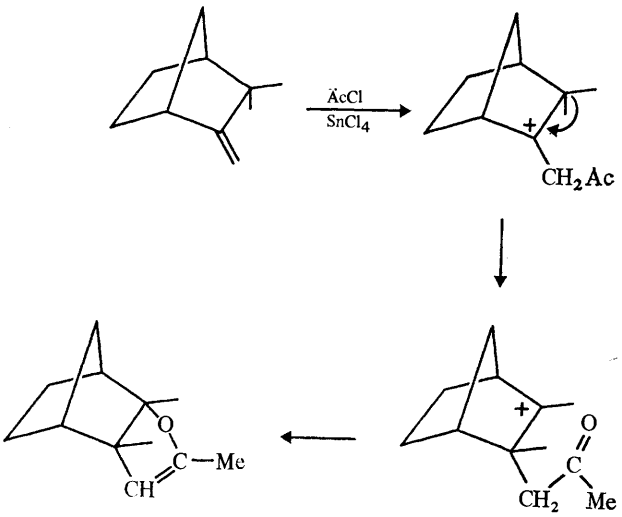
ticipation was obtained by Baddeley's observation that acetylation of octahydronaphthalene (formed by *in situ* de-hydrogenation of decalin) results in the formation of 1,1′-epoxy-10-vinyl-*trans*-decalin (35) as the major product.[74] This was interpreted as involving the formation of a four-membered cyclic bridged structure which rearranges to the less strained five-membered bridge.



(35)

[74] G. Baddeley, B. G. Heaton, and J. W. Rasburn, *J. Chem. Soc.*, 1960, 4713.

The products may alternatively be accounted for by bridging only after hydride migrations have located the charge at the geometrically more favourable γ (and δ) positions. In the acetylation of camphene an *exo*-3,2-methyl shift appears to precede bridge formation to afford (36).[75] Although (36) is probably a primary

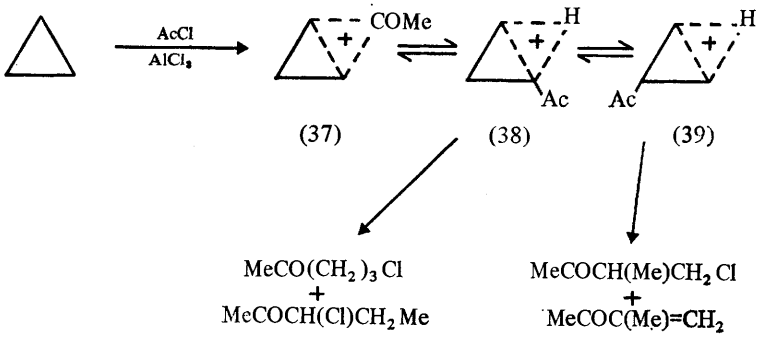


(36)

product it should be noted that $\beta\gamma$-unsaturated ketones can also form dihydrofuran derivatives in acidic media.[76] Benzoylation of camphene and subsequent hydrolysis was originally reported to afford 10-benzoylborneol but reinvestigation showed the product to be 10-benzoylisoborneol.[77] Norbornene reportedly undergoes acetylation without rearrangement affording a chloroketone to which the authors tentatively assign a *cis-exo* configuration.[78]

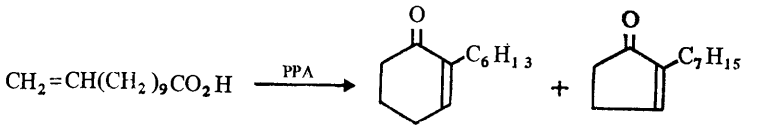
Finally, we mention the acylation of the quasi-unsaturated cyclopropanes.[79] Hart and Schlosberg suggest that the acetylation products of cyclopropane are best accounted for in terms of the ion (37) which undergoes equilibration with the more stable ions (38) and (39). Nucleophilic attack upon, or proton ejection from, these ions explains the products. Surprisingly, acetylcyclopropane formation does not occur. The results obtained for the acetylation of methylcyclopropane do not yet permit a distinction between the involvement of conventional and bridged intermediates, whilst 1,1-dimethylcyclopropane undergoes isomerization to 2-methylbut-2-ene more rapidly than it acetylates.

[75] J. A. Crosby and J. W. Rasburn, *Chem. and Ind.*, 1967, 1365.
[76] D. D. Faulk, W. H. Corkern, I. Ookuni, and A. Fry, *J. Org. Chem.*, 1970, **35**, 1518.
[77] W. R. Vaughan, J. Wolinski, R. R. Dueltgen, S. Grey, and F. S. Seichter, *J. Org. Chem.*, 1970, **35**, 400.
[78] R. J. Poel, *Diss. Abs.*, 1965, B27, 766.
[79] H. Hart and R. H. Schlosberg, *J. Amer. Chem. Soc.*, 1968, **90**, 5198.



