ORGANIC REACTION MECHANISMS · 1973

An annual survey covering the literature dated December 1972 through November 1973

Edited by

A. R. BUTLER
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Preface

This year's edition of *Organic Reaction Mechanisms*, the eighth in the series, does not differ greatly from the highly successful pattern developed by the previous editors. The literature dated December 1972 to November 1973 has been covered and the aim has been, as in past years, to make the coverage comprehensive. Over 5000 papers have been reported and many of the important ones discussed in some detail.

One modification which will be immediately apparent to those familiar with the series is the changed order of the Chapters. This change has been made to facilitate separate publication of selected sections of the book at prices more likely to be within the reach of the individual researcher. It should be stressed that not all of this book will be available in sectional form; however, if it is successful, sectional publication may be extended with the 1974 Volume. We have also decided to omit the chapter on Photochemistry. This topic is covered comprehensively in a Specialist Report published annually by the Chemical Society.

A further change, made with great reluctance, but as an economy measure necessitated by spiralling publishing costs, has been the relegation of references to the ends of the chapters. If this innovation or any other aspect of the book's format is found irksome, please do not hesitate to let us know. Indeed, it is our intention to offer *Organic Reaction Mechanisms* as a service, and we shall always be pleased to consider suggestions for its improvement.

We are grateful to the established contributors for their continued support, and welcome those who have joined this year. The British office of John Wiley and Sons have given us every possible help and have made the rapid publication of this volume possible. We sincerely hope that *Organic Reaction Mechanisms 1973* will be of as great a value to organic chemists as its predecessors.

August 1974

A. R. B.
M. J. P.

Contents

CHAPTER 1

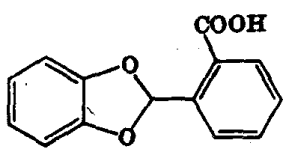
Reactions of Aldehydes and Ketones and their Derivatives

B. CAPON

Chemistry Department, Glasgow University

Formation and Reactions of Acetals and Ketals[1]

3-(2-Hydroxyphenoxy)phthalide (**2**) is an intermediate in the hydrolysis of *O,O'*-(2-carboxybenzylidene)catechol (**1**) in aqueous buffers of pH 2.9–5. The sponaneous reaction is about 30 times faster than that of *O,O'*-(4-carboxybenzylidene)catechol and may involve nucleophilic catalysis by the carboxylate group. The rate constants for catalysis by acetic and formic acid are similar for the two compounds. The pH–rate profile for the conversion of 2,3-(4-carboxybenzylidenedioxy)benzoic acid (**3**) into the phthalide



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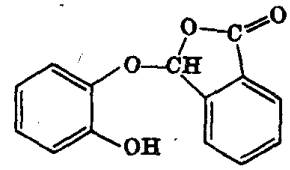

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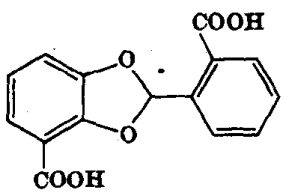

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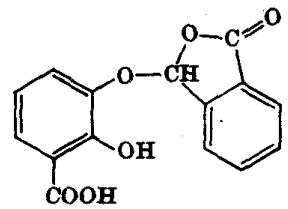
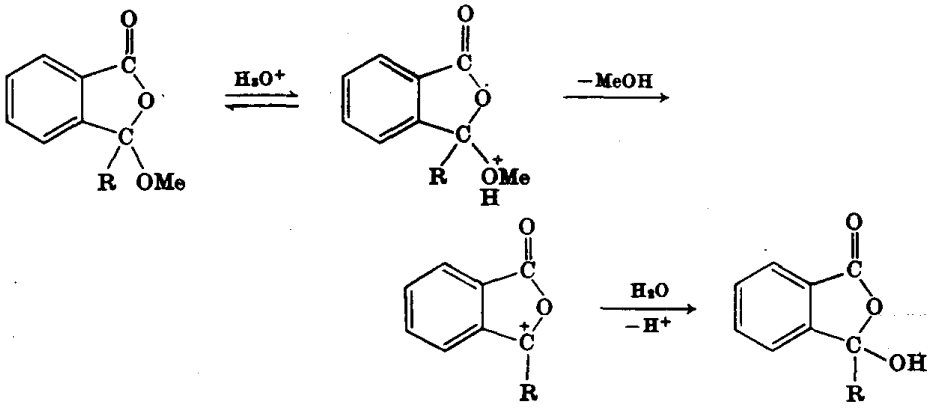


(4)

(**4**) is bell-shaped, but this reaction occurs only about three times faster than the hydrolysis of the acid (**3**) and hence there can be little nucleophilic assistance.[2]

