ORGANIC REACTION MECHANISMS · 1999

An annual survey covering the literature dated December 1998 to November 1999

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Preface

The present volume, the thirty-fifth in the series, surveys research on organic reac-
tion mechanisms described in the literature dated December 1998 to November 1999. In order to limit the size of the volume, we must necessarily exclude or restrict overlap with other publications which review specialist areas (e.g. photochemical reactions, biosynthesis, electrochemistry, organometallic chemistry, surface chemistry and heterogeneous catalysis). In order to minimize duplication, while ensuring a com-
prehensive coverage, the editors conduct a survey of all relevant literature and allocate publications to appropriate chapters. While a particular reference may be allocated to more than one chapter, we do assume that readers will be aware of the alternative chapters to which a borderline topic of interest may have been preferentially assigned.

There has been only one change of authorship since last year. We welcome Drs D.M. Hodgson, M. Christlieb, and E. Gras who co-author ‘Carbenes and Nitrenes’. They replace Dr J. Knight whose expert contribution to the series since 1993 we wish to acknowledge.

We regret that publication has been delayed by late arrival of manuscripts, for reasons out of the control of the editors. In order to reduce the impact of such ongoing delays we have had to take exceptional steps. Thus, a belated chapter covering ‘Radical Reactions Part 2’ for 1998 appears in this volume since we had available the 1999 review to include in place of a void in the 1998 volume. We have also encouraged contributors to cooperate with a colleague in alternate year authorship, where this may help to relieve pressure of work.

Once again, we wish to thank the production staff of John Wiley and Sons and our team of experienced contributors for their efforts to ensure that the review standards of this series are sustained.

A.C.K.
W.E.W.
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CHAPTER 1

Reactions of Aldehydes and Ketones and their Derivatives

B. A. MURRAY

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**Formation and Reactions of Acetals and Related Species**

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Formation and Reactions of Acetals and Related Species

Hammett plots have been constructed for the acid- and base-catalysed decomposition of methyl hemiacetals of benzaldehydes in aqueous solution. The data are analysed in terms of three-dimensional More O’Ferrall–Jencks diagrams and of Cordes interaction effects.
Diazidooxopropyl acetal (1) undergoes rhodium(II)-catalysed ring expansion to (3) in the presence of TMS chloride; the latter reagent acts as a Lewis acid–base catalyst for ring expansion of the oxonium ylid intermediate (2).

\[
\begin{align*}
\text{(1)} & \quad \text{(2)} & \quad \text{(3)} \\
\text{O} & \quad \text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} & \quad \text{O} \\
\text{N}_2 & \quad \text{O} & \quad \text{O} \\
\end{align*}
\]

\(t\)-Butyl chloromethyl ketone forms a cyclic acetal with sucrose: the 2-hydroxy group of the sugar reacts with the carbonyl, with ring closure via the 3-position, yielding a \(t\)-butyl hydroxymethyl acetal. The results are part of a study of the relative reactivities of the hydroxy groups of (unprotected) sucrose.

An unusual case of cyclopropanol formation from a hemiacetal of a \(\beta\)-silyl aldehyde is ascribed to an enhanced reactivity of the silicon, due to an appropriately placed oxyanion generated from the hemiacetal.

Activated \(N, O\)-acetals (4) can undergo a nucleophilic alkylation which replaces the oxygen (via an imine intermediate) to yield an amine (5a), or by replacement of the nitrogen (via an aldehyde) to yield an alcohol (5b). Such amine or alcohol products are valuable, especially if obtainable as single isomers. A catalytic, enantioselective alkylation has been reported to yield the amines (5a), using a copper–BINAP catalyst, and a variety of alkene sources for the alkylating group (enol silanes or allylsilanes, ketene silyl acetals). \(^1\)H NMR spectroscopy was used to elucidate mechanistic details concerning the transsilylations involved. For example, a simple \(N, O\)-acetal (4; \(X = p\)-Ts, \(R^1 = H, R^2 = Et\)) does not give amine (5a) with 1 equiv. of the enol silane of acetophenone; rather, \(O\)-silylation occurs. A second equivalent of enol silane is required to form (5a), and the catalyst. The paper also reports similar transformations of \(N, N\)-acetals.

\[
\begin{align*}
\text{(5b)} & \quad \text{(5a)} \\
\text{Nu} & \quad \text{Nu} \\
\text{R}^2\text{O}_2\text{C} & \quad \text{R}^2\text{O}_2\text{C} \\
\text{OH} & \quad \text{N}X & \quad \text{N}X \\
\end{align*}
\]

Catalytic, enantioselective alkylations of \(N, O\)-acetals have been reported.