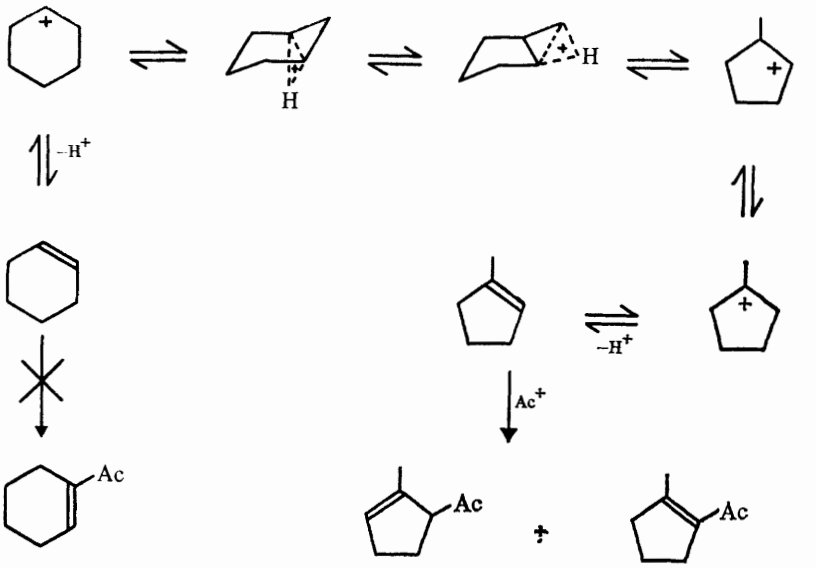
13 Side reactions of Alkenes

Alkenes readily undergo acid-catalysed isomerization and if the rate of acylation is not markedly greater than that of isomerization then the product composition will depend upon the rates of acylation and isomerization of the alkenes present. Brönsted acid catalysts are particularly prone to induce side reactions; thus polyphosphoric-acid-catalysed cyclizations of olefinic acids usually yield five- and six-membered ketones, irrespective of the initial positions of the acyl and alkenyl groups.[80] Obviously, the double bond migrates freely and the products reflect the acylation rates of the isomers present. Such bond migration may be prevented



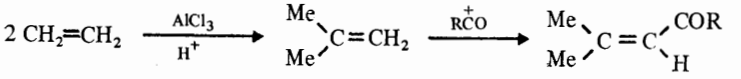
by choice of a more suitable catalyst. Trifluoroacetic anhydride effects olefinic acid cyclizations without inducing bond migration[81] and acylation obviously forestalls isomerization in the aluminium-chloride-catalysed cyclization of 6-heptenoyl chloride to β-chlorocycloheptenone.[82] Cyclohexanol, cyclohexyl chloride, and cyclohexane each react with aluminium chloride–acetyl chloride to afford a cyclohexylium cation. Reversible ring contraction, possibly by the mechanism shown in Scheme 7, permits formation of both cyclohexene and 1-methylcyclopentene, but the acylation products are normally derived entirely from the more branched alkene.[83] Nitro-compounds tend to prevent ring contractions by assisting in rapid proton loss from the initial cycloalkyl cation.[2]

[80] M. F. Ansell and M. H. Palmer, *Quart. Rev.*, 1964, **18**, 211; M. F. Ansell and T. M. Kafka, *Tetrahedron*, 1969, **25**, 6025.
[81] M. F. Ansell, J. C. Emmet, and R. U. Coombs, *J. Chem. Soc.* (*C*), 1968, 217.
[82] W. S. Trahanovsky, M. P. Doyle, P. W. Mullen, and Ching Ching Ong, *J. Org. Chem.*, 1969, **34**, 3679.
[83] I. Tabushi, K. Fujita, and R. Oda, *Tetrahedron Letters*, 1968, 4247.



Scheme 7

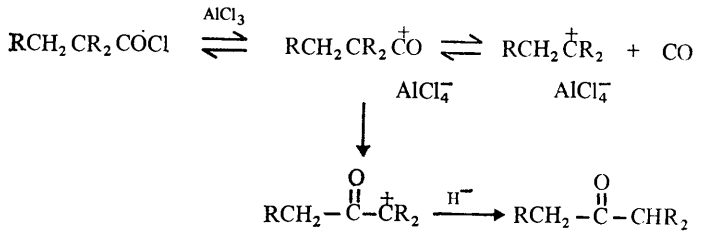
Apart from rearrangements, alkene protonation may also induce nucleophilic attack. Reactions employing carboxylic acids or anhydrides frequently result in carboxylate addition and the ester (or lactone)-to-ketone ratio of the product parallels the stability of the protonated alkene.[72] In certain instances the nucleophile involved is a second molecule of alkene, and thus the acylation of ethylene in the presence of an excess of aluminium chloride affords products which are, at least formally, derived from dimerization and rearrangement of the alkene:[84]



