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The Cleavage of the Carbon-Carbon Bond in Carbonyl Compounds and Alcohols under the Influence of Bases

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The characteristics of the cleavage of the carbon-carbon bond in carbonyl compounds and alcohols of different types are considered. It is shown that the ease of dissociation of this bond is determined primarily by the stability of the carbanion formed. Among other factors, the nature of the solvent, the base, and the counterion are important. The importance of the latter factor has the greatest influence on the stability of the O-M bond in alcohols and hydroxycarbonyl compounds. The bibliography includes 281 references.

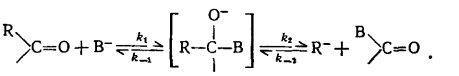
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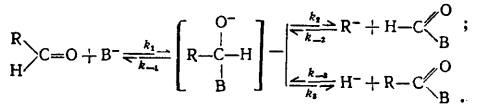
I. INTRODUCTION

The heterolytic cleavage of the carbon–carbon bond is a fairly rare although important reaction in organic chemistry. Such cleavage is usually associated with the formation of carbanions (in a free or cryptoanionic state) and proceeds reversibly, so that, if the stability of the carbanions is insufficient, the occurrence of the reaction requires the presence of special carbanion acceptors. The reactions considered here include the following:

1. The reaction of carbonyl compounds with bases:

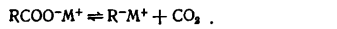


In the general case we have here competition between the abstraction of B^- and R^- (stages with the rate constants k_{-1} and k_2). The bases employed in this reaction are usually OH^- or OR^-, but amides and other nucleophiles, including carbanions, can also be used. We may note that for aldehydes there is also the possibility of the abstraction of a hydride ion (stage with the rate constant k_3):

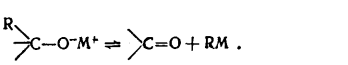


The reactions of the type considered include also the retro-Claisen condensation, in particular, the so called acid cleavage of the acetoacetic ester.

2. Decarboxylation of carboxylic acids with participation of the anion:

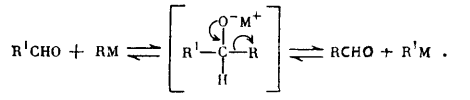


3. Decomposition of carbinolates (alkoxides)—the reaction which is the opposite of the addition of organometallic compounds to the carbonyl group—the most important process leading to the formation of the carbon–carbon bond:



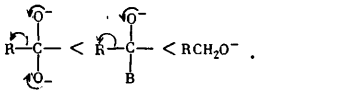
Such reactions include the retroaldol condensation (the reverse reaction, i.e. the aldol condensation, involves the addition of an alkali metal enolate to the carbonyl group).

Naturally, the decisive factor in all the reactions considered is the stability of the carbanion split off, so that, in the presence of several substituents in the carbinolate RR^1R^2COM, the C–C bond ruptured is that having the substituent which corresponds to strongest CH acid RH. Thus, in principle, it is possible to formulate the equilibrium in which one carbanion induces the displacement from an aldehyde or ketone another more stable carbanion:



However, there exist also other factors, which likewise determine the possibility of the cleavage reactions considered. These are primarily the nature of the base and the solvent and, when a specific type of base is used, the nature of the counterion. The role of the last factor is associated with the difference between the effects of the counterion on the ease of ionisation of the O–M and B–M bonds and is determined by the exclusively strong dependence of the stability of the O–M bond (in relation to ionisation) on the nature of M (which is much more pronounced than in the case of, for example, the C–M bond).

As was to be expected, the free anion is cleaved most readily. If anions such as the carbinolate, the tetrahedral anionic intermediate formed when the base adds to the carbonyl group, as well as the dianion arising on treatment with an excess of alkali are compared, then their stabilities are seen to vary in the sequence



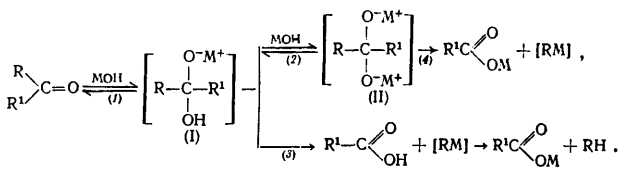
Thus it is possible to trace the general characteristics of the reactions involving the cleavage of the C–C bond occurring in compounds of different classes and having at first sight little in common. The present review is devoted to the analysis of the available data concerning the influence of the stability of the carbanion, the nature of the solvent, and the nature of the counterion on the ease of cleavage of the carbon–carbon bond.

II. THE CLEAVAGE OF KETONES AND ALDEHYDES BY BASES

1. General Considerations

Ketones are usually cleaved by bases with difficulty. An exception is ketones containing in the α-position strong electron-accepting groups, for example, NO_2 or SO_2,[1] quaternary ammonium,[2] and keto- or ester groups.[3] The last case represents the well known reaction involving the acid cleavage of β-dicarbonyl compounds.[4] Trihalogenomethyl ketone and trihalogenoacetaldehydes are readily cleaved (haloform cleavage reaction).[5] The study of the kinetics of the cleavage of such carbonyl compounds by alkalis in aqueous solution showed that all these processes can be represented by a single scheme (Scheme 1):[1-3]

Scheme 1

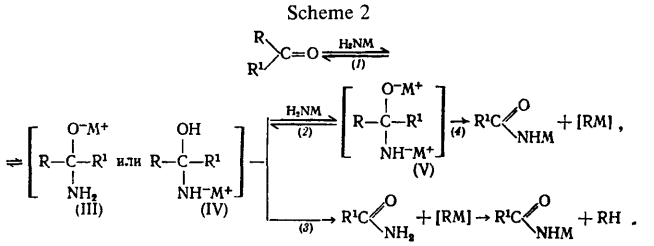


where R is a stronger electron-accepting group than R^1.

Kinetic studies have made it possible to postulate that, depending on the nature of the carbonyl compound, the rate-limiting stage can be both stage (1), involving the addition of the hydroxide anion to the carbonyl group (for example, for nitroacetone, ω-nitroacetophenone,[1] αα-dimethylacetophenone,[3] and thienyltrifluoroacetone[1,6]) and the formation of the dianion (II) (for ketoalkylpyridinium salts and sulphonylketones[1,2]) or its decomposition (for example, for acetylacetone, methylacetylacetone,[3] chloral hydrate, and 2,6-dihalogenobenzaldehydes[7,8]).

Potassium or sodium amides in liquid NH_3 or in aromatic hydrocarbons such as benzene, toluene, and xylenes (Haller–Bauer cleavage) are frequently used as bases for the cleavage of ketones.[9-11] The fundamental scheme for these processes (Scheme 2) is analogous to that presented above:[9,12,13]

Scheme 2

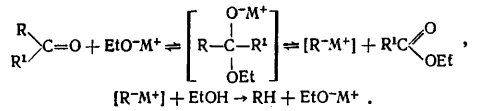


It follows from Schemes 1 and 2 that the first stage in the cleavage of carbonyl compounds by bases involves the addition of bases to the carbonyl group with formation of the intermediate (I) or (III)/(IV). Adducts of type (III) have been frequently isolated in reactions with NH_3 or amides at low temperatures; on decomposition with water, they regenerated the initial ketones.[14-17] Similar adducts with alkalis, alkoxides, and other bases are probably less stable. We may note that the adducts of formaldehyde with hydroxide and methoxide ions have been recently detected in the gas phase.†[18]

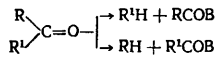
† The adduct of an alkoxide with *NN*-dimethyltrifluoroacetamide has been recently detected in solution.[19]

The majority of cleavage reactions of carbonyl compounds apparently require the formation of the dianions (II) or (V), which follows from kinetic data (second order with respect to the alkali).[1-3,8,12,13] The heterolysis of such dianions should naturally proceed more readily than that of the monoanions. The formation of the dianions is indicated also by the fact that, in the absence of a proton donor, the hydrocarbon RH is not formed.[20] When fairly stable carbanions R^-, such as the nitromethyl or trifluoromethyl carbanions, are formed, the monoanion (I) can apparently also undergo heterolysis;[1] in this case it may be protonated by the acid formed, giving rise to the hydrocarbon RH.

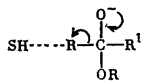
When carbonyl compounds are cleaved by alkoxides in alcohols, there is a possibility of the formation of only the monoanion, but it has been demonstrated nevertheless that acetylacetone and 2-ketoalkylpyridinium salts are readily cleaved under these conditions:[21]



In the general case, when asymmetric ketones are cleaved by bases, there is a possibility of the formation of a mixture of two acids (or their derivatives) and two hydrocarbons:[9,22,23]

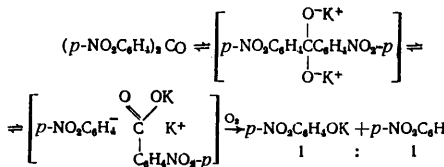


The mode of reaction is determined by the relative stabilities of the carbanions R^- and $(R^1)^-$—the most stable carbanion is split off. Therefore, if the stabilities of the carbanions are approximately identical, i.e. the pK_a of the corresponding RH and R^1H are similar, then a mixture of four products is formed. The ease of cleavage of carbonyl compounds is also determined by the stabilities of the carbanions produced (see below). The question arises whether these reactions lead to the formation of the carbanion R^- as a kinetically independent species or is it possible, as has in fact been suggested,[24] that the product RH is formed as a result of the attack by the proton-donating compound (SH) directly on R in the adduct:

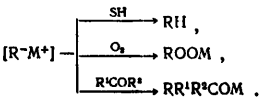


According to Artamkina et al.,[20] the ion pair VI participates in the reaction, as shown in Scheme 3 for the cleavage of $(p\text{-}NO_2C_6H_4)_2CO$, where oxygen functions as the trapping agent for R^-:

Scheme 3



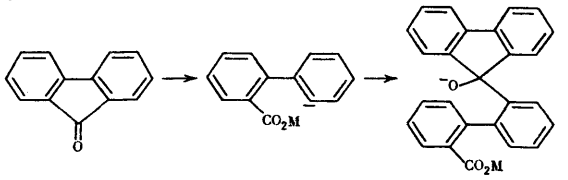
Naturally, the organometallic compound RM itself can also be formed in these reactions if R^- is a sufficiently stable carbanion. On the other hand, in the majority of cases the reaction requires the presence of a suitable compound functioning as the trapping agent for the carbanion:



The cleavage of carbonyl compounds is usually carried out in aqueous or alcoholic solutions and the trapping is a proton-donating compound. This role can sometimes be assumed by O_2.[20] In the absence of a proton donor, the ketone itself can act as the trapping agent. For example, in the cleavage of benzophenone and its *pp'*-difluoro-derivative, triarylcarbinols have been obtained in 75–86% yield by treatment with KOH in dimethoxyethane (DME):[20]

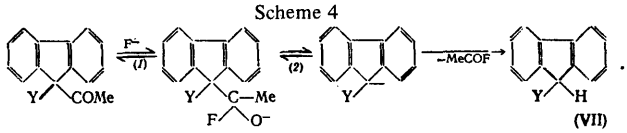
$$[XC_6H_4^-K^+] \xrightarrow{(XC_6H_4)_2CO} (XC_6H_4)_2COK,$$
$$X = H,\ p\text{-F}.$$

The formation of small amounts of triarylcarbinols (X=H or *p*-Cl) has also been noted in other studies.[23–26] A similar reaction has likewise been observed in the cleavage of fluorenone;[27–29] the yield of the carbinol reached 94% in some cases:[28]



In the absence of carbanionic trapping agents, the stages (3) and (4) (in Schemes 1 and 2) are as a rule reversible and the process as a whole therefore becomes reversible. This has been clearly demonstrated for the cleavage of 9-substituted 9-acetylfluorenes by the fluoride ion (KF-18-crown-6 ether or Bu_4NF/SiO_2) and it was shown that both stage (1) and stage (2) (Scheme 4) are reversible:[30]

Scheme 4

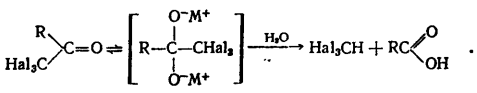


(VII)

When Y = CN, the equilibrium is strongly displaced towards the reaction products. Subsequent hydrolysis showed that the yield of RH (VII) diminishes in the sequence Y = CN > $PhCH_2$ > Me and on passing from a non-polar to a polar solvent.[30]

Specific examples of the cleavage of carbonyl compounds by various bases are examined below.