Reactions of Glucosides and Nucleosides

A theoretical study of the mutarotation of glucose has evaluated the energies of the two transition states (i.e. \(\alpha\)-anomer to aldehyde and aldehyde to \(\beta\)-anomer), placing
Reactions of Aldehydes and Ketones and their Derivatives

$n = 0–3$ water molecules as part of a specific proton-transfer network. The transition states are lowered by ca 28 kcal mol$^{-1}$ with even one water, but significant further stabilizations are observed for $n = 2$ and 3, both of which exhibit very strong hydrogen-bonded networks. A variant with secondary hydrogen bonding ($n = 2$, with two ‘outer’ waters) is also evaluated.

A m-xylylene moiety has been used as a rigid spacer to align an intramolecular glycosylation at room temperature. The systems used, involving 15- or 14-membered ring formation, exhibit good face selectivity (i.e. towards formation of $\alpha$- or $\beta$-anomer). They also show promise for oligosaccharide synthesis, with a simple protocol for post-synthesis cleavage of the spacer.

Alkaline hydrolyses of $p$-nitrophenyl $\alpha$-D-glucoside and the corresponding galactosides are accelerated by a factor of up to 110 on addition of boric, boronic, or borinic acids, relative to their $\beta$-anomers. The selectivity is reversed in the case of the mannoses, indicating that a cis-relationship between the 2-hydroxy and the $p$-nitrophenoxy groups is central to the stereoselection. An acceleration of the hydrolysis of $p$-nitrophenyl-D-glucosides in the presence of $\alpha$-cycloextrins depends on this same stereochemical relationship. With $\alpha$-cycloextrin (20 mmol dm$^{-3}$), hydrolysis of the $\alpha$-D-mannoside is accelerated 7.6-fold, whereas the $\beta$-anomer is unaffected. For the D-glucoside, -galactoside, and -xyloside, complexation by cycloextrins favours hydrolysis of the $\beta$-sugars, by similar factors. These selectivities are achieved without particularly strong binding ($110 < K / \text{mol}^{-1} \text{dm}^3 < 260$), and are not due to binding selectivity: $K_\alpha$ never differs from $K_\beta$ by more than 60%.

The Maillard reaction involves condensation of an aldose with an amino function (e.g. of a protein), yielding an imine that can undergo rearrangement to an amino form (the Amadori rearrangement), followed by subsequent reactions involving both volatile and polymeric products. In the light of the increasing use of high pressure in food processing, the effect of such pressures on the formation of volatiles has been studied for a model Maillard reaction.

TMS triflate catalysis of transglycosylations between permethylated methyl D-glucopyranosides and simple alcohols has been reported.

Reactions of Ketenes and Related Species

Mechanistic investigations of additions to ketenes continue to focus on which double bond reacts first, and on the role of the solvent: many theoretical studies probe the latter by systematic incremental inclusion of a series of solvent molecules in the calculation. Experimentally, similar effects for the catalyst are often seen in its kinetic order.

Gas-phase and solution-phase calculations on the hydration of ketene to produce acetic acid, using water clusters of two, three, and four molecules to attack the ketene, show a two-step addition via the 1,1-enediol intermediate, i.e. initial addition to $\text{C}=\text{O}$, rather than to $\text{C}=\text{C}$. The preference is slight, but consistent.

Solvent isotope effects, $k_{\text{H}_2\text{O}} / k_{\text{D}_2\text{O}}$, have been measured for the hydration of five ketenes, $R^1R^2\text{C}=\text{C}=\text{O}$, catalysed by hydroxide ion.

Rate constants for hydration of ketene, and of carbon dioxide, have been calculated using No Barrier Theory, Marcus Theory, and a multi-dimensional Marcus treatment.
The methods agree except in the case of the un catalysed hydration of ketene, where the multi-dimensional method predicts $\Delta G^{\text{act}}$ to be lower for addition to C=O, whereas the No Barrier results favour C=C addition. A calculation of $k_{HO}$ for ketene hydration agrees with preliminary experimental results.

Addition of amines to the silylketene PhMe$_2$SiCH=C=O to form amides exhibits kinetics in acetonitrile in which the order in amine lies between second and third,$^{16a}$ as found in recent theoretical studies of the parent ketene, H$_2$C=C=O, and ammonia.$^{16b}$ The result contrasts sharply with a straightforward first-order dependence found for more reactive substrates, such as diphenylketene. The influence of amine basicity is discussed for the silylketene and compared with results for hindered compounds. The reasons for the failure to observe higher order terms for the more reactive substrates are also discussed.

The amination of ketenes to produce amides (see Scheme 1) has been subjected to a variety of computational methods, including several treatments of the solvent, with explicit roles for actively participating amine and water molecules.$^{17}$ All the results favour a two-step process with initial addition to the C=O bond, rather than a concerted reaction involving the C=C bond. The former involves a 1-amino-1-hydroxy ene intermediate (6), formally the enol of the amide. Inclusion of a second amine molecule lowers the barrier to the two-step reaction. Replacing the second amine with a water molecule lowers it even further, an effect which should be even greater when water is the bulk solvent. Some experimental evidence is presented for the highly hindered substrates, bis(mesityl)ketene and bis(pentamethylphenyl)ketene. Addition of primary or secondary amines clearly shows, from IR and UV spectra, the build-up and subsequent tautomerization of the intermediate enols. The kinetics of these more hindered substrates are first order in amine; this is not inconsistent with the theoretical results, as such hindered ketenes may only react rather slowly with amine dimer, which is also in low concentration under the conditions used.

