ORGANIC REACTION MECHANISMS · 1976

An annual survey covering the literature dated December 1975 through November 1976

Edited by

A. R. BUTLER, University of St. Andrews
M. J. PERKINS, Chelsea College, University of London

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An Interscience® Publication

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Preface

This twelfth volume, continuing the pattern now established for the series, surveys work on organic reaction mechanisms appearing in the literature dated December 1975 to November 1976. The aim has, as before, been to provide a concise and comprehensive coverage of work published in the period under review. Where, at the time of writing, any particular results seemed of outstanding significance, these are described and discussed; the remainder are listed.

This is the last volume which we are editing, and perhaps we might be permitted to reflect upon the role of a book of this type. Annual surveys are not new. In 1821 the great Swedish chemist Jac. Berzelius published his *Årsberattelser öfver Vetenskapernas Framsteg* and in the first volume discussed developments in physics, chemistry, astronomy, zoology, botany, and technology. By 1840 the contents were restricted to topics in chemistry and mineralogy. The process of specialization and condensation has continued and one can only envy the spacious manner in which Berzelius discussed the great discoveries of his time. However, he found the task of producing the volume an arduous one. His colleague Wöhler had complained of the work involved in translating the report into German. Berzelius wrote to him: "The Herr Professor complains of so much writing. Yes, it's boring but let's be clear that without it we could not do our best. I curse the *Annual Report* when I begin it, but I praise it at the end when I see how much the work has added to my own stock of knowledge." As editors we found the task of allocating published papers to the different contributors and editing the reports arduous, but it will have been worthwhile if it has helped chemists to add to their "stock of knowledge". We are grateful to all those who have written to us with their comments, and we are especially grateful to those who have contributed Chapters to the four volumes which have appeared under our names. Two of them, Dr. A. C. Knipe and Dr. W. E. Watts, have agreed to become the new editors; we know that they share our enthusiasm for the series, and we wish them every success in their efforts to continue to provide what we believe is a valuable service to organic chemists.

Our thanks are also due to the staff of the British office of John Wiley and Sons for their patient friendship and their help, not least in expediting the publication of each volume.

July 1977

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

Contents

CHAPTER 1

Reactions of Aldehydes and Ketones and their Derivatives

B. CAPON

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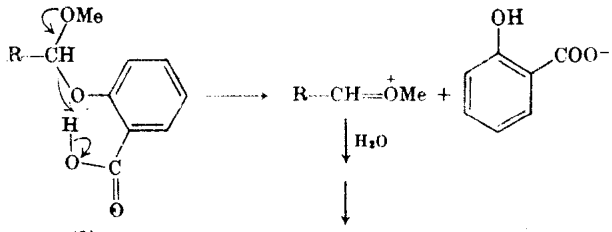
Formation and Reactions of Acetals and Ketals

Two mechanisms are possible for the spontaneous hydrolysis of acetals derived from salicylic acid:[1] either there is an intramolecularly general-acid catalysed reaction of the un-ionized form (equation 1) or a specific-acid catalysed reaction of the ionized form (equation 2) where the high rates of reaction are caused by an electrostatic effect. The latter has been excluded for the hydrolysis of benzaldehyde 2-carboxyphenyl methyl acetal (**1**; R = Ph) since the rate constant k_2 would have to have an unreasonably high value (*ca.* 10^{16} s^{-1}) and hence the mechanism of equation 1 was preferred for the hydrolysis of this compound.[2] However, it was argued that the acetals derived from formaldehyde (R = H) probably react by the mechanism of equation 2.[2,3] The basis for this argument was that acetals such as (**1**; R = Ph) which lack the carboxyl group undergo an intermolecular general-acid catalysed hydrolysis and therefore it was reasonable to suppose that the compounds with the carboxyl group would react with intramolecular catalysis. On the other hand acetals such as (**1**; R = H) which lack the carboxyl group do not react with intermolecular general-acid catalysis and it was therefore argued that the



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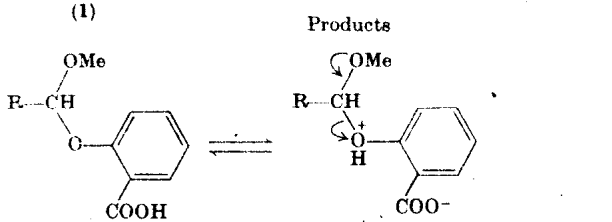


(1)

(2)

compounds with the carboxyl group would not be expected to react with general-acid catalysis.[3] The weakness of this argument has been pointed out[4] and Craze and Kirby[5] have shown that the effect of substituents in the salicylic acid residue of (**1**; R = H) leads to a value for ρ(carboxy) = 0.02 ± 0.08 which is consistent only with a mechanism in which there is a small amount of proton transfer in the transition state, and hence not consistent with the mechanism of equation 2. Now Buffet and Lamaty[6] have carried out a similar investigation of the reactions of the acetals analogous to (**1**; R = Ph) with the methoxyl group replaced by an ethoxyl group. They report a similar value of ρ (carboxyl) (0.2 ± 0.1) to that reported by Craze and Kirby. As seen from Table 1 the effect of substituents in the salicylate residue on the rate constants for the two reactions are similar, which supports the view that similar mechanisms are followed.

