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CHAPTER 2

Reactions of Carboxylic, Phosphoric, and Sulfonic Acids and their Derivatives

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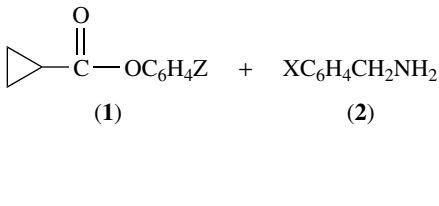
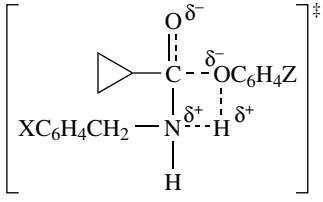
CARBOXYLIC ACIDS

Tetrahedral Intermediates

Kinetic studies of the reaction of Z-phenyl cyclopropanecarboxylates (**1**) with X-benzylamines (**2**) in acetonitrile at 55 °C have been carried out. The reaction proceeds by a stepwise mechanism in which the rate-determining step is the breakdown of the zwitterionic tetrahedral intermediate, $T^{\pm}$, with a hydrogen-bonded four-centre type transition state (**3**).[1] The results of studies of the aminolysis reactions of ethyl Z-phenyl carbonates (**4**) with benzylamines (**2**) in acetonitrile at 25 °C were consistent with a four- (**5**) and a six-centred transition state (**6**) for the uncatalysed and catalysed path, respectively.[2] The neutral hydrolysis of *p*-nitrophenyl trifluoroacetate in acetonitrile solvent has been studied by varying the molarities of water from 1.0 to 5.0 at 25 °C.[3] The reaction was found to be third order in water. The kinetic solvent isotope effect was $(k_{H_2O}/k_{D_2O}) = 2.90 \pm 0.12$. Proton inventories at each molarity of water studied were consistent with an eight-membered cyclic transition state (**7**) model.



(**1**) (**2**)



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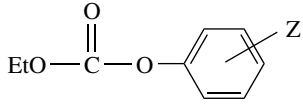

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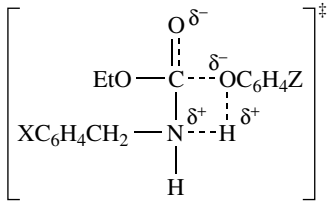

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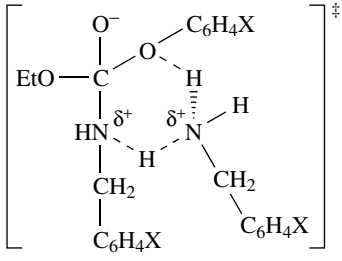

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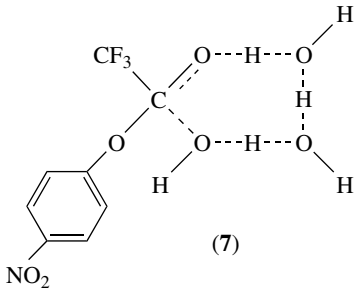

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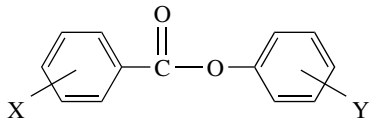

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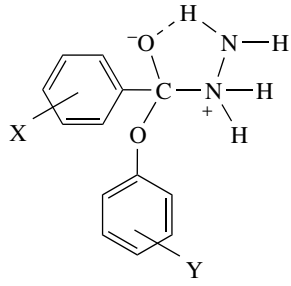


(**9**)

The kinetics of the aminolysis reactions of the α-effect nucleophiles hydrazine and hydroxylamine with Y-phenyl X-benzoates (**8**) have been reported.[4,5] The results demonstrated that the magnitude of the α-effect decreases with increasing electron-withdrawing ability of the acyl substituents. The authors propose that hydrazine stabilizes the transition state (**9**) by intramolecular H-bonding.[5]

Intermolecular Catalysis and Reactions

Reactions in Hydroxylic Solvents

(a) *Esters*

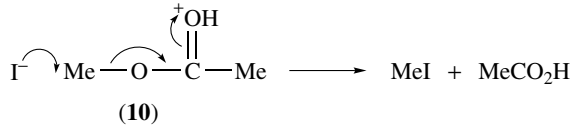
(i) *Formation*

In a kinetic study of the esterification of acetic acid with methanol in the presence of hydrogen iodide, iodimethane was identified as a by-product. The authors propose that this derives from iodide ion attack on protonated methanol.[6] However, attack by iodide ion on protonated methyl acetate (**10**) is more likely, since acetic acid is a better leaving group than ethanol.

(ii) *Transesterification*

The mechanism and thermodynamics of transesterification of acetate–ester enolates in the gas phase have been investigated.[7] The catalytic effect of alkali-metal *t*-butoxide clusters on the rate of ester interchange for several pairs of esters has been determined in non-polar and weakly polar solvents. Reactivities increase in the order ($Li^+ < Na^+ < K^+ < Rb^+ < Cs^+$) with the fastest rates reaching 10^7 catalytic

turnovers per hour. The heavier metals (K, Rb, Cs) exist in solution (and in the solid state) as tetrameric structures (**11**). The authors propose that the roles of the clusters in facilitating the rate of transesterification are to supply multiple cations within the cluster framework, these sites stabilizing developing negative charge in the transition state, and to provide scaffolding for first pre-coordinating the ester, potentially activating it, and then delivering the alkoxide nucleophile via a six-membered transition state along the stereoelectronically preferred Bürgi–Dunitz angle.[8]



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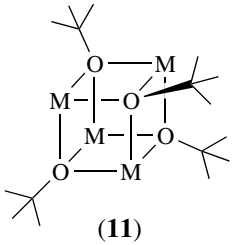

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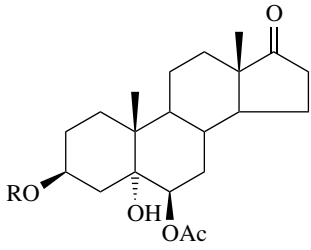
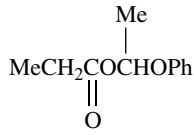


(**12**)

a; R = Ac
b; R = H



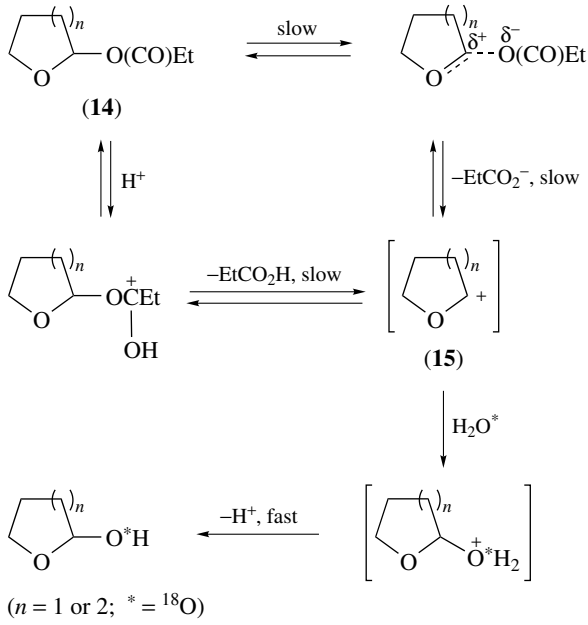
(**13**)

(iii) *Other reactions*

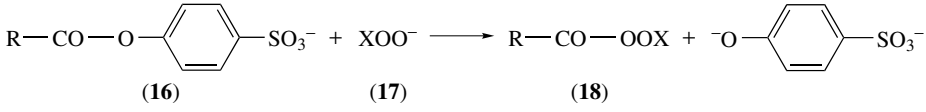
A comparison of the kinetics of alkaline hydrolysis of methyl, isopropyl and butyl acetates in propan-2-ol–water and *t*-butanol–water has revealed that the observed effects correlate with solvent structure.[9]

Tetracyanoethylene (TCNE) has been shown to be a mild catalyst, which possessed some stereoselectivity, for the hydrolysis of the esters of steroidal alcohols. For example, 3β, 6β-diacetoxy-5α-hydroxyandrostan-17-one (**12a**), when treated with TCNE in toluene–methanol (1:1) at 50 °C for 8 h, yielded the 3β-hydroxy compound (**12b**), the 6β-acetoxy group having survived unscathed.[10]

The acid-catalysed hydrolysis of the acylal, 1-phenoxyethyl propionate (**13**), has been studied using the PM3 method in the gas phase.[11] The kinetics and mechanism of the hydrolysis of tetrahydro-2-furyl and tetrahydropyran-2-yl alkanoates (**14**) in water and water–20% ethanol have been reported. In acidic and neutral media, kinetics, activation parameters, ^{18}O isotope-exchange studies, substituent effects, solvent effects and the lack of buffer catalysis pointed clearly to an A_{A1}-1 mechanism with formation of the tetrahydro-2-furyl or tetrahydropyran-2-yl carbocation as the rate-limiting step (Scheme 1). There is no evidence of a base-promoted $B_{AC}2$ mechanism up to pH 12.[12]

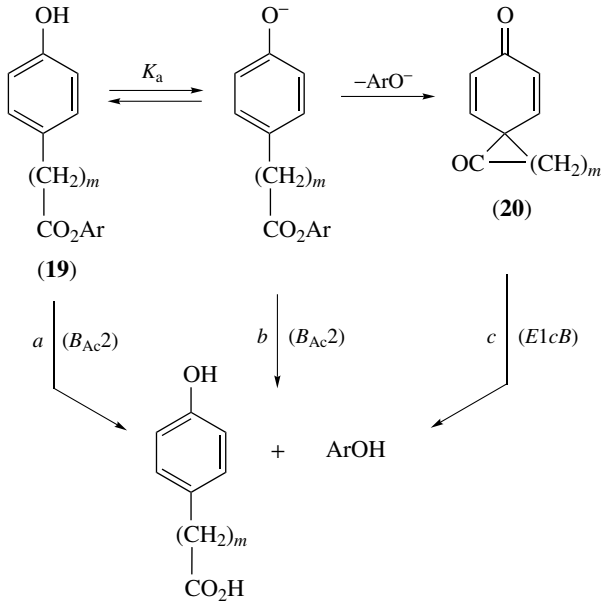


SCHEME 1



Structure–reactivity studies of the reactions between a range of anionic peroxide nucleophiles (**17**; R = H, MeCO, SO_3^-, PO_3^{2-}) and four 4-acyloxybenzenesulfonates [**16**; R = Me, Bu, $Me(CH_2)_7$, $Me_3CCH_2CH(Me)CH_2$] have been reported.[13] The rate data for 4-acetyloxybenzenesulfonate (**16**; R = Me) conformed to a Brønsted-type relationship with $\beta_{nuc} = 0.42 \pm 0.01$, similar to a value of 0.40 ± 0.01 for *p*-nitrophenyl acetate and the same range of peroxide nucleophiles determined earlier by the same group. A larger value of $\beta_{nuc} = 0.56 \pm 0.05$ was obtained for *n*-nonanoyloxybenzenesulfonate [**16**; R = $Me(CH_2)_7$], which was interpreted in terms of steric and polar interactions between the acyl substituents and the attacking peroxide nucleophile.[13] The effect of surfactants on this type of reaction[14] is discussed later on p. 41. These kinetic studies[13,14] were undertaken to provide a set of fundamental data that would provide a backdrop to the action of commercial 'peroxide bleach activators' (e.g. *n*-nonanoyloxybenzenesulfonate) which convert hydrogen peroxide to a better oxidant, an organic peracid (**18**; X = H).

Kinetic studies of the alkaline hydrolyses (pH 11–14) of a series of pentachlorophenyl esters of ω-(*p*-hydroxyphenyl)alkanoic acids (**19**; $m = 1$–4) have been reported.[15] The reasonably high nucleofugality of the pentachlorophenoxide (pK_a

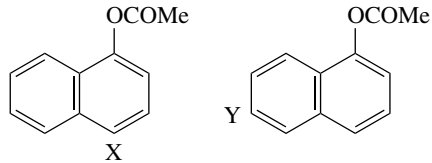


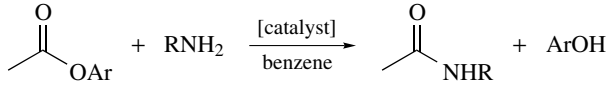
SCHEME 2

of C_6Cl_5OH is 4.79) was considered to be a driving force for the intervention of an *E*l*cB* pathway (path *c*) leading to spiro intermediates (**20**) (Scheme 2). In the event, there was no evidence for that pathway and the hydrolysis of all four esters (**19**; $m = 1–4$) occurred through the usual $B_{AC}2$ mechanism (path *a* or *b*).

Reactions of a wide range of substituted phenyl acetates with six α-effect nucleophiles have revealed little or no difference, compared with phenolate nucleophiles, in the values of the Leffler parameters. As a result, the case for a special electronic explanation of the α-effect is considered unproven.[16] Studies of the kinetics and mechanism of the aminolysis and alkaline hydrolysis of a series of 4-substituted (**21**)[17] and 6-substituted naphthyl acetates (**22**)[18] have revealed that, for electron-withdrawing substituents, aminolysis for both series proceeds through an unassisted nucleophilic substitution pathway.

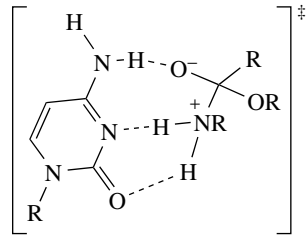
The catalysis by a protected nucleoside of the aminolysis by butylamine of *p*-nitrophenyl acetate in benzene (Scheme 3) has been reported. Interestingly, only 2′, 3′, 5′-*O*-tris(*t*-butyldimethylsilyl)cytidine showed any marked catalytic effect, the adenosine, guanosine and uridine analogues behaving merely as weak general base





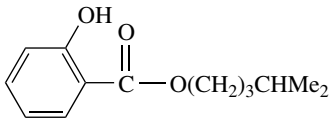
R = $(CH_2)_3Me$
Ar = *p*-$O_2NC_6H_4$

SCHEME 3



(**23**)

catalysts. The authors propose that a bifunctional mechanism operates, with the protected nucleoside stabilizing the aminolysis transition state (**23**) by simultaneous donation and acceptance of protons.[19]



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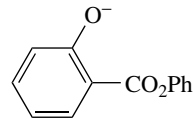

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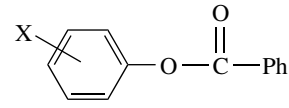
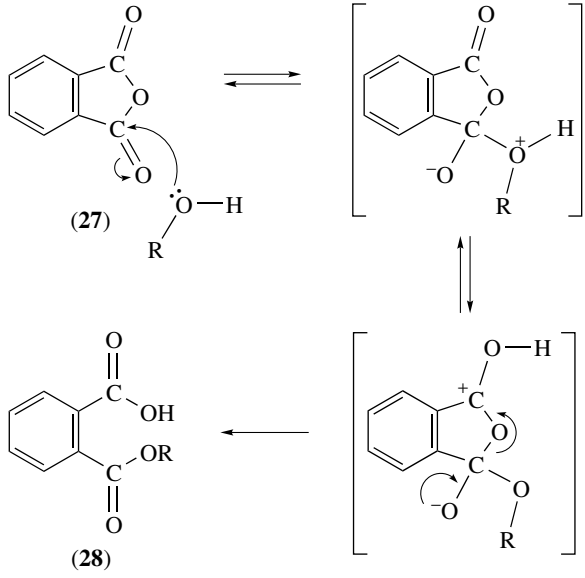


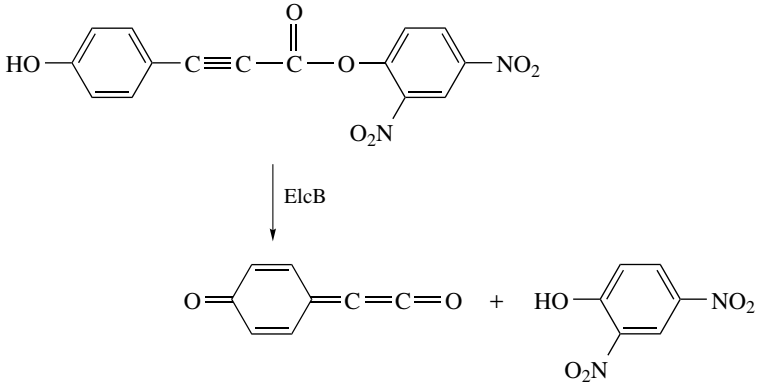
(**26**)