Calculations and low-temperature NMR experiments have been used to investigate the course of reactions of diphenylketene with dienes.$^{18}$ While the reaction of cyclic (s-cis) 1,3-dienes such as cyclopenta- and cyclohexa-1,3-diene yield 2 + 2 (Staudinger) products, the low-temperature experiments indicate initial formation of 4 + 2 (Diels–Alder) intermediates. For the open-chain reactants, 2,3-dimethyl- and 1-methoxy-1,3-butadiene, both product types are formed initially, with conversion of the Staudinger to the Diels–Alder over time, via a retro-Claisen rearrangement.

Methyleneketene, H$_2$C=C=O, could undergo cycloaddition at any of its double bonds. Theoretical calculations on its reaction with pyrroline-1-oxide predict
an asynchronous concerted mechanism leading to (7), the 2,3-adduct, the same regioselectivity as is observed in experiment.¹⁹

The mechanisms of dimerization of ketene imine and its bis(trifluoromethyl) derivative have been studied by *ab initio* methods.²⁰ Each process identified was found to be concerted but asynchronous, with a four-membered transition state.

An isodesmic reaction has been employed to study substituent effects on the stability of ketenimines, XCH=CH=NH.²¹ A (negative) correlation with the electronegativity of the substituent X was found. The sensitivity to the substituent effect is less than that for ketenes or isocyanates, but more than that found for diazomethanes or allenes. Particular stabilizing effects are found for π-acceptors, e.g. X = AlH₂, BH₂, O=CH, HO₂C, CN, NO₂, and HSO₂ (suggesting cyano-cation resonance structures are important), and for X = Li (i.e. ynamine resonance).

Keteniminium cations and imines can undergo a formal 2 + 2 thermal cycloaddition to yield 2-azetidinones [β-lactams (8)]; see Scheme 2. A computational study suggests the cycloaddition occurs via a stepwise mechanism, with N–C bond formation occurring first.²² Stereochemistry is determined in the second step, by torquoelectronic effects. However, the nature of the anion can affect the stereochemistry, which appears to explain the change in stereochemistry found when X = Cl, i.e. when chloro-enamines are used as precursors of keteniminium ions.

The chemistry of bis(trimethylsilyl)-1,2-bisketene (9) has been extended to its reaction with amines.²³ The facile reaction occurs in two steps: the first amine gives a ketenylcarboxamide (10) and the second gives a succinamide (11); the latter can be a mixed product if the bisketene (9) is treated with two different amines successively. Phenylhydrazine reacts with (9) to give a succinimide, while treatment with an amine and then an alcohol (or vice versa) gives an ester amide. Diamines...
give polymeric products, unless an excess of the bisketene is employed, to give an \( \alpha,\omega \)-bisketenylldiamide. Kinetic studies of each of the steps in the formation of the succinamide are reported. It is noted that reaction of methanol with ketenylcarboxamidine (10) to give the ester amide is much faster than the formation of a diester from a ketenyl ester. This and other lines of evidence point to a coordination between the carboxamide group of (10) and incoming nucleophiles in the formation of the ‘homo-’ and ‘hetero-’ succinic acid derivatives.

Bromofluoroketene ethyl trimethylsilyl acetal \([\text{Br(F)}\text{C}=\text{COEt(OSiMe}_3)]\), \( E/Z \)-mixture undergoes enantioselective aldol reactions with aldehydes in the presence of Masamune’s catalyst. The enantioselectivity is markedly temperature dependent, with examples of high \( ee \) at \(-78 \) and \(-20^\circ C \), but of opposite rotation sign.

Lewis acid-mediated addition of silyl ketene acetics to a chiral sulfimine gives precursors of \( \beta \)-amino acids in fair to excellent \( de \).

Mixed diesters of both symmetrical and unsymmetrical diols have been prepared by reaction of carboxylic acids with cyclic ketene acetals of the diols, with the less substituted carbon of the cyclic dioxonium ion intermediate being attacked in most cases.

Hydration of trifluoroacetylketene is discussed later under Enolization.

**Formation and Reactions of Nitrogen Derivatives**

**Imines**

Proton affinities of imines and heats of formation of immonium ions have been calculated for the gas phase by \( ab \) \( initio \) methods. \( cis \)-Imines are more basic than their \( trans \)-isomers, reflecting the unusually high \((15-17 \text{ kJ mol}^{-1})\) energy difference between the \( cis \)- and \( trans \)-isomers, which decreases significantly in the immonium ions. An additivity scheme for group contributions in immonium ions is proposed.