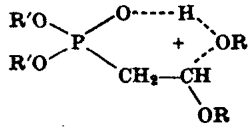
Table 1. The relative rate constants for the spontaneous hydrolysis of acetals (I).

	Unsubstituted	5-Me	5-MeO	5-Cl
R = H[a]	1	0.68	0.75	1.9
R = Ph[b]	1	0.71	0.83	2.3

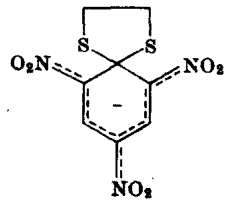
[a] I = 1.0M, 39°. [b] I = 0.1M, 25° for ethyl acetals.

Hydrolyses of the phosphonated acetals $(R^1O)_2P(O)CH_2CH(OR)_2$ have negative entropies of activation (*ca.* −25 cal mol^{-1} K^{-1}) and low energies of activation *ca.* 15 kcal

mol^{-1}. It was suggested that the transition state is stabilized by intramolecular hydrogen-bonding to the P—O group (**2**).[7]



(**2**)



(**3**)

Opening of the dithiolan ring of (**3**) is only very feebly catalysed by H_3O^+ if at all: it is strongly catalysed by mercuric ions, however. The ratio $k(H_2O)/k(D_2O)$ is 1.15 which suggests that the spontaneous opening is not water-catalysed. The analogous oxathiolane was also studied.[8]

It has been estimated that the energy of the "perpendicular conformation" of the α-methoxymethyl cation is 18.4 kcal mole^{-1} higher than that of the "parallel conformation".[9,10]

The (2-methoxyethoxy)methyl group has been used as a protecting group for alcohols. The resulting acetal is cleaved with zinc bromide in methylene chloride followed by an aqueous work-up. Possible mechanisms were discussed.[10]

Equilibrium isotope effects for ketal formation from α-deuteriated ketones have been determined.[12]

The following reactions have also been studied: salt effects on hydrolysis[13a] and formation[13b] of benzaldehyde dimethyl acetals, decomposition of peroxyacetals,[14a] cleavage of acetaldehyde aryl methyl acetals with ethylmagnesium bromide,[14b] hydrogenolysis of acetals with chloralane,[15] reductive cleavage of acetals with borane,[16] halogen-promoted cleavage of 1,3-oxathiolanes,[17] solvolysis of cyclopropanone dithioacetals,[18] methanolysis of 1,3-dioxanes,[19] isomerization of pentaerythritol acetals,[20] hydrolysis of acetylene derivatives of dioxolane,[21] formation of acetals from glycoxal,[22] glycolaldehyde,[23] *o*-benzoquinone,[24] and 1-deoxy-D-glucitol and 3-*O*-methyl-D-glucitol with butyraldehyde,[25] formation of acetals catalysed by montmorillonite,[26] formation of acetals and orthoesters from methyl pentopyranosides,[27] reactions of sugar orthoesters,[28] and hydrolysis of fluoromethyl methyl ether.[29]

There have been several investigations of the conformations of cyclic acetals.[30]

Hydrolysis and Formation of Glycosides

Non-enzymic Reactions

Further work has been reported on neighbouring amido-group participation in reactions of 2-carboxyphenyl 2-acetamido-2-deoxy-β-D-glucoside.[31a,b] Neighbouring-group participation was also demonstrated in the reactions of 2,4-dinitrophenyl 2-acetamido-2-deoxy-β-D-glucopyranoside and of 2-acetamido-2-deoxy-β-D-glucopyranosyl fluoride. The intermediate oxazoline was detected in the methanolysis of the latter compound in the presence of base.[31a]

Details of Cocker and Sinnott's linear-free-energy relationship between the rates of acetolysis of some 2,4-dinitrophenyl glycosides and the acid-catalysed methanolysis of the corresponding methyl glycosides have been published.[32] Anchimeric assistance in the

acetolysis of 2,4-dinitrophenyl 2-acetamido-2-deoxy-β-D-glucoside is greater than in the acid-catalysed hydrolysis of methyl 2-acetamido-2-deoxy-β-D-glucoside.[32,31b]

Further work on the hydrolysis of methyl chlorodeoxyglycosides has been reported,[33a] and the hydrolysis of thioglycosides catalysed by mercuric ions has been investigated.[33b]