14 Side-reactions of the Acylating Agent

The formation of acid chlorides from Lewis acids and acid anhydrides has already been noted. Acylium ions are reduced to aldehydes by hydrocarbon solvents[85] and for tertiary acyl halides such hydride abstraction may be accompanied by alkyl group migration.[86] The decarbonylation reaction indicated in Scheme 8 occurs only if the resulting alkyl cation is tertiary and near planar.[87]

[84] H. T. Taylor, *J. Chem. Soc.*, 1958, 3922; T. Matsumoto, K. Hata, and T. Nishida, *J. Org. Chem.*, 1958, **23**, 106.
[85] G. Baddeley, E. Wrench, and R. Williams, *J. Chem. Soc.*, 1956, 2110.
[86] A. T. Balaban and C. D. Nenitzescu, *Tetrahedron*, 1960, **10**, 55.
[87] D. G. Pratt and E. Rothstein, *J. Chem. Soc.* (*C*), 1968, 2548.

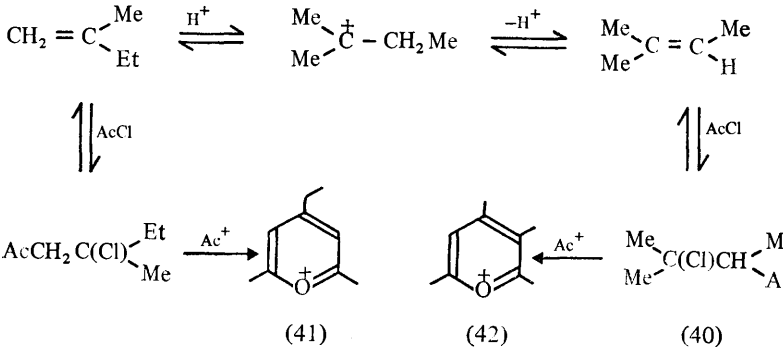


Scheme 8

In certain instances dehydrogenation of the alkyl portion of an acid chloride and subsequent intramolecular acylation have been reported, as in the formation of α-tetralone from cyclohexylbutyryl chloride.[88]

15 Side-reactions of the Ketones

Diacylation studies have raised the question of the reversibility of monoacylations. Baddeley postulated a deacetylation–reacetylation in the formation of the pyrylium salt (41) from 4-methyl-4-chloropentan-2-one (40) and acetyl chloride–aluminium chloride.[89] Balaban and co-workers confirmed this by using labelled

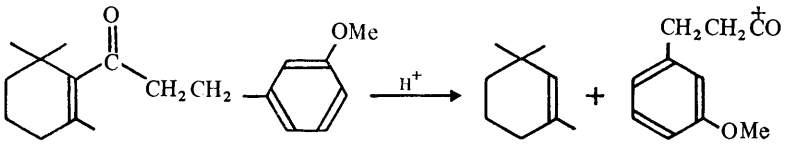


(41) (42) (40)

acetyl chloride and showing that the acetyl group of the ketone and acylating agent become equivalent during the reaction.[90] Zinc chloride does not effect deacylation and hence yields the different pyrylium salt (42). Other investigations[91] employing labelled ketones have confirmed deacylation of the chloroketone (40) but show that mesityl oxide undergoes deacylation less readily and that acetophenone does not at all. The reluctance of unsaturated ketones to undergo

[88] N. Jones, E. Rudd, and H. T. Taylor, *J. Chem. Soc.*, 1963, 2354.
[89] G. Baddeley and M. A. R. Khayat, *Proc. Chem. Soc.*, 1961, 382.
[90] M. Frangopol, A. Genunche, P. T. Frangopol, and A. T. Balaban, *Tetrahedron*, 1964, **20**, 1881.
[91] M. Frangopol, A. Genunche, N. Negoita, P. T. Frangopol, and A. T. Balaban, *Tetrahedron*, 1967, **23**, 841.

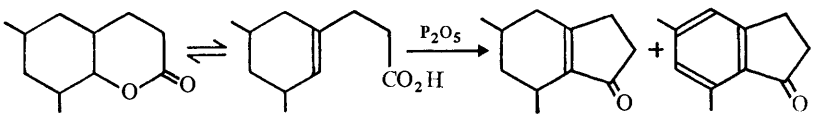
deacylation is perhaps related to conjugation energies. The ketone (43), which has a non-planar enone system, readily undergoes deacylation.[92]



(43)