Equilibrium addition of methanol to benzylideneanilines (12; \( X = H, 3-\text{Cl, 3- and 4-NO}_2 \)) to give \( \alpha \)-amino ethers (13) has been studied in methanol solvent, using carboxylate buffers. The reaction is general acid-catalysed, with fast iminium ion formation as the initial step. Brønsted \( \alpha \) exponents range from 0.67 to 0.88, with electron-withdrawing \( X \) giving larger \( \alpha \), an observation also true of the equilibrium constant, which follows \( \sigma^- \).

The kinetics and mechanisms of acid catalysis of intramolecular cyclization of 1,3-diaryl-3-(2-aminophenylsulfenyl)propan-1-ones (14) to yield cyclic imines in mixtures of methanol and various acids have been described. The \( X \) substituent significantly affects the rate.
Oxazolinylaziridines have been prepared by addition of (chloromethyl)oxazolines to imines.$^{30}$

A range of imines derived from trifluoromethyl aryl ketones have been converted into heterocyclic products via intramolecular cyclization with loss of the CF$_3$ group.$^{31}$ For example, $o$-aminoimine (15), when treated with strong base, cyclizes to benzimidazole (16), with loss of trifluoromethyl anion. The corresponding $o$-phenols yield benzoazoles, and examples using an external amine lead to aziridines.

Furfural and nitromethane, in the presence of isobutylamine, form 1-(fur-2-yl)-2-nitroethane, a bioactive material; an aldimine intermediate, $N$-(fur-2-ylmethylene)isobutylamine, has been characterized.$^{32}$

A simple disulfonamide catalyses reaction of aldehydes and amines to give imines, via hydrogen bonding to the transition state for nucleophilic attack of the amine.$^{33}$

Amino–imino tautomerism in simple 1-substituted-2-aminopyrroles (17a ⇄ 17b) ⇄ (17c) has been studied by NMR spectroscopy and by \textit{ab initio} calculations for R = H, Me, Et, Bu', and Ph.$^{34}$ 1-Methyl-2-aminopyrrole (17a; R = H) is predicted to show observable imino tautomers in water.
1-Phenyl-4-(phenylhydroxymethylidene)pyrrolidine-2,3,5-trione (18) can exist as endo-(shown) or exo-enol, depending on the solvent. This equilibrium appears to affect its site reactivity with amines. Ethanolic condensation with glycine (R = CH₂CO₂H) or β-alanine (R = CH₂CH₂CO₂H) gives C(6) products (19) which exist in two tautomeric forms: a keto–enamino or enaminone (shown), and an enol–imine. In contrast, reaction of the hydrochloride of glycine ethyl ester (R = CH₂CO₂Et) in the same solvent at reflux gave condensation at C(3), i.e. structure (20) (enol–imine shown), which again exhibited a similar equilibrium with an enaminone tautomer. This compound was also found to undergo transamination with benzylamine (i.e. R = CH₂Ph), as did several others.

The products of reactions of two methyl 2-aryl-2H-azirine-3-carboxylates (21; aryl = 2,6-Cl₂C₆H₃ or 4-MeC₆H₄) with a range of nucleophiles are reported. Although a wide range of compounds have been added (thiols, propargyl alcohol, amines, enamines, enones and β-diketones), all appear to involve initial addition to the C=N bond.

Aryl alkyl ketones undergo a two-step homologation to give α-aryl-α-alkynitriles (23), via an imine [an N-(1-aryalkylidene)cyanomethyl amine (22)]. A mechanism is proposed, and several are ruled out. For example, a series of para-substituted...
imines (22) give reaction rates with a Hammett $\rho$ value of 1.86, suggesting electron-withdrawing substituents enhance the rate by favouring an initial deprotonation. However, alkylation of (22) $\alpha$ to the nitrile prevents reaction, indicating that both methylene hydrogens are required. Imine–imine tautomerism was also ruled out, as was photochemical activation. Isotope-labelling experiments ($^{13}$CN and $^{15}$N) suggest an intramolecular nucleophilic substitution, as the cyano group of (23) is derived from the $=\text{N}--\text{CH}_2-$ fragment of (22). On this basis, an intermediate three-membered nitrogen heterocycle is proposed.

The mechanism of the Gibbs reaction, an assay for phenols using, e.g., 2,6-dichlorobenzoquinone $\text{N}$-chloroimine, has been probed for a wide range of imines and phenols. The first step of single-electron transfer to produce the $\text{N}$-chloroimine radical anion is followed by a mechanistic divergence into three routes, depending on the reactivity of the pair of reactants.

The kinetics of the nucleophilic addition of potassium cyanide to $\alpha,N$-diphenyl-nitrone have been reported.

**Stereoselective Imine Reactions**

Enthalpic and entropic contributions to diastereofacial selectivity have been explored in the addition of $n$-butyllithium to the C=N bond of $\text{R}^1\text{CH(OR)}^2\text{CH}=\text{NSiMe}_3$. Using THF or $n$-hexane as solvent, temperature ranges of up to 150°C can be covered, over which a change in the $\text{anti}$: $\text{syn}$ ratio of the products from 3:1 to 1:3 can be achieved. The results are discussed in terms of stereospecific solvation effects on the reacting $\pi$-system, an area in need of an appropriate computational approach.