Treatment of D-glucose, D-xylose and L-idose with methanolic hydrogen chloride in the presence of strontium or calcium chloride leads to formation of the dimethyl acetals.[34]

The following reactions have also been studied: acid-catalysed hydrolysis of glycosides and oligosaccharides,[35] hydrolysis of sucrose in a reversed micelle of dodecylbenzenesulphonic acid in dioxan–water mixtures,[36] methanolysis of disaccharides,[37] equilibration of methyl α- and β-coumerosides and of their C-2 epimers,[38] alkaline degradation of xylotetraose[39] and other oligosaccharides,[40] and formation of 3,4:5,6-di-*O*-isopropylidene-D-glucose dimethyl acetal and 2,3;5,6-di-*O*-isopropylidene-D-glucose dimethyl acetal by the acid-catalysed reaction of glucose with acetone and methanol.[41]

Enzymic Reactions

There have been reviews on the following topics: "Some Pertinent Aspects of (Enzyme) Mechanism as Determined with Small Molecules",[42] "Enzyme Models",[43] "The Mechanism of Action of Glycosidases",[44] "Transition State Analog Inhibitors and Enzyme Catalysis",[45] "Enzyme Mechanism",[46] and "Hydrolysis of Acetals and Approach to the Modelling of Enzymic Reactions with the Participation of Lysosyme".[47]

(a) *Galactosidases.* It has been shown that the β-galactosidase from *E. Coli* catalyses formation of allolactose (β-D-galactosyl(1→6)-D-glucose) and of tri- and tetra-saccharides from lactose (β-D-galactosyl(1→4)-D-glucose) at pH 7.2 when its concentration is relatively high (0.5M). At lower concentrations (<0.05M) tri- and tetra-saccharides are no longer formed but allolactose is, and formation of the ultimate products D-glucose and D-galactose proceeds partly via this species. The reaction was carried out in the presence of hexakinase and ATP in order to phosphorylate rapidly any free glucose at position 6. At short reaction times this had no effect on the rate of formation of allolactose and it was concluded that the conversion of lactose into allolactose was a direct "intramolecular" transglycosylation. However, the crucial experiment of starting with a mixture of lactose labelled in the glucose and galactose residues and unlabelled lactose and looking for crossed products was not carried out. The proportion of direct hydrolysis to conversion into allolactose depends on the anomeric configuration of the lactose. Thus the ratio of allolactose to glucose formed is 0.25 with α-lactose and greater than 2.0 with β-lactose. This proportion also depends strongly on the pH.[48]

Inhibition of human liver β-galactosidase and β-glucosidase by *N*-(bromoacetyl)-β-D-galactosylamine has been studied.[49]

N^3-β-D-Galactosylmethyl-N^1-*p*-nitrophenyltriazene is an active-site-directed irreversible inhibitor for β-galactosidase from *E. coli*.[50]

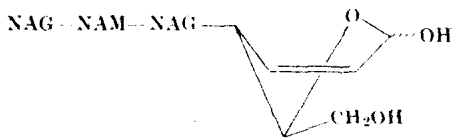
6-*O*-Tosylgalactosides have been investigated as inhibitors of lactose phosphotransferase from *Staphylococcus aureus*.[51]

There have been other investigations of α-[52] and β-galactosidases[53] and of bovine-milk galactosyl transferase.[54]

(b) *Lysozymes.* The binding of $(NAG)_n$, $n = 1, 2$ or 3, to hens' egg-white lysozyme in the presence of Biebrich Scarlet has been investigated by studying the change in the circular dichroism (CD) spectrum on binding.[55] The conclusions differ from those made previously[56] from an investigation of the ultraviolet difference spectra and it appears that sugars which are thought to bind only in the upper portion of the cleft affect the binding constant of Biebrich Scarlet.

2-Acetamido-2,3-dideoxy-D-glucose is bound 3-10 times more weakly to hens' egg-white lysozyme than is 2-acetamido-2-deoxy-D-glucose (NAG), and, in contrast to the situation with the latter, no transition between pH 5 and pH 8 was observed in the plot of log K_I against pH.[57] X-Ray crystallographic studies showed that in the complex of lysozyme and NAG the 2-hydroxyl group is hydrogen-bonded to the NH of tryptophan 63 and hence these results suggest that this interaction is an important one.

The compound (**4**) has been shown to be bound 100 times more strongly than $(NAG\ NAM)_2$ by hens' egg-white lysozyme. The glucoseen ring has a half-chair conformation



(**4**)

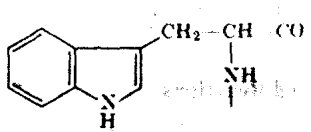
and (**4**) was claimed to be a transition-state analogue;[58] this seems to be an unsatisfactory description, however, since the half-chair of (**4**) has C-1, C-2, C-3 and C-4 in one plane whereas the usually accepted intermediate cation has C-1, C-2, C-5 and the ring-oxygen in one plane.