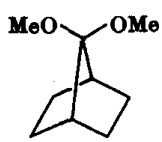
Details of Anderson and Fife's work on the hydrolysis of benzaldehyde disalicylyl acetal have been published.[3]

The kinetics of hydrolysis of a series of 3-alkyl-3-methoxyphthalides have been measured and interpreted in terms of the mechanism of equation (1), which was preferred to the *A*2 mechanism previously proposed.[4]

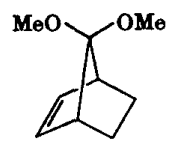


...(1)

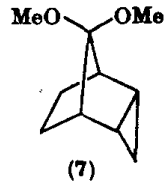
The relative rates of hydrolysis of compounds (**5**),(**6**), and (**7**) are 1 : 2.3 : 120. Therefore, if the faster rates for compounds (**6**) and (**7**) are the result of participation by the double bond and the cyclopropane ring, the rate enhancements are much less than found with the analogous *p*-nitrobenzoates and arenesulphonates.[5] This result is not surprising in view of known reduction of anchimeric assistance brought about by an α-carbonium ion stabilizing group.[6]



(**5**)



(**6**)



(**7**)

The kinetics of alcohol-exchange of acetals and exchange of the α-hydrogen atom have been studied. It was thought that the latter reaction proceeded by way of the vinyl ethers, and the equilibrium constants for the interconversion of the acetals and the vinyl ethers were evaluated from these results together with the rate constants for the addition of alcohols to the vinyl ethers.[7]

Tracer studies have shown that the formation of the formal from benzyl alcohol and paraformaldehyde in aqueous sulphuric acid involves aldehyde—oxygen fission, not benzyl—oxygen fission.[8]

Other related reactions studied include that between acetylferrocene and triethyl orthoformate,[9] formation of cyclic acetals from enones,[10] formation of 2-furyl-1,3-dioxans catalysed by ion-exchange resins,[11] and ketone-exchange of 2,3 : 4,5-di-isopropylidene-α-L-sorbofuranose with butan-2-one.[12]

There have been numerous investigations of the conformations of cyclic acetals. The classes of compounds studied include 1,3-dioxans,[13–15] 1,3-dioxolans,[16] spirodioxolans,[17,18] bicyclic 1,3-dioxans,[19] 1,3-oxathians,[20a] and 1,3-dioxacycloheptanes.[20b]

It has been shown that independent estimates of hydrogen-ion activity in moderately concentrated acids are in good agreement. This is of considerable potential use for studies of reaction mechanism.[21]

Hydrolysis and Formation of Glycosides

Non-enzymic Reactions

A reinvestigation of the hydrolysis of ferrocenylmethyl β-D-glucopyranoside has shown that it proceeds with ferrocenylmethyl—oxygen fission, not glucosyl—oxygen fission as previously supposed. Acid-catalysed methanolysis gave glucose and methoxymethylferrocene.[22]

Details of Sinnott and his co-workers' investigation of the hydrolysis of 1-adamantyl glycosides[23] and of Clark and Hay's investigation of the metal-ion catalysis of 8-quinolyl β-D-glucoside[24] have been published. It was suggested that the acid-catalysed hydrolysis of 8-quinolyl β-D-glucoside proceeds by an *A*2 pathway.[24]

Other glycosides whose acid-catalysed hydrolysis has been studied include alkyl[25] and aryl[26] β-D-galactopyranosides, methyl 4-*O*-alkyl-α- and -β-D-galactopyranosides,[27] β-D-fructofuranosides,[28a] the methyl glycoside of *O*-acetylated *N*-acetylneuramic acid,[28b] sucrose,[29] and cellulose.[30] The alkaline degradation of sucrose has also been studied.[31]

There has been an investigation of the Fischer glycoside synthesis with glucose and galactose.[32]

Brown and Bruice[33] have studied the hydrolysis of 1-β-D-glucopyranosyl benzoate, 2,3-di-*O*-methyl-1-β-D-glucopyranosyl benzoate and a mixture of α- and β-2,3,4,6-tetra-*O*-methyl-D-glucopyranosyl benzoates. These reactions show acid-catalysed and neutral components. The acid-catalysed hydrolysis is 10–100 times faster than that of methyl or phenyl β-D-glucoside and, on the basis of $\Delta S^{\ddagger}$ and the solvent isotope effect, it appears to follow an *A*1 mechanism with glycosyl—oxygen fission. The neutral hydrolysis also appears to be a unimolecular process with glycosyl—oxygen fission, as benzoate esters are not normally hydrolysed under these conditions. In alkaline solution the hydrolysis of 1-β-D-glucopyranosyl benzoate shows complex kinetics and must occur with benzoyl migrations. Since complex kinetics are also found with the 2,3-di-*O*-methyl compound, migration to the 6- as well as to the 2-hydroxy-group must occur.[33]