The Exterior Frontier Orbital Extension (EFOE) model has been applied to predict $\pi$-facial selectivity in nucleophilic additions to imines and iminium ions of the cyclohexanone, tropinone, and adamant-2-one systems. A review of the EFOE model and other references to its use, are described later under **Regio-, Enantio-, and Diastereo-selective Aldol Reactions**.

Stereoselective aldol reactions, allylations, and aziridinations of imines, including activated imines, have been reported. The Sakurai–Hosomi reaction of allylsilane with imine in the presence of tetrabutylammonium fluoride is found not to be strictly catalysed by fluoride; rather, a fluoride-triggered autocatalytic route is suggested.

$\text{N}$-Benzylimine [(24); derived from ($R$)-glyceraldehyde], undergoes a tandem Mannich–Michael reaction with Danishefsky’s diene (25) to give cyclic enaminoones (26). The diastereoselectivity of the reaction, and the effects of temperature, solvent,
and Lewis acid catalyst, have all been studied. Replacing the N-benzyl group of (24) with an (S)-α-methylbenzyl residue leads to double stereodifferentiation.

![Diagram](image)

A related reaction of N-benzylmethylimine, MeCH=NCH2Ph, has been investigated by NMR and computational methods. Distinct differences in chemical behaviour are observed when the di- or tri-fluoromethyl analogues are studied.

Aldimines, R1CH=NR2, react with allyltrimethylsilane in the presence of n-butylammonium fluoride to give homoallylamines, R1CH(NHR2)CH2CH=CH2; fluoride-triggered autocatalysis is again proposed. Allylation of imines has been achieved via in situ formation of an N-tosyliminium species from aldehydes or ketones.

As part of an asymmetric route to α-arylglycinols, a chiral lithium methyl p-tolyl sulfoxide has been added to N-arylidine-p-anisidines (ArCH=NNC6H4-p-OMe). Under thermodynamically controlled conditions (0°C), de ≈0%, regardless of the nature of the C-aryl substituent. However, kinetic control at −70°C allows high diastereoselectivity to be achieved, and its direction can be controlled by the electronic nature of the aryl group.

A new enantioselective Strecker synthesis of α-aminonitriles and α-amino-acids reacts N-benzhydrylimines with hydrogen cyanide in the presence of a chiral guanidine catalyst; the mechanistic basis of the enantioselectivity is analysed.

N-t-Butanesulfinylimines derived from aldehydes and ketones undergo highly diastereoselective 1,2-addition of organometallic reagents. The product sulfinamides are readily hydrolysed in acidic methanol, providing enantio-enriched α-branched and α,α-dibranched amines. Steric, electronic, and solvent effects are explored.

Enamines of cyclohexylamine have been enantioselectively cyclized to bicyclo[3.3.1]nonanedione systems, using acryloyl chloride and chiral pyrrolidine catalysis. Enantiopure N-sulfinylimines have been used in asymmetric synthesis of isoquinolone alkaloids, and a stereocontrolled synthesis of 3,4,5,6-tetrahydroprymidine-based amino acids from imino ethers has been reported. Diastereoselective additions of chiral acetals of (2-lithiophenyl)acetaldehyde to arylimines have been used in an asymmetric synthesis of 1-aryltetrahydroisoquinolines. Organolithiums react with chiral imines, in the presence of Lewis acids or bases, to give amines in up to 100% de. Diastereoselective additions of copper reagents to imines derived from (S)-1-phenylethylamine have been reported.

Catalytic enantioselective addition to imines has been reviewed.
Hydrolysis of Imines

pH–rate profiles and transition metal ion catalysis are reported for hydrolysis of o- and p-hydroxybenzylidene-4-benzidines (27) in aqueous dioxane at 20°C.\textsuperscript{58}

\[
\begin{align*}
\text{H} & \quad \text{C} \quad \text{N} \quad \text{O} \\
\text{X} & \quad \text{H} & \quad \text{N} & \quad \text{H}_{2}\text{N} & \quad \text{NH}_{2}
\end{align*}
\]

(27)

Acidic hydrolysis of a bis(salicylidenamino)diimine, \(\text{CH}_2\{4-\text{C}_6\text{H}_4\text{N}=\text{CHC}_6\text{H}_4-2\text{-OH}\}\text{2}\), has been studied from 30 to 45°C.\textsuperscript{59} Ni(II) accelerates the hydrolysis, as does Zn(II) to a lesser extent, while Cu(II) has a more complex effect. Activation parameters are reported.