2. The Haloform Reaction

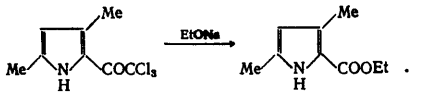


Such reactions occur frequently and usually readily,[5] because trihalogenomethyl anions are fairly stable (the pK_a of the corresponding CH acids are 13.7–15.5 [31]). The cleavage sometimes occurs simply on treatment with water, as happens, for example, for hexabromo- and hexachloro-acetones,[32,33] but usually bases have to be employed. Thus ααα-trichloroacetophenone can be heated for 7 h at 170 °C without change, but in the presence of catalytic amounts of MeCOOK it is immediately cleaved.[34] αα-Dibromoacetophenone is cleaved on boiling with a sodium carbonate solution.[35] Perfluoro-t-butylphenyl ketone is entirely stable, but decomposes rapidly in the presence of catalytic amounts of CsF in DME:[36]

$$PhCOC(CF_3)_3 \xrightarrow{F^-} PhCOF + (CF_3)_3C^- \xrightarrow{-F^-} (CF_3)_2C{=}CF_2 .$$

However, KOH and NaOH are usually employed as bases in the haloform reaction, $Ca(OH)_2$ and $Ba(OH)_2$ being more rarely used.[5]

The haloform reaction is used to synthesise bromoform and iodoform, the determination of the structures of organic compounds, and sometimes for the synthesis of acids or their esters.[5] For example, ferrocenemonocarboxylic and ferrocenedicarboxylic acid are obtained by treating mono- or diacetylferrocenes with hypohalites.[37] Aliphatic acids with branched groups of the type of Me_3CCOOH and Me_3CCH_2COOH or unsaturated acids, which are sometimes difficult to obtain in other ways, can be synthesised with the aid of this reaction; in the presence or alcohols, esters are produced,[34,38] for example:



Phenylesters can also be obtained by a similar procedure:[38]

$$PhCOCCl_3 \xrightarrow[\text{80\%}]{PhOH,\ KOAc} PhCOOPh,$$
$$PhCOCCl_3 \xrightarrow[\text{90\%}]{(o,\ p)\text{-}MeC_6H_4OH} PhCOOC_6H_4Me\text{-}(o,\ p).$$

Hexachloroacetone is used for the trichloroacetylation of alcohols and phenols:[39–41]

$$Cl_3CCOCl_3 + ClCH_2CH_2OH \xrightarrow[\text{pentane, 20°C, 16 h}]{K_2CO_3} Cl_3CCOCH_2CH_2Cl + CHCl_3 .$$

In aprotic dipolar solvents such as nitromethane,[40] dimethyl sulphoxide (DMSO), dimethylformamide, (DMF), pyridine, and hexamethylphosphoramide (HMP),[41] the reaction can be carried out in the absence of a catalyst. DMF proved to be especially effective.[41]

The decomposition of hexachloro- or hexabromo-acetone is also induced by ammonia[33] and amines, even aromatic amines:[42]

$$CCl_3COCCl_3 + RC_6H_4NH_2 \xrightarrow[20–60°]{H_2O} Cl_3CCONHC_6H_4R,$$
$$R = H;\ MeO,\ Me,\ OH,\ Cl .$$

The trichloroacetylation of peptides has been carried out in an analogous manner.[43]

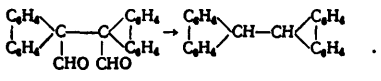
On treatment with hypohalites, carbonyl compounds of other classes are also cleaved—α-ketoesters, β-diketones, or β-ketoesters. In essence, these reactions are analogous to the haloform cleavage reactions. Some of them have been described in a review.[5]

3. The Cleavage of Aldehydes by Bases

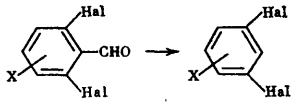
Aldehydes without α-hydrogen atoms usually enter into the Cannizzaro reaction,[44] but there are a number of exceptions whereupon treatment of aldehydes with alkali results in their cleavage:

$$RCHO + MOH \begin{cases} \xrightarrow{(1)} RCH_2OH + RCOOH, \\ \xrightarrow{(2)} RH + HCOOH . \end{cases}$$

Naturally, the second mode of reaction occurs in those cases where the Group R is sufficiently electron accepting. The well-known examples of such reactions are the cleavage of chloral,[45] bromal,[46] mixed bromochloroacetaldehydes,[47] and even aldehydes containing the SO_3K or SO_3H group in the α-positions[48–51] on treatment with alkalis. On heating with 20% KOH (130 °C, 5 h) [52,53] or with alcoholic KOH (120 °C, 5 h),[54] triphenylacetaldehyde is cleaved to triphenylmethane. Aldehydes containing an acetylenic group in the α-position (propargyl, phenylpropargyl,[55] and tetrolic[56] aldehydes) are cleaved by dilute KOH solutions at 20 °C. Other examples of the ready cleavage of aldehydes, for example, bisdiphenylene succinic aldehyde[52] or trichloroacrolein,[57] can also be quoted



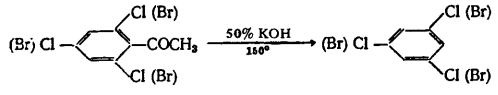
In the series of aromatic aldehydes, an essential condition for their cleavage in an alkaline medium is the presence of two electron-accepting substituents, and halogen atoms, for example, must be in the *ortho*-positions. 2,6-Dihalogenobenzaldehydes are cleaved by refluxing with 50% KOH and under these conditions the aromatic ring can contain also other substituents, including electron-donating substituents (Me, MeO):[58]



Dinitrobenzaldehydes react much more readily and in this case not only 2,6-dinitro- but also 2,4-dinitro-benzaldehydes are cleaved.[59] Trinitrobenzaldehyde is cleaved especially easily—it is sufficient to heat it with alcoholic solutions of NaOH or NH_3, Na_2CO_3 (10%), or even aniline (the yield of trinitrobenzene is up to 95%).[59] Thus the general trend is evident: the reaction is faster, the more stable the carbanion formed. A single chlorine atom in the *ortho*-position in benzaldehyde is insufficient to alter the mode of reaction—the usual Cannizzaro reaction takes place in this case.[58]

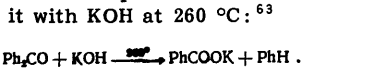
4. The Cleavage of Ketones by Alkalis and Alkoxides

As will be seen from the data presented below, the cleavage of ketones obeys the rules which have been noted above for aldehydes. Thus acetophenone and its monochloro-derivatives are cleaved by alkali with difficulty. It is of interest that the cleavage proceeds with abstraction of the methyl and not the phenyl group.[60] It may be that the ease of protonation of the more nucleophilic group plays a role in this case. The reaction is accompanied by charring and the yield of benzoic acids is insignificant.[60] Even when acetophenone is heated with KOH melt at 220–250 °C, only 20% of benzoic acid is formed.[61] The same has been observed for methylacetophenones.[60] The situation changes sharply when two chlorine or bromine atoms are introduced in the *ortho*-positions in the benzene ring; the process proceeds even more readily with 2,4,6-trichloro-, 2,4,6-tribromo-, and 2,3,4,5,6-pentachloro-acetophenones (50% KOH, 150 °C), but the products of these reactions are halogenobenzenes and not benzoic acids:[60]



Naturally 2,4,6-tribromo-ααα-trichloroacetophenone gives rise to 2,4,6-tribromobenzoic acid on cleavage.[62]

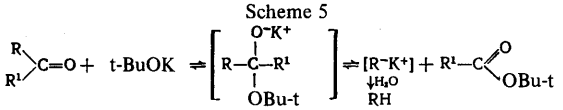
Acetophenone and other enolisable ketones undergo the condensation reaction more readily than the cleavage reaction and cleavage has therefore been investigated for non-enolisable ketones, in the first place benzophenone and its derivatives.[22,23,63–67] Benzophenone was cleaved as early as 1849 by fusing it with KOH at 260 °C:[63]



Under just as severe conditions, mono- and di-methylbenzophenones are cleaved with formation of toluic acids.[64–67] The introduction of even one chlorine atom in the *ortho*-position in the benzene ring proved to be sufficient to increase significantly the rate of reaction, whereupon chlorobenzene and benzoic acid are formed.[23] The influence of chlorine is so great that 2,4,6-trichlorobenzophenone is cleaved even by refluxing for 2 h with a dilute (20%) alcoholic solution of KOH.[68] Benzophenone itself and many of its substituted derivatives (with methyl and halogeno-substituents) are reduced under these conditions to diphenylmethanols, while benzophenones with strong electron-donating substituents do not react or char.[24,68,69] It is noteworthy that at the present time a method is available for the cleavage of benzophenone under much milder conditions—refluxing the ground KOH in DME or tetrahydrofuran (THF).[20] Fluorenone and its substituted derivatives are cleaved in a KOH melt[27] or in diphenyl ether.[70]

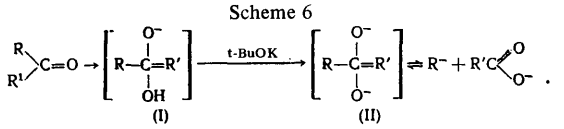
In recent years, t-BuOK has been most widely used for the cleavage of ketones, usually in aprotic dipolar solvents.[25,26,71–76] This method was proposed by Swan as early as 1948.[24] Ether, dioxan, pyridine, DMSO, HMP, and DME and also benzene and hexane can be used as solvents in these reactions. A very important factor is the presence of small amounts of water in the reaction mixture. Careful experiments have shown that t-BuOK : H_2O = 3 : 1 is the optimum ratio. In the absence of a proton source, the yields of acid are insignificant (the reaction usually does not occur at all). The mechanism initially proposed by Swan[24] (Scheme 5) includes the attack by t-BuOK on the ketone; water serves as the trapping agent for the carbanion and generates under these conditions the OH^- anion, which is essential for the hydrolysis of the t-butyl ester:

Scheme 5



However, it was shown subsequently that t-butyl esters are not intermediates in these reactions[73] and an alternative mechanism (Scheme 6) was therefore proposed in which the carbonyl group is initially attacked by the OH^- anion with formation of the adduct (I), while t-BuOK abstracts a proton from it, affording the dianion (II):[25,73,74,76]

Scheme 6

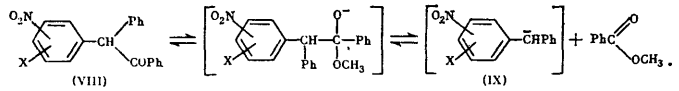


In this version, the role of water consists in generating the hydroxide from t-BuOK. There exists yet another point of view on the mechanism of this reaction—the 3 : 1 : 1 t-BuOK–t-BuOH–H_2O mixture gives rise to an aggregate, which is soluble in organic solvents and in which OH^- is only slightly solvated and is therefore extremely reactive. In this case KOH should cleave ketones in aprotic solvents also in the absence of the t-BuOK–t-BuOH mixture. Indeed, a suspension of KOH, obtained by adding water to an excess of KH in THF, cleaves nortricyclanone in 2 h at 30 °C.[73] However, as mentioned above, ground KOH in THF or DME cleaves even benzophenone under relatively mild conditions.[20] Other di- and tri-cyclic ketones are cleaved in the t-BuOK–H_2O–aprotic solvent system. The authors believe that the driving force of their cleavage is the removal of strain from the system and the formation of stable cyclopropyl and allyl carbanions.[71–73] According to this view, camphenilone and fenchone, which are less strained than, for example, nortricyclanone, dehydronorcamphor, or 7-oxonorbornene, are not cleaved or are cleaved with difficulty.[72] The possibility of the cleavage of ketones such as $PhC(Me_2)COPh$ or $MeOC.(Me_2)COPh$ is also explained by the elimination of steric strain.[77,78]