Acetylation of lysozyme converts six amino-groups into their acetylated derivatives and leaves one amino-group free, namely that of Lys 33. Titration of this modified lysozyme was investigated.[59]

The individual ^{13}C resonances of some of the carboxyl groups of hens' egg-white lysozyme have been studied at 68 MHz. The variation of chemical shift with pH enabled the microscopic dissociation constants to be determined.[60]

A theoretical discussion of catalysis by lysozyme has emphasized the importance of electrostatic stabilization of the transition state.[61]

Ozone oxidation of lysozyme converts tryptophan-62 into an inactive *N'*-formylkynurenine derivative (**5**→**6**). Hydrolysis of the formyl group restores 80% of the enzymic activity.[62]



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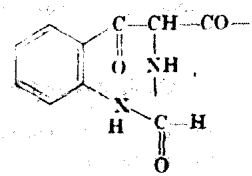


(**6**)

The ^{13}C-NMR spectrum of the product of the reaction of lysozyme with iodine has been studied.[63] There have also been investigations of the binding of $(NAG)_n$, $n = 1, 2$ or 3, to the oxidized lysozyme[64] and of the oxidation of lysozyme by *N*-bromosuccinimide[65] and by singlet oxygen.[66] Lysozyme has been modified by reaction with 2,3-dioxoindoline-5-sulphonic acid[67] and with 7-chloro-4-nitrobenz-2-oxa-diazole,[68] by photo-oxidation,[69] by carboxymethylation of the lysine residues[70] and by esterification of the carboxyl groups.[71]

Further work has been done on the colorimetric assay of lysozyme with 3,4-dinitrophenyl tetra-*N*-acetylchitotetraoside.[72]

The properties of lysozyme and α-lactalbumin have been compared.[73]

The effect of ethylene glycol on the difference UV spectrum and the CD spectrum of lysozyme has been studied.[74] The effect of temperature on the structure of lysozyme in solution has been investigated by ^{13}C-NMR spectroscopy.[75]

The antigenic reaction site of lysozyme has been studied.[76]

There have been several investigations of the binding of substrates and inhibitors to hens' egg-white lysozyme[77] and to turkey egg-white lysozyme.[78]

The pH-dependence of the rate of hydrolysis of the cell wall of *M. luteus* catalysed by human leukemic lysozyme has been studied.[79]

The specificity requirements of bacteriophage *T4* lysozyme have been explored.[80]

There have been many other investigations of the lysozyme from hens' egg-white,[81] turkeys' egg-white,[82] chachalcas' egg-white,[83] geese's egg-white.[84a] humans,[84b] rats,[85a] mice.[84b] and *Asterias rubens*.[86]

(c) *Amylases*. The assay of amylases,[87] and the anomeric form of maltose produced on the hydrolysis of phenyl α-maltoside catalysed by amylases,[88] have been reviewed.

It has been shown that the α-amylase from hog pancreas which is 2,4-dinitrophenylated on the free ε-amino-group of lysine cannot bind chloride ion and has the enzymic activity of the chloride-free α-amylase.[89]

Taka amylase from *A. oryzae* has been shown to hydrolyse maltotriose via a transglycosylation mechanism.[90] Inhibition by D-gluconolactone and phenyl α-D-glucoside of the hydrolysis of maltodextrin catalysed by glucoamylase from *Rhizopus nivens* has been studied.[91] There has been an investigation of pH induced conformation changes of bacterial-liquefying α-amylase and Taka amylase.[92]

There have been numerous other investigations of amylases.[93]

(d) *β-D-Fructofuranosidases*. The active site of external yeast β-fructofuranosidase has been labelled with conduritol β-epoxide and it was speculated that there is a carboxyl group present at the active site.[94] Presumably the conduritol β-epoxide binds at the same site as does the glucose residue of fructose. There have been several other investigations of β-fructofuranosidases.[95]

(e) *Other Glycosidases*. Other enzymes which have been investigated include cellulases,[96] chitinase,[97] mannanases,[98] xylanases,[99] exo-β-*N*-acetylmuraminidase,[100] β-glucanases,[101] xylosidases,[102] β-D-acetyl-D-hexoseaminidases,[103] fucosidases,[104] mannosidases,[105] glucosidases,[106] glucuronosidases,[107] and neuraminidase.[108]

Hydration of Aldehydes and Ketones and Related Reactions

Bell and Sorensen have measured the rate constants, k_1, for the addition of hydroxide ion to a series of aromatic aldehydes and those, k_{-1}, for the reverse reaction, the decomposition of the anion of the aldehyde hydrates. The values of k_1 increase with the number and power of the electron-withdrawing groups in the aromatic ring but those of k_{-1} are almost independent of structure. It was suggested that the transition state was the desolvated anion of the hydrate.[109]