The kinetics of the alkaline hydrolysis of 2-methylpentyl salicylate (**24**) have been studied in various aqueous propanol and *t*-butanol mixtures and in mixtures of water and ethane-1,2-diol.[20] Further studies of the aminolysis of ionized phenyl salicylate (**25**) have been reported, in which it was observed that, in mixed acetonitrile–water solvents, glycine, 1,2-diaminoethane and 3-aminopropanol all reacted as did simple amines, via an intramolecular general-base-catalysed process.[21]

The influence of temperature on the *ortho* effect has been evaluated in the alkaline hydrolysis in aqueous DMSO solutions of *ortho*-, *meta*- and *para*-substituted phenyl benzoates (**26**).[22] The alcoholysis of phthalic anhydride (**27**) to monoalkyl phthalates (**28**) occurs through an *A*-2 mechanism via rate-determining attack of the alcohol on a carbonyl carbon of the anhydride (Scheme 4). Evidence adduced for this proposal included highly negative $\Delta S^{\ddagger}$ values and a ρ value of +2.1. In the same study, titanium tetra-*n*-butoxide and tri-*n*-butyltin ethanoxide were shown to act as effective catalysts of the half-ester formation from (**27**), the mechanism involving alkoxy ligand exchange at the metal as an initial step.[23]

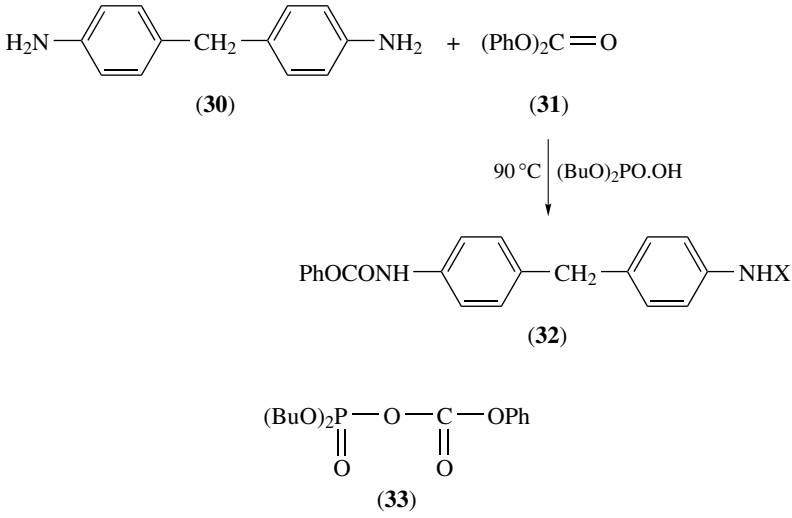


SCHEME 4



As an extension of studies of esters that hydrolyse by dissociative mechanisms, evidence for the operation of the *ElcB* pathway in the alkaline hydrolysis of 2,4-dinitrophenyl 4′-hydroxyphenylpropiolate (**29**) has been sought.[24] No firm conclusion was made, the data merely suggesting the occurrence of the *ElcB* pathway; the data were also consistent with the conventional $B_{AC}2$ pathway.[24]

In the presence of dibutyl phosphate as catalyst, 4,4′-methylenedianiline (**30**) reacts with diphenyl carbonate (**31**) in tetrahydrofuran at 90 °C to give the corresponding mono- (**32**; X = H) or di-carbamate (**32**; X = CO_2Ph), depending on



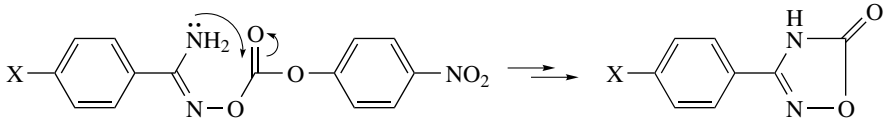
(**30**) (**31**)

(**32**)

(**33**)

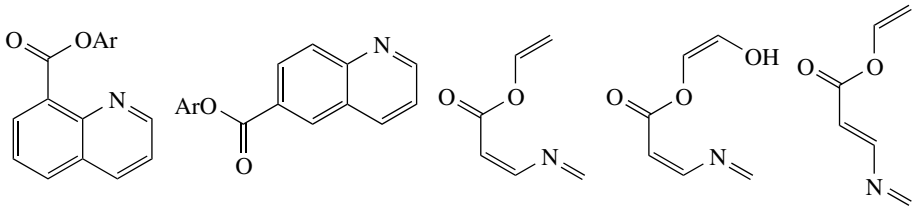
the reaction time.[25] Other organophosphorus acids, e.g. $Ph_2P(O)OH$, $(PhO)_2P(O)OH$ and $BuOP(O)(OH)_2$, are equally effective. The proposed mechanism involves the initial formation of a phosphocarbonate species (**33**), which is a more active carbonylating agent than the parent carbonate.[25]

The kinetics of the cyclization of 4-substituted benzamidoxime 4-nitrophenyl carbonates (**34**; X = H, Me, OMe, Cl, NO_2) in the pH range 8–11 to yield the corresponding heterocycles (**35**) have been studied.[26] At acidic pH, cyclization does not occur and the hydrolysis reaction predominates.



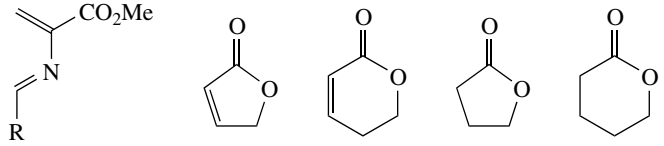
(**34**) (**35**)

The mechanisms of aminolysis of substituted phenyl quinoline-8- and -6-carboxylates, (**36**) and (**37**), have been evaluated using AM1 semiempirical and HF/6–31+G(d) *ab initio* quantum mechanical methods to study the ammonolyses of the model systems vinyl *cis*-3-(methyleneamino)acrylate (**38**), *cis*-2-hydroxyvinyl *cis*-3-(methyleneamino)acrylate (**39**) and vinyl *trans*-3-(methyleneamino)acrylate (**40**). Both experimental and computational results support the formation of a tetrahedral intermediate in the reaction. The results of this study are fully consistent with the experimental observations for the aminolyses of variously substituted phenyl quinoline-8- (**36**) and -6-carboxylates (**37**).[27]



(**36**) (**37**) (**38**) (**39**) (**40**)

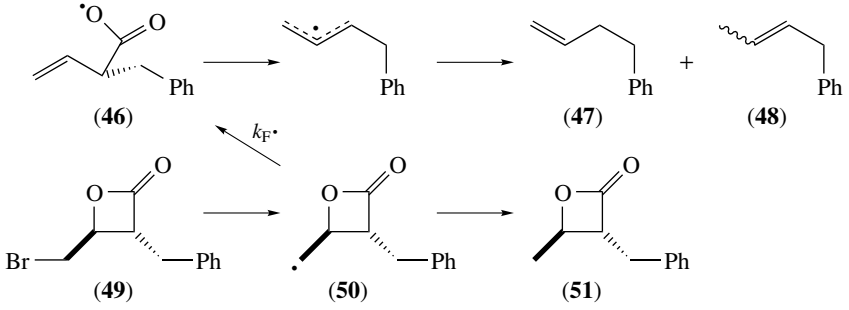
The azadiene bearing a carboxymethyl group (**41**; R = Ph) participates in the Diels–Alder reaction with both electron-rich and electron-deficient dienophiles. However, when groups of greater electron-withdrawing power replace the phenyl group (e.g. R = 4-$O_2NC_6H_4$, COPh, CO_2Et), reaction with only electron-rich dienophiles occurs. A rationale for these observations was made on the basis of a semiempirical molecular orbital study.[28]



(**41**) (**42**) (**43**) (**44**) (**45**)

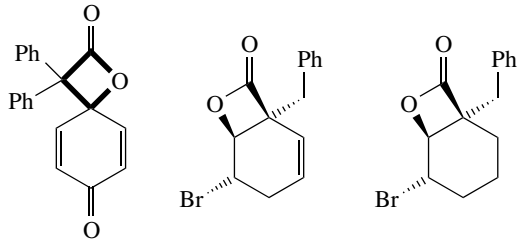
(b) *Lactones and derivatives*

Using Fourier transform ion cyclotron resonance techniques, the proton affinities of the prototypical α, β-unsaturated γ- (**42**) and δ-lactones (**43**) have been determined as 836 and 862 kJ mol^{-1}, respectively. This increase in basicity with the size of the ring also prevails for the saturated analogues (**44**) and (**45**).[29]



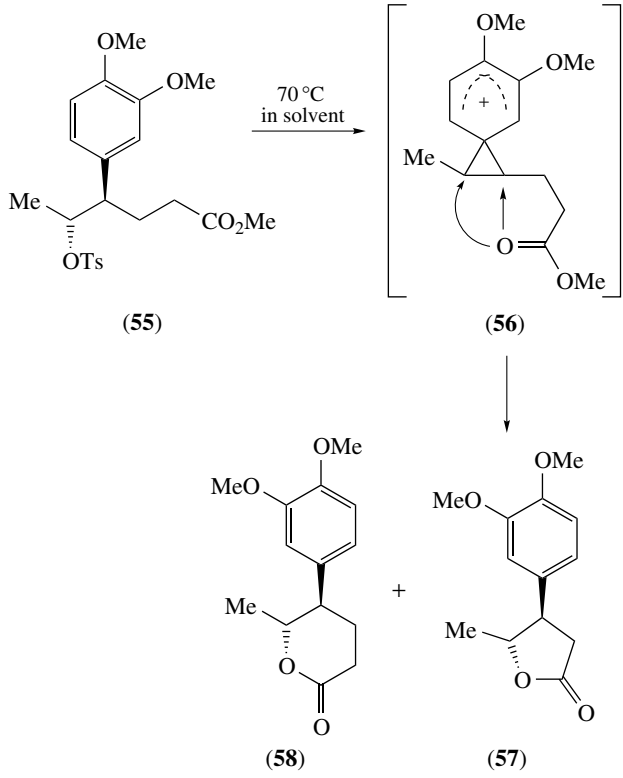
(**46**) (**47**) (**48**) (**49**) (**50**) (**51**)

In an investigation of the free-radical chemistry of β-lactones, a facile decarboxylative cleavage has been observed.[30] For example, the 4-bromo-β-lactone (**49**) reacted with $Bu_3SnH + 5\%(PhSe)_2$ to yield mainly (>95%) the isomeric alkenes (**47**) and



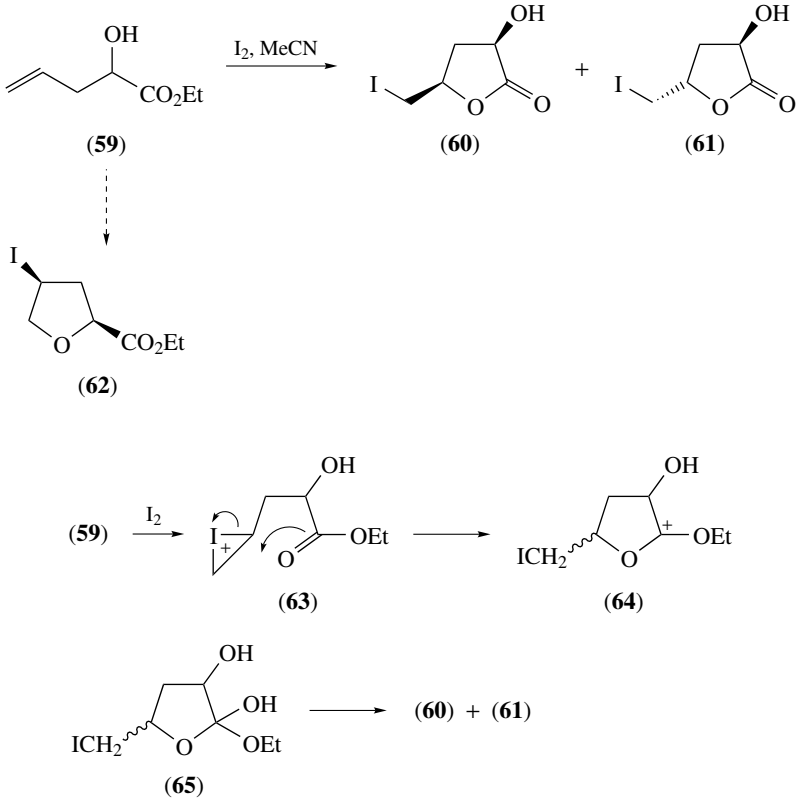
(**52**) (**53**) (**54**)

(**48**), the products of decarboxylation of the ring-opened radical (**46**). The precursor of (**46**) is the 2-oxetanon-4-ylcarbinyl radical (**50**), which is the first-formed intermediate from the 4-bromo-β-lactone (**49**). The ring system of the radical (**50**) remained intact when a molar equivalent of $(PhSe)_2$ was employed, and the saturated β-lactone (**51**) formed by hydrogen atom transfer from PhSeH [produced *in situ* from $(PhSe)_2$] was the major (80%) product. Three bicyclic β-lactones, (**52**), (**53**) and (**54**), were also studied and gave analogous products.[30]



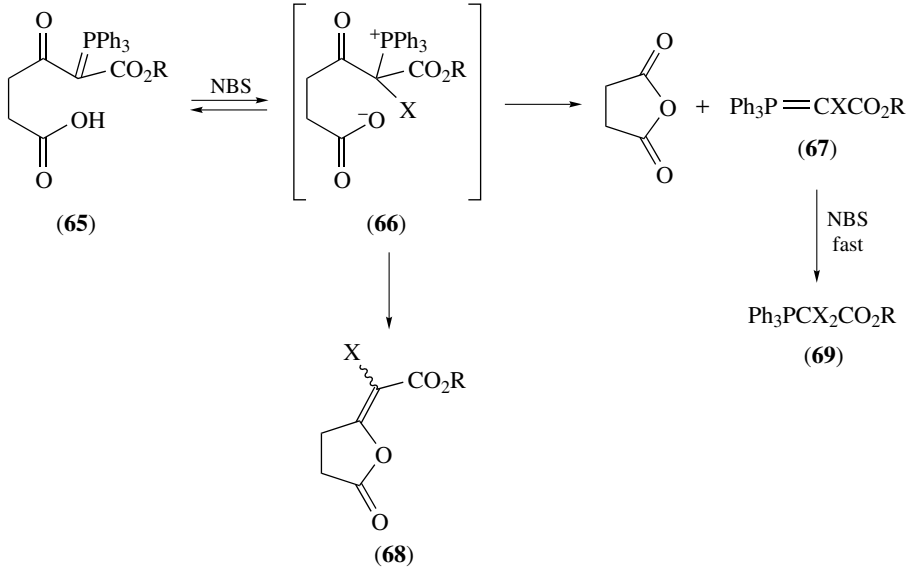
(**55**) (**56**) (**58**) (**57**)

Methyl 4-(3′, 4′-dimethoxyphenyl)-5-tosyloxyhexanoate (**55**) was transformed by heating in acetonitrile solvent at 70 °C into a mixture (2.6:1) of a γ- (**57**) and a δ-lactone (**58**). It is proposed that the products are formed via an intermediate phenonium ion (**56**).[31]