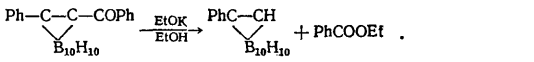
We may note that dehydronorcamphor, which is an enolisable ketone, is fairly smoothly cleaved by t-BuOK.[71,73,79] Yet another interesting example is the cleavage of α-(p- and

o-nitrophenyl)deoxybenzoins (VIII), which leads to the formation of benzoic acid and products of the further reaction of the carbanions (IX)—substituted anthranilic acid derivatives and tetraphenylethanes (Scheme 7):[80]

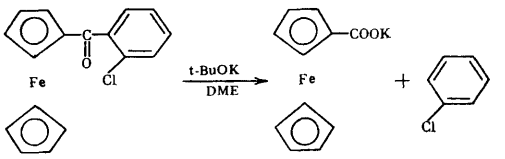
Scheme 7



Ketones of the carbaborane series are readily cleaved by treatment with EtOK in ethanol,[81] because the carbaborane formed is a fairly strong CH acid ($pK_a \cong 18$):[31]



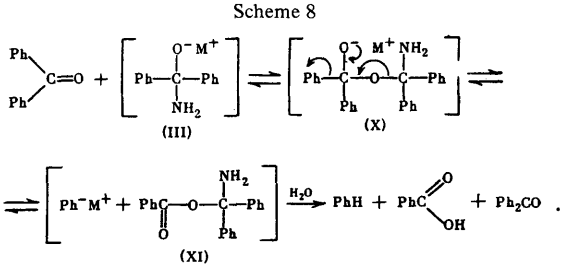
The t-BuOK–DME system has been used for the synthesis of carboxylic acids of the ferrocene and cymantrene series:[82]



5. The Cleavage of Ketones by Alkali Metal Amides

Potassium amide in liquid ammonia does not cleave benzophenone,[12,13] but it does partly cleave benzopinacol[83] and readily cleaves o-halogenobenzophenones.[12,13,17,84] Under more severe conditions, i.e. on refluxing ketones with H_2NK. .(H_2NNa) in toluene or xylene, both Ph_2CO and its *ortho*, *para*, and *meta*-substituted derivatives (with the Me, Cl, and Br substituents) are cleaved.[9,85] As a rule, when ketones are cleaved by alkali metal amides, not only amides but also the corresponding acids are formed.[9,12,84] Under the mild conditions used in the isolation of the reaction products, the amide cannot hydrolyse to the acid. The acid is apparently formed in the course of the reaction itself. It has been suggested that the mechanism of the formation of acids on cleavage of ketones by alkali metal amides[12] is analogous to the mechanism of the formation of benzilic acid on treatment of benzil with H_2NNa or RO^- in aprotic solvents.[86] The anion (III) acts as a base, attacking a second ketone molecule, and the heterolysis of the intermediate adduct (X) affords compound (XI), which is converted on hydrolysis into benzoic acid (Scheme 8):

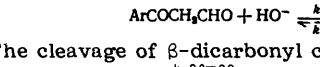
Scheme 8



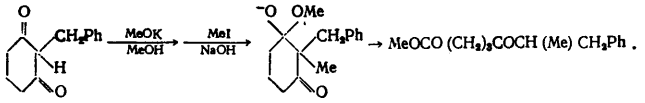
We may note that the intermediate formation of o-halogenophenyl anions has been demonstrated in the reaction with o-halogenobenzophenones.[12,13]

6. The Cleavage of β-Dicarbonyl Compounds

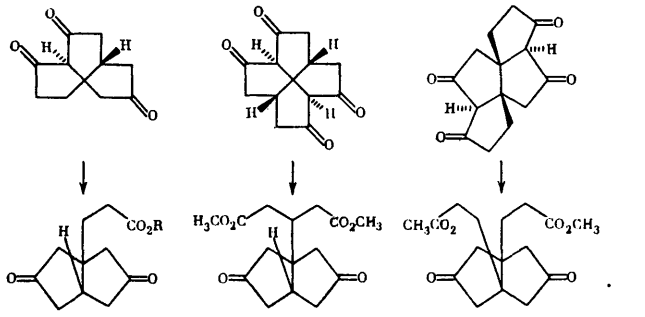
The best evidence that β-dicarbonyl compounds are cleaved by bases in the keto-form is probably provided by the finding that αα-disubstituted β-diketones or β-ketoesters, which are incapable of enolisation, are cleaved most readily.[3,87,88] It has been convincingly demonstrated for thenoyltrifluoroacetone that the enolate is stable in an alkaline medium and that the corresponding hydrate decomposes rapidly.[6] The stage involving the protonation of the enolate of the β-dicarbonyl compound can therefore become important for acid substrates which exist in the enolic forms in alkaline solutions. This situation obtain, for example, in the alkaline cleavage of aroylacetaldehydes, which are fully enolised in 0.1–1 M NaOH solutions:[89]



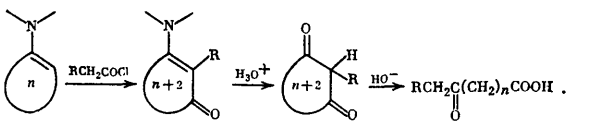
The cleavage of β-dicarbonyl compounds is used fairly often in synthesis.[4,90–92] This method is most important for the series of cyclic β-diketones, where it is used to synthesise oxocarboxylic acids:[4,90–92]



Recently this method has been used to cleave standard tri- and tetra-spiro-β-diketones:[95]



As an example, one may also quote the synthesis of 13-keto-acids, including the reaction of 1-morpholinocyclododecene with an acid chloride and the subsequent cleavage of the 1,3-diketone in an alkaline medium:[93,94]

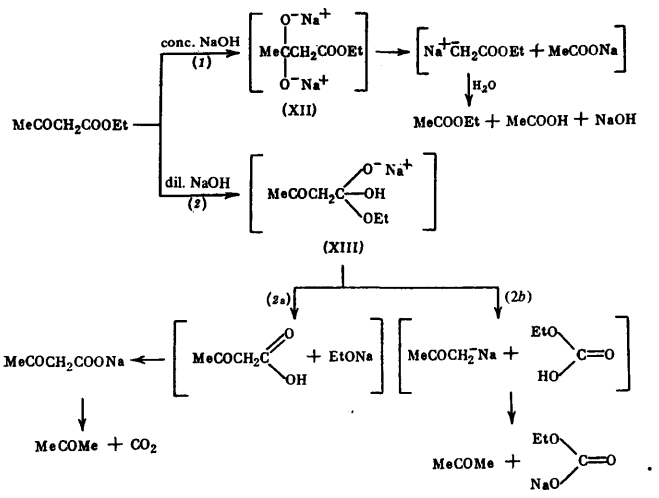


Dibasic ketoacids can be obtained by the reaction of an enamine with the chloride of a dibasic acid.[93,94]

The cleavage of β-dicarbonyl compounds in an alkaline medium is frequently an undesirable side reaction in the alkylation of β-diketones or β-ketoesters. However, the cleavage can be reduced to a minimum by carrying out the reactions at low temperatures, using sterically hindered bases, for example, t-BuOK in t-BuOH, or using NaH in aprotic dipolar solvents.[4]

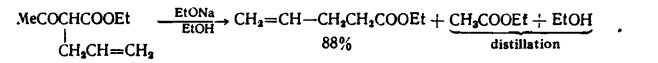
An unusual problem arises in the so called acid cleavage of acetoacetic ester and its analogues (the reaction which is the opposite of its synthesis, i.e. is the retro-Claisen condensation), which is always accompanied by the formation of ketones (ketone degradation) (Scheme 9).

Scheme 9



The first of these reactions involves the addition of the alkali to the keto-group [the adduct (XII)], which should proceed more readily than the addition to the ester group [the adduct (XIII)]. Nevertheless, both reactions [(*1*) and (*2*)] take place almost simultaneously. A possible explanation of this finding is that the dissociation of the C–C bond requires as a rule the formation of the dianion, which is indicated by the second (or higher) order of the reaction with respect to the alkali, while the cleavage of the C–O bond (hydrolysis) can occur in the monoanion. In fact, the intermediate (XIII) can decompose not only via the hydrolysis stage (*2a*) but also via the other pathway (*2b*), especially since this entails the formation of the acetonyl carbanion, which is more stable than the ethyl acetate anion [pK_a(MeCOMe) = 20 and pK_a(Me.COOEt) = 24 [31])]. The operation of this pathway [pathway (*2b*) as well as pathway (*1*) should be promoted by concen-t trated alkali. It may be that the high reactivity of the keto-group has an effect in the competition between pathways (*1*) and (*2b*).

In practice, the cleavage of dialkyl- or even monoalkyl-acetoacetic esters at the carbonyl group can be successfully achieved when the reaction is carried out in the presence of an excess of alcohol with catalytic amounts of an alkoxide and with continuous distillation of ethyl acetate from the reaction mixture, [92,96] for example:



It is noteworthy that unsubstituted β ketoesters are not cleaved under these conditions but are converted into enolates, which are fairly resistant to the action of bases.

III. DECARBOXYLATION OF CARBOXYLIC ACIDS AND DEALKOXYCARBONYLATION OF ESTERS

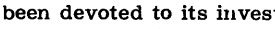
The decarboxylation of carboxylic acids and their derivatives is an important process both in synthetic organic chemistry [97–99] and in biochemistry (the latter applies mainly to the decarboxylation of β-ketoacids [100,101]) and this is why much attention has been devoted to its investigation. The unimolecular thermal decarboxylation of acids, involving the formation of a carbanion, has been thoroughly studied: [97]



Both the neutral acid and its anion or zwitter-ion, for example in the case of acids of the pyridine series, can be decarboxylated. [97] However, we shall not be interested in the decomposition of the carboxylate ion, which may arise both on treatment of the acid with bases and as a result of the dissociation of the acid. It is therefore natural that, when one is dealing with the decarboxylation of neutral acid, one has in mind fairly strong acid and fairly polar solvents. The decomposition of carboxylate ions leads to carbanions, whose formation has been unambiguously demonstrated with the aid of electrophilic trapping agents—bromine, aldehydes, ketones, nitro-compounds, D_2O, etc. [97]

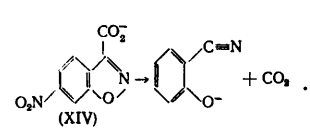
1. Decarboxylation of Monocarboxylic Acids

Fairly strong acids such as trihalogenoacetic, 2,4,6-trinitrobenzoic, and α-nitrocarboxylic acids are almost fully dissociated in aqueous solutions even in the absence of bases and it has been shown that they are decarboxylated in the anionic forms: [102–111]