There have been several measurements of the equilibrium constants for the addition of hydroxide ion to aromatic aldehydes[110–112] and ketones.[113]

The rate constant for the spontaneous hydration of acetaldehyde by localized water in micellar Triton X-100 in carbon tetrachloride is 1.5×10^4 times greater than that for hydration in bulk water.[114]

Although hexachloroacetone is not hydrated to an appreciable extent in water it forms stable adducts in wet organic solvents (e.g. cyclohexanone, DMSO, dioxane). This was

attributed to strong hydrogen-bonding between the hydrate and the organic solvent.[115]

The order with respect to water for the uncatalysed addition of water to chloral in water–dioxane mixtures varies from 4 to 2. This was interpreted as evidence for a cyclic transition state.[116] The dehydration of chloral hydrate in acetone,[117] the hydration of pyruvamide,[118] and the addition of water and of sodium hydrogen sulphite to 1,3-dimethoxyacetone[119] have also been investigated.

It has been shown that decomposition of the benzaldehyde methylhemiacetal is the rate-limiting step in the hydrolysis of α-acetoxy-α-methoxytoluene in the pH range 3.69 to 6.27. In acetate buffers decomposition of the hemiacetal is general-acid and general-base catalysed.[120]

The reaction of 4-methylpent-4-en-2-ol with acetaldehyde to form a tetrahydropyran proceeds via the hemiacetal which then cyclizes.[121]

It has been shown that 2-hydroxypyridine and 2-pyridone are present in approximately equal amounts in their equilibrium mixture in non-polar solvents at low concentrations (*ca.* 10^{-7}M) but that at higher concentrations the predominant form is the dimer of the 2-pyridone.[122] It is still not clear which is the catalytic species in the mutarotation of tetramethylglucose in non-polar solvents in the presence of this mixture. The self-association of Δ^4-thiazoline-2-thiones has also been studied.[123] There has been an investigation of the mutarotation of tetramethylglucose catalysed by di-*n*-butylphosphinic acid and some carboxylic aids (in benzene?).[124]

There has been more work on the composition of solutions of aldoses and ketoses using ^{13}C-NMR spectroscopy.[125] The CD spectra of the individual anomeric forms of some aldoses have been measured down to 165 nm.[126] The hydration of glucose in aqueous dimethyl sulphoxide has been studied by NMR spectroscopy.[127]

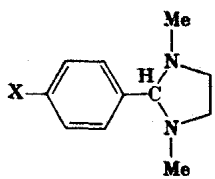
The reactions of carbonyl compounds with peroxides[128] and with cysteine[129] have been investigated.

NMR spectroscopic evidence has been reported which argues against the covalent attachment of an aldehyde "transition state analogue" to α-chymotrypsin.[130]

Reactions with Nitrogen Bases

Schiff Bases

The hydrolyses of 2-aryl-1,3-dimethylimidazolines (**7**) have been investigated by Fife and Hutchins.[131] In moderately concentrated solutions of hydrochloric acid the intermediate cationic Schiff base was detected spectrophotometrically but at higher pH's it



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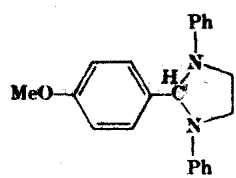
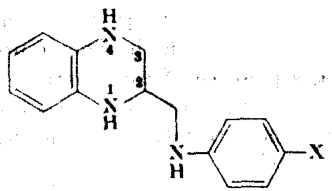


(8)

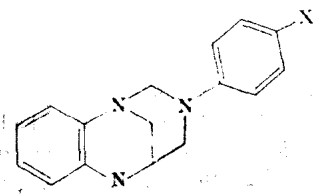
could no longer be observed. It seems likely that this is because at these pH's the re-cyclization to imidazoline is faster and that the rate-limiting step is hydrolysis of a rapidly and reversibly formed cationic Schiff base. It was thought likely that the ring-opening step would be general-acid catalysed. The reaction of 2-(*p*-methoxyphenyl)-1,3-diphenylimidazoline (**8**), which is much slower, was also studied but this was not general-

acid catalysed in formate buffers in 50% aqueous dioxane. It is possible that the structural change on going from (**7**) to (**8**) leads to the reaction of (**8**) no longer being general-acid catalysed because the intermediate carbonium ion is less stable. It is interesting to note, however, in the context of this paper that the hydrolysis of benzaldehyde diphenyl acetal is general-acid catalysed[132] and it is possible that it is not valid to compare the hydrolysis of acetals with that of imidazolines.