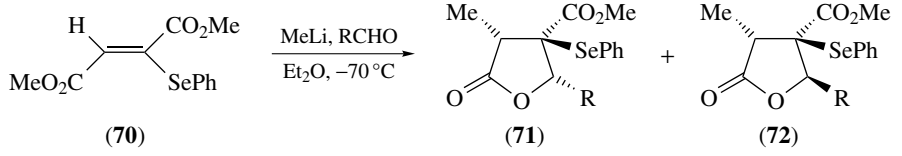


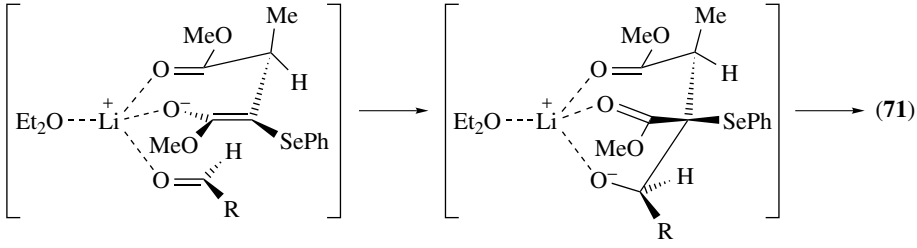
Attempted iodocyclization with iodine in moist acetonitrile of ethyl 2-hydroxypent-4-enoate (**59**) to give the iodotetrahydrofuran (**62**) gave instead a 2:1 mixture (80%) of *syn*- and *anti*-γ-lactones (**60**) and (**61**). Labelling studies with $H_2{}^{18}O$ indicated that the probable mechanism of the reaction involved initial attack of the ester group upon the iodonium ion (**63**) to yield a mixture of epimeric carbocations (**64**), which upon attack by water would yield the orthoesters (**65**), elimination of ethanol from which giving the epimeric γ-lactones (**60, 61**).[32]

The ketophosphorane (**65**; R = Me), the product of reaction between succinic anhydride and carbomethoxymethylenetriphenylphosphorane, undergoes reaction with *N*-bromosuccinimide (NBS) to yield the bromo enol lactone (**68**; X = Br, R = Me) as a 67:33 mixture of *E* and *Z* isomers. The *t*-butyl ester (**65**; R = Bu^t) gave 100% of the corresponding *E* isomer (**68**; X = Br, R = Bu^t).[33] The corresponding



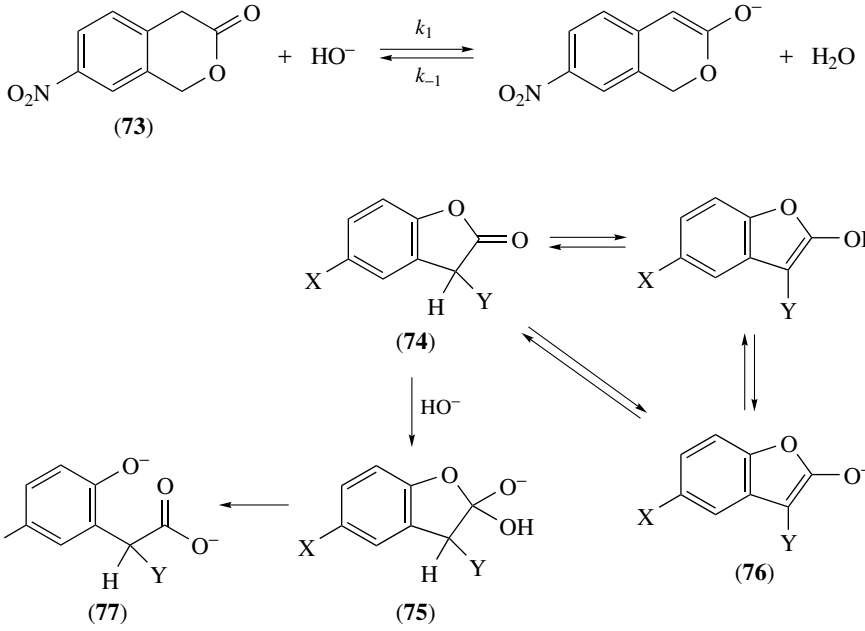
chloro and fluoro enol lactones were preparable using *N*-chlorosuccinimide or *N*-fluorodiphenylsulfonamide, respectively, in place of NBS. Other anhydrides such as glutaric, maleic, phthalic and phenylmaleic anhydrides were also used to prepare the analogous halo enol lactones.[33] The general mechanism of the reaction, illustrated by the ketophosphorane from succinic anhydride (**65**), involves attack by NBS to yield a tetrahedral bromo intermediate (**66**; X = Br) which can either break down to the anhydride and the bromo ylide [which is rapidly brominated by NBS to the dibromo ylide (**69**)], or progress to the bromo enol lactone (**68**; X = Br) via elimination of Ph_3PO.[33]





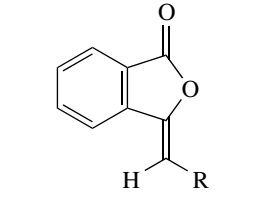
SCHEME 5

Aldehydes react with dimethyl 2-phenylselenofumarate (**70**) at −70 °C in diethyl ether in the presence of MeLi to give good yields of highly substituted 4-phenylselenobutano-γ-lactones (**71**) and (**72**). High diastereoselectivity [for benzaldehyde, (**71**):(**72**)−89:11] was rationalized by assuming the formation of a chelated intermediate between MeLi and (**70**), with approach of the aldehyde from the favoured *si*-face (Scheme 5).[34]

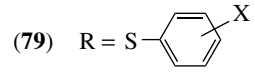


In solutions of sufficient basicity ([NaOH] $\gtrsim$ 0.1 mM) 7-nitroisochroman-3-one (**73**) undergoes reversible deprotonation to form the corresponding enolate. Although ester hydrolysis accompanies enolization, observable quantities of the enolate persist for several seconds. Rate constants for deprotonation by hydroxide ion [$k_1 = 1.31(\pm 0.06) \times 10^4\,\mathrm{l\,mol^{-1}s^{-1}}$], protonation of the enolate by water ($k_{-1} = 212 \pm 24\mathrm{s^{-1}}$), and lactone hydrolysis ($k_{OH} = 19.0 \pm 0.3\,\mathrm{l\,mol^{-1}\,s^{-1}}$) have been determined by monitoring the rates of formation and disappearance of the enolate. The kinetic data were used to calculate the acid dissociation constant for (**73**) (pK_a11.98).[35] Studies of the alkaline hydrolysis of the aromatic lactones coumaran-2-one (**74**; X,Y = H) and some 5-X-substituted 3-phenylcoumaran-2-ones (**74**; Y = Ph) have shown that at high pH the first step is the reversible formation of an enolate ion (**76**), but hydrolysis probably occurs via rate-limiting hydroxide addition to the carbonyl group of the parent compound (**74**) to yield a tetrahedral intermediate (**75**), which breaks down to the dianionic product (**77**).[36] Studies of the base-catalysed hydrolysis in 70% (v/v) aqueous dioxane at 30 °C of substituted 3-phenoxy- and 3-thiophenoxy-methylenephthalides (**78**) and (**79**) have been reported.[37] The rate-determining step in

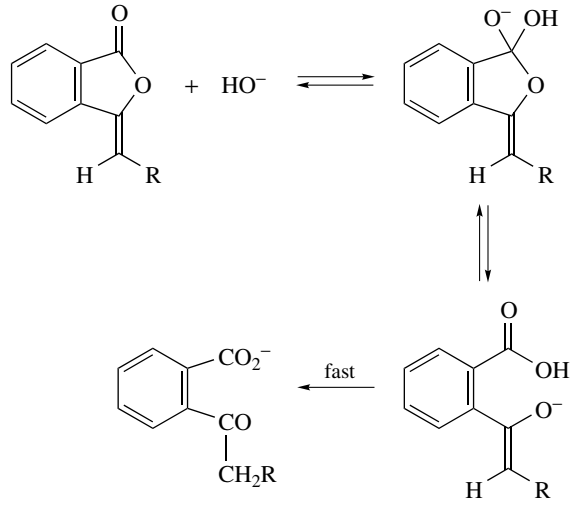
the reaction is considered to be the addition of hydroxide ion to the lactone carbonyl group, as shown in Scheme 6. An excellent correlation was found between the rates of alkaline hydrolysis, the carbonyl stretching frequencies measured in $CHCl_3$ or CCl_4 and Hammett σ constants.[37]



(**78**) R = O–C$_6$H$_4$–X



(**79**) R = S–C$_6$H$_4$–X

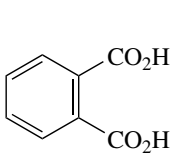


SCHEME 6

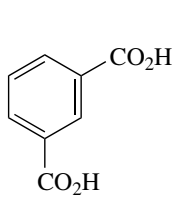
(c) *Acids and anhydrides*

Studies of the thermal degradation of several aromatic acids have been reported. Phthalic acid (**80**), but not isophthalic acid (**81**) or terephthalic acid (**82**), decomposes via dehydration to its anhydride at 140–160 °C. However, (**81**) and (**82**) and benzoic acid are thermally stable below 200 °C.[38] Dissociation constants of all 19 isomers of methyl-substituted benzoic acids (**83**) have been measured in methanol and DMSO. From the pK_a values, the substituent effects of the methyl groups were calculated and tentatively divided into polar and steric effects. Also, in the case

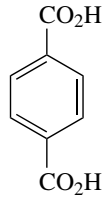
of polymethyl derivatives, the buttressing effect was calculated with reference to monomethyl derivatives. The steric effects may be classified as steric hindrance to resonance—observed only in derivatives with two *o*-methyl groups, and electrostatic induction in the deprotonated molecules—observed in all derivatives. Both effects make the acids stronger and both are attenuated in solution, in methanol more than in DMSO.[39]



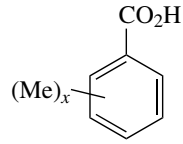
(**80**)



(**81**)

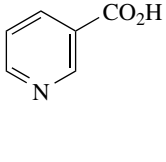


(**82**)

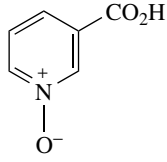


(**83**) $x = 1–5$

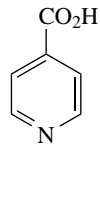
Kinetics of the reaction of diazodiphenylmethane (**92**) in a wide range of alcohols with pyridine and pyridine-*N*-oxide 3- and 4-carboxylic acids (**84**)–(**87**), 4-substituted benzoic acids (**88**),[40] *cis*-4-substituted cinnamic acids (**89**),[41] 2-(4-phenyl-substituted)cyclohex-1-enyl carboxylic acids (**90**), and 4′-substituted-biphenyl-2-carboxylic acids (**91**)[42] have been reported. Comparison of the new results for 4-substituted benzoic acids with the published results of data for 3-substituted benzoic acids was made,[40] and it was concluded that the most important solvent property influencing the rate of reaction appears to be the polarity of the alkyl group expressed as Taft's polar constant σ^*. Transmission coefficients in the cinnamic acids (**89**) were compared with those in the bicyclic acids (**90**) and (**91**).[41,42]



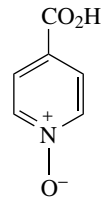
(**84**)



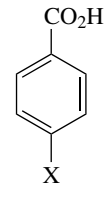
(**85**)



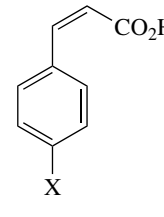
(**86**)



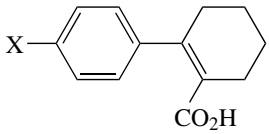
(**87**)



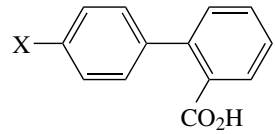
(**88**)



(**89**)



(**90**)

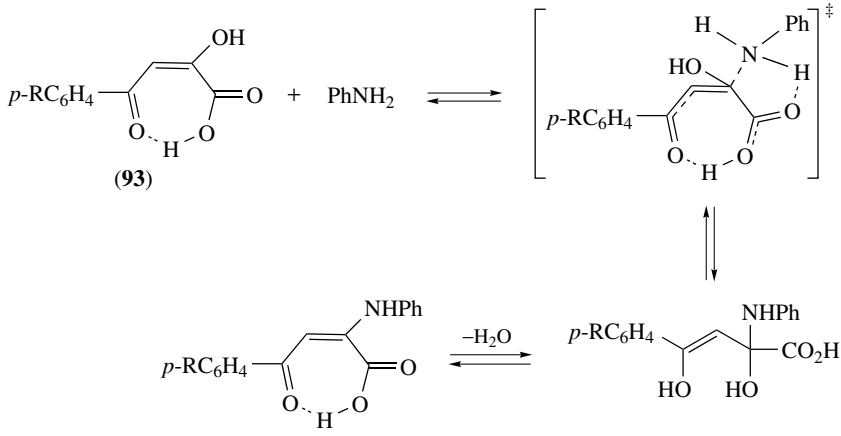


(**91**)

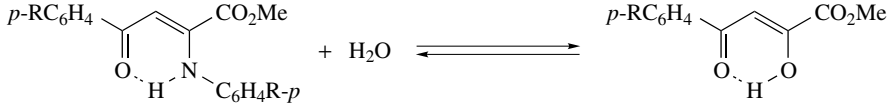
Ph_2CN_2

(**92**)

In the reactions of 4-substituted-benzoylpyruvic acids (**93**) with arylamines in toluene, intramolecular catalysis by the carboxyl group is observed (Scheme 7).[43] By extending these studies in a range of solvents using aniline only,[44] it was observed that the efficiency of intramolecular catalysis by the carboxyl group in these reactions increases with a decrease in the polarity of non-specific solvating solvents; for example, no catalysis is observed with dioxane as solvent.[44] A study of the reverse reaction by the same group[45] has shown that it proceeds via general acid catalysis (Scheme 8).

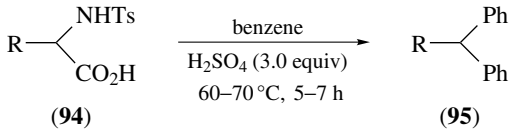


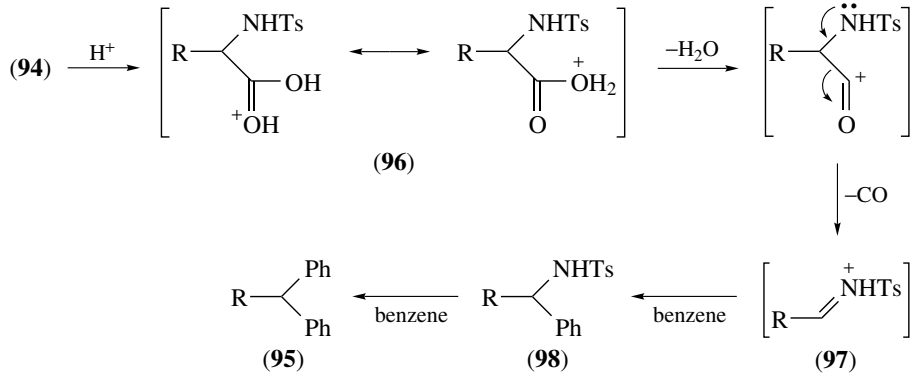
SCHEME 7



SCHEME 8

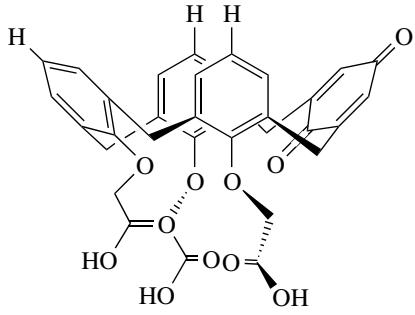
The reaction of various *N*-tosylated α-amino acids (**94**) with benzene in concentrated sulfuric acid yielded diphenyl derivatives (**95**).[46] The mechanism proposed for the reaction (Scheme 9) involves initial protonation of the carboxyl group to give (**96**), which suffers decarbonylation to the *N*-tosyliminium salt (**97**). This reactive electrophile (**97**) interacts with benzene to give a monophenyl compound (**98**) which, via a Friedel–Crafts reaction, interacts with another molecule of benzene to yield the diphenyl compound (**95**).[46] Toluene and *p*-xylene reacted analogously[46] to yield diarylated products.