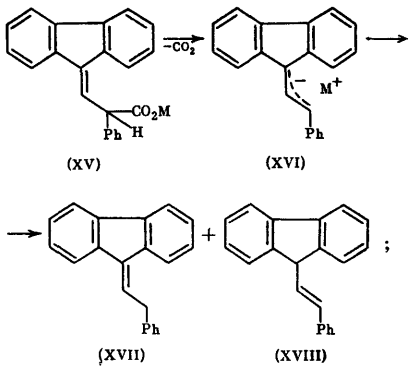


This has been confirmed by the identity of the activation energies for the decarboxylation of the acids and their salts. In non-aqueous solvents, where the acids are insignificantly ionised, the rate of reaction after the addition of the base is proportional to the concentration of the anion formed. The unionised acids are entirely stable. [102–111] Although water promotes the dissociation of acids and salts, which should facilitate the decarboxylation, it can also stabilise the carboxylate anion as a result of solvation. Indeed, it has been shown that an increase of the fraction of ethanol or formamide in water up to a certain concentration increases the rate of decarboxylation of CCl_3CCOH or its sodium salt. [104,106] Analogous behaviour has been observed for trinitrobenzoic acid after the addition of ethanol or dioxan to the aqueous solution. [108,109] In the decarboxylation of (4-chlorophenyl)-α-cyanoacetate anion, the rate increases sharply in alcohol and increases almost by a factor of 3000 in dioxan compared with water. [112] However, a certain amount of water is apparently necessary to suppress the reversibility of the reaction even in fairly strong aprotic solvents, because water serves as a "trap" for the carbanion. Thus the rate of decarboxylation of potassium triphenylacetate in THF proved to be a maximum after the addition of 1–3 moles of H_2O per mole of the substrate. At higher concentrations of water, the rate of reaction falls, whilst at lower concentrations the decarboxylation ceases altogether (more precisely the degree of reaction is determined by the concentration of water): [113]

An especially marked increase of the rate of decarboxylation has been observed in aprotic dipolar solvents, for example, the rate of decarboxylation of the anion of 3-carboxy-6-nitrobenzoisoxazole (XIV) increases by a factor of 10^5 in DMSO or benzonitrile and by a factor of 10^6 in HMP compared with water: [114–116]



An exceptionally great role of the solvent has been noted also in the decarboxylation of the 3-(fluoren-9-ylidene)-2-phenylproprionate anion (XV): [117]



(XV) (XVI) (XVII) (XVIII)

M = H (a), Na (b).

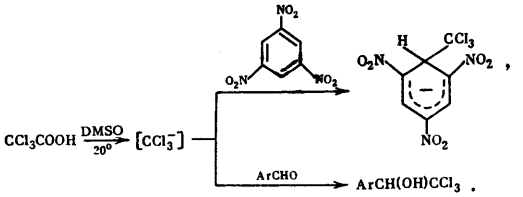
It is of interest that the dissolution of the acid (XVa) in DMSO leads to the instantaneous and quantitative formation of the products (XVII) and (XVIII). On the other hand, the addition of toluene-*p*-sulphonic acid fully suppresses the decarboxylation, which demonstrates yet again that the acid (XVa) is decarboxylated via the anion (XVI).[117]

The addition of crown ethers acts in the same direction as aprotic dipolar solvents.[113,117] It is believed that the main role of crown ethers consists in increasing the solubility of the salts in THF or dioxan, although, apart from this, the formation of complexes with the crown ether apparently increases the resistivity of RCOOM.[113,117]

The influence of the structure of the substituent (R = 9-phenylfluorenyl, fluorenyl, phenylethynyl, triphenylmethyl, and diphenylmethyl) on the rate of decarboxylation of RCOOM in THF or dioxan in the presence of 18-crown-6 ether has been investigated[113] and it has been shown that there is a correlation between the rate of reaction and the pK_a of the CH acids formed during the reaction. Sodium 9-phenylfluorene-9-carboxylate, which forms the most stable carbanion (for the substituents R investigated) (pK_a = 17.9 for 9-phenylfluorene), is decarboxylated at the highest rate, while sodium diphenylacetate, to which corresponds the diphenylmethylanion whose stability is fairly low (pK_a = 32 for Ph_2CH_2), is decarboxylated at the lowest rate.[113] In the presence of 18-crown-6 ether, the rate of decarboxylation increases by a factor of 13–500 depending on the structure.

The extremely marked dependence of the rate of decarboxylation on the nature of the solvent and the added crown ethers undoubtedly indicates the important role of the ions and ion pairs in this process. This is also indicated by data concerning the influence of the counterion. The rate of decarboxylation of triphenylacetates Ph_3CCOOM in THF diminshes in the sequence K > Na > Li. In the presence of 18-crown-6 ether, the rate of reaction increases approximately by a factor of 100.[113] In the decarboxylation of trichloroacetate salts in ethanol, the tetra-alkylammonium salts decompose fastest.[106]

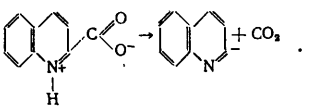
The decarboxylation of acids or their salts in aprotic solvents has long been used to obtain carbanions. Thus trichloroacetic acid in DMSO proved to be the best source of the CCl_3^- anion, because the latter is fairly stable# in this system and can be used in various syntheses:[118–120]



The decarboxylation of 4-nitro-, 2,4-dinitro-, and 2,4,6-trinitro-phenylacetates in DMSO, THF, or DME has been proposed for the generation of nitrobenzyl carbanions, which are difficult to obtain by other methods. The reactions in THF or DME are accelerated by crown ethers.[121]

2. Decarboxylation of Heterocyclic Acids

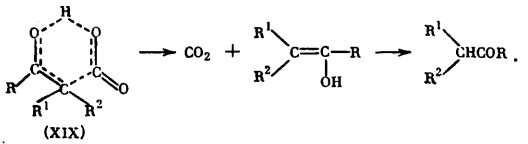
It has been suggested that heterocyclic acids—picolinic, quinaldinic, isoquinaldinic, pyridine-4-acetic, etc. acid—are decarboxylated via zwitter-ions:[97]



Indeed, these acids are stable in highly basic or acid solutions but decompose in neutral solutions.

3. Decarboxylation of β-Ketoacids or β-Dicarboxylic Acids

The decarboxylation of β-ketoacids and β-dicarboxylic acids differs from the decarboxylation of acids with other electron-accepting groups (see above) by certain features. In such cases, both the anions and the undissocated acids are decarboxylated in water and aqueous solutions, the undissociated acids being cleaved more rapidly than the ionised forms.[97,122–125] For example, acetoacetic acid is decarboxylated approximately 50 times faster and malonic acid approximately 10 times faster than the corresponding anion.[97,122–125] The dianions of malonic and phenylmalonic acids are stable in aqueous media.[125,126] It is believed that the decarboxylation of such keto-acids or dicarboxylic acids proceeds via a six-membered transition state of type (XIX)[97,111,122–124,127–129] with the intermediate formation of the enolic forms of the ketones or acids:[97,111]



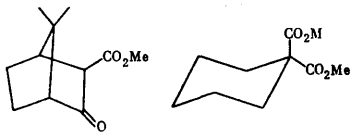
(XIX)

It is of interest that in the case of dibromomalonic acid the monoanion is decarboxylated incomparably faster than the undissociated acid.[126] Phenylmalonic acid occupies an intermediate position—the rate of cleavage of its monoanion is approximately 5 times higher than the rate of cleavage of the undissociated acid.[126] The monoanions of oxalylacetic acid are also decarboxylated faster, whilst the dianions are stable, as for malonic acid.[130–132]

It is noteworthy that at present there are virtually no data on the decarboxylation of β-ketoacids or β-dicarboxylic acids in anionic forms. There has been only one study in which the influence of the cation and crown ether on the decarboxylation of the acid (XX) and (XXI) was investigated and

The CCl_3^- anion, formed, for example, on treating chloroform with a base, decompses fairly rapidly with elimination of Cl^-, affording dichlorocarbene.

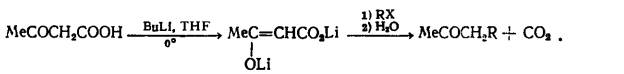
it was shown that the same tendency is observed for these acids as for triphenylacetic acid.



(XX) (XXI)

The potassium salt is decarboxylated faster in dioxan than the sodium salt and the reaction is accelerated by 18-crown-6 ether.[133] In the decarboxylation of benzoylacetate anions, a fairly marked influence of the substituents was noted, in contrast to the decarboxylation of the undissociated acids.[101,124]

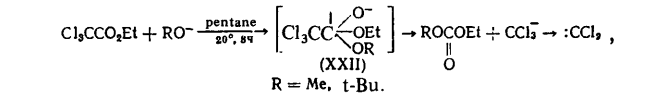
It has been suggested that the lithium enolate of acetoacetic acid be used for the synthesis of ketones:[134]



The decarboxylation proceeds smoothly at 0 °C.

4. Dealkoxycarbonylation of Carboxylic Acid Esters

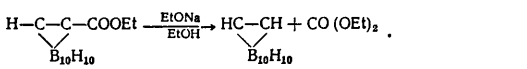
Carboxylic acid esters can be cleaved by strong bases (the dealkoxycarbonylation reaction) as happens with carbonyl compounds. Thus ethyl trichloroacetate is cleaved by sodium alkoxides:[135]



(XXII)

R = Me, t-Bu.

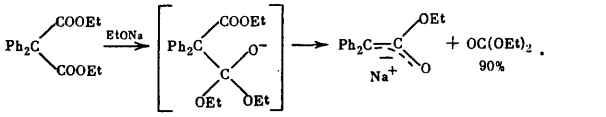
The intermediate formation of the adducts (XXII) has been unambiguously demonstrated by the isolation of dialkyl carbonates (73–94%). On treatment with catalytic amounts of EtONa and EtOH, the esters of carbaboranemonocarboxylic and carbaboranedicarboxylic acids are cleaved:[136]



We may note that the amides of methyl- and phenyl-barenic acids are just as readily cleaved by H_2NNa in liquid NH_3.[137]

Malonic esters can be cleaved with sodium ethoxide in certain cases, although as a rule this requires high temperatures.[4,138] The cleavage of the diphenylmalonic ester with EtONa in EtOH results in the quantitative formation of diethyl carbonate and the enolate of diphenylacetic ester§ (Scheme 10):[138]

Scheme 10

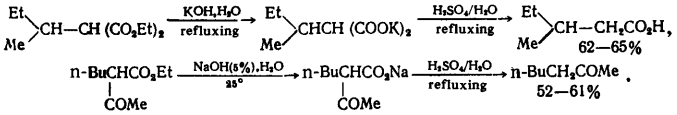


This version of the reaction is the reverse of the synthesis of malonic esters from diethyl carbonate and acetic esters.[139]

§ When dialkylmalonates are cleaved by EtONa, another pathway predominates: $R_2C(COOEt)_2$ + EtONa → $R_2CHCOOEt$ + CO + CO_2 + C_2H_6, etc.; α-vinyl, α-ethyl-, and phenylethylmalonic esters, which are cleaved simultaneously via both pathways, constitute an intermediate case.[138]

The equilibrium is displaced by distilling of diethyl carbonate. However, in contrast to the cleavage of carbonyl compounds by alkali or alkoxides, this reaction involving esters is not so well known and has not found extensive applications. In many cases it appears as a side reaction, for example, in the acid cleavage of β-ketoesters (see Section II) and in all cases where malonic or cyanoacetic esters have to be heated for a long time with alcoholic alkoxides.[4]

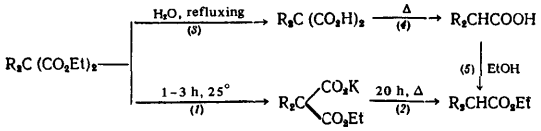
The decarboxylation of β-ketoacid or *gem*-dicarboxylic acid esters is widely used in the synthesis of ketones and monocarboxylic acids. The hydrolysis is usually carried out with acids or dilute alkalis using so far as possible an insignificant excess of the latter in order to avoid the side reaction involving the acid cleavage in the case of ketoesters. Examples are presented below:[4]



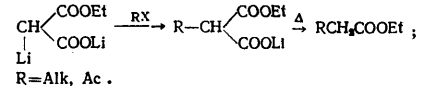
Thus the problem reduces to obtaining acids or their anions, which are then subjected to thermal decarboxylation (already described above).