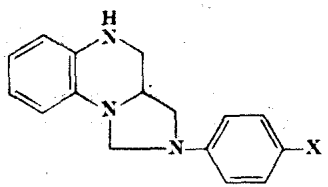
The reaction of the 2-(*p*-*X*-anilinomethyl)-1,2,3,4-tetrahydroquinoxalines (**9**) with formaldehyde is more complex than previously thought.[133] It has been shown by two groups[134,135] that the benzotriazocine (**10**) accumulates in the formation of the imidazoline (**11a**) and that this is formed via the Schiff base at *N*-4.[135] The benzotriazocine



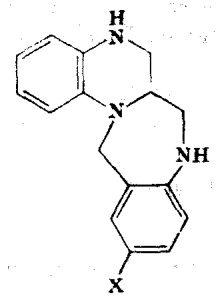
(**9**)



(**10**)



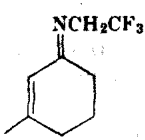
(**11a**)



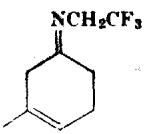
(**11b**)

(**10**) is in equilibrium with a small concentration of (**9**) which reacts more slowly with formaldehyde at *N*-1 to form imidazoline (**11a**) and at high acidities (pH 2) there is a further reaction to yield the benzodiazepine (**11b**).

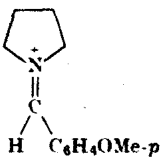
The reactions of aromatic amines with formaldehyde to form carbinolamines have been studied. The reactions are general-acid catalysed and Brønsted plots with a series of



(**12**)



(**13**)



(**14**)

acids of varying structural types were non-linear with some of the amines.[136] The reactions with heteroaromatic amines were also studied.[137]

The hydrolysis of the α,β-unsaturated Schiff base (**12**) has been studied. The overall kinetic behaviour is similar to that shown by other Schiff bases and there is a break in the pH–rate curve at about pH 0 which corresponds to a change in the rate-determining step. The reaction is much slower than that of (**13**), probably mainly as a result of the lower basicity of (**12**).[138] It was also shown that the hydrolysis of the protonated form of (**12**) is increased on changing the solvent from water to aqueous dioxan, k(90% v v aq. dioxan)/k(H_2O) = 18. The reaction catalysed by chloroacetate ions is accelerated much more, k_{cat} (70% v/v aq. dioxan)/k_{cat}(H_2O) = *ca.* 250. It was suggested that the increase in the rate of the water-catalysed reaction arises because the rate-determining step involves dispersion of charge and the greater increase in the chloroacetate-catalysed reaction because the rate-determining step involves destruction of charge. It was conjectured that enzymes which involve Schiff bases as intermediates "use a combination of general-base catalysis and an apolar active site to facilitate the formation and hydrolysis of these imines".[139]

There is a rate-depressing effect by salts on the spontaneous and acetate-catalysed hydrolysis of the *N*-*p*-methoxybenzylidenepyrrolidinium ion (**14**). This leads to a non-linear plot of k_{obs} against concentration of acetate when the ionic strength is maintained constant at 1M by the addition of other salts. This work indicates that great care must be taken in interpreting non-linear plots of k_{obs} against concentration of buffer, especially *when the ionic strength is high*.[140]

The reaction of phenalene-1,2,3-trione dihydrate with amino-acids has been studied. The small concentration of free trione in equilibrium with the hydrate reacts with the amino-group to form a carbinolamine which then undergoes the Strecker degradation.[141]

The hydrolysis of 3-anilinophthalides, which exist in equilibrium with the *o*-carboxylbenzylideneaniline, has been studied.[142] There has also been an investigation of the hydrolysis of 3-phenylimino-oxindole.[143]

There have been several other investigations of the hydrolysis[144] and tautomerism[145] of Schiff bases. The following reactions have also been studied: reaction of morpholine with anthracene-9-carbaldehyde to form a carbinolamine,[146] the cyanide-catalysed reaction of benzils with amines,[147] interaction of glutaraldehyde with amino-groups of 6-aminohexanoic acid and of α-*N*-acetyl-lysine,[148] photoisomerization of a Schiff base of retinal,[149] formation of a Schiff base from *N*-methylated pyridoxal and tryptophan,[150] the reaction of phthalaldehyde with thiols and amines,[151] condensation of 4,6-diamino-*s*-triazine with formaldehyde,[152] cycloaddition of Schiff bases with diphenylketene,[153] condensation of acetylenic carbonyl compounds with amines,[154] reaction of arylidenealkylamines with dialkyl phosphates,[155] reaction of hexuloses with amino-acids,[156] anomerization of glucosylamines,[157] covalent hydration[158] and amination[159a] of heterocyclic compounds, and transamination.[159b]

The conformations of Schiff bases[160] and of thiazolidines[161] have been studied.