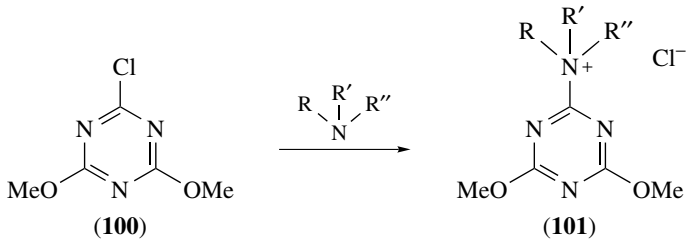
SCHEME 9

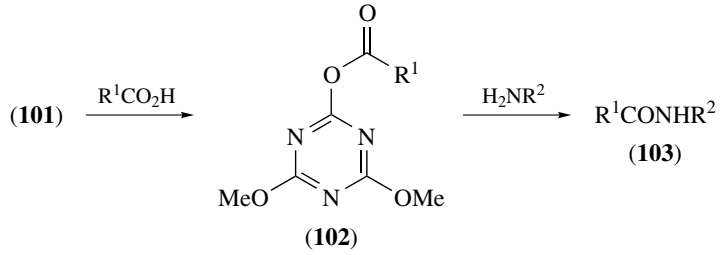
A new water-soluble calix[4]arene-triacid-monoquinone (**99**) has been synthesized and its ion-binding properties in aqueous solution were investigated by means of voltammetry and UV–visible spectrophotometry. The electrochemical behaviour of (**99**) is dependent on the concentration of Ca^{2+} ion rather than that of other alkaline earth metal ions or alkali metal cations. The selective response towards Ca^{2+} was achieved even in the presence of a large excess (>1000-fold) of interfering Na^{+} ion.[47]

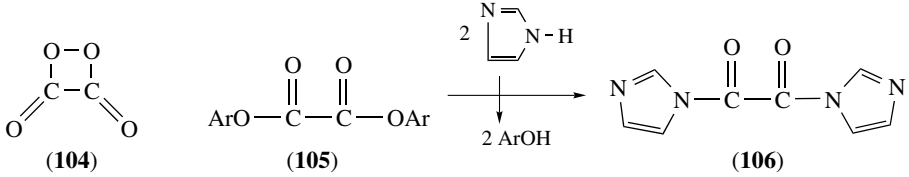


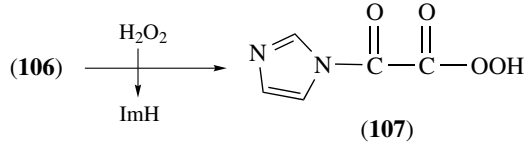
(**99**)

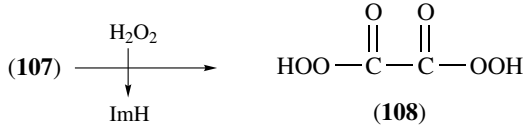
2-Chloro-4,6-dimethoxy-1,3,5-triazine (**100**) reacts with *N*-methylmorpholine at 20 °C to yield an isolable quaternary triazinylammonium salt (**101**; R = Me, R′, R″ = C_4H_8O). This salt can then be reacted with a carboxylic acid to yield a 2-acyloxy-4,6-dimethoxy-1,3,5-triazine (**102**), which, in turn, can be reacted with an amine to yield an amide (**103**).[48] This sequence of reactions provides an explanation for the 'activation' (formation of reactive ester) of the carboxylic acid function by 2-chloro-4,6-disubstituted-1,3,5-triazines (**100**) in the presence of hindered amines. Several other hindered amines may replace *N*-methylmorpholine in the process, but unhindered amines such as triethylamine and tributylamine were inactive.[48]

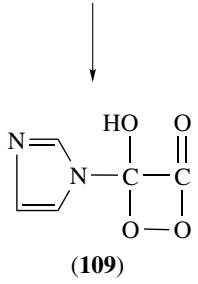

Cl
N
N
MeO
N
OMe
R
R′
R″
N
Cl⁻
N+
(100)
(101)


(101)
R¹CO₂H
O
O
R¹
N
N
MeO
N
OMe
H₂NR²
R¹CONHR²
(102)
(103)


O
O
C
C
O
O
(104)
ArO
O
C
C
O
OAr
(105)
2
N
N-H
2 ArOH
N
N
C
C
N
N
(106)


(106)
H₂O₂
ImH
N
N
O
O
C
C
OOH
(107)

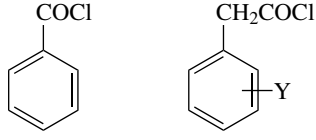

(107)
H₂O₂
ImH
HOO
O
O
C
C
OOH
(108)


N
N
HO
O
C
C
O
O
(109)

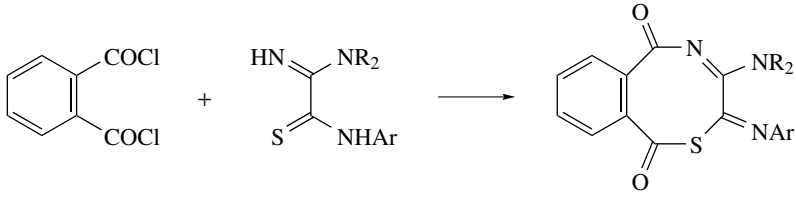
A stopped-flow kinetic investigation[49] of the imidazole-catalysed peroxyoxalate chemiluminescence reaction has led to the proposal that a dioxetanone (**109**) may be responsible for the chemiluminescence, rather than 1,2-dioxetanedione (**104**) which had been suggested previously. The reaction studied, that between bis (2,4,6-trichlorophenyl) oxalate (**105**) and hydrogen peroxide catalysed by imidazole, involves initial formation of 1,1′-oxalyldiimidazole (**106**); (**106**) then reacts with H_2O_2 to yield the monoperoxy acid (**107**), which can progress either to the diperoxy acid (**108**) or to imidazoylhydroxydioxetanone (**109**).[49]

(d) *Acid halides*

A kinetic study of the acylation of ethylenediamine with benzoyl chloride (**110**) in water–dioxane mixtures at pH 5–7 showed that the reaction involves mainly benzoylation of the monoprotonated form of ethylenediamine.[50] Stopped-flow FT-IR spectroscopy has been used to study the amine-catalysed reactions of benzoyl chloride (**110**) with either butanol or phenol in dichloromethane at 0 °C. A large isotope effect was observed for butanol versus butanol-*O*-*d*, which is consistent with a general-base-catalysed mechanism. An overall reaction order of three and a negligible isotope effect for phenol versus phenol-d_6 were observed and are consistent with either a base- or nucleophilic-catalysed mechanism.[51] Mechanistic studies of the aminolysis of substituted phenylacetyl chlorides (**111**) in acetonitrile at −15 °C have revealed that reactions with anilines point to an associative S_N2 pathway.[52]

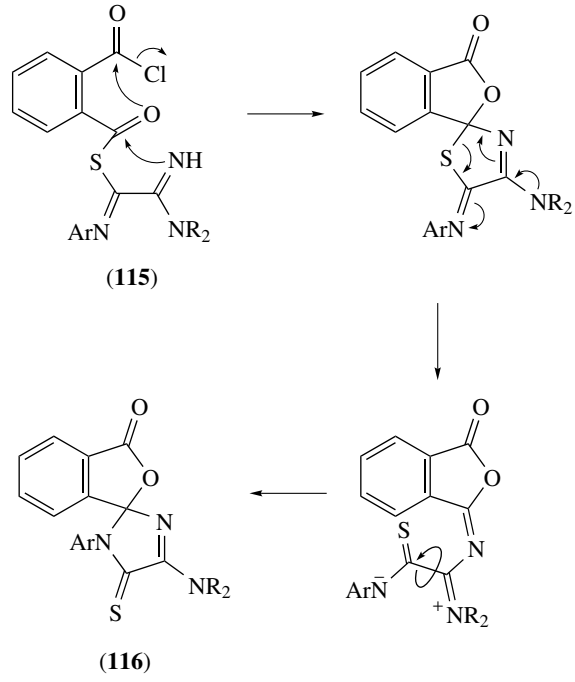


(**110**) (**111**)



(**112**) (**113**) (**114**)

The proposed formation of 2,5-benzothiazocine-1,6-diones (**114**; R = Pr) from the reaction of phthaloyl chloride (**112**) and amidino thioamides (**113**; R = Pr, Ar = 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$) in pyridine has been disproved. Instead, supported by an X-ray structure, the products have been shown to be spiro[4,4]lactones (**116**; R = Pr, Ar = 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$). The proposed mechanism of formation of

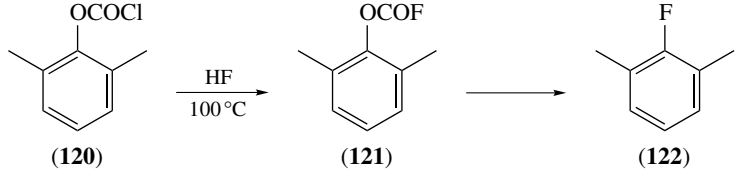


(**115**)

(**116**)

SCHEME 10

(**117**) (**118**) (**119**)

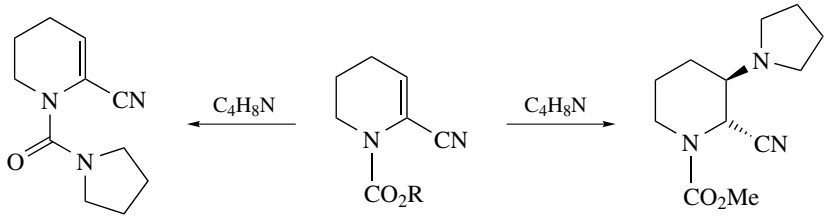


(**120**) (**121**) (**122**)

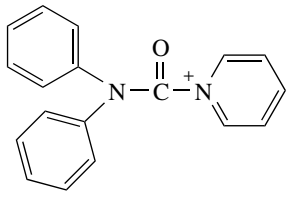
(**116**) involves initial intramolecular attack of the amidine group in a monosubstituted intermediate (**115**), as shown in Scheme 10.[53]

The extended (two-term) Grunwald–Winstein equation has been applied to the solvolyses of ethyl chloroformate (**117**) and ethyl chlorothioformate (**118**). For each substrate, there is evidence for two competing reaction channels.[54] Solvolysis

studies of substituted phenyl chloroformates (**119**) at various temperatures and pressures have revealed that reaction proceeds either via an addition–elimination reaction or via a synchronous S_N2-type process.[55] Kinetic studies of the solvolyses of 4-substituted phenyl chloroformates (**119**) in ethanol- and methanol–water mixtures have been reported.[56–58] The kinetic solvent isotope effects determined in D_2O, CH_3OD, and 50% D_2O–CH_3OD for the 4-MeO[57] and the 4-O_2N[58] compounds are consistent with a general-base-catalysed addition–elimination pathway. Treatment of 2,6-dimethylphenyl chloroformate (**120**) with anhydrous HF at 100 °C yields the corresponding fluoroformate (**121**), which upon heating at 200 °C decarboxylates to 2,6-dimethylfluorobenzene (**122**).[59]



(**123**) (**124**) (**125**)



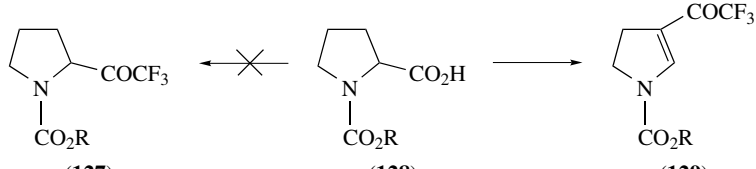
(**126**)

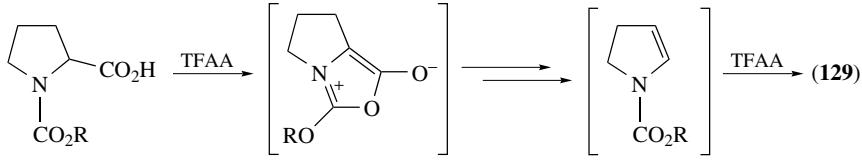
(e) *Ureas, carbamates, hydroxylamine, and derivatives*

A bicyclic urea (**123**) was an unexpected product of the reaction between pyrrolidine and the phenyl ester of 2-cyano-1,4,5,6-tetrahydro-1-pyridinecarboxylic acid (**124**; R = Ph); the corresponding methyl ester (**124**; R = Me) reacted, as expected, to give the product of Michael addition (**125**).[60] The better leaving ability of phenoxide vs methoxide presumably tilted the reaction towards the substitution rather than the addition product, although thiols (e.g. PhSH) underwent only the addition reaction.

Solvolyses of the *N,N*-diphenylcarbamoylpyridinium ion (**126**) were found to be subject to specific and/or general base catalysis, which could be eliminated by addition of perchloric acid or increased, especially in fluoroalcohol-containing solvents, by addition of pyridine. The uncatalysed solvolyses in aqueous methanol and aqueous ethanol involve a weakly nucleophilically assisted ($l = 0.22$) heterolysis and the solvolyses in the pure alcohols are anomalously slow.[61]

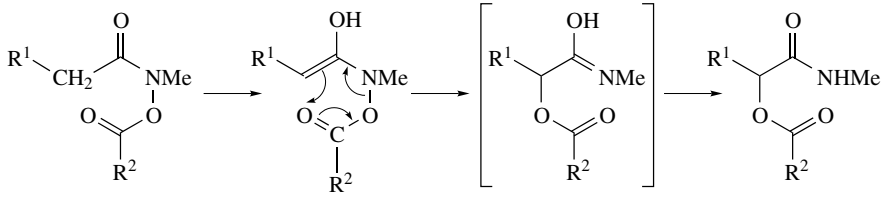
Under Dakin–West reaction conditions (trifluoroacetic anhydride–MeCN/80 °C/5 h), *N*-methoxycarbonylproline (**128**; R = Me) yielded *N*-methoxycarbonyl-4-trifluoroacetyl-2,3-dihydropyrrole (**129**; R = Me) and none of the expected Dakin–West product, the trifluoromethyl ketone (**127**).[62] A possible mechanism proposed by the authors[62] involves initial formation of a mesoionic 1,3-oxazolium-5-olate (**130**; R = Me), but the pathway to the *N*-methoxycarbonyl-2,3-dihydropyrrole (**131**; R = Me) and thence the final product (**129**; R = Me) was unexplained.[62]





An appraisal has been made of the available kinetic data on the acid hydrolyses of hydroxyamic acids. For *N*-substituted hydroxamic acids both *A*-2 and *A*-1 paths are recognized, but for primary hydroxamic acids there is evidence only for the *A*-2 pathway.[63]

The *O*-benzoyl derivative of *N*-methylphenylacetohydroxamic acid (**132**; R^1, R^2 = Ph) upon treatment with Et_3N in toluene at 110 °C for 1 h rearranged to *N*-methyl-2-benzoyloxyphenylacetamide (**134**; R^1, R^2 = Ph).[64] Most variations of R^1 (2-napththyl, PhCH=CH_2, PhCMe=CH_2, PhCBu=CH_2) or R^2 (Me, Bu^t, 4-$O_2NC_6H_4$) also gave the analogous products, the fastest reaction occurring with the 4-nitrobenzoyl compound (**132**; R^1 = PhCH=CH_2, R^2 = 4-$O_2NC_6H_4$). The mechanism proposed for the reaction was a novel [3,3]-sigmatropic rearrangement of the enol form of the *N*-methyl-*O*-acylhydroxamic acids (**133**) (Scheme 11).[64]

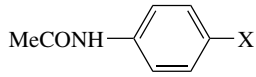


SCHEME 11

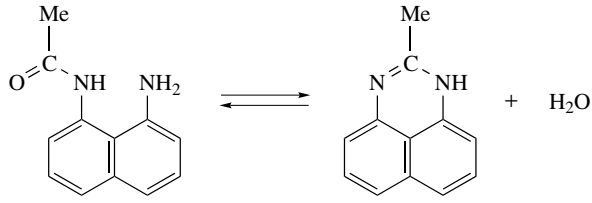
(f) *Amides and anilides*

The neutral and acid-catalysed mechanisms of hydrolysis of formamide, $HCONH_2$, have been revisited and a comparison made between *ab initio*, semiempirical and DFT results.[65] *Ab initio* MO calculations on the alkaline hydrolysis of *para*-substituted acetanilides (**135**) in the gas phase have shown that the activation energy depends on the nature of electron-withdrawing groups (e.g. $X = NO_2$, CN, Cl) but is invariant for electron-donating groups ($X = NH_2$, OMe).[66]