Enzymic Reactions[34]

(a) *Lysozymes.* A detailed kinetic investigation of the hydrolysis of hexa-*N*-acetylchitohexaoside (NAG-6) catalysed by lysozyme from hens' egg-white has been reported. From the pH-dependence of k_{cat} and k_{cat}/K_m it was concluded that the pK_a of glutamic acid[35] is 6.1 in the free enzyme and 6.7 in the non-productive complex of the enzyme and NAG-6, and that the pK_a of aspartic acid 52 is 3.4–3.7 in the free enzyme and 3.8 in the complex.[35]

The α-tritium isotope effect on the lysozyme-catalysed hydrolysis of NAG-3 to NAG-2 and NAG is $k_H/k_T = 1.19$, corresponding to an α-deuterium isotope effect $k_H/k_D = 1.14$, from which it was concluded that the rate-limiting step is an S_N1-type ionization. Unfortunately it is difficult to judge this conclusion since there are few if any models for the possible nucleophilically assisted processes for this system, i.e. reactions at a glycosyl-carbon atom where the nucleophile is an amido or carboxylate group.[36]

The enthalpy of binding of NAG-4 to lysozyme is 2.8 kcal/mol less negative than that for the binding of NAG-3, but the free energies of binding differ only by 0.3 kcal/mol at 25°. It was suggested that two complexes are formed between lysozyme and NAG-4, one similar to that formed by NAG-3 and the other in which the terminal residue partly fills site D.[37]

The fluorescence of human lysozyme has been studied. NAG-3 and NAG-4 are bound less strongly to human lysozyme than to lysozyme from hens' egg white.[38]

The binding of aryl di-*N*-acetylchitobiosides to lysozyme appears to be more complex than hitherto thought. Whereas at 32° only the signal in the PMR spectrum of the acetamido-group proximal to the aglycone of *p*-methoxyphenyl di-*N*-acetyl-β-chitobioside is shifted in the presence of lysozyme, at 65° the signals of both acetamido-groups are shifted so that they coalesce. It was suggested that there was a temperature-dependent transition of the interaction between lysozyme and the aryl di-*N*-acetylchitobioside.[39]

An X-ray study has confirmed that when 2′,3′-epoxypropyl di-*N*-acetylchitobioside reacts with lysozyme it becomes attached to the carboxyl group of aspartic acid 52.[40] Further work on the reaction of iodine with lysozyme has been reported.[41]

A polypeptide with lysozyme activity has been synthesized.[42]

There have been numerous other investigations of lysozyme from hens' egg white[43] and also of the lysozymes from human leukocytes,[44] baboon milk,[45] bacteriophage T4,[46] turkeys' egg white,[47] and geese's egg white.[48]

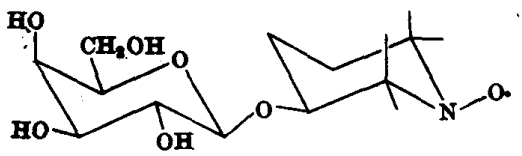
(b) *β-Galactosidases.* The α-deuterium isotope effect for the hydrolysis of some β-galactosides catalysed by β-galactosidase from *E. coli* has been determined. It was suggested that a conformational change of the enzyme is the rate-limiting step in the reactions of the more reactive galactosides.[49]

Nucleophilic competition by alcohols in the hydrolysis of galactosides catalysed by the β-galactosidase from *E. coli* has been extensively re-investigated. It now seems that the levelling off of the rate at high methanol concentrations arises from factors other than a change in rate-limiting step from degalactosylation to galactosylation.[50,51]

The β-D-galactopyranosylpyridinium cation is a poor substrate for β-galactosidase from *E. coli*. As electrophilic catalysis is not possible with this substrate, substrate distortion and electrostatic or nucleophilic catalysis must be responsible for the enzymic catalysis.[52] The binding of β-D-galactopyranosyltrimethylammonium bromide to β-galactosidase has been studied,[53a]

Although the acid-catalysed hydrolysis of *tert*-butyl, 1,1-diethylpropyl and diphenylmethyl β-D-galactopyranoside proceed partly with alkyl—oxygen fission, the hydrolyses catalysed by β-galactosidase proceed wholly with galactosyl—oxygen fission.[53b]

Compound (8) has been used as a spin-labelled substrate for β-galactosidase.[54]



(8)

The β-galactosidase from bovine testes has been studied.[55]

(c) *Other glycosidases.* Evidence for the presence of 2–3 carboxyl groups at the active site

of glucoamylase I from *A. niger* has been presented. When the enzyme reacts with glycine methyl ester and a water-soluble carbodiimide, maltose prevents the reaction of between two and three carboxyl groups per molecule of enzyme.[56]

Inhibition of the α-glucosidase from yeast and of the β-glucosidase from almond emulsin by α- and β-D-glucosylimidazole,[57] and of the glycosidases from almond emulsin by *C*-glycosides,[58] has been studied.