The steric course of nucleophilic attack on the carbonyl group has been further discussed.[162]

Enamines

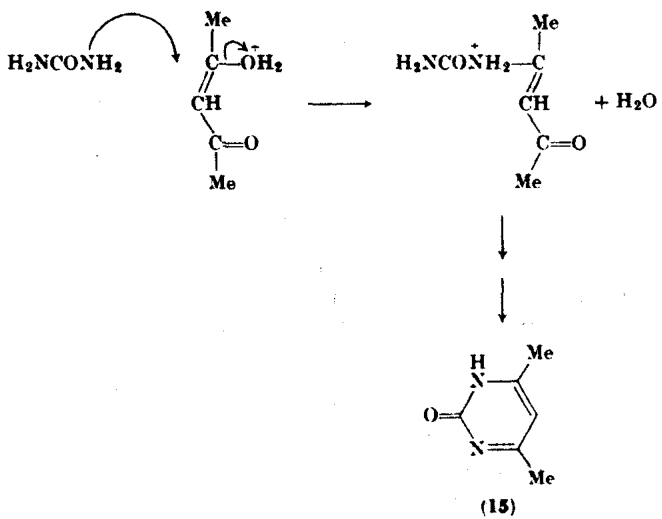
Enamines of optically active α-pipecoline yield optically active ketones on hydrolysis.[163] There have also been investigations of the hydrolysis of the enamine of 3,6,6-trimethylnorpinan-2-one[164] and of the isomerization of enamines.[165]

Hydrazones, Oximes, Semicarbazones and Related Compounds

The reaction of *N*-methylpyridiniumcarbaldehydes with semicarbazide occurs with rate-limiting dehydration of the intermediate carbinolamine. Generally the rate is much slower than the rate of dehydration of the aldehyde but at high concentrations of semicarbazide and low pH values the two rates approach one another. The reactions of *N*-methylpyridinium-2-, -3- and -4-carbaldehyde with hydroxylamine and phenylhydrazine were also studied.[166]

The intermediate carbinolamine in the reaction of acetaldehyde with hydroxylamine has been detected by determining the NMR spectrum of a flowing reaction solution, and the kinetics of its conversion into a mixture of oximes has been measured.[167] In the NMR spectrum of a flowing mixture of hydroxylamine and acetone at pH 7.70 there is a time-averaged signal for the methyl groups of the acetone and of the carbinolamine which decreases when the flow is stopped with concurrent formation of the signal of the methyl group of the oxime.[168] The addition of hydroxylamine to ethyl acetoacetate was also studied.[169] In a flowing solution of 20 ml min^{-1} at pH 7.50 and 30° the time-averaged spectrum of ethyl acetoacetate and the carbinolamine was observed. When the flow was stopped the spectra of the *syn*- and *anti*-oximes appeared. That of the *anti*-oxime increased continuously but that of the *syn*-oxime first increased and then decreased with concurrent formation of the spectrum of 3-methylisoxazol-5-one. It was estimated that the effective concentration of the internal oxime group in the latter reaction was 10^4 M.[169] It was also shown that the reaction of acetylacetone with hydroxylamine to yield 3,5-dimethylisoxazole involves formation of the carbinolamine, cyclization, and finally elimination of two mol of water.[170] Substituent effects on the equilibrium constants for the cyclization of the mono-oximes of 1,3-diketones have been determined.[171]

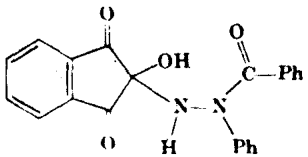
The reaction of pentane-2,4-dione with urea in acid solution has been studied: the product is the pyrimidone (**15**) and there is no accumulation of an intermediate. The mechanism shown in Scheme 1 was proposed.[172]



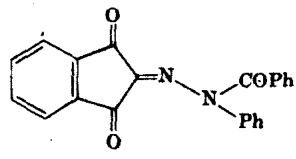
(**15**)

SCHEME 1.

The structure of the carbinolamine (**16**) has been determined by X-ray crystallography and the conversion into the hydrazone (**17**) in the solid state has been studied.[173]



(**16**)



(**17**)

The α-carbonyl intermediate in the racemization of lactic acid catalysed by lactic acid racemase derived from *Clostridium butylicum* has been trapped as its oxime.[174]

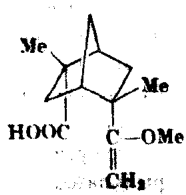
There have been further investigations of the reactions of carbonyl compounds with hydroxylamine,[175] hydrazines,[176] semicarbazide,[177] salicylhydrazines,[178] and phenylmethanesulphonamide,[179] and of the reaction of nitrosobenzene with phenylhydroxylamines.[180]

The *cis-trans*-isomerization of hydrazones[181] and amidoximes[182] has been investigated.