The well-known affinity of saccharides for boronic acids has been exploited to activate imine hydrolysis. Imine (28) is hydrolysed much faster in the presence of saccharides, and the acceleration follows the same order as the stability constants of a range of saccharide complexes.\textsuperscript{60} The phenomenon is not merely a substituent effect because (i) it is not observed at all in the absence of the boronate substituent, and (ii) its magnitude is not significantly altered if the substituent is placed on the other side of the imine instead. Using pH–rate profiles and kinetic isotope effects, the mechanism is proposed to involve covalent attachment of saccharide, followed by binding of water to boron, producing an intermediate (29) with a very acidic ‘bound water,’ which sets up protonation of nitrogen through a solvent chain.

Forward and reverse rate constants have been reported for the reversible ring opening of a triazolo-1,4-thienodiazepine (30a) over a range of pH values in water, using a combination of UV spectrophotometry and polarography.\textsuperscript{61} The results have been analysed in terms of several protonated forms of the reactant (30a) and product (30b), and similar forms of potential carbinolamine intermediates.

Rate constants for the formation and hydrolysis of Schiff bases derived from pyridoxal 5’-phosphate and co-polypeptides have been determined in the pH range 4–11 at 25°C.\textsuperscript{62} The co-polypeptides contain L-lysine, and aromatic L-amino acids, and
the interaction of such aromatic moieties with pyridoxal (and, by extension, such interactions in enzymes) are discussed.

Iminium Ions and Related Species

One of the mechanisms operating in ageing and degenerative disease is lipid peroxidation: this can produce 4-hydroxyalk-2-enals (31), giving rise to both cross-linking and fluorophore generation. A major fluorophore appears to be derived from \((E)-4\)-hydroxy-2-non- (or -hex)-enal \([i.e. \text{ (31; } R^1 = C_3H_{11} \text{ or } C_2H_5)]\). These aldehydes cross-link with lysine residues in protein, and model compounds have been prepared using simple amines. The model fluorophores are 2-alkyl-2-hydroxy-1,2-dihydropyrrol-3-one iminium cations \((32a; R^2 = \text{Pr, Bu, CH}_2\text{CH}_2\text{OMe})\). The structure and chemistry of these ions have been studied by \(^{15}\text{N} \text{ labelling, } ^1\text{H} \text{ and } ^{13}\text{C} \text{ NMR spectroscopy, and fluorescence spectroscopy.} \) Typical of vinylogous amidinium cations, H(4) is exchanged by a tautomeric equilibrium \((32a \Leftrightarrow 32b)\). A mechanism for the formation of the fluorophores, involving initial Schiff base formation and subsequent oxidation, is proposed.

\[\text{R}^1\text{CHO} \overset{R^2\text{NH}_2}{\rightarrow} \text{NHR}^2\text{OH} \]  

\[\text{(31)} \rightarrow \text{(32a)} \rightarrow \text{(32b)}\]

\(\alpha\)-Silylnitrosamine (33) easily generates azomethine imine (34), via a 1,4-silatropic shift. Subsequent reaction with dipolarophilic alkynes yields pyrazole derivatives.

The iminium ion chemistry of activated indoles has been reviewed (47 references). Focusing particularly on the Vilsmeier formylation, this reaction has been generalized over time to include a greater variety of amide types. The traditional Vilsmeier protocol
of activating amides by reaction with phosphoryl chloride has also been broadened by the use of triflic anhydride as an alternative.

**Oximes**

Rate constants have been measured for oxime formation in water for several substituted benzaldehydes and hydroxylamine, over a range of pH from 7 down to 2. Hammett plots have been constructed for carbinolamine formation and its dehydration.

The use of reversible transformations to set up dynamic combinatorial libraries has received considerable attention recently. In such systems, molecular diversity can be generated and screened by allowing a target compound to ‘identify’ a species from the pool in dynamic equilibrium, based on a strong interaction. A kinetic and mechanistic study of imine exchange in $O$-aryl and $O$-alkyl oximes has been undertaken in aqueous solution, to assess the reaction’s suitability for a water-based dynamic library. Of particular importance for such an application is the stability of the system, i.e. the rate of exchange must be substantially greater than the rate of hydrolysis. For the example of the $O$-alkyl case, a typical equilibrium that was studied is shown in Scheme 3. In this case, the kinetic behaviour was consistent with fast $N$-protonation, followed by attack of alkoxylamine to give a tetrahedral adduct, which can then back-or exchange-eliminate. In contrast, the $O$-aryl exchange involves slow hydration of the $C=\text{N}$ bond to give a tetrahedral intermediate, which can then go on to exchange, or to hydrolyse.