Other glycosidases that have been investigated include α-amylases,[59] β-amylases,[60] α-mannosidase from bakers' yeast,[61] α-glucosidase from *Mucor javanicas*[62a] and rabbit muscle,[62b] β-L-arabinosidase from *Cajanus indicus*,[63] *N*-acetyl-β-D-glucosaminidase from *A. oryzae*,[64a] and the β-D-glucuronidases from bovine liver and *E. coli*.[64b]

Hydration of Aldehydes and Ketones and Related Reactions

Equilibrium constants for the addition of hydroxyl ion to a series of substituted benzaldehydes have been measured and the results used to establish an acidity-function scale.[65]

The kinetics of dehydration of glycolaldehyde hydrate have been measured by determining the rate of scavenging of free aldehyde with semicarbazide and with sulphite. The reaction is general-acid and general-base catalysed.[66]

The kinetics of hydration of isobutyraldehyde have been studied by temperature-jump and NMR spectroscopy,[67] and the hydration of acetaldehyde has also been studied by NMR spectroscopy.[68]

The effect of pressure on the equilibrium constants for the hydration of aliphatic aldehydes has been determined.[69]

Hydration and polymerization of succinaldehyde, glutaraldehyde, and adipaldehyde,[70] and the oligomerization reaction of formaldehyde,[71] have been studied. An X-ray structure determination of the dimer of DL-glyceraldehyde has been reported.[72]

There have been investigations of the chemistry of hemiacetals[73] and of ring–chain tautomerism of 8-acyl-1-naphthoic acids.[74]

Diphenyl phosphate, phenylphosphinic acid, and trichloroacetic acid appear to act as tautomeric catalysts for the mutarotation of tetra-*O*-methylglucose in benzene as they are more effective catalysts than expected from a Brønsted plot for catalysis by phenols.[75]

The mutarotation of glucose in mixtures of water with dimethyl sulphoxide (DMSO) has been studied. The rate of the acid-catalysed reaction varies only slightly with solvent composition, but that for the water-catalysed reaction decreases strongly with increasing DMSO concentration in the range $\chi_{DMSO} = 0$–0.3 and remains approximately constant at higher concentrations. It was proposed that the acid-catalysed reaction proceeds by a stepwise mechanism without the intervention of a water molecule and that the water-catalysed reaction involves three water molecules.[76]

Glucose shows a complex mutarotation in aqueous dimethylformamide (DMF) at high DMF concentrations. This has been attributed to formation of a furanose form and one has been detected in solutions of glucose in pure DMF by gas chromatography plus mass spectrometry of the trimethylsilyl ethers.[77]

The mutarotation of β-L-arabinopyranose yields furanose forms as well as the α-pyranose form, but the *aldehydo*-form does not appear to cyclize more rapidly to furanose forms than to pyranose as reported for 2-deoxyribose.[78]

The equilibrium composition of fructose 6-phosphate has been shown by ^{13}C-NMR to be 19% of α- and 81% of β-furanose with less than 1.5% of the keto-form.[79]

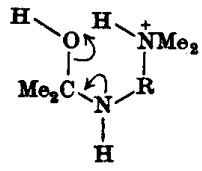
The mutarotatase from bovine kidney cortex has been investigated.[80]

Reactions with Nitrogen Bases

Schiff Bases

On the basis of X-ray crystal-structure determination of compounds that have a carbonyl group close to an amino-group it has been suggested that the preferred angle of attack by nitrogen nucleophiles is not perpendicular to the carbonyl group but at an angle of 107°.[81]

Imine formation from acetone and the monoprotonated forms of 2-(dimethylamino)-ethylamine and *trans*-(2-dimethylaminomethyl)cyclopentylamine is, respectively, 1000- and 60-fold faster than expected on the basis of a Brønsted plot for the reactions with other amines. Smaller rate enhancements are found with the monoprotonated forms of 3-(dimethylamino)propylamine, 4-(dimethylamino)butylamine, and 5-(dimethylamino)-pentylamine. It seems likely that intramolecular catalysis of dehydration of the carbinolamine intermediate is occurring, as symbolized by (**9**).[82]