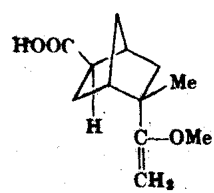
There have been investigations of the tautomerism of hydrazones and enehydrazines,[183] of the ring-chain tautomerism of the hydrazones of hydroxy-carbonyl compounds,[184] of pentose oximes[185] and of thio-oximes.[186]

Hydrolysis of Enol Ethers

Ryono and Loudon[187] have carried out a detailed kinetic investigation of the hydrolysis of the enol ethers (**18**) and (**19**) prepared by complex synthetic paths; the intermolecular general-acid catalysed hydrolysis of the ionized form of (**18**) does not appear to be

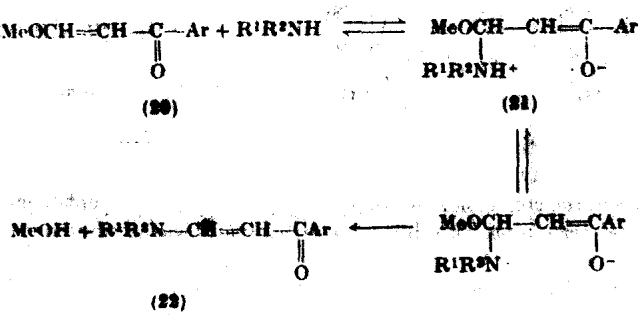


(**18**)



(**19**)

enhanced electrostatically but the un-ionized form reacts with weak intramolecular catalysis.



(**20**) (**21**) (**22**)

An investigation of the hydrolysis of vinyl sulphides suggests that they are hydrolysed by a mechanism similar to that for the hydrolysis of enol ethers.[188]

There have been kinetic investigations of the hydrolyses of 1-alkoxybut-1-en-3-ynes[189] and 1-(alkylthio)but-1-en-3-ynes.[190]

The conversion of the enol ethers (**20**) into the enamines (**22**) is thought to proceed via the addition–elimination sequence shown with formation of Zwitterion (**21**) as the rate-determining step. The ρ-value for the reaction with aminoethanol is 1 and the solvent isotope effect, $k(H_2O)/k(D_2O) = 1$.[191]

The concentration of the vinyl ether $CH_2{=}C(OMe)CH_3$ in equilibrium with the acetal $CH_3C(OMe)_2CH_3$ has been estimated to be $5 \times 10^{-3}\%$.[192]

The thermodynamic stability of vinyl ethers has been further investigated.[193]

Enolization and Related Reactions

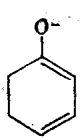
Intramolecular catalysis for the enolization of a number of 2-carboxyacetophenones has been investigated by studying their iodination and the detritiation of analogous tritium compounds. The introduction of 3,6-dimethyl substituents causes a substantial increase in the equilibrium constant for cyclization to form the lactol but a decrease in the rate of the intramolecularly catalysed enolization. The tritium isotope effects, k_H/k_T, are lower than for the analogous intermolecular process which was ascribed to the non-linearity of the transition state of the intramolecular reaction.[195]

The detritiation of [$^3H_1$]-2,6-dihydroxyacetophenone does not show an enhanced rate compared to that for detritiation of 2-hydroxyacetophenone and hence does not proceed with intramolecular general-acid and general-base catalysis.[196]

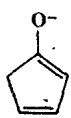
Further work on dedeuteriation of [$^2H_6$]acetone catalysed by diamines has been reported.[197]

The enolization of oxalacetic acid does not show a second-order dependence on buffer concentration in imidazole and phosphate buffers, thus excluding the previously proposed concerted mechanism. In 3-quinuclidinol buffer the values of k_{obs} at buffer concentrations greater than 0.04M fall below the straight line defined by the plot of k_{obs} *vs* buffer concentration at lower concentrations. This was interpreted by a mechanism that involves formation of the enol in an elimination reaction of the ionized carbinolamine.[198]

The general-base catalysed exchange of the α-hydrogen atoms of cyclohex-3-enone catalysed by DPO_4^{2-} is 575 times faster than its conversion into cyclohex-2-enone. The enolate ion (**23**) is therefore deuteriated (and presumably protonated) preferentially at the α-position. In contrast, the enolate ion (**24**) derived from cyclopent-3-enone is



(**23**)



(**24**)

$CH_2{=}CH{-}\bar{C}HCOSBu^t$

(**25**)

deuteriated only 3.2 times faster at the α- than at the γ-position. Thus the rate-determining step in the conversion of cyclohex-3-enone into cyclohex-2-enone is protonation of (**23**), whereas in the conversion of cyclopent-3-enone into cyclopent-2-enone enolization is partly rate-determining. This difference in behaviour was attributed to the geometry of the dienolate ions. In (**24**) the π-system is almost planar and on protonation at the γ-position the charge should be transmitted to the oxygen, whereas in (**23**) the π-system