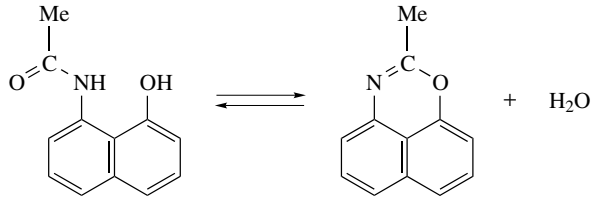
Theoretical calculations of minimum energy structures and thermodynamic terms using SCF theory with thermodynamic and solvation corrections have been made of the cyclization of 1-amino-8-(acetylamino)naphthalene (**136**) to give 2-methylperimidine



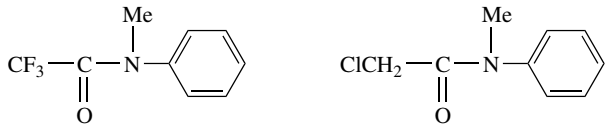
(**135**)



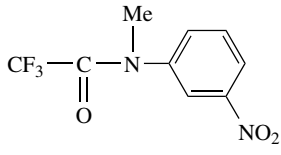
(**136**) (**137**)



(**138**) (**139**)



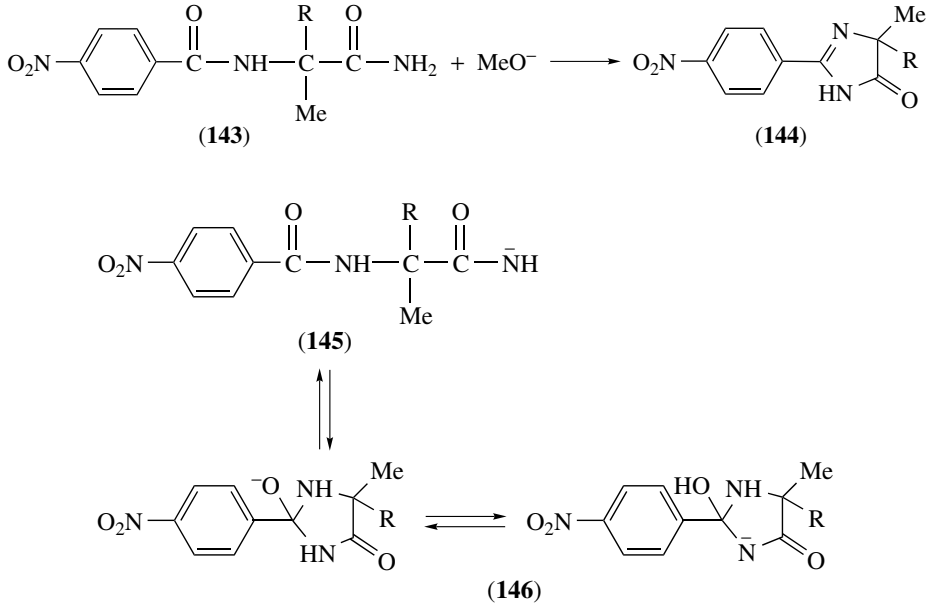
(**140**) (**141**)



(**142**)

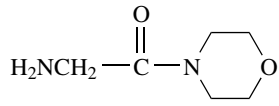
(**137**) with the liberation of water and of the related reaction of 1-hydroxy-8-(acetylamino)naphthalene (**138**) to 2-methylnaphtho[1,8-*b,e*][1,3]oxazine (**139**). The calculations predict that in the gas phase the former reaction is strongly thermodynamically favourable whereas the latter is much less favourable. The results are in qualitative agreement with experimental observations for the reaction in solution.[67]

Alkaline earth (Ba, Sr) metal ethoxides have been found to be more reactive than free ethoxide in the ethanolysis of simple activated amides such as *N*-methyl-2,2,2-trifluoroacetanilide (**140**), *N*-methyl-1-chloroacetanilide (**141**) and *m*-nitro-*N*-methyl-2,2,2-trifluoroacetanilide (**142**); enhanced catalysis was observed upon addition of equimolar amounts of 18-crown-6.[68]

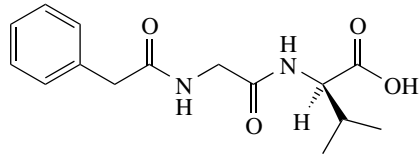


2-(4-Nitrobenzoylamino)-2,2-dimethylpropanamide (**143**; R = Me) reacts in methanol–DMSO solution with sodium methoxide to yield 5,5-dimethyl-2-(4-nitrophenyl)imidazol-4(5*H*)-one (**144**; R = Me).[69] The 4-methoxyphenyl derivative and the parent phenyl derivative react similarly, as do compounds in which variation of the 2-substitutent (R = Pr^i, Ph, 4-$O_2NC_6H_4$) was made. The mechanism of the cyclization probably involves initial formation of the anion of the alkanamide (**145**), which adds to the carbonyl group of the benzamido moiety to yield the tetrahedral oxyanion (**146**); proton transfer and dehydration then yield the heterocycle (**144**).[69]

The kinetics of hydrolysis in water at 70 °C and pH 2–11 of *N*-glycidylmorpholine (**147**) have been reported.[70]

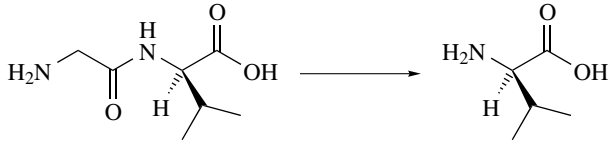


(**147**)



N-(phenylacetyl)glycyl-D-valine

(**148**)



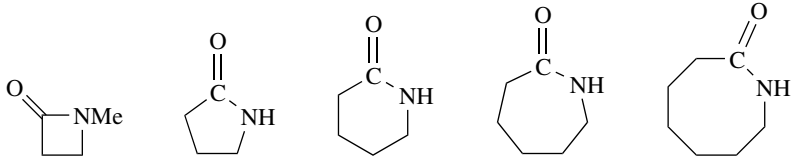
glycyl-D-valine D-valine

SCHEME 12

Except at extremes of pH and high temperature, peptide bond hydrolysis is a slow process that is difficult to quantify accurately. Using a new, highly fluorescent derivative of amines to quantify by HPLC the amine products of hydrolysis of *N*-(phenylacetyl)glycyl-D-valine (**148**), an acylic analogue of penicillin G, its pH–rate profile over the range pH 0–14 has been constructed.[71] Both hydrolysis products, glycyl-D-valine and D-valine (Scheme 12), are formed at all pHs, and it is shown that the rate constants (k_1, k_3) are very similar. At pH 7, where k_{H_2O} is dominant, the half-life of the glycyl-D-valine bond was found to be ca 265 years.[71]

(g) *Lactams*

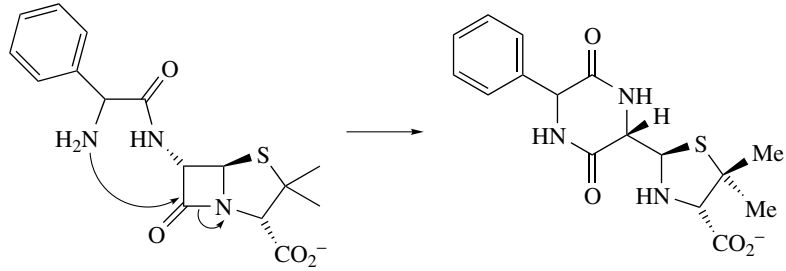
An *ab initio* study of the acid hydrolysis of β-lactams has yielded a value of 14.23 kcal mol^{-1} for the energy barrier for the opening of the ring.[72] Two theoretical studies of *N*-methyl-2-azetidinone (**149**) have been reported. In the first, semiempirical calculations



(**149**) (**150**) (**151**) (**152**) (**153**)

(PM3) were used to investigate solvent effects on the alkaline hydrolysis of (**149**)[73] and in the second, the effect of an ancillary water molecule on the neutral and alkaline hydrolysis mechanisms of *N*-methylazetidinone (**149**) was studied at the Hartree–Fock and MP2 levels using the 6–31G* and 6–31 + G* basis sets.[74]

Reaction rate constants obtained in moderately concentrated sulfuric acid for the hydrolysis of simple lactams of ring sizes five, six, seven and eight (**150**)–(**153**) as a function of acidity and temperature have been analysed using the excess acidity kinetic method.[75]



(**154**) (**155**)

$CH_3CH_2CH_2CN$

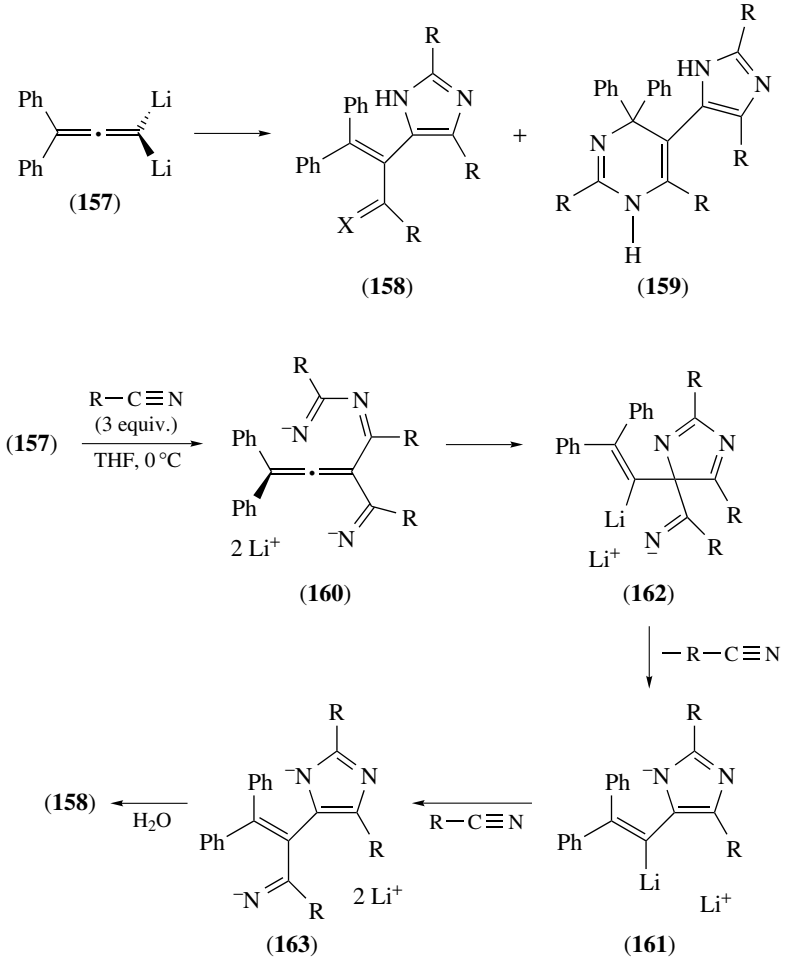
(**156**)

Kinetic studies of the 'unnatural' 6-α-epimer of ampicillin, 6-*epi*-ampicillin (**154**), have revealed an intramolecular process not undergone by ampicillin (or other 'natural' β-substituted penicillins).[76] At pH 6–9, intramolecular attack of the β-lactam carbonyl group by the side-chain amino group of (**154**) yields a stable piperazine-2,5-dione derivative (**155**). Theoretical calculations show that the intramolecular aminolysis of 6-*epi*-ampicillin nucleophilic attack occurs from the α-face of the β-lactam ring with an activation energy of 14.4 kcal mol^{-1}.[76] In other respects, the hydrolysis of the 6-α-epimer is unexceptional.

(h) *Non-heterocyclic nitrogen centres*

The effect of high pressure (128–2600 bar) and high temperature (330 °C) on the hydrolysis of butyronitrile (**156**) has been reported.[77]

A domino reaction of 1,1-diphenyl-3,3-dilithioallene (**157**) with benzonitrile yields both a yellow imidazole (**158**; R = Ph X = NH) (12%) and a colourless 5-imidazol-5-yl-1,4-dihydropyrimidine (**159**; R = Ph) (51%), the products, respectively, of the incorporation of three and four nitrile molecules.[78] The proposed mechanism (Scheme 13) involves initial formation of an intermediate (**160**) that is the product of the interaction of three molecules of benzonitrile with 1,1-diphenyl-3,3-dilithioallene (**157**), which cyclizes to (**162**; R = Ph) and then eliminates a molecule of benzonitrile to produce (**161**; R = Ph). Re-addition of benzonitrile at a different locus produces

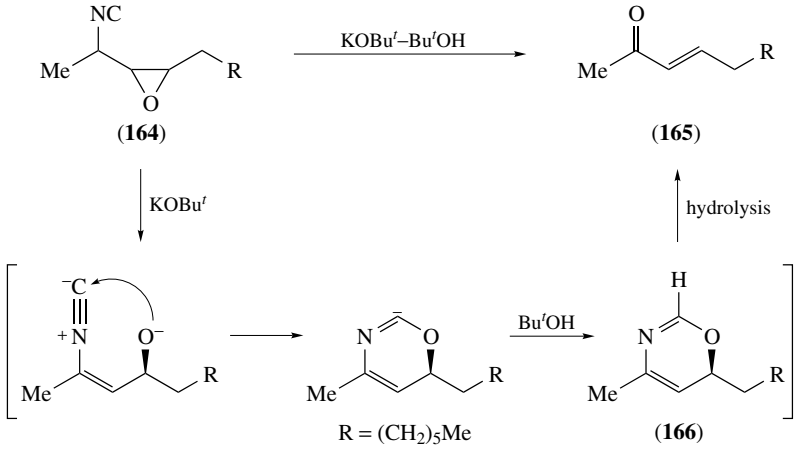


SCHEME 13

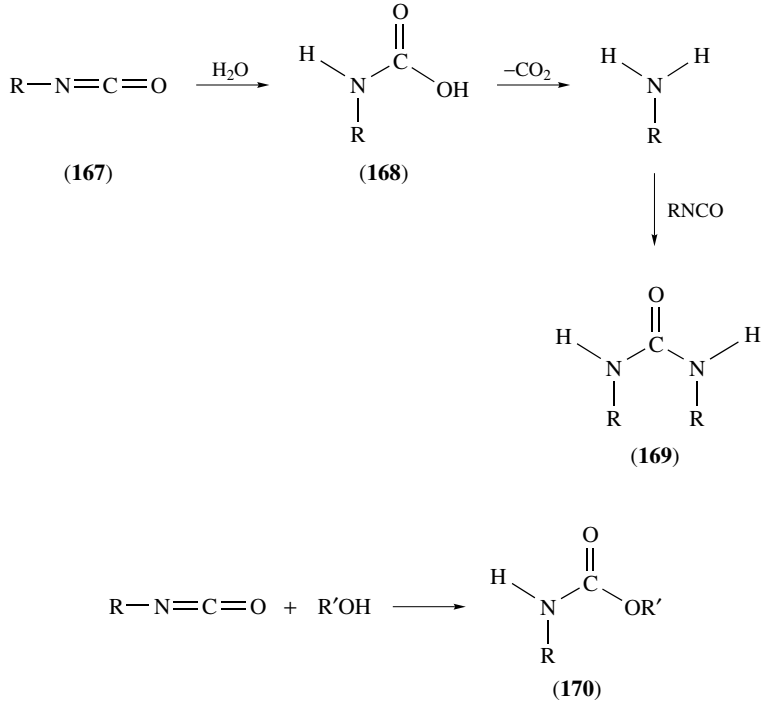
(**163**; R = Ph), which either can suffer protonation to give the imidazole (**158**; R = Ph) or can react with a further molecule of benzonitrile to yield, after several steps, the imidazoyl-1,4-dihydropyrimidine (**159**; R = Ph).[78]

The epoxyisonitrile [**164**; R = $(CH_2)_6Me$] upon treatment with Bu^tOK in Bu^tOH yielded the α, β-unsaturated ketone [**165**; R = $(CH_2)_6Me$], the mechanism of formation of which (Scheme 14) plausibly involving the intermediacy of the 5,6-dihydro-4*H*-1,3-oxazine [**166**; R = $(CH_2)_6Me$].[79]

A theoretical study of the reaction of water and methanol with HNCO has led to a prediction of a four-centred transition state for both reactions.[80] The interactions of water[81] and of alcohols[82] with alkyl isocyanates have been the subject of both experimental and theoretical study. In the case of hydration, evidence for initial interaction of water and water clusters (n = 1–3) across the N=C bond of the alkyl isocyanate