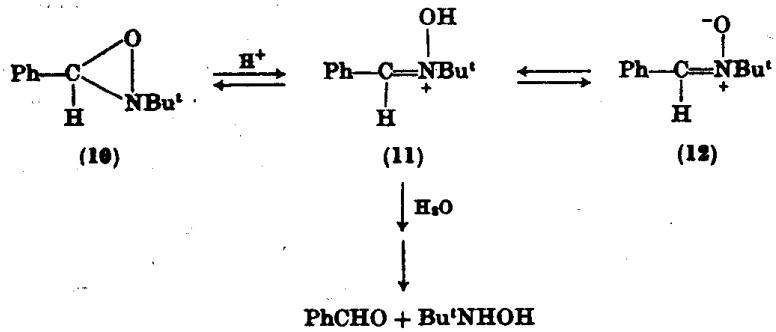


(**9**)

The condensation of isobutyraldehyde with diamines to form imidazolines has been studied.[83]

The rate constants for the uncatalysed reaction of piperazine (pK_a 9.97) and piperazine monocation (pK_a 5.80) with pyridine-4-aldehyde to form the carbinolamine are 2.3×10^5 and 65 l mol^{-1} s^{-1}, respectively. The reaction of piperazine shows general-base catalysis which was thought to involve catalysis of the proton-transfer step, i.e. conversion of the zwitterionic carbinolamine into the anionic form.[84]

The hydrolyses of 2-*tert*-butyl-3-phenyloxaziridine (**10**) and *N*-benzylidene-*tert*-butylamine *N*-oxide (**12**) are thought to proceed through the same ion (**11**). The effect of micelles on the rates of these reactions was studied.[85]



(**10**) (**11**) (**12**)

The hydrolysis and synthesis of benzylideneaniline in the presence of micelles of sodium dodecyl sulphate[86a] and the hydrolysis of Schiff bases derived from ferrocenyl aldehyde and ketones[86b] have been studied.

The kinetics of hydrolysis of salicylideneanilines in acidic solutions with H_0 down to –4 have also been studied.[87] So have amine exchange reactions of substituted benzylideneanilines.[88,89]

The reaction of glycine with benzaldehyde in ethanol in the presence of potassium hydroxide to form phenylserine is thought to involve formation of the Schiff base which forms a carbanion by loss of the α-proton. Reaction of this carbanion with another molecule of benzaldehyde would then lead to the product.[90]

The reaction of substituted benzylideneanilines with diethylmagnesium has been studied. Electron-withdrawing substituents in either benzene ring increase the rate of reaction and electron-releasing substituents decrease it.[91]

Dehydration of the β-ketol 9-hydroxy-10-methyl-*cis*-2-decalone by secondary and primary amines proceeds via iminium ions.[92]

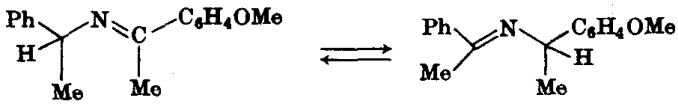
There have been PMR studies[93] and MO calculations[94] on the protonated imine group.

The reaction of the following compounds have been studied: glycine with glyoxal,[95] imidazole with formaldehyde,[96] isoxazol-5-ones with Schiff bases,[97] aldehydes with ammonia,[98,99] and Schiff bases with nitrosonium borofluoride.[100]

Ring–chain tautomerism of *o*-benzoylbenzamides has been investigated.[101]

Transamination

The interconversion of *N*-(α-methyl-4-methoxybenzylidene)-1-phenylethylamine (**13**) and *N*-(α-methylbenzylidene)-1-(4-methoxyphenyl)ethylamine (**14**) catalysed by potassium *tert*-butoxide in *tert*-butyl alcohol occurs with about 50% of intramolecular proton-transfer and about 60% of racemization. The starting material also undergoes substantial racemization. It was suggested that reaction proceeds through twisted carbanions.[102a]



(**13**) (**14**)

Transamination of the imine derived from 3-hydroxypyridine-4-carboxaldehyde and alanine is 2–3 times faster than racemization in aqueous buffers, the exact value depending on the catalyst and the prototropic state of the imine. This indicates that the intermediate carbanion is protonated with approximately equal facility at the two sites.[102b]

Other workers on transamination are cited in reference 103.