Re-ionization of chloroketones may induce reactions other than deacylation; thus 1-benzoyl-2-chlorocyclohexane undergoes aluminium-chloride-catalysed isomerization to the 4-chloro-isomer.[64] More surprisingly, treatment of 1-acetyl-4-chlorocyclo-octane with tin(IV) chloride affords 4-acetylcyclo-octene (15%) and 1-acetylcyclo-octene (25%).[93] Formation of the latter, which presumably involves ionization followed by hydride migration, appears contrary to Cope's generalization that transannular hydride shifts are important only when a more stable cation results.[94]

Interconversions of tautomeric ketones are particularly common in Brönsted-acid-catalysed acylations,[80] and base-catalysed isomerizations[95] of $\beta\gamma$-unsaturated ketones to their conjugated tautomers may occur during isolation procedures.‡ The formation of an aromatic system may induce various further reactions of an initial product. Alka-2,4-dienoic acids afford dienones which enolise to the corresponding phenol.[97] Dehydrogenation reactions, *e.g.* formation of (44), may also occur.[98]



(44)

Although β-chloroketones are normally readily dehydrohalogenated,[99] in certain instances the synthetic usefulness of alkene acylations is limited by an inability to effect dehydrochlorination without effecting concurrent isomerization.

‡See footnote to ref. 95, and ref. 96.

[92] J. A. Barltrop and N. A. J. Rogers, *J. Chem. Soc.*, 1958, 2566.

[93] T. S. Cantrell, personal communication.

[94] A. C. Cope, M. M. Martin, and M. A. McKervey, *Quart. Rev.*, 1966, **20**, 119.

[95] J. K. Groves and N. Jones, *J. Chem. Soc.* (*C*), 1968, 2898. ‡The reverse isomerisation may be effected photochemically or by enol esterification followed by mild hydrolysis (see ref. 96).

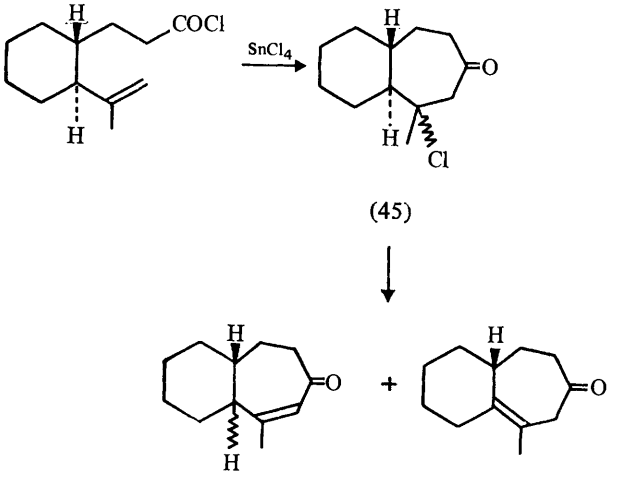
[96] D. Amar, V. Permutti, and Y. Mazur, *Tetrahedron*, 1969, **25**, 1717.

[97] G P. Chiusoli and G. Agnes, *J. Chem. Soc.*, 1963, 310.

[98] R. L. Frank and R. C. Pierle, *J. Amer. Chem. Soc.*, 1951, **73**, 724.

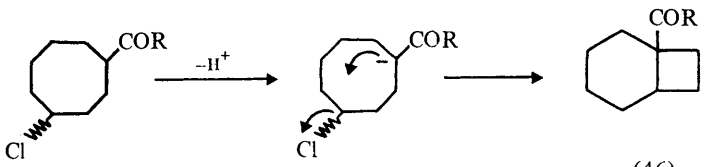
[99] R. Braidy, *Compt. rend.*, 1966, **263***C*, 810.

For example, dehydrochlorination of (45) results in isomerization at the alkene bond and at the ring junction.[100]



(45)

Finally, we mention the dehydrochlorination of chloroketones in which chloride addition was preceded by hydride migration. These compounds are considerably more reluctant to undergo dehydrochlorination and, in certain instances, the major reaction is an intramolecular anionic displacement within the enolate anion. Useful syntheses of bicyclic systems [*e.g.* (46)] may result.[101]



(46)

16 Concluding Remarks

An attempt has been made to provide a broad coverage of the various types of reaction possible. Despite the variety of reaction pathways available viable syntheses of unrearranged saturated or conjugated ketones are frequently possible. Syntheses of $\beta\gamma$-unsaturated ketones proceed satisfactorily for many alkenes which afford a tertiary intermediate ion, but anion addition reactions may preclude the application of this method to less branched alkenes. Additional unsaturated centres in the alkene or acylating agent behave in a relatively predictable manner but the same is only superficially true of rearrangement

[100] J. A. Marshall, N. H. Anderson, and J. W. Schlicher, *J. Org. Chem.*, 1970, **35**, 858.
[101] J. K. Groves and N. Jones, *J Chem. Soc.* (*C*), 1969, 2350.

reactions. Friedel–Crafts acylations of alkenes clearly provide much interesting chemistry, the serious study of which has hardly begun.

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