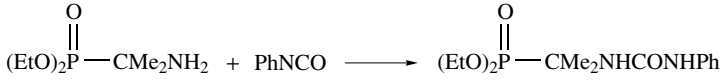
SCHEME 14



rather than the C=O bond was adduced by *ab initio* methods, both in the gas phase and in aqueous solution. The C=O bond of the alkyl isocyanate thus remains intact in the first-formed intermediate, the carbamic acid (**168**), but this rapidly breaks down to CO_2 and an amine, which reacts with a further molecule of isocyanate to give the 1,3-disubstituted urea (**169**).[81] By contrast, alcohol addition to an alkyl isocyanate yields a

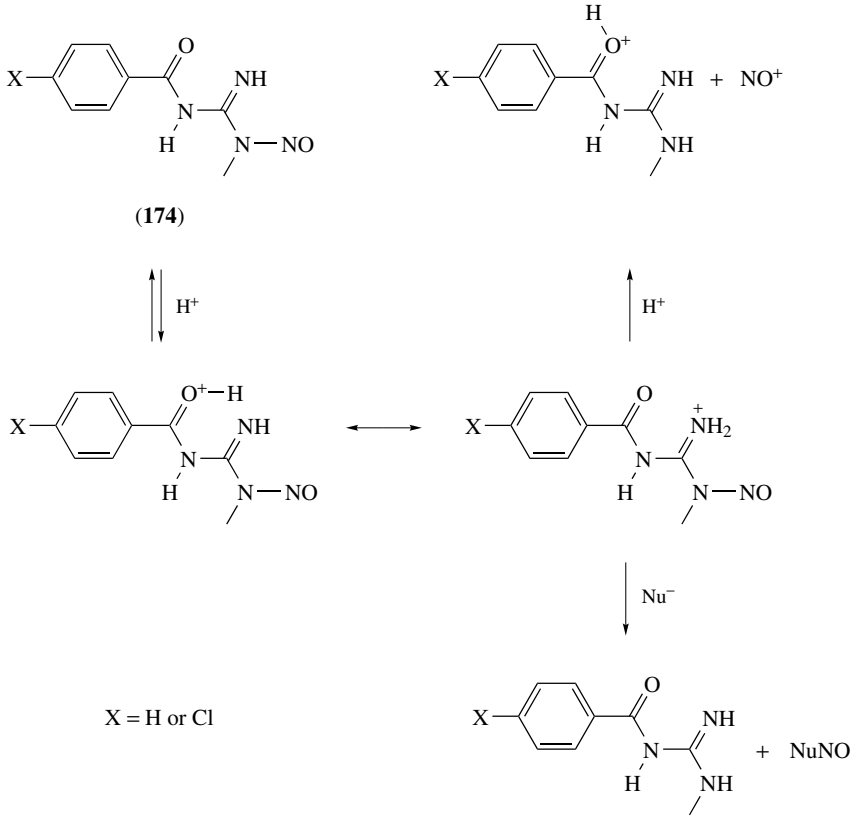
stable carbamate (**170**). The experimental study of this reaction, which was undertaken employing propan-2-ol and cyclohexanol in low and high concentrations, suggested that either two or three molecules of alcohol are involved in the initial interaction with the isocyanate; like the hydration reaction, the addition of alcohol occurs in a concerted way across the N=C bond of the isocyanate, rather than the C=O bond.[82]

A study of the kinetics of the reaction between *O,O*-diethyl 1-amino-1-methylethanephosphonate (**171**) and phenyl isocyanate (**172**) has been reported. The product of the adduction (**173**) is considered to have an autocatalytic effect on the reaction.[83]

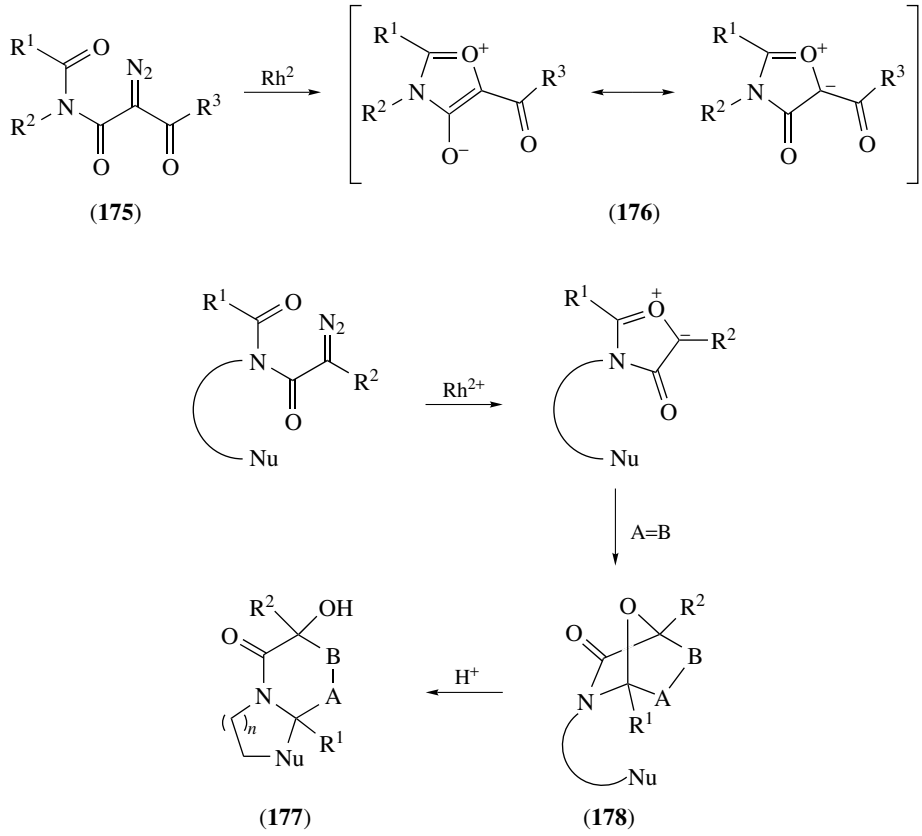


(**171**) (**172**) (**173**)

1-Methyl-1-nitroso-3-benzoylguanidine (**174**; X = H) undergoes denitrosation by two parallel pathways (Scheme 15). One involves a slow nucleophilic attack concerted



SCHEME 15



(**175**) (**176**)

(**177**) (**178**)

SCHEME 16

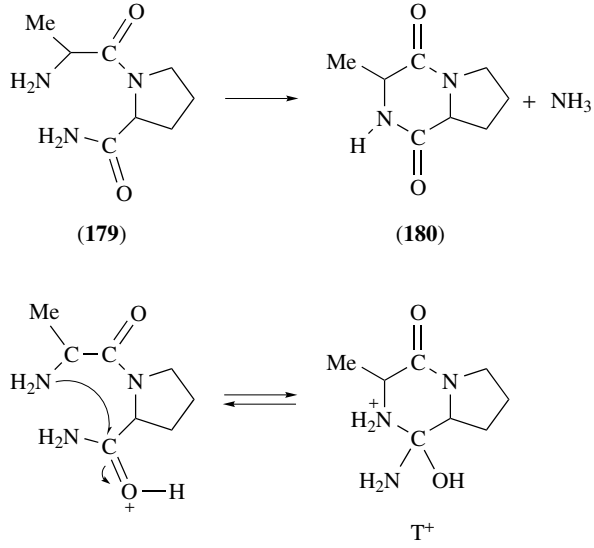
with an intramolecular proton transfer, and the other a slow concerted denitrosation, where a second proton transfer and NO^+ expulsion are simultaneous.[84]

A domino carbenoid cyclization/4 + 2-cycloaddition/cationic π-cyclization protocol as a method for construction of complex nitrogen heterocycles such as lycopine and aspidospermine indole alkaloids has been reviewed.[85] The constructs for this process are diazoimides (**175**), which upon treatment with a rhodium(II) catalyst yield 1,3-oxazolium 4-oxides (isomunchones) (**176**). As cyclic equivalents of carbonyl ylides, the isomunchones (**176**) readily undergo 4 + 2-cycloaddition with electron-rich or electron-deficient dipolarophiles. By incorporating an internal nucleophile on a tether, annulation of the original cycloadduct (**178**) allows for the construction of more complex nitrogen heterocyclic systems, e.g. (**177**); see Scheme 16.[85]

(i) *Other heterocyclic nitrogen centres*

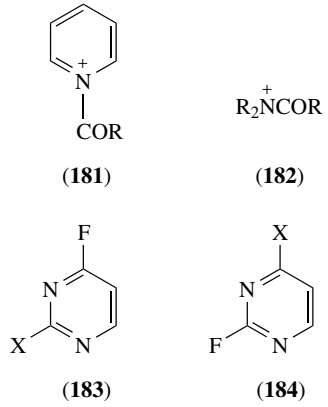
2,5-Dioxopiperazines are products of sometimes unwanted cyclizations of the *N*-terminal residues of di- and oligo-peptides and proteins. As a model for this process,

in which the nitrogen atom of the *N*-terminal deprotonated amino group attacks the C=O group of the second residue, the cyclization of H-Ala-Pro-NH_2 (**179**) to the bicyclic 2,5-dioxopiperazine (**180**) has been studied.[86] At low pH, the protonated amide carbonyl undergoes attack by the free amino group to give T^+ (Scheme 17). At high pH the pH–rate profile levels off, and this is interpreted as a *trans* → *cis* isomerization of the Ala-Pro peptide bond, rendering the cyclization unattainable.[86]



(**179**) (**180**)

SCHEME 17



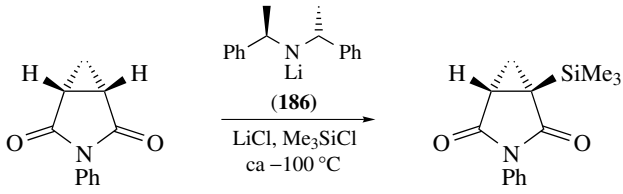
(**181**) (**182**)

(**183**) (**184**)

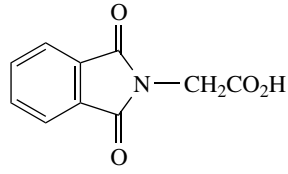
The general chemistry of acylpyridinium salts (**181**) and their role in the nucleophilic catalysis by pyridine of carbonyl substitution reactions have been reviewed and compared with the role of acylammonium salts (**182**).[87]

The rates of alkaline hydrolysis of a series of amino derivatives of 4-fluoro-(**183**; X = NH_2) and 2-fluoro-pyrimidines (**184**; X = NH_2) have been compared, revealing that the former hydrolyse more rapidly.[88] Some difluoro analogues (**184**; X = F) with amino and alkyl substituents were also studied, the 4-fluoro substituent departing the more readily.

The desymmetrization of the *N*-phenylcyclopropylsuccinimide (**185**) has been effected by its reaction at low temperature with a chiral base (**186**) and an *in situ* electrophile, trimethylsilyl chloride. The silylated product (**187**) was obtained in 80% yield and 95% *ee* (Scheme 18).[89]



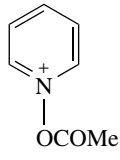
SCHEME 18



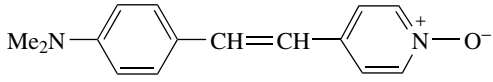
(**188**)

Kinetic evidence has been obtained for ion-pair formation when the effects of inorganic salts on the alkaline hydrolysis of *N*-phthaloylglycine (**188**) were investigated.[90]

Kinetic studies have been reported of acetyl transfer in acetonitrile from *N*-acetyloxypyridinium cations (**189**) to 4-(4′-*N,N*-dimethylaminostyryl)pyridine *N*-oxide (**190**), pyridine *N*-oxide (**191**) and 4-dimethylaminopyridine (**192**).[91] In a follow-up



(**189**)



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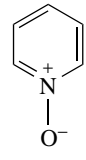
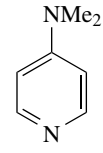


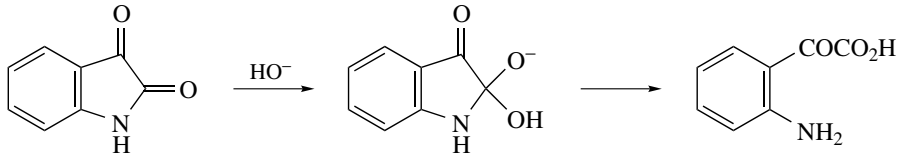
(**191**)



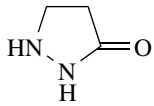
(**192**)

study,[92] methoxycarbonyl transfer to and from similar and analogous reactants have been reported. Generally, it was found that the methoxycarbonyl transfer was a concerted process and reactivity depended on the ionization potential of the nucleophile and the electron affinity of the acylonium salt.[92]

Solvent effects have been investigated in isatin (**193**) hydrolysis.[93] Results from ethanol–water and acetonitrile–water mixtures revealed that for alkaline hydrolysis log k was correlated with the reciprocal of the dielectric constant. A tetrahedral intermediate (**194**) is involved, which breaks down to yield the ring-opened amino acid (**195**).[93] A comparison has been made of the lability of isatin (**193**) towards diethylamine and hydroxide ion, the latter showing the greater effect.[94]



(**193**) (**194**) (**195**)

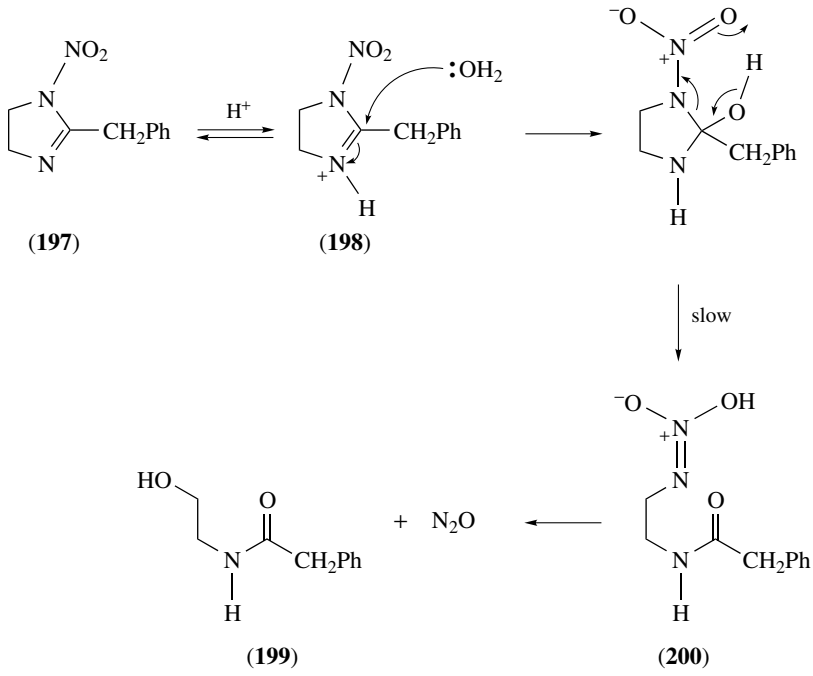


(**196**)

A complete study of the basic hydrolysis of pyrazolidinone (**196**) by *ab initio* calculations at RHF/6–31+G*//RHF/6–31+G* and MP2/6–31+G*//MP2/6–31+G* levels has been carried out. The alkaline hydrolysis has been studied through a $B_{AC}2$ mechanism, characterized by a nucleophilic attack of the hydroxyl group on the carbonyl of the γ-lactam ring, formation of the tetrahedral intermediate, and cleavage of the C(2)–N(3) bond to yield the final reaction product.[95]

Studies of the acid-catalysed kinetics of a simple cyclic N-nitroamidine have been reported.[96] N-Nitrotolazoline (**197**) (i.e. N-nitro-2-benzyl-4,5-dihydro-1H-imidazole), which was formed from the α-adrenergic blocking agent, tolazoline (**197**; H for NO_2) by treatment with N_2O_4, undergoes acid-catalysed hydrolysis to form N-(2-hydroxyethyl)phenylacetamide (**199**). The proposed mechanism involves rapid water attack of a protonated intermediate (**198**) followed by a slow, intramolecular rearrangement involving proton transfer to yield a zwitterion (**200**), which eliminates N_2O to yield the product (**199**) (Scheme 19).[96]