Enamines

The stereochemistry of the acidic hydrolysis of 2,6-disubstituted cyclohexanone enamines has been studied,[104] as also has the formation of dienamines.[105]

Hydrazones, Oximes, Semicarbazones and Related Compounds[106]

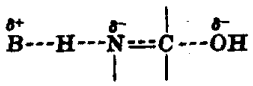
The pH–rate profile for the reaction of methoxyamine with *p*-chlorobenzaldehyde shows two breaks. That at low pH (ca. 1) was interpreted as arising from a change in rate-determining step from attack of the methoxyamine below this pH to proton-transfer to the zwitterionic form of the carbinolamine above it.[107] Details of Sayer and Jencks's investigation of the reaction of 2-methylthiosemicarbazide with *p*-chlorobenzaldehyde have been reported;[108] and there has been a review of "Encounter-Limited Rate-determining Steps in Carbonyl and Acyl Group Reactions".[109]

The rate of the base-catalysed dehydration of carbinolamines formed from substituted hydrazines and *p*-chlorobenzaldehyde is enhanced by electron-withdrawing substituents

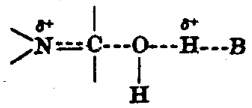
in the hydrazine. A transition state (**15**) involving a large degree of negative charge on nitrogen and little double-bond formation was proposed. The reaction is also general-acid catalysed and the rate of that reaction is also decreased by electron-withdrawing substituents in the hydrazine, a transition state (**16**) being here proposed.[110]

Details of the investigation by Cordes and his co-workers on the α-deuterium isotope effect for addition of semicarbazide and phenylhydrazine to benzaldehyde have been published.[111]

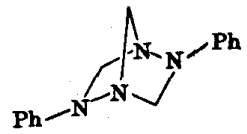
Other work on hydrazone formation is cited in reference 112. There have been several investigations of the formation of osazones.[113] Molecular-orbital calculations for the products of reaction of glyoxal with phenylhydrazine have been reported.[114] Formaldehyde phenylhydrazone reacts with an excess of formaldehyde to yield (**17**).[115] The reaction of butane-2,3-dione dihydrazone with formaldehyde in the presence of metal ions has been studied.[116]



(**15**)

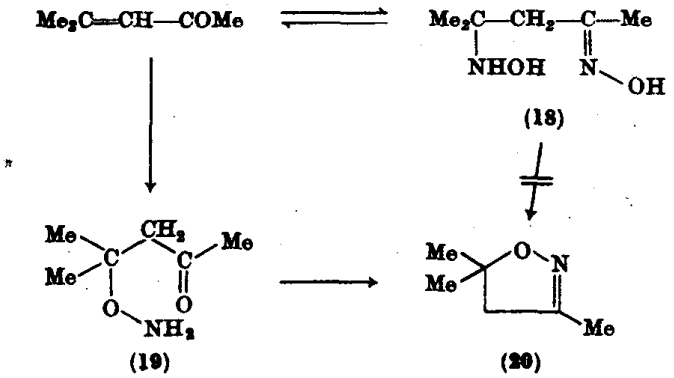


(**16**)



(**17**)

On investigation of the reaction of mesityl oxide with hydroxylamine to form 3,5,5-trimethyl-2-isoxazoline (**20**) it was shown that (**18**) is not an intermediate as it is not converted into (**20**) under the reaction conditions, but an NMR investigation of the reaction solution showed that (**19**) is an intermediate.[117]



(**18**)

(**19**) (**20**)

There have been several investigations of the hydrolysis of oximes.[118]

The reaction of *N*-arylhydroxylamines with nitrosoarenes appears not to be a simple reaction analogous to oxime formation but to be a radical process involving transfer of hydrogen.[119]

Hydrolysis of Enol Ethers

The rate constants for the hydrolysis of ethyl vinyl ether catalysed by positively charged amino-acids gives a Brønsted plot that is almost parallel to that for neutral carboxylic acids but lying about 0.3 logarithm unit below it. On the other hand, the points for negatively charged acids fall above the line for neutral carboxylic acids. An electrostatic interaction in the transition state was proposed as an explanation of these observations.[120]

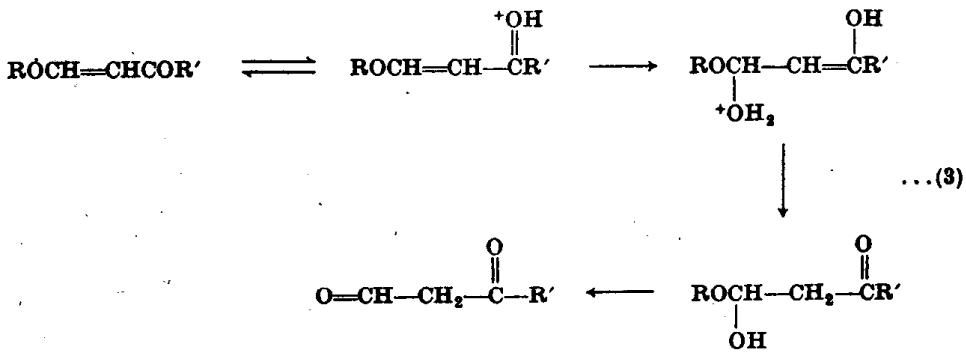
The hydrolysis of ethoxypropadiene (equation 2) is general-acid catalysed with $\alpha = 0.62$. The rate constant for hydronium-ion catalysis shows a negative deviation from the Brønsted plot. The isotope effect $k(H_3O^+)/k(D_3O^+) = 3.05$, $\Delta S^{\ddagger} = -10$ cal mol^{-1} K^{-1}, and Bunnett's w parameter is 0.36. A mechanism similar to that for the hydrolysis of ordinary enol ethers seems likely.[121]