A method has been proposed recently for the decarboxylation of dicarboxylic acids involving the selective hydrolysis of the diester to the monoester and its decarboxylation in the presence of 18-crown-6 ether [the KOH/crown ether/benzene/dioxan/ethanol system (5%)].[133] Since acid esters and not the acids themselves are used in the synthesis, this method is a convenient single-stage alternative to the traditional three-stage synthesis of esters [stages (3)–(5) in Scheme 11]:[133]

Scheme 11



Enolisation may take place as a side reaction, which has already been observed for phenylmalonic esters; nitromalonic ester enolises wholly under these conditions. In this system, it has been possible to carry out the dealkoxycarbonylation of certain ketoesters.[133] Another procedure involves the synthesis of acid esters by alkylating or acylating the dilithio-derivative of monoethyl malonate with subsequent decarboxylation:[140,141]



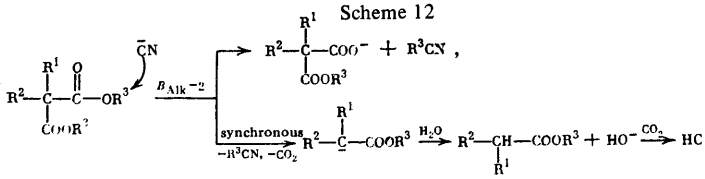
R=Alk, Ac.

Yet another method has been vigorously developed recently—the decarboxylation of β-ketoesters, malonates, α-cyanoesters, etc. in aprotic dipolar solvents in the presence of small amounts of added water (1–2 moles per mole of the substrate) and salts such as NaCN, NaCl, NaBr, NaI CaI_2, and LiCl (possibly even in catalytic amounts) as 140–180 °C.[98,99,142–147] This method, whieh had been used earlier to convert monocarboxylic esters into acids (a reaction of the S_N2 type),[148,149] proved to be convenient in many instances for the decarboxylation of substrates sensitive to attack by alkalis or acids. In many cases the best results have been achieved by employing $Me_4NOCOMe$ in DMSO (130 °C) or in HMP (100 °C).[150–152] The *p*-aminothiophenol–Cs_2CO_3–DMF system (130 °C) is probably still more effective, making it possible to eliminate immediately two methoxycarbonyl groups from a single molecule.[153]

It has been suggested that moist DMSO be used in the dealkoxycarbonylation of reactive substrates such as $NCCH_2$. .COOEt, $PhCH(COOEt)_2$, 2-ethoxycarbonylcyclopentanone, etc.;[145–147] the cleavage can also be carried out in dry DMSO, but the addition of water lowers the reaction temperature.[146,147] For less reactive substrates, it is essential to add water and frequently also a salt. The greatest effect is produced by NaCN.[144–146]

It is assumed that, in the absence of a salt, the ester is hydrolysed in moist DMSO by the $B_{AC}2$ route. In the KCN–DMSO mixture, the reaction pathway depends on the substrate. Thus in the case of dimethyldiethylmalonate, the formation of MeCN indicates that the $B_{Alk}2$ mechanism of the cleavage reaction predominates[98] (Scheme 12):

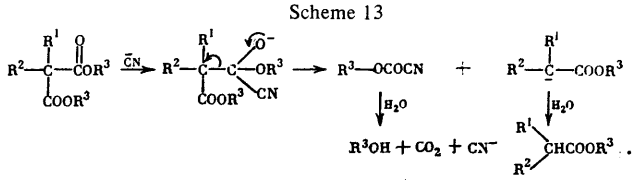
Scheme 12



This scheme is probably valid for other salts MX and for other substrates such as β-ketoesters and α-cyanoesters.[98]

The $B_{AC}2$ mechanism should be preferred for reactions of monosubstituted malonic esters when the process is catalytic (Scheme 13):

Scheme 13

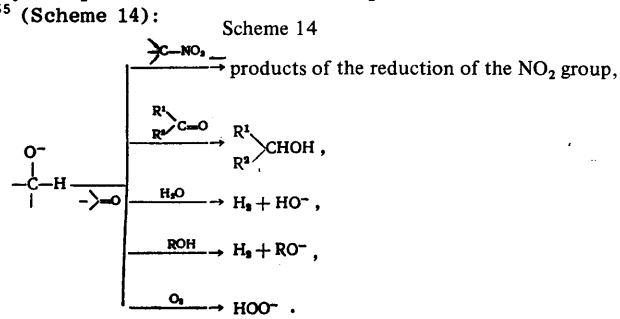


The intermediate formation of carbanions in these reactions can not only be readily demonstrated (by stereoselectivity data and by obtaining α-deuteriated esters and ketones), but can also be used in synthesis. For example, the cleavage of β-ketoesters, α-cyanoesters, or malonates in anhydrous DMSO in the presence of LiCl makes it possible to obtain α-alkylated ketones, acids, and nitriles. Dealkoxycarbonylation in the presence of PhSSPh in HMP affords α-phenylthioketones or α-phenylthioesters.[99] Numerous examples of the synthetic application of the method are quoted in Krapcho's review.[98,99] It has also been suggested that a non-ionic base—1,4-diazabicyclo[2.2.2]octane in xylene—be used for the decarboxycarbonylation of β-ketoesters; the yields of ketones are 84–90%.[154]

IV. THE CLEAVAGE OF ALKOXIDES

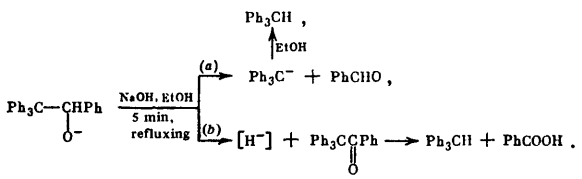
The alkoxides derived from primary and secondary alcohols are known to be potential sources of the hydride ion, which they can transfer to suitable acceptors such as carbonyl compounds, olefins, nitro-compounds, alcohols, etc.[155] (Scheme 14):

Scheme 14

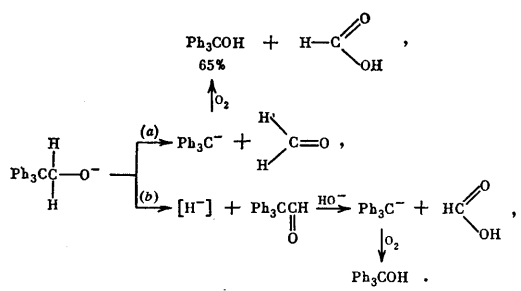


It is assumed that water behaves as the hydride ion acceptor in the dehydrogenation of primary aliphatic and aliphatic-aromatic alcohols by heating with caustic alkalis in aqueous solutions as 200–300 °C (the Dumas–Stass reaction[156]).[157] An alcohol molecule can also serve as the acceptor (200–225 °C).[158,159] In all these reactions (see Scheme 14) a C–H bond is ruptured and they are usually regarded as dehydrogenation or oxidation of alcohols. However, in this Section we shall be interested only in reactions in which C–C bonds are dissociated. This pathway occurs fairly rarely for alkoxides derived from primary or secondary alcohols and requires the presence in the latter of a group R which gives rise to a sufficiently stable carbanion. An example may be provided by the cleavage of phenyltritylcarbinol in an alcoholic solution of NaOH with formation of a mixture of triphenylmethane and benzaldehyde (65% of each) [pathway (*a*), Scheme 15].[160] In principle, the second pathway (*b*) is also possible, because the stabilities of Ph_3C^- and H^- are comparable,[161] but in this case this does not occur (Scheme 15):

Scheme 15



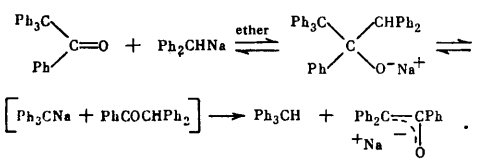
1-Aryl-2,2,2-trichloro- and 1-aryl-2,2,2-tribromo-ethanols are cleaved even more readily.[162] Alcohols of the carbaborane series likewise tend to be cleaved in an alkaline medium.[81] Even a primary alcohol containing the trityl group, namely 2,2,2-triphenylethanol (DME, KOH–O_2), is easily cleaved in an alkaline medium:[163]



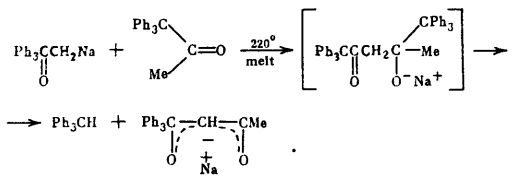
Here it is impossible to make an unambiguous choice between pathways (*a*) and (*b*), since the compositions of the products are identical.

Tertiary alcohols have the greatest tendency to be cleaved, the reaction involving only the rupture of a C–C bond in such compounds. As will be seen below, the ease of cleavage of alkoxides is determined by three most important factors: (1) the presence in the alkoxide RR^1R^2COM of a group to which corresponds a stable carbanion; (2) the bulk of the groups R, R^1, and R^2, because steric compression is eliminated in the transition state of this reaction; (3) the nature of the counterion giving rise to a fairly stable carbanion, in order to achieve their cleavage the introduction into the reaction mixture of trapping agents for the carbanion has been frequently resorted to. The trapping agent is the proton and the cleavage is therefore usually carried out in the presence of water or alcohol. Sometimes the carbonyl compound formed can serve as the source of the proton in the decomposition of alkoxides if it is capable of enolisation. Thus, when an attempt was made to obtain a tertiary alcohol from benzopinacolone and the sodio-derivative of diphenylmethanol,

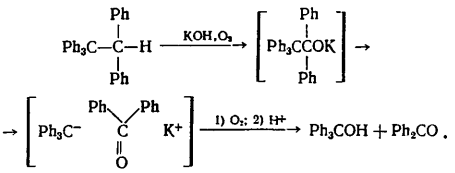
the spontaneous decomposition of the resulting carbinolate was observed:[164]



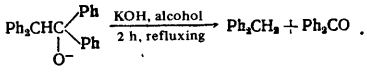
Because of the possibility of the ready elimination of the trityl anion, it has been possible to achieve an unusual Claisen–type condensation of methyl trityl ketone, where the leaving group is, however, the trityl anion:[165]



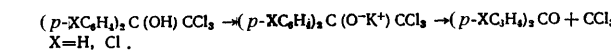
The alkoxides derived from pentaphenylethanol are apparently also unstable. At any rate, all attempts to obtain pentaphenylethanol by the reaction of Ph_2CO with Ph_3CM (M = Li, Na, or MgBr) proved unsuccessful.[166,167] The extreme instability of this alkoxide is probably to be explained by the steric strain in the molecule combined with the presence of the Ph_3C group, which gives rise to a fairly stable carbanion. This view is confirmed by the results of the oxidation of pentaphenylethane in an alkaline medium.[163] The reaction products in the THF(DME)–KOH–18-crown-6 ether system are triphenylmethanol and benzophenone. Evidently, the alkoxide formed in the reaction is unstable and decomposes to Ph_2CO and Ph_3C^-:[163]



Under mild conditions, the diphenylmethyl anion is split off:[168,169]

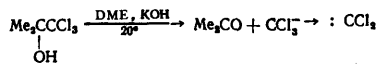


In aqueous alcoholic solutions in the presence of KOH, tertiary alcohols containing the CCl_3 group are readily cleaved:[170,171]

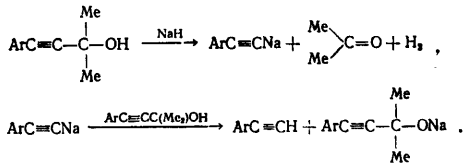


It has been shown that the rate of reaction increases linearly with increase of the concentration of the base.