3-(Dimethylamino)propanol (**201**; R = H) is known to be acetylated by N-acetylimidazole (**206**) by a mechanism that involves intramolecular general base

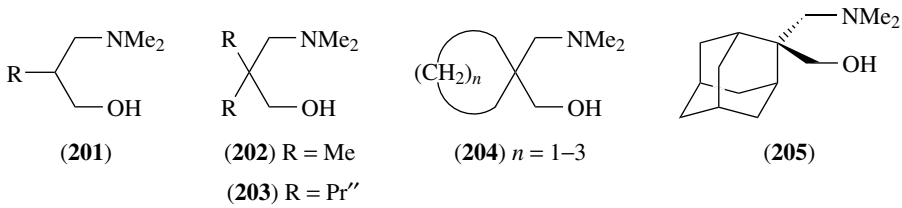


(**197**) (**198**) (**199**) (**200**)

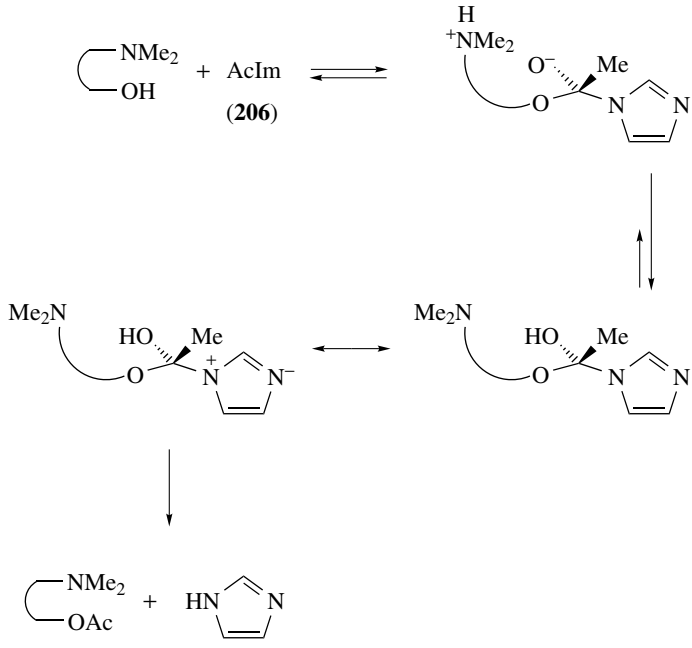
SCHEME 19

catalysis (Scheme 20). Now a study of the rates of acetylation of 2-alkyl (**201**; R = Bu^t) and 2,2-dialkyl analogues (**202**)–(**205**) by *N*-acetylimidazole (**206**) in MeCN have been reported.[97] Only a modest increase in acetylation rate was detected for the series, the highest rate being seen with the adamantyl compound (**205**), where the magnitude of the internal bond angle at the 2-position, $\alpha = 107°$, was the smallest. Effective molarities were estimated to be 13–14 M.[197]

An electron-withdrawing group (EWG) on the nitrogen of a pyrrole of the type (**210**) is thought to suppress the formation of a highly electrophilic azafulvenium species (**208**) in nucleophilic substitution reactions (Scheme 21). In the absence of such deactivation, the analogous pyrroles (**207**) readily react with a nucleophile, via the postulated azafulvene intermediate (**208**) to give products of the type (**209**). If the EWG is an *N*-protected α-aminoacyl group, e.g. (**212**), then it is feasible that *in vivo* esteratic removal of the EWG could lead to a reactive azafulvene (**208**) which would be capable of inactivating the enzyme by alkylation (Scheme 21, where Nu^- is an amino acid in the enzyme's active site). Such a latent reactive inhibitor of serine proteases has been developed in which the EWG is *N*-phthalylleucinyl, i.e. (**212a**).[98] Now studies of the fate of each of the ^{2}H-labelled hydrogens of the methylene group of (**212a**) in which (**212b**) and (**212c**) were base-hydrolysed in the presence of an external nucleophile, (+)-*sec*-butylamine (**215**), have shown that



(**201**) (**202**) R = Me (**203**) R = Pr″ (**204**) *n* = 1–3 (**205**)

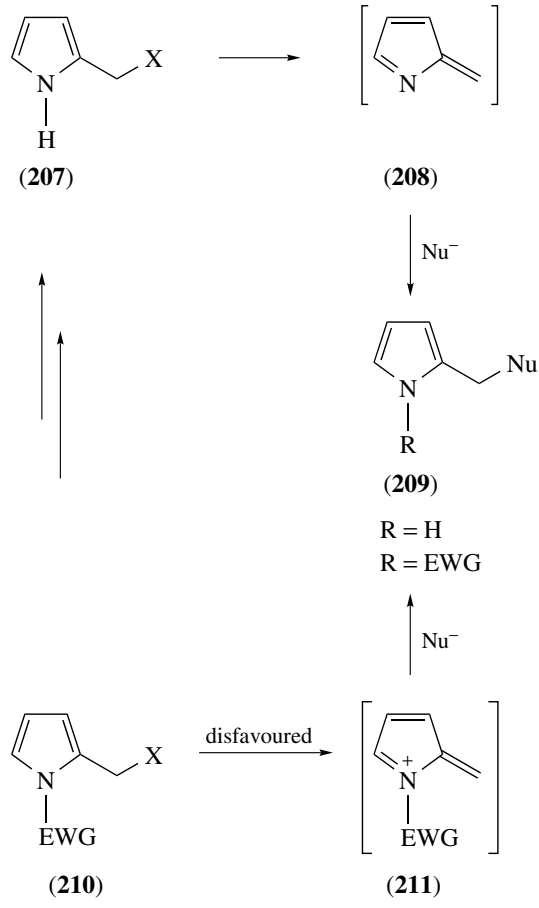


SCHEME 20

the reaction proceeds by an initial intramolecular *N*- to *O*-acyl transfer to yield (**214**) (pathway *a*, Scheme 22), which upon deacylation yields an azafulvene (**213**). Evidence for the intervention of the azafulvene (**213**) was the isolation of the (*S*)- and (*R*)-*sec*-butylamino[^{2}H]methylpyrroles (**216**; R = D) formed by its reaction with (+)-*sec*-butylamine (**215**) (pathway *b*).[98]

Reactions in Aprotic Solvents

Several reactions that have been conducted in aprotic solvents have been dealt with earlier; see references 1, 2, 19, 25, 31, 39, 43, 44, 51, 52, 91, 92 and 97. The following references ahead also deal with reactions in aprotic solvents: 101, 113, 139, 165–167, and 179–181.



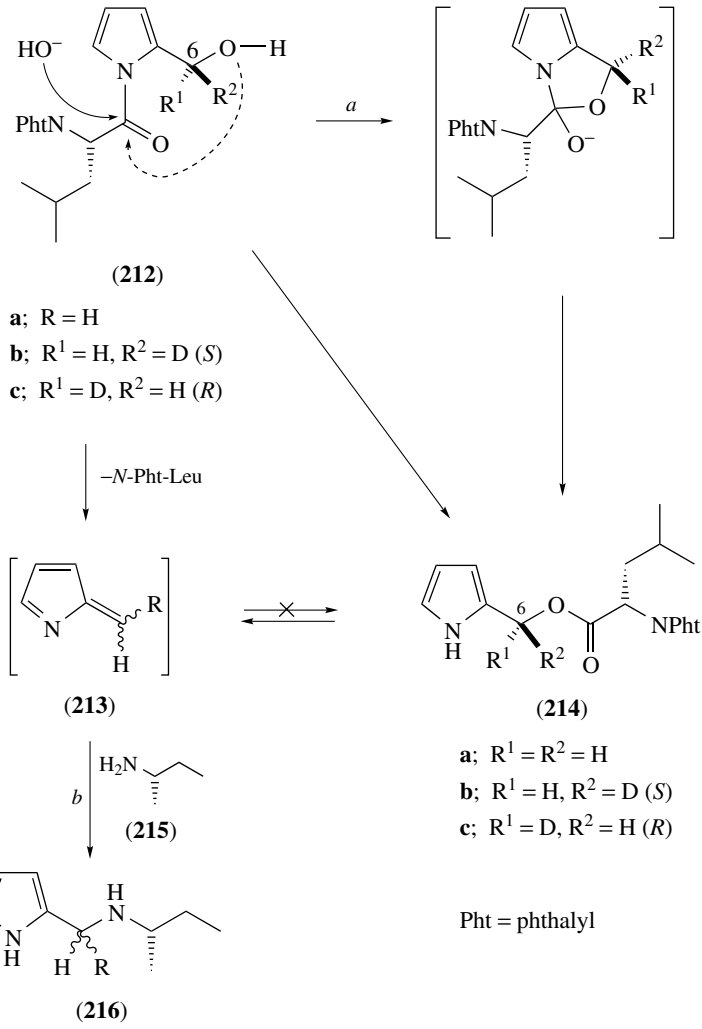
EWG = electron-withdrawing group

SCHEME 21

Intramolecular Catalysis and Neighbouring-group Participation

Neighbouring-group participation in the hydrolysis of esters and amides has been reviewed.[99] The effects of urea, Na^+ and Li^+ on the intramolecular general-base-catalysed glycolysis of phenyl salicylate (**217**) in glycol–acetonitrile solvent at constant water concentration have been reported.[100]

The stereoisomeric bicyclic amino alcohols (**218**) and (**219**) each undergo in tetrahydrofuran solvent ready acetylation with acetyl chloride and ready mesylation with methanesulfonyl chloride. Reaction of the *endo* isomer (**219**) very probably proceeds via the intramolecular 5-*exo-Trig* pathway, similar intermediates being formed in

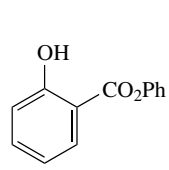


SCHEME 22

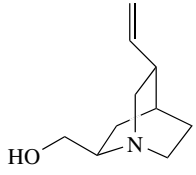
both acetylation (Scheme 23) and mesylation (Scheme 24).[101] However, although not discussed by the authors, the *exo* isomer (**218**) cannot react in a similar way, and intermolecular catalysis presumably occurs.

Association-prefaced Catalysis

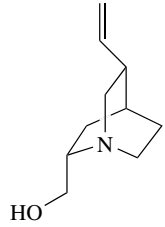
Hydrolysis of substituted phenyl acetates is catalysed by the Zn(II) complex of 1,5,9-triazacyclododecane (**220**). The results support the mechanism in which the ester is first complexed to the metal centre, and then water or hydroxide ion makes a nucleophilic attack at the complexed ester.[102]



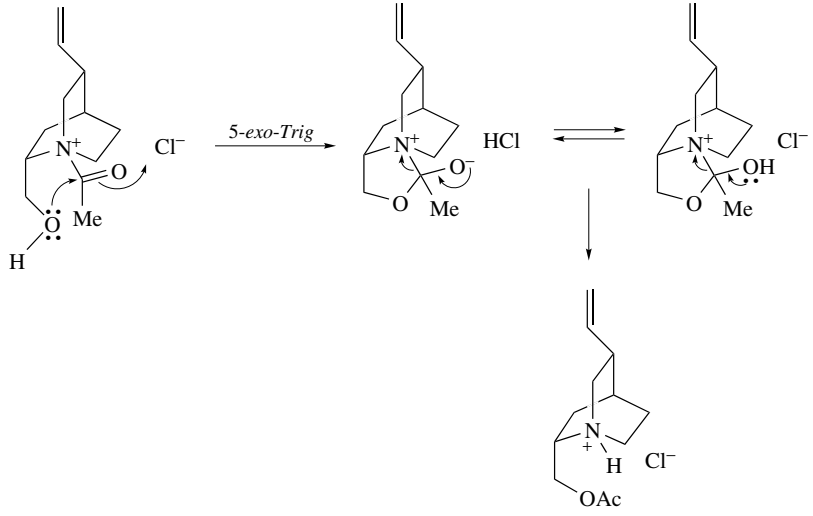
(**217**)



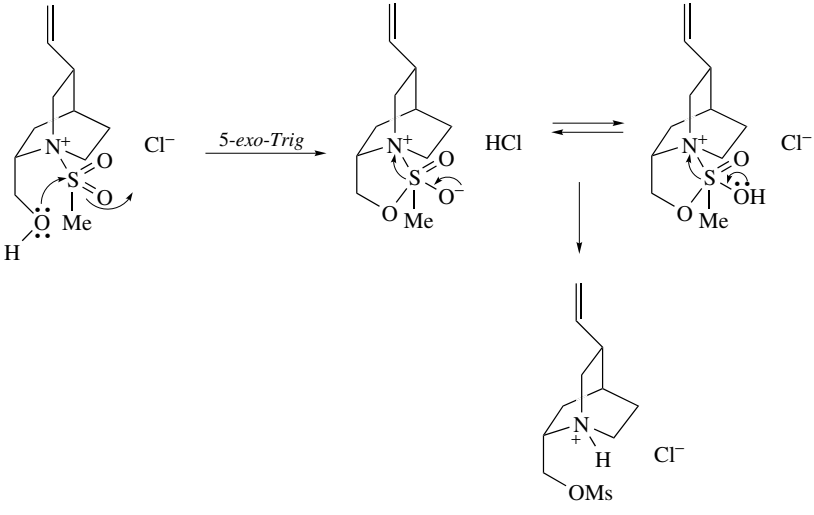
(**218**)



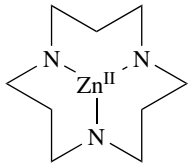
(**219**)



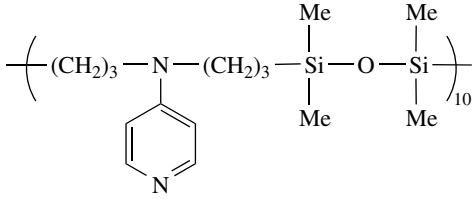
SCHEME 23



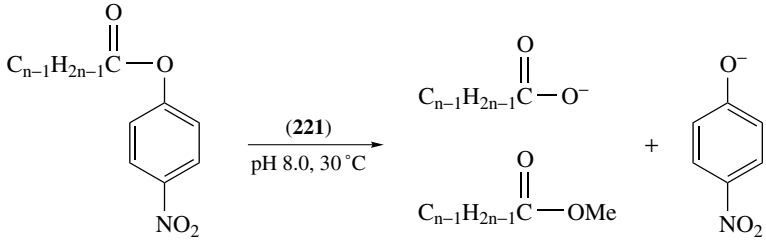
SCHEME 24



(**220**)



(**221**)



(**222**)

$n = 2, 4, 6, 8, 10, 12, 14, 16, 18$

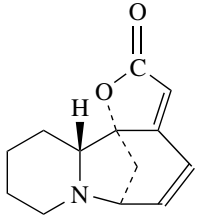
The substrate specificity in solvolysis reactions of *p*-nitrophenyl alkanoates (**222**; $n = 2–18$) catalysed by 4-(dialkylamino)pyridine-functionalized polymer (**221**) can be controlled by the concentration of (**221**) in 50:50 (v/v) methanol–aqueous phosphate buffer solution at pH 8.0 and 30 °C. Below 1.0×10^{-5} unit mol l^{-1}, macromolecule (**221**) exhibits substrate specificity for (**222**; $n = 14$). As the concentration of (**221**) increases to 2.5×10^{-5} unit mol l^{-1}, the substrate preference changes from (**222**; $n = 14$) to (**222**; $n = 12$). The substrate specificity changes again from (**222**; $n = 12$) to (**222**; $n = 10$) when the concentration of (**222**) increases further to 7.5×10^{-5} unit mol l^{-1}. The control of substrate specificity by polymer catalyst concentration is claimed to be unprecedented for catalysis of ester solvolysis.[103]

The cleavage of *p*-nitrophenyl alkanoates (**222**; $n = 1–8$) at high pH is modestly catalysed by micelles formed from cetyltrimethylammonium bromide (CTAB) in aqueous solution. Rate constants exhibit saturation behaviour with respect to [CTAB], consistent with substrate binding in the micelles. The strength of substrate binding and transition state binding to the micelles increases monotonically with the acyl chain length, and with exactly the same sensitivity. As a result, the extent of acceleration