(Z)-$O$-Methylbenzohydroximoyl cyanide (35; $R = \text{CN}$) reacts with methoxide ion in DMSO–methanol to give the corresponding substitution product (35; $R = \text{OMe}$), even though this is thermodynamically the less stable product, and, under the conditions, all the staggered conformations of the tetrahedral intermediate should have been accessible. The $E$-reactant isomer was also found to isomerize to the $Z$-isomer faster than it underwent nucleophilic substitution. Theoretical calculations have now been carried out on the tetrahedral intermediate, with phenyl replaced by hydrogen for computational expediency. Conformation (36b), which would lead to $E$-product, is found to be 7 kcal mol$^{-1}$ less stable than (36a), and the transition states also differ by ca 5 kcal mol$^{-1}$ in the same sense.
α-Oxooximes [or α-(hydroxyimino) ketones] are potentially useful synthons. *N*-Hydroxy-α-oxobenzeneethanimidoyl chloride (37) is a chloro derivative of such a compound, and can be prepared in one step from acetophenone. Acid-catalysed methanolysis yields methyl α-oxobenzacetate (38a) and methyl α-(hydroxyimino)benzeneacetate (38b). Mechanistic investigation of the solvolysis, using $^{13}$C labelling, rules out 1,2-arene migration in the formation of (38b). Treatment of pure (38a) under the same conditions as solvolysis yielded some (38b), indicating that it forms via an intermolecular pathway, but also tending to rule out hopes of boosting the yield of (38b) from the solvolysis. Compound (37) has the configuration and conformation shown i.e. benzoyl and OH are trans-, and the oxo- and imino-double bonds are in an $s$-trans relationship; there is no intramolecular hydrogen bonding. These structural factors, found also for several related compounds in the literature, are in sharp contrast to the isostructural enols of β-diketones.

4-Aminopyridinone (39a) reacts with hydroxylamine to give isoxazolo[4,3-c]pyridinone (40a), while the 4-hydroxy reactant (39b) yields the isomeric [4,5-c] structure (40b). Semiempirical calculations have been used to tease out four different mechanisms for the reactions, as well as the effects of tautomeric equilibria in the reactants.
Formation of oxime (41) from 4-dimethylaminobenzaldehyde ($X = \text{NMe}_2$) and 4-trimethylammoniobenzaldehyde ($X = +\text{NMe}_3\text{I}^-$) has been interpreted in terms of a standard two-step mechanism: initial carbinolamine formation, followed by dehydration.\footnote{71} pH–rate profiles have been constructed for both compounds: the amine shows evidence of a change in rate-determining step at low pH (and of the intervention of the reaction of the protonated amine), while the ammonium salt shows a change from acid-catalysed to uncatalysed carbinolamine formation. Equilibrium constants for oxime formation are also reported and discussed.

Arrhenius parameters are reported for pyrolysis of six $p$-toluenesulfonyl arencarb-oxaldoximes (42) in the range ca 334–401 K, giving the sulfonic acid and benzonitrile as products.\footnote{72} The reaction is a thermal electrocyclic elimination, and has been established as being clearly unimolecular and polar in mechanism. The variation of the Arrhenius parameters and relative rates suggest that the polarity of the N–O bond is the major determinant of their high reactivity: the corresponding sulfinyl hydrazones undergo a similar reaction, but ca $10^4$ times more slowly (at 500 K).

The reaction kinetics of acetamide and benzamide $\omega$-(phenoxy carbonyl)oximes have been studied in aqueous buffers over a wide pH range, with cyclization dominant at high pH, and hydrolysis at lower values.\footnote{73} A Hammett plot for the benzamide series suggests that $N$-deprotonation occurs, followed by a rate-limiting step involving concerted $N$–C bond formation and C–O bond breaking.

Ketoximes have been reacted with aliphatic aldehydes and diphenylborinic acid.\footnote{74} $\alpha$-Hydroxyalkylation at the oxime oxygen is favoured by a bulky substituent in the aldehyde (leading subsequently to a ‘BOCON’ diphenylboron chelate), while formaldehyde reacts by $N$-alkylation (giving a ‘COBON’ chelate).
The kinetics of the oxidation of oximes of substituted acetophenones by vanadium(V) have been measured in aqueous acetic acid, using NaVO₃. A two-electron oxidation to the carbocation is proposed, ultimately yielding the ketone.

The kinetics and mechanism of the reaction of sodium methoxide with para-substituted O-benzoylbenzamidoximes, \( p-XC₆H₄C(NH₂)=NO₂CC₆H₄-p-Y \), in methanol have been described.

Oximoyoxytris(dimethylamino)phosphonium salts, derived from oximes of ketones, undergo the Beckmann rearrangement.

A review of synthetic methods for arylpyrroles focuses particularly on the Trofimov reaction of oximes of alkyl aryl ketones with acetylene (192 references).

### Hydrazones, Semicarbazones, and Related Species

Tosylhydrazones of benzaldehyde have been reacted with a benzotriazole-stabilized benzyl anion, formed from an (arylmethyl)benzotriazole and butyl lithium, to provide a stereoselective, one-step synthesis of stilbenes, with lithium chelation probably setting up the geometric preference for \( E \)-product.

An attempted Fischer-type bis-indolization of cyclohexane-1,3-dione (43; \( R = H \)), and (separately) of dimeredone (43; \( R = Me \)) involved treatment with 2 equiv. each of phenylhydrazone and phosphorus trichloride, in anhydrous benzene. In addition to the expected bis(phenylhydrazones) (44a), an oxidation product (44b) was also formed. A mechanism is proposed.