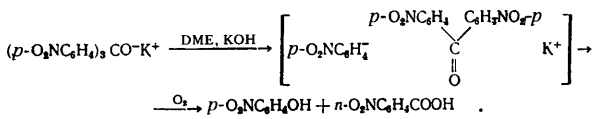
When dimethyl(trichloromethyl)methanol was maintained in the DME–KOH system in the presence of cyclohexene, dichlorononcarane was obtained,[163] which is associated with the formation of $:CCl_2$ from the trichloromethyl anion:



Acetylenic alcohols[172–175] and β-nitroalcohols[176] are fairly readily cleaved. It has been suggested that Ag_2CO_3 on celites in toluene,[174] Ag_2CO_3 and Ag_2O in DMSO (20 °C),[175] or K_2CO_3 at 150–160 °C[173] be used for the cleavage of acetylenic alcohols. Such cleavage can sometimes be conveniently used for the synthesis of arylacetylenes:[177,178]

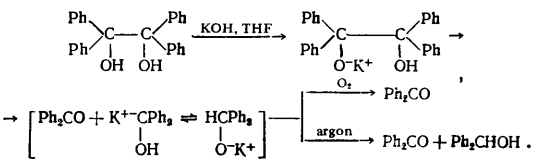


In the examples enumerated above, the proton usually serves as the "trap" for carbanions. Oxygen can sometimes be conveniently used as such a "trap".[20,163] Thus tris(*p*-nitrophenyl)methanol is readily cleaved in the DME–KOH–O_2 system, forming *p*-nitrophenol and *p*-nitrobenzoic acid.[20,163,179] We may note that, in the cleavage of alcohols as well as carbonyl compounds (see Section II), the attack by the electrophile or oxidant may be directed to a polarised C–C bond or ion pair and not to the free carbanion R^-:

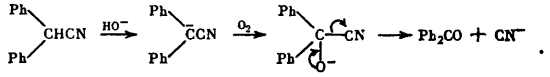


In the absence of O_2, a mixture of products which is difficult to separate, including the products of the reduction of the NO_2 group is formed. Lithium carbinolate is stable under these conditions. Triphenylmethanol is recovered unchanged even after heating for 48 h at 60–70 °C in the KOH–HMP–O_2 system, but the introduction of even one NO_2 group in the *para*-position in the benzene ring is sufficient for the rapid cleavage of the carbinolate (DME–KOH–O_2) with formation of *p*-nitrophenol and benzophenone. Even benzyldiphenylmethanol is cleaved in this system (60–70 °C, yield of PhCOOH 70–75%). The stability of the benzyl anion ($pK_a = 35$ for PhMe[31]) is apparently critical for the given conditions,[163] because the phenyl anion is not split off.

Aromatic ditertiary alcohols, for example, benzopinacol, are extremely readily cleaved:[163]

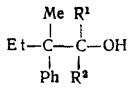


From the standpoint of the stability of alkoxides, the ready decomposition of cyanohydrins into the initial components in an alkaline medium can be readily understood, because the stable cyanide anion is split off.[180,181] This reaction apparently constitutes the basis of the oxidative decyanation of secondary nitriles in an alkaline medium:[182–184]



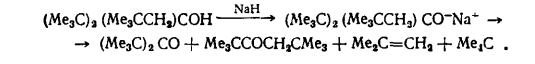
In the examples quoted above, the tendency of alcohols to be cleaved was determined mainly by the stability of the carbanion formed, although one cannot fully rule out also the influence of steric factors. This influence becomes of

primary importance in the cleavage of tertiary alcohols of the benzyl type,[77,78] i.e.



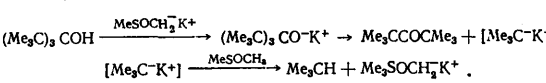
The rate of cleavage of these alcohols varies within wide limits as a function of the experimental conditions—the nature of the solvent and the base, etc. However, in general the ease of cleavage increases gradually in the following sequence of R^1R^2 groups: Ph_2 < PhMe < EtMe < Me_2, which corresponds overall to a gradual decrease in the size of the leaving group. This fact led to the conclusion that the weakening of the steric compression is one of the driving forces in anionic cleavages of this kind.[77,78] We may note that, in the given instances, a fairly stable carbanion is nevertheless formed.

Under more severe conditions (200–300 °C), the alkoxides derived from purely aliphatic tertiary alcohols are cleaved, the rate of cleavage being higher the greater the degree of branching.[185] Triethylmethanol is not cleaved even on heating to 335 °C in the presence of $NaNH_2$, but sodium di-t-butylneopentylmethoxide is cleaved when an attempt is made to obtain it from the corresponding carbinol and NaH:[185]

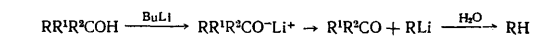


The carbanionic character of the cleavage of these alcohols, which do not give rise to stable carbanions, is emphasised by the just as marked influence of the counterion as that noted for alcohols capable of splitting off fairly stable carbanions R^-: Li > K > MgX [185] (see below). The successful use of organolithium compounds, in contrast to RMgX, for the synthesis of branched alcohols can apparently be accounted for precisely by the stability of the alkoxides,[186,187] Thus diisopropylneopentylmethanol is formed in 70% yield by the reaction of iso-Pr_2CO with neopentyl-lithium,[185] but the yield is only 4% in the reaction with neopentylmagnesium chloride.[188]

The influence of the solvent is usually very great in reactions with participation of carbanions. The reaction involving the cleavage of alcohols is not exceptional in this sense. Thus, on treatment with dimsylpotassium in DMSO, tri-t-butylmethanol undergoes exothermic cleavage with formation of bi-t-butyl ketone and isobutane:[189]



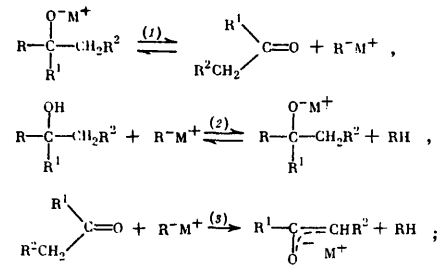
Even more stable alcohols are cleaved in HMP on treatment with BuLi:[190]



R, R^1, and R^2 represent different combinations of adamantyl, norbornyl, and 1-bicyclo[2.2.2]octyl and t-butyl groups. We may note that even lithium alkoxides are readily cleaved in this case.

In connection with the possibility of cleaving alkoxides, the question of the reversibility of the reaction involving the addition of organometallic compounds to aldehydes and ketones must inevitably arise. In contrast to other carbonyl compound condensation reactions (for example, the aldol and Claisen condensations), the reversibility of this reaction is not quite so widely known. Apparently, the reaction of RM with ketones as a reversible process was first† considered by Zook et al.[185] Their study of the decomposition of alkoxides derived from tertiary alcohols led them to the conclusion that the process is general for alkoxides with a branched structure and represents the reaction which is the reverse of the addition of RM to ketones (Scheme 16):

Scheme 16

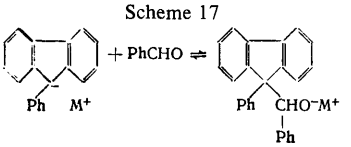


M = alkali metal.

According to the authors, the process can be reversible even when the equilibrium position in stage (*1*) is displaced far to the left, because, in the presence of an excess of the tertiary alcohol or the enolisable ketone, the equilibrium is displaced or is altogether disturbed by the conversion of RM into a hydrocarbon [stages (*2*) and (*3*) in Scheme 16].[185] It is noteworthy that the very possibility of the decomposition of the alkoxide with formation of a ketone and RM is evidence in support of the reversibility of reaction (*1*) in the general case. At the present time convincing evidence has been obtained for the existence of such equilibrium in various systems.

It is known that in aprotic media the stability of alcohols falls significantly compared with protic media.[192] Furthermore, the stability of the alkoxides ROM depends very markedly on the counterion M, diminishing in the sequence Li > Na > K.[193–195] The influence of the counterion on the association constant is manifested particularly strongly in aprotic dipolar solvents. Thus in DMSO the ionic association constants for t-BuOK are 10^8, 10^6, 270, and 200 litre mol^{-1} for M = Li, Na, K, and Cs respectively.[194] The equilibrium position (Scheme 16) can therefore vary significantly as a function of the nature of the counterion. Indeed, in the study of the reaction of benzaldehyde and cyclohexanone with fluorenyl and 9-phenylfluorenyl salts it was shown that the equilibrium in ether and DME is displaced wholly to the right for M = Li and Na and wholly to the left for M = Cs (scheme 17):[196,197]

Scheme 17



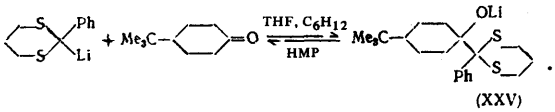
(XXIII) M=Cs

(XXIV) M=Li, Na

¶ Some indication of the reversibility of the reaction of RLi with ketones may be found in the paper of Swain and Kent,[191] although in the equation presented only the stage involving the formation of the complex between the carbonyl compound and RLi was reversible.

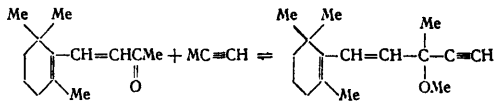
For M = K, it was possible to observe a "living" equilibrium in which both the alkoxide (XXIV) and the initial carbanion (XXIII) are involved. The equilibrium position depends significantly also on the solvent. Thus, if at the end of the reaction with the lithium salt in DME the solvent is replaced by HMP, the reaction equilibrium is fully displaced towards the initial reactants.[196,197]

A similar situation has been observed in the reaction of 2-lithio-2-phenyl-1,3-dithiane with t-butylcyclohexanone:[198]



(XXV)

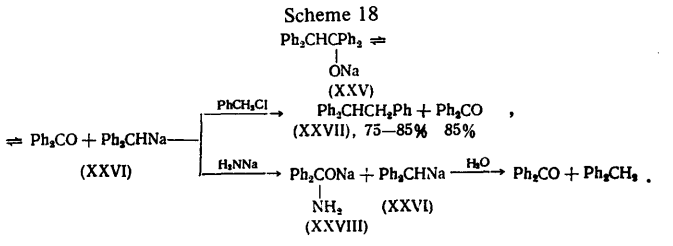
The carbinolate (XXV) is formed in 90% in C_6H_{12} and 75% yield in THF, while in HMP the reaction does not occur. The authors showed that this is associated with the reversibility of the reaction, because the carbinolate (XXV), known to be formed *a priori* in HMP, was converted into the initial compound. The changes in the degree of reaction of α- and β-ionones and benzylideneacetone with metal acetylides can probably be accounted for precisely by the different stabilities of the alkoxides (or, in other works, by the reversibility of the reaction).[199] Thus, in the reaction with β-ionone, the yield of the alcohol is low for M = K, increases to 15–27% for M = Na, and reaches 63–86% for M = Li:



An analogous picture has been observed in the reaction with benzylideneacetone (the yield of the alcohol is 40% for M = K, 71% for M = Li, and 96% for M = Ca) and with β-ionone (30% for M = Na, 67% for M = Li, and 67% for M = Ca).[199] The failure of the attempt to synthesise tertiary alcohols of the carbaborane series from ketones and lithio-derivatives of barenes has been explained[81] by the instability of such alcohols.