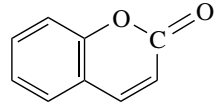
(or catalytic ratio) is independent of the ester chain. These and earlier results are consistent with the reaction centre being located in the Stern layer of the micelle, with the acyl chain of the ester being directed into the hydrophobic micellar interior.[104]

Complexation with caffeine and theophylline-7-acetate depresses the rate of alkaline hydrolysis of substituted phenyl benzoates and is consistent with the formation of molecular complexes with 1:1 stoichiometry between the hosts and esters; stacking of the xanthines is excluded as an explanation in the range of concentrations studied. Inhibition of hydrolysis is attributed to repulsion of the hydroxide ion from the host–ester complex by the extra hydrophobicity engendered by the xanthine host, as well as by the weaker binding of the transition state to the host compared with that in the host–ester complex.[105]

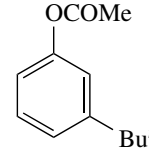
The effects of micelles of cetyltrimethylammonium bromide (CTABr), tetradecyltrimethylammonium bromide (TTABr) and sodium dodecyl sulfate (SDS) on the rates of alkaline hydrolysis of securinine (**223**) were studied at a constant [HO^-] (0.05 M). An increase in the total concentrations of CTABr, TTABr and SDS from 0.0 to 0.2 M causes a decrease in the observed pseudo-first-order rate constants (k_{obs}) by factors of ca 2.5, 3, and 7, respectively. The observed data are explained in terms of pseudophase and pseudophase ion-exchange (PIE) models of micelles.[106] Cationic micelles of CTABr speed attack of hydroxide ion upon coumarin (**224**) twofold owing to a concentration effect.[107]



(**223**)



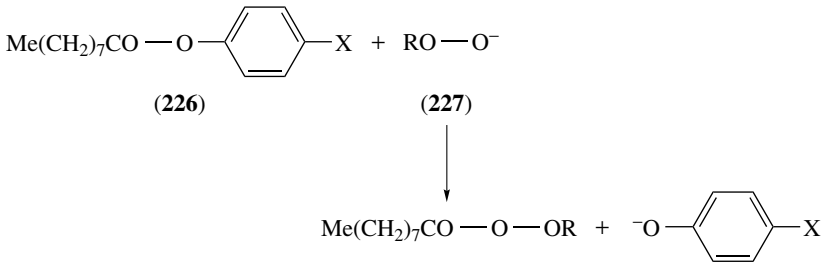
(**224**)



(**225**)

Molecular dynamics free-energy perturbation simulations utilizing the empirical valence bond model have been used to study the catalytic action of β-cyclodextrin in ester hydrolysis. Reaction routes for nucleophilic attack on *m-t*-butylphenyl acetate (**225**) by the secondary alkoxide ions $O(2)^-$ and $O(3)^-$ of cyclodextrin giving the *R* and *S* stereoisomers of ester tetrahedral intermediate were examined. Only the reaction path leading to the *S* isomer at O(2) shows an activation barrier that is lower (by about 3 kcal mol^{-1}) than the barrier for the corresponding reference reaction in water. The calculated rate acceleration was in excellent agreement with experimental data.[108]

The micellar kinetics of the acyl transfer from *n*-nonanoyloxybenzenesulfonate (**226**; X = SO_3^-) and phenyl nonanoate (**226**; X = H) to hydrogen peroxide (**227**; R = H) and pernonanoic acid [**227**; R = $Me(CH_2)_7CO$] have been reported. The



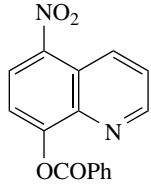
(**226**) (**227**)

micellar association constant of phenyl nonanoate with SDS is four orders of magnitude greater than that of *n*-nonanoyloxybenzenesulfonate owing to the absence of the negatively charged sulfonate group, whilst the apparent micellar association constant of the transition state for its reaction with pernonanoate is more than an order of magnitude less.[14]

Metal-ion Catalysis

Ruthenium(III) catalyses the oxidative decarboxylation of butanoic and 2-methylpropanoic acid in aqueous sulfuric acid.[109] Studies of alkaline earth (Ba, Sr) metal alkoxides in amide ethanolysis[68] and of alkali metal alkoxide clusters as highly effective transesterification catalysts[8] were covered earlier. Kinetic studies of the ethanolysis of 5-nitroquinol-8-yl benzoate (**228**) in the presence of lithium, sodium, or potassium ethoxide revealed that the highest catalytic activity is observed with Na^+.[110]

In the hydrolysis of methyl (**229**; X = OMe) and ethyl esters of α-amino acids (**229**; X = OEt) the catalytic effectiveness of Ce(III) and Nd(III) was the highest for a set of 20 lanthanide ions; Ln(III) and Yb(III) were the least effective. For the hydrolysis of amides of α-amino acids (**229**; X = NH_2), however, the Ce(IV) ion is much more active than any of the lanthanide(III) ions.[111]



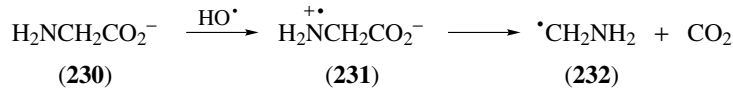
(**228**)

$RCH(NH_2)COX$

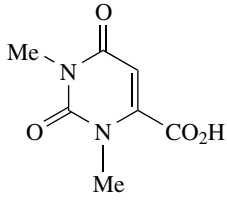
(**229**)

Decarboxylation

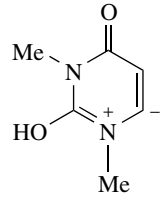
Glycine anion (**230**) is decarboxylated when exposed to hydroxyl radicals. The major initial product is an amino radical cation (**231**), which suffers rapid ($\leqslant$100 ns) fragmentation into CO_2 and a carbon-centred radical (**232**).[112] Oxidative decarboxylation



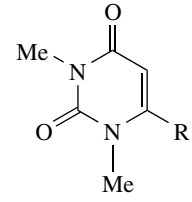
(**230**) (**231**) (**232**)



(**233**)

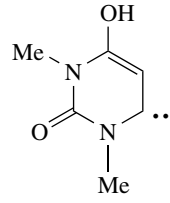


(**234**)



(**235**) R = H

(**236**) R = CH_2Ph



(**237**)

of butanoic and 2-methylpropanoic acid in aqueous sulfuric acid is catalysed by ruthenium(III).[109]

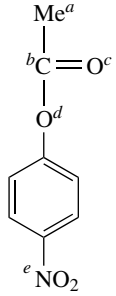
When 1,3-dimethylorotic acid (**233**) was heated at 198 °C in benzyl bromide for 3 h, 6-benzyl-1,3-dimethyluracil (**236**) was formed in 10% yield together with the product of decarboxylation, 1,3-dimethyluracil (**235**). This finding supports the involvement of a carbon-6-centred nucleophilic intermediate in the decarboxylation reaction; a carbanion (**234**) could be involved or a carbene (**237**).[113]

Oxalic acid, tartaric acid, and other hydroxylated di- and tricarboxylic acids are decarboxylated to varying extents by radical pathways when reacted at 25 °C with Ce(IV) in 1 M sulfuric acid solution.[114]

Enzymic Catalysis

General

Isotope effects have been measured for the reaction of *p*-nitrophenyl acetate with chymotrypsin, papain and an acid protease and the results compared with data from its uncatalysed reactions with oxygen and sulfur nucleophiles. The isotope effects, which were measured by the competitive method and are therefore effects on *V/K,* were determined at the β-deuterium (^{D}k), carbonyl carbon (^{13}k), carbonyl oxygen ($^{18}k_{C}{=}O$), leaving-group phenolic oxygen ($^{18}k_{lg}$) and leaving-group nitrogen (^{15}k) positions (see Scheme 25).[115] All of the enzymatic reactions showed isotope effects consistent with a concerted mechanism like that seen in uncatalysed aqueous reactions, but exhibited



(**a**) $^{D}(V/K)$

(**b**) $^{13}(V/K)$

(**c**) $^{18}(V/K)_{carbonyl}$

(**d**) $^{18}(V/K)_{lg}$

(**e**) $^{15}(V/K)$

SCHEME 25

smaller inverse β-deuterium effects than seen in the non-enzymatic reactions. This phenomenon may be explained by greater hydrogen bonding or electrostatic interaction with the ester carbonyl group in enzymatic transition states relative to non-enzymatic aqueous transition sates.[115]

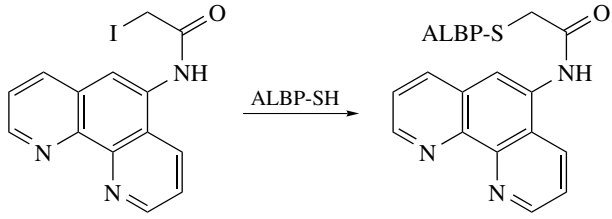
A new, more general, way to combine *ab initio* quantum mechanical calculations with classical mechanical free-energy perturbation approach (QM/FE approach) to calculate the energetics of enzyme-catalysed reactions and the same reaction in solution has been reported.[116] The calculated free energies were in fairly good agreement with the experimental data for the activation energies of the first test case, amide hydrolysis in trypsin and in aqueous solution.[116]

β-Lactamases

The mechanism of catalysis and the inhibition of β-lactamases have been reviewed (75 references).[117]

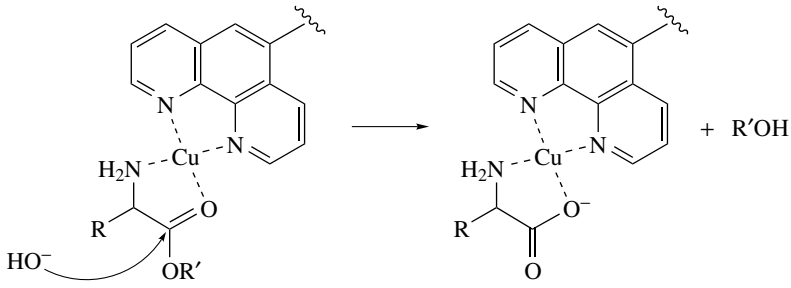
Other Enzymes

A semi-synthetic metalloenzyme that catalyses the enantioselective hydrolysis of simple amino acid esters has been reported.[118] Iodoacetamido-1,10-phenanthroline (**238**) was interacted with a cysteine residue in adipocyte lipid binding protein (ALBP) to produce the conjugate ALBP–Phen (**239**), which was converted into its Cu(II) complex. The ALBP–Phen–Cu(II) was found to catalyse the enantioselective



(**238**) (**239**) (ALBP-Phen)

hydrolysis of several amino acid esters under mild conditions (pH 6.1, 25 °C) at rates 30–250-fold above the spontaneous rate. A possible mechanism involves the positioning of the amino acid ester around the copper such that the C=O group is activated towards attack by water or hydroxide ion (see Scheme 26).[118]



SCHEME 26

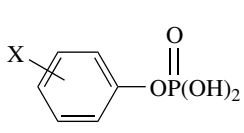
NON-CARBOXYLIC ACIDS

Phosphorus-containing Acids

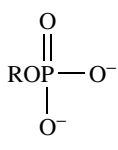
Phosphates and Phosphonates

Solvolysis studies of *meta*- and *para*-substituted phenyl phosphates (**240**) in anhydrous Bu^{t}OH and in Am^{t}OH have revealed that generally reactions of dianions are much faster in alcohols than in water. For example, the dianion of *p*-nitrophenyl phosphate (**240**; $X = 4\text{-}NO_2$) reacts 7500- and 8750-fold faster in Bu^{t}OH and Am^{t}OH, respectively, than in water.[119] The results of a theoretical study of the reactivity of phosphate monoester anions in aqueous solution do not support the generally accepted view that Brønsted coefficients $\beta_{lg} = -1.23$ and $\beta_{nuc} = 0.13$ determined more than 30 years ago for the uncatalysed reaction of water and a monophosphate dianion (**241**) represent conclusive evidence for the dissociative mechanism. It is suggested that, instead, the observed LFERs could correspond to a late transition state in the associative mechanism.[120]

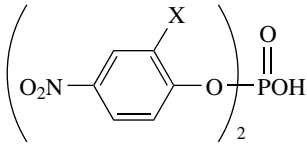
An aquahydroxy complex of Co(III) with 1,4,7,10-tetraazacyclododecane (**243**) has been shown to be an effective catalyst for the hydrolysis of *p*-nitrophenyl phosphate (**240**; $X = 4\text{-}NO_2$), bis(*p*-nitrophenyl) phosphate (**242**; X = H) and bis(2,4-dinitrophenyl) phosphate (**242**; $X = NO_2$).[121] Whereas Th^{4+} had no effect, Ce^{4+}



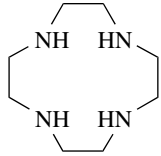
(**240**)



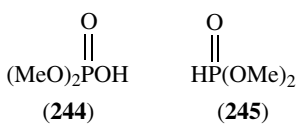
(**241**)



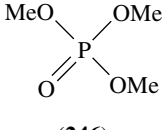
(**242**)

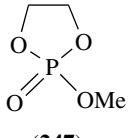


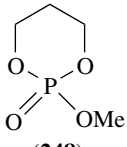
(**243**)


(**244**)

(**245**)


(**246**)


(**247**)

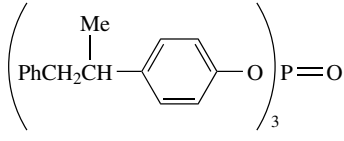

(**248**)

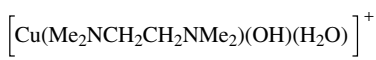
caused an acceleration of 2×10^8-fold in the acid hydrolysis of dimethyl phosphate (**244**). The mechanism of the catalytic process is uncertain and is undergoing investigation.[122]

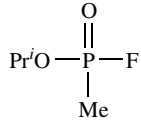
Quantitative ^{31}P NMR examination of the hydrolysis of dimethyl phosphonate (**245**) using ^{18}O-enriched water under base-catalysed conditions supports a mechanism involving P−O rather than C−O bond cleavage.[123]

Ab initio calculations to map out the gas-phase activation free energy profiles of the reactions of trimethyl phosphate (TMP) (**246**) with three nucleophiles, HO^-, MeO^- and F^- have been carried out. The calculations revealed, *inter alia,* a novel activation free-energy pathway for HO^- attack on TMP in the gas phase in which initial addition at phosphorus is followed by pseudorotation and subsequent elimination with *simultaneous* intramolecular proton transfer.[124] *Ab initio* calculations and continuum dielectric methods have been employed to map out the lowest activation free-energy profiles for the alkaline hydrolysis of a five-membered cyclic phosphate, methyl ethylene phosphate (**247**), its acyclic analogue, trimethyl phosphate (**246**), and its six-membered ring counterpart, methyl propylene phosphate (**248**). The rate-limiting step for the three reactions was found to be hydroxyl ion attack at the phosphorus atom of the triester.[125]

The kinetics and mechanism of the acid hydrolysis of tris[4-(2′-phenylisopropyl) phenyl] phosphate (**249**) have been reported.[126]

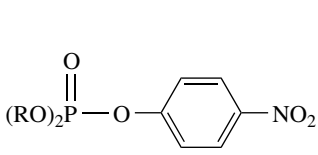

(**249**)


(**250**)

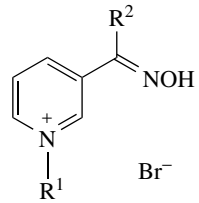

(**251**)

A hydroxoaqua copper complex containing *N*, *N*, *N*′, *N*′-tetramethyl-1,2-diaminoethane (**250**) is an excellent catalyst for the hydrolysis of sarin, *O*-isopropyl methylphosphonofluoridate (**251**), and diethyl *p*-nitrophenyl phosphate (**252**; R = Et). The mechanism of the reaction probably involves bound hydroxide attacking the phosphoryl group with concomitant electrophilic catalysis by copper.[127]

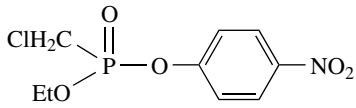
Two types of amphiphilic quaternary 3-pyridinium ketoximes (**253a**, **b**) with different positioning of the hydrophobic alkyl chain have been synthesized and tested as hydrolytic micellar catalysts. A considerable positive deviation from the expected first-order curve was observed in the absorbance vs time plot when *p*-nitrophenyl diphenyl phosphate (**252**