Aromatic SAMP-hydrazones [45; SAMP = (S)-aminomethoxymethylpyrrolidine] react with the lithio derivative of methoxyallene to yield enantiopure 3-pyrrolines.

Homochiral nitrile imines (46) can be generated \textit{in situ} by base treatment of hydrazonyl chlorides (47); (46) undergoes diastereoselective formation of furo[3,4-c]pyrazole derivatives [(48), easily separable isomers], via intramolecular cycloaddition.
Oxidative cyclization of (thio)semicarbazones is a common route to five-membered rings with three heteroatoms. A quantitative study of the reaction of 2,4-diaryl-substituted aldehyde thiosemicarbazones (49) reports rate constants for formation of 1,2,4-triazole (50), together with the isomeric thiadiazole (51), the latter only being formed when the Ar¹ moiety has a strongly electron-withdrawing substituent (CF₃, NO₂) in the para-position. The products are not interconvertible under the reaction conditions (FeCl₃ · 6H₂O in refluxing ethanol), indicating that intramolecular attack by nitrogen predominates over sulfur in all cases. The aldehyde-derived ring (i.e. Ar¹) has the most effect on the rate of cyclization: a ρ value of −3.0 ± 0.2 is reported.

Kinetics of the aminolysis of phenyl and methyl 4-nitrophenyl thionocarbonates [Ph- and Me-OC(=S)OC₆H₄-4-NO₂] by secondary cyclic amines, to give the corresponding thionocarbamates, have been measured in aqueous solution at 25°C.
Using an excess of amine, pseudo-first-order rate coefficients were recorded, but not all plots against amine concentration were linear. The observed behaviours are interpreted in terms of a tetrahedral zwitterionic intermediate, the formation of which is rate-determining for the phenyl substrate. The relative rates of the steps of the mechanism are more finely balanced for the methyl case. The effect of changing from C=S to C=O in the reactant is also examined.

Para-substituted methyl phenylcarbamates have been chloromethylated, using formaldehyde and hydrogen chloride.85

C–C Bond Formation and Fission: Aldol and Related Reactions

Regio-, Enantio-, and Diastereo-selective Aldol Reactions

Chemical Reviews (1999), Volume 99, issue 5, was devoted to the theme of diastereo-selection, with the majority of articles dealing predominantly with ketones, aldehydes, and their derivatives. The titles (and principal authors) indicate how comprehensively the field is reviewed. Topics covered include ‘Catalytic Enantioselective Addition to Imines’ (Kobayashi)57 and ‘Synthesis and Diastereoselective Reactions of N,N-Dibenzylamino Aldehydes and Related Compounds’ (Reetz).86 The range of electronic and steric influences, and the need for tightly controlled model systems to test theories, are exemplified in ‘Around and Beyond Cram’s Rule’ (Reiser),87 ‘Using Perturbation and Frontier Molecular Orbital Theory to Predict Diastereofacial Selectivity’ (Danzenberg),88 ‘Inductive and Resonance Effects of Substituents on π-Face Selection’ (Cieplak),89 ‘Orbital-controlled Stereoselections in Sterically Unbiased Cyclic Systems’ (Ohwada),90 ‘Structure Distortions in Heteroatom-substituted Cyclohexanones, Adamantanes, and Adamantanones: Origin of Diastereofacial Selectivity’ (Gung),91 ‘Face Selection in Addition and Elimination in Sterically Unbiased Systems’ (Le Noble),92 ‘Nature of the Electronic Factor Governing Diastereofacial Selectivity in Some Reactions of Rigid Saturated Model Substrates’ (Adcock),93 ‘Electronic Control of Facial Selection in Additions to Sterically Unbiased Ketones and Olefins’ (Mehta),94 and ‘Nucleophilic Additions to 4,4-Disubstituted 2,5-Cyclohexadienones: Can Dipole Effects Control Facial Selectivity?’ (Wipf).95

A computational approach is applied in ‘The Exterior Frontier Orbital Extension Model’ (Tomoda).42 Indeed, Tomoda has used the EFOE model in several other papers that are mentioned together here for convenience.

The method involves calculating the accessible space outside the van der Waals radii above and below the carbonyl- (or other π-) plane. The stereoselectivity is then predicted from the difference between the π-plane-divided accessible space on each side. Several hydride reductions of cyclohex- and cyclohept-anones and of adamantant-2-ones have been used to exemplify the method, which does not require consideration of transition-state effects.96 For 5-substituted adamantant-2-ones (52), π-facial stereoselection is found to arise mainly from steric effects in most cases, except for aryl substituents, where orbital control appears dominant.97 In assessing the steric, electronic, and orbital contributions to π-facial stereoselectivity in nucleophilic addition to bicyclo[2.2.1]heptan-7-ones (53),98 the results are compared with Mehta’s experimental data for the system.99a,b In the case of nucleophilic additions to