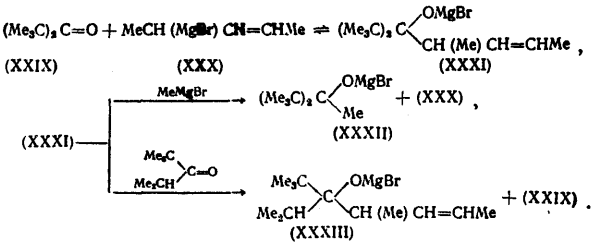
The reversible reactions quoted above involve stable carbanions of the type of fluorenyl or ethynyl carbanions. In the case of less stable carbanions, the reversibility of the reaction can be demonstrated by employing "trapping agents"—a carbonyl compound or RM. The existence of equilibrium in the reaction of benzophenone with diphenylmethylsodium was apparently first demonstrated precisely with the aid of this procedure (Scheme 18):[17,200]

Scheme 18

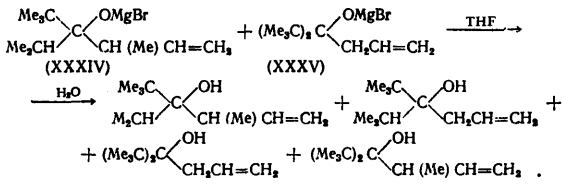


Indeed the addition of benzyl chloride to the reaction mixture leads to the formation of the alkylation product (XXVII), while the introduction of sodium amide results in the isolation of the adduct (XXVIII). The latter reaction is accompanied by the appearance of a red colour due to the carbanion (XXVI).[17]

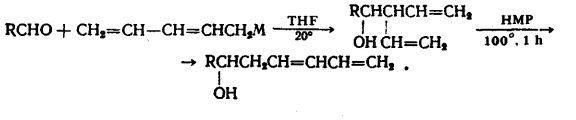
The reversibility of the reaction with ketones has been convincingly demonstrated also for organometallic compounds of the allyl type (M = Li, MgX, or ZnX).[201–214] One of the procedures used for this purpose is similar to that quoted by Hamrick and Hauser.[17] On treatment of the adducts (XXXI) with an excess of RMgX (R = Me or CH_2=CHMe), the tertiary alkoxide (XXXII) was obtained, in which the dimethylallyl group had been replaced by R, while on heating compound (XXXI) with iso-PrCOBu-t, which is more reactive than the ketone (XXIX), the adduct (XXXIII) was isolated together with t-Bu_2CO (XXIX):



In the case of CH_2=CH=CH_2MgX or α- and γ-dimethylallylmagnesium halides, where the initial and rearranged products are identical, the reversibility of the reaction was demonstrated by means of a "cross" reaction—when a mixture of the two carbinolates (XXXIV) and (XXXV) is refluxed, a mixture of four carbinolates is formed evidently as a result of the decomposition of compounds (XXXIV) and (XXXV) into the initial reactants and their subsequent interaction:[206]

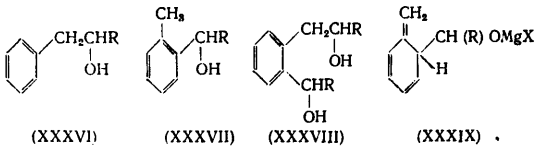


The thermal decomposition of carbinolates of the allyl type has also been carried out.[202,207,215] As was to be expected, the rate of decomposition increases with increase of the bulk of the substituents: t-Bu > iso-Pr ≅ cyclo-C_6H_{11} > Ph > Et.[207] It has been suggested that the reactions of allylic organometallic compounds, containing a strained diene system, with ketones and even with aldehydes are also reversible.[218,219] As already reported, the ratios of the products in these reactions depend significantly on their conditions. The strong influence of the nature of the cation M (Li, Na, Zn, and Al) on the mode of reaction has been noted in many communications.[204,215–218] It is therefore evident that the reversibility of such reactions can be used for synthesis purposes. Indeed, studies in which alcohols with a specified structure were synthesised by the reaction of such RM with carbonyl compounds have already been published.[215–218] For example, when the aldehydes RCHO are treated with CH_2=CHCH=$CHCH_2$M (M = ZnBr or Li) at the usual temperature, alcohols with a branched structure are formed exclusively, but, with increase of temperature and after the replacement of THF by HMP, the formation of only linear alcohols is observed:[216]



Thus the ability of allylic carbinolates to decompose into the initial ketone and allylmetal has been established. The possibility of the cleavage of magnesium carbinolates with formation of the benzyl Grignard reagent has been comparatively recently demonstrated. Throughout many years, chemists have been interested in the reaction of benzylmagnesium halides with aldehydes, in which the formation of "anomalous" products, namely o-tolylmethanol (XXXVII)[220–225]

and the diol (XXXVIII) or its dehydration product, [222–231] was observed together with the formation of the so called "normal" alcohols (XXXVI):



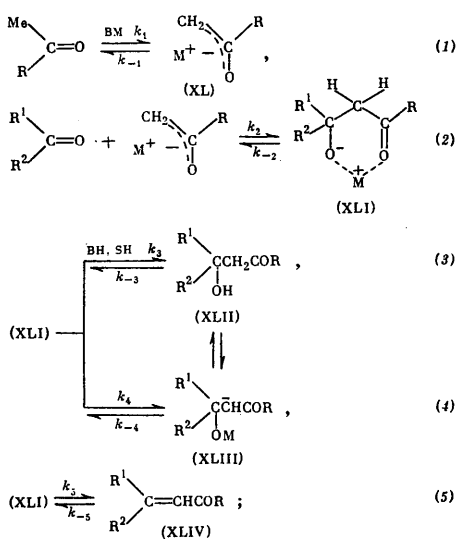
(XXXVI) (XXXVII) (XXXVIII) (XXXIX).

Convincing evidence showing that the diol (XXXVIII) and possibly also the "normal" alcohol (XXXVI) are secondary products, whose formation can be explained by the reversible dissociation of the adduct (XXXIX) arising initially and subsequent reactions, has been obtained only comparatively recently.[232–234]

V. THE RETROALDOL CONDENSATION

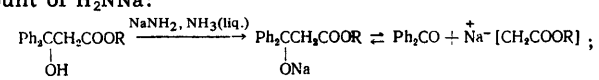
As shown in Section IV, tertiary alcohols containing a group R to which corresponds a sufficiently stable carbanion are cleaved in an alkaline medium, the ease of such cleavage depending primarily on the stability of the carbanion. It is quite evident that the alkoxides derived from β-hydroxycarbonyl compounds (the products of aldol condensation) must be unstable, because their cleavage results in the formation of the enolates of aldehydes, ketones, and esters, i.e. fairly strong CH acids (pK_a = 25–20).[31] Indeed, aldol condensation in an alkaline medium is a reversible process (Scheme 19) and all its stages are reversible:

Scheme 19



a) $R^1 = R^2$ = Alk or Ar; b) R^1 = Alk, Ar; R^2 = H; c) R^1 = Alk, Ar; R^2 = OAlk.

In order to obtain the target products, it is therefore necessary to select special conditions. However, in general, one may say that the condensation is promoted by the use of strong bases in stoichiometric or even larger amounts [in order to shift the equilibrium (*1*) to the right], by the removal of the condensation product from the reaction sphere [for example by its precipitation as the carbinolate (XLI) or the dianion (XLIII)], by a low temperature, and by a short reaction time.[4,92] On the other hand, the retroaldol cleavage will be promoted by the employment of catalytic amounts of bases, by an elevated temperature, by a long reaction time, and by the presence of trapping agents (for example, water or alcohol), which are capable of reacting with the enolates (XL), displacing thereby the equilibrium in stage (*1*) to the left. Indeed, retroaldol cleavage is as a rule carried out in aqueous or alcoholic solutions. In non-aqueous media there is also a possibility of retroaldol decomposition, because the initial reactants are more stable than the condensation products. However, since in non-aqueous media the hydroxycarbonyl compound (XLII) can itself function as a trapping agent for the enolate (XL), in the presence of stoichiometric amounts of bases, whereupon only the carbinolate (XLI) is present in solution, the retroaldol decomposition may not occur. Such a situation has been observed for the β-hydroxyester (XLV), which is cleaved by catalytic amounts of H_2NNa in liquid ammonia, but is not cleaved by the stoichiometric amount of H_2NNa:[235]



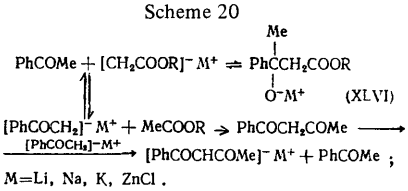
(XLV)

R = Et, iso-Pr, t-Bu.

As an example illustrating the influence of the reaction time on the yield of products, one may quote the condensation of benzophenone with alkyl acetates MeCOOR (R = Et or iso-Pr) in the presence of equimolar (and larger) amounts of H_2NNa in liquid ammonia.[235] For a short reaction time (neutralisation 5 min after the addition of Ph_2CO to the enolate), β-hydroxyesters (XLV) are formed in yields of ~70%, but, following an increase of the reaction time to 1 h, only the initial reactants are recovered.

Yet another procedure which is resorted to in order to shift the equilibria in aldol condensations involves the selection of the corresponding cations M^+. The dependence on the nature of the cation is the most interesting feature of these reactions. Thus acetophenone readily condenses in liquid ammonia with the enolates of alkyl acetates $[CH_2COOR]M^+$, where M = Li or ZnCl, but the adducts are not formed under these conditions with the Na enolates. Comparison of the alkoxides (XLVI), know to have been obtained *a priori*, showed that the lithium alkoxides are much more stable than the sodium or potassium alkoxides. Indeed, the sodium salt (XLVI) decomposes on refluxing in ether for 2 h, while the lithium or ZnCl salts are cleaved only on refluxing in toluene or dibutyl ether[235,236] (Scheme 20):

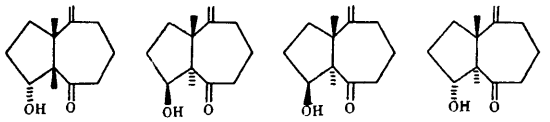
Scheme 20



M = Li, Na, K, ZnCl.

We may note that the decomposition of compound (XLVI) can lead not only to the initial reactants but also to products of other condensations, for example, to benzoylacetone and acetophenone, which are formed as a result of the transmetallation and subsequent Claisen acylation. A similar influence of the cation M^+ has been noted also for the adducts (XLV).[235] In the series of the usual alcohols ROH, the dependence of the stability of the alkoxides on the nature of the counterion is well known (see Section III). In the case of β-hydroxycarbonyl compounds, the dependence of the stability of the enolate on the nature of the metal is determined not only by the strength of the O–M bond but also by the ability of the carbonyl group to form chelates, which promotes a shift of the equilibrium in the second stage of the condensation to the right (see Scheme 19). The ability of a

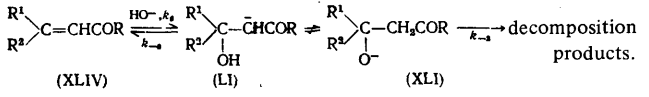
definite series of metals (Li, Zn, B, etc.) to form stable chelates is widely used to achieve high regio- and stereoselectivities of aldol condensations.[4,237,238] Consequently, it is best to employ potassium or sodium as the cation for the retroaldol reaction. An interesting application of the retroaldol–aldol condensation sequence has been proposed[239] for the synthesis of isomeric perhydroazulene hydroxyketones (XLVII)–(L). Depending on M^+ in the base (Li, Na, or K) and the reaction time, it is possible to obtain predominantly the isomers (XLIX) or (L) or an equilibrium mixture of all four isomers from the isomers (XLVII) and (XLVIII).[239]



(XLVII) (XLVIII) (XLIX) (L)