$$H_2C{=}C{=}CHOEt + H_2O \rightarrow H_2C{=}CHCHO + EtOH \qquad (2)$$

The hydration of the β-oxy-α,β-unsaturated ketones (**21**) and (**22**) is specific-acid catalysed with $k(D_3O^+)/k(H_3O^+) =$ ca. 2.6. The ρ^+-values are −0.18 and +0.26, respectively. These results are clearly inconsistent with the normal mechanism of vinyl ether hydrolysis and that shown in equation (3) was proposed.[122]

The alkylation of vinyl ethers has also been studied.[123]

ArOCH=CHCOMe (**21**) MeOCH=CHCOAr′ (**22**)



...(3)

Enolization and Related Reactions*

A detailed investigation of the halogenation of butan-1-one has shown that the previously reported anomalies can be explained in terms of the heterogeneity of the system, reaction of the halogen with DMF (for reactions in aqueous DMF), formation of iodate, and nucleophilic displacement of the halide by hydroxide ion.[124]

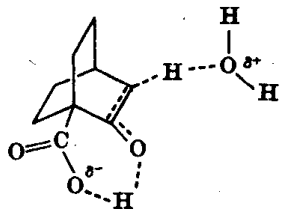
The enolization of 2-oxobicyclo[2.2.2]octane-1-carboxylic acid (RCO_2H) follows a rate law of the form:

$$\text{Rate} = \{k_H[H^+] + k_0\}[RCO_2H]$$

k_H is similar to that for the methyl ester. k_0 could arise from the acid-catalysed enolization of the carboxylate form and if this were so the catalytic constant would be 230 times greater than k_H for enolization of the methyl ester. This rate enhancement was attributed to hydrogen bonding or electrostatic stabilization as symbolized by (**23**) or (**24**).[125] More work on the stereochemistry of hydrogen-exchange of bicyclic ketones has also been reported.[126]

The rates of enolization (measured as iodination) of 4-(diethylamino)butan-2-one and 5-(diethylamino)pentan-2-one are much greater than normally found for aliphatic ketones, which was attributed to intramolecular catalysis as symbolized by (**25**) and (**26**).[127]

* See also Chapter 10.



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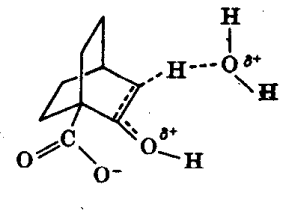

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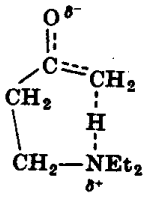

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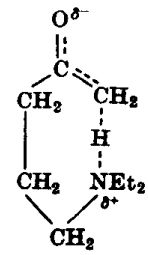


(26)

Diamines of type $Me_2N(CH_2)_nNH_2$, where $n = 2$, 3, 4 or 5, are not better catalysts than monoamines for the dedeuteriation of [2-^{2}H]isobutyraldehyde, showing the absence of any intramolecularly catalysed reaction of the Schiff base. This was thought to be because the Schiff bases have the *anti*-structure, but even the diamines undecane-1,11-diamine and dodecane-1,12-diamine, which have sufficiently long chains to permit catalysis even with this structure, showed no catalysis. However, evidence for catalysis was found with N^1,N^1-dimethyloct-2-yne-1,8-diamine.[128] Catalysis of dedeuteriation of [2-^{2}H]isobutyraldehyde by polyethyleneimines is also thought to involve reversible transformation of the aldehyde group into an iminium ion, followed by intramolecular removal of a deuteron by another amino-group.[129]

Ethylenediamine causes an increase in the rate of deuterium exchange of [2-^{2}H]-isobutyraldehyde (0.06M) up to a concentration of 0.03M and then a decrease at higher concentration. This decrease arises from conversion of the aldehyde into 2-isopropyl-imidazoline. At concentrations of diamine above 1M the rate increases again owing to catalysis by the imidazoline.[130]