Thus, when $(iso\text{-}Pr)_2NLi$ was used in THF, the selective conversion of the isomer (XLVII) into (XLIX) and of (XLVIII) into (L) was observed. The stereoselective course of the reaction was promoted by the low temperature and the short reaction time. For example, when the isomer (XLVII) is treated with $(iso\text{-}Pr)_2NLi$ for 5 min (THF, 20 °C), then the isomer (XLIX) is formed in 65% yield, but, when the reaction mixture is kept for 45 min, almost equal amounts of the isomers (XLIX) and (L) are isolated. When the isomer (XLVII) or (XLVIII) is treated with a methanol solution of NaOH, virtually identical mixtures of all four isomers are formed, i.e. equilibrium is established in the system.[239]

Kinetic study of the decomposition of β-hydroxyketones (ketols) in an alkaline medium showed that ketols undergo two competing reactions—decomposition into the initial carbonyl compounds and dehydration.[204–205] Dehydration (crotonic condensation, Claisen–Schmidt condensation) is the reaction by means of which it is sometimes possible to displace the equilibria in such reactions towards the formation of the products. However, enones can also be unstable in alkaline media; by combining with the hydroxide anion via the Michael reaction, they are reconverted into the ketols and further into cleavage products, the ketol being present in such cases at a stationary concentration. Under certain conditions, it is possible to observe also an equilibrium mixture of all the components:[240–245]

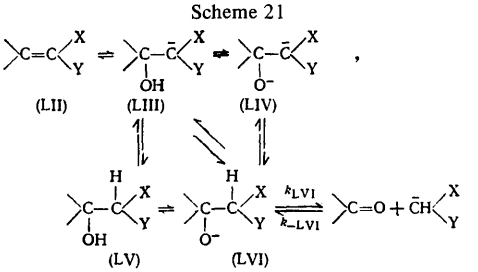


(XLIV) (LI) (XLI)

Each of the processes—dehydration and cleavage of the ketols into the initial reactants—is of second order overall and of first order with respect to each reactant (sometimes even higher with respect to the alkali) and the rate-determining stages are usually the reactions on the anions (XLI) and (LI) (k_{-2} and k_{-6}).[240–251]

Naturally in an alkaline medium not only enones but also other compounds with an activated double bond are cleaved (for example, the products of the Knoevenagel condensation). It has been established qualitatively that the ease of cleavage of compounds of the type  (LII) (X and Y are electron-accepting groups and R^1 and R^2 = alkyl or aryl) depends primarily on the number and strength of the electron-accepting groups X and Y, which determines the stability of the carbanions formed. The influence of alkyl and aryl groups is not so great, but alkyl derivatives are as a rule cleaved more readily than aryl derivatives. The presence of electron-accepting groups in the substituents R^1 and R^2 inhibits the reaction, which is in fact understandable, since the "expelling force" of the group R^1R^2CO diminishes.[252–254] However, despite the simple and understandable qualitative pictures, the mechanism of this reaction is fairly complex and depends significantly on the pH of the medium.[256–263] An overall mechanism of the hydrolytic cleavage of activated olefins (Scheme 21) has been proposed on the basis of the analysis of kinetic data for the cleavage of a series of olefins using a flow technique with spectrophotometric recording:[258–263]

Scheme 21



(LII) (LIII) (LIV) (LV) (LVI)

The most general mechanism in basic media involves the addition of the base to the olefin (LII) with formation of the anion (LIII), which is followed by its protonation to compound (LV), the formation of the anion (LVI), and its decomposition into products. In a highly alkaline medium, there is a possibility of another pathway—the formation of the dianion (LIV) and its subsequent protonation to compound (LVI) or intramolecular proton transfer in the anion (LIII) with formation of the anion (LVI). For example, it has been shown that, in the cleavage of 1,1-dinitro-2,2-diphenylethylene in 50% DMSO (H_2O) at pH 13.5, the rate-determining stage is the protonation of the dianion (LIV); at pH 12.5–13.5, the rate is determined by the protonation of compound (LIII) and at pH 11–12 it is determined by the attack by the hydroxide ion with formation of compound (LIII); at pH 10, the slow stage probably involves the attack by water on the substrate (LII).[259] The conversion of compound (LV) into the reaction products (in which the present authors are interested) using the stopped flow technique can be identified as an independent two-stage process,[258–263] the rate-determining stage of which may be also the deprotonation of the adduct (LV), while the rapid stage is the decomposition of compound (LVI) into the products.[258,259,263]

Table 1. Kinetic data for the retrodecomposition of the anion (LVI) and for its formation in water at 25 °C.[261]

Kinetic data	$PhCH{=}C(CN)_2$	$ArCH{=}C(NO_2)_2$*	$PhCH{=}C(COO)_2$
k_{LVI}, s^{-1}	$4.66\cdot10^4$	$6\ 32\cdot10^2$	$5\cdot10^8$
k_{-LVI}, litre mol^{-1}	$1.70\cdot10^5$	0.2	—
K, mol $litre^{-1}$	$2.74\cdot10^{-1}$	$3\ 16\cdot10^3$	$1.09\cdot10^8$
pK_a for CH_2X_2	11.19	10.2	4.83

*Ar = 3,4-methylenedioxyphenyl.[257]

However, on comparing the rate constants for the decomposition of the anion (LVI) into the products, it was found that, for the olefins investigated, there is no correlation between these rates and the pK_a of the corresponding

hydrocarbons (Table 1). Dicyanomethane is a weaker CH acid than dinitromethane, while the rate of abstraction of the dicyanomethyl anion from the adduct (LVI) is higher almost by two orders of magnitude than the rate of abstraction of $\bar{C}H(NO_2)_2$.[261] The causes of this are so far not understood. Table 1 also lists the rate constants k_{-LVI} for the condensation stage and the equilibrium constants.

An analogous picture has been observed in the hydrolytic cleavage of activated olefins by amines.[264] It has been shown that an adduct of type (LVII) is formed as an intermediate in this process and subsequently decomposes into the product [264–267] (Scheme 22).

Comparison of the rates of cleavage of several such adducts showed that in this case there is no correlation between the rate of cleavage and the pK_a of the hydrocarbon CH_2XY. Thus, as was to be expected, the adduct of the olefin (LVIII) is cleaved faster than the adduct of the olefin (LIX) but more slowly than the adducts of benzylidenemalonitrile, although, judging from the pK_a of the hydrocarbon CH_2XY, the opposite sequence should have been obtained (Table 2).

Scheme 22

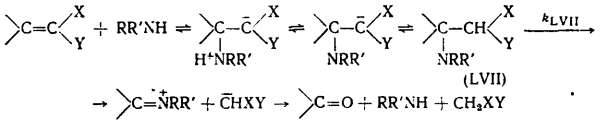
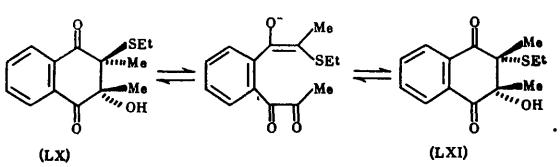


Table 2. The rate constants for the decomposition of the adducts (LVII) with piperidine (RR'NH = piperidine).[264]

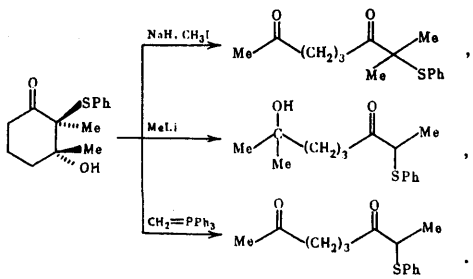
Kinetic data	PhCH=C(CN)C$_6$H$_3$(NO$_2$)$_2$-2,4 (LVIII)	PhCH=C(CN)C$_6$H$_3$(NO$_2$)-4 (LIX)	PhCH=C(CN)$_2$
k_{LVII}, s^{-1}	9.4	$4.5 \cdot 10^{-3}$	33
pK_a for CH_2XY	8.06	12.62	10.21

The retroaldol decomposition is frequently an undesirable side reaction, which must be borne in mind in carrying out condensations of the aldol or crotonic type. However, this reaction has also found some applications in synthesis. As an example, one may quote its use for the *cis–trans*-isomerisation of β-hydroxycarbonyl compounds.[268,269] Thus the *trans*-dihydronaphthoquinone derivative (LX) undergoes a base (EtS^- or EtO^-)-catalysed rearrangement to the *cis*-isomer (LXI) via a sequence of retroaldol–aldol condensations [and conversely (LXI) → (LX)]:[268,269]



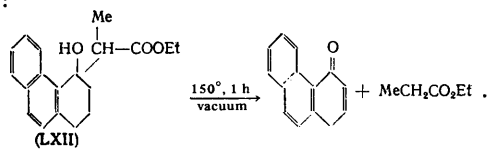
(LX) (LXI)

It has been suggested that the enolates formed in retroaldol processes be made to react with electrophilic trapping agents in order to obtain acyclic compounds with functional groups from cyclic compounds:[270]



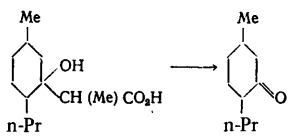
The cleavage of unsaturated acids or nitriles is used to synthesise isotope-labelled acids having two carbon atoms less than in the initial compounds.[271] The cleavage of β-hydrocarbonyl compounds and activated olefins can be usefully employed in all cases where the cleavage products are less readily available than the initial compounds.[91,272]

In conclusion, we may note that cases of ready thermal decomposition of β-hydroxycarbonyl compounds are known. Thus the hydroxyketone (LXII) is cleaved quantitatively into ethyl propionate and 4-oxo-1,2,3,4-tetrahydrophenanthrene at 150 °C:[273]

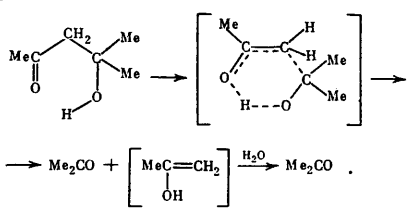


(LXII)

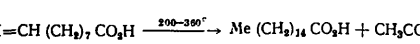
α-Menthylpropionic acid is cleaved on distillation:[274]



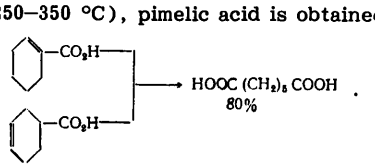
It has been suggested that a six-membered transition state is formed on thermal decomposition in the gas phase or in inert solvents:[275]



The examples listed above do not exhaust the possible types of cleavage of C–C bonds in alkaline media. Fairly numerous complex reactions involving to some extent retrodecomposition (retro-Claisen, retroaldol, etc.) stages, examined above, are known. We shall quote here several such reactions which are of practical importance. For example, the cleavage of unsaturated aliphatic acids constitutes a method of synthesis of saturated acids having two carbon atoms less than the initial acids:[276]



By heating cyclohexene-1-carboxylic or cyclohexene-3-carboxylic acid or their nitriles with alkalis in autoclaves at high temperatures (250–350 °C), pimelic acid is obtained:[277–279]



Azelaic acid is obtained in exactly the same way from cyclooctene-1-carboxylic and cyclooctene-4-carboxylic acids.[280] In most such reactions, the mechanism cannot be always readily traced, although it is evident that the unsaturated acids isomerise to αβ-unsaturated acids, combine with water via the Michael reaction, and the resulting hydroxyacids are dehydrogenated to ketoacids, which then undergo the retro-Claisen decomposition.

The cleavage of ricinoleic acid (obtained by hydrolysing castor oil) to sebacic and ω-hydroxydecanoic acids, which has found an application in industry, is even more complex:[281]

$$\mathrm{Me(CH_2)_5CH(OH)CH_2CH{=}CH(CH_2)_7COOH} \begin{cases} \rightarrow \mathrm{Me(CH_2)_5COCH_3 + HOCH_2(CH_2)_8CO_2Na}, \\ \rightarrow \mathrm{Me(CH_2)_5CH(OH)Me + NaOOC(CH_2)_8COONa}. \end{cases}$$

The mechanism of this reaction is unknown.

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