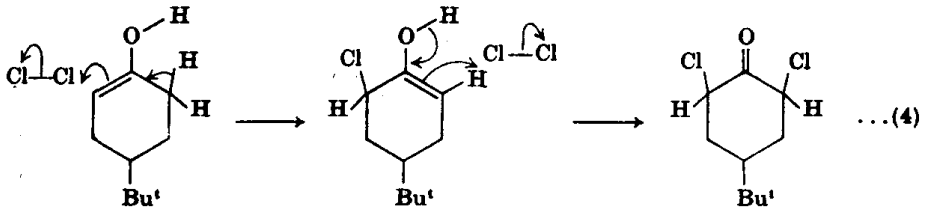
The kinetics of iodination of acetone have a term that is of the second order in amine when this is 2-aminomethylpyridine but not when it is 2-aminoethylpyridine. It was thought that this term arose from a rate-limiting dehydration of a carbinolamine with another molecule of the 2-aminomethylpyridine acting as a bifunctional catalyst. This would yield an imine which should be iodinated rapidly.[131]

The Brønsted β-coefficient for the enolization of 3-methylacetylacetone (measured as bromination) is 0.49. The kinetics were also measured in H_2O–D_2O mixtures and the results analysed in terms of the Gross–Butler equation.[132]

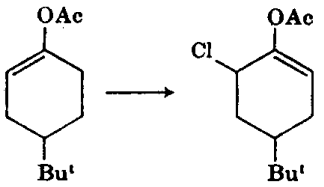
The hydroxide-ion-catalysed enolization of 2,4-dimethylpentan-3-one and 3,5-dimethylheptan-4-one show primary deuterium isotope effects $k_H/k_D = 6.09$ and 3.67, respectively, at 25°, but no primary tritium isotope effect. Possible explanations of this surprising observation were discussed.[133]

On treatment with chlorine in carbon tetrachloride 4-*tert*-butylcyclohexanone yields 4-*tert*-butyl-*cis*-*trans*-2,6-dichlorocyclohexanone under conditions where 4-*tert*-butyl-*cis*- and -*trans*-2-chlorocyclohexanone are not further chlorinated. It was suggested that the dichloro-ketone was formed by the mechanism of equation (4). A process analogous

to the conversion of (**27**) into (**28**) was demonstrated by treating the enol acetate (**29**) with chlorine in carbon tetrachloride to yield (**30**). It seems that, in carbon tetrachloride, C—H bond-cleavage of the enol (**27**) is competitive with O—H bond-cleavage.[134] Other work on the halogenation of ketones in carbon tetrachloride solution is reported in reference 135.



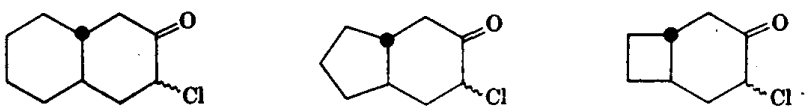
(**27**) (**28**) ...(4)



(**29**) (**30**)

The protonation and epimerization of 4-*tert*-butyl-2-halocyclohexanones and of 1-halo-2-decalones in strong acids has been studied. The epimerization was thought to proceed via the enol,[136] as is that of 1,1-trichloro-2-hydroxy-3-methylhexan-4-one in glacial acetic acid.[137]

The rates of enolization of the ketones (**31**), (**32**) and (**33**) at the α-carbon atom vary only slightly with the size of the fused ring but the rates of enolization at the α'-carbon decrease strongly as the size of the fused ring is reduced.[138]

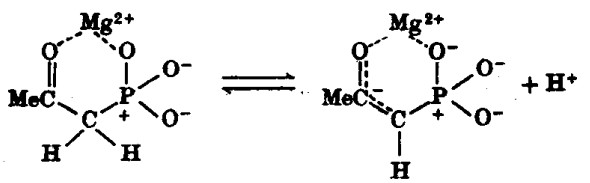


(**31**) (**32**) (**33**)

The rate constants for the acid-catalysed bromination, chlorination and iodination of acetone under conditions where formation of the enol is not rate-limiting are approximately equal. It seems that the equilibrium constant for enolization is 1.5×10^{-5}, which is considerably smaller than hitherto thought, and that the reactions of the halogens with the enol are diffusion-controlled with rate constant ca. 10^9 mol^{-1} s^{-1}.[139]

The kinetic solvent isotope effects for the enolization of ketones in alcohols ROH and ROD have been measured.[140]

Magnesium ions catalyse the exchange of hydrogen atoms of the methylene group of acetonyl phosphate in alkaline solutions, the reaction being thought to involve a chelate as shown in equation (5).[141]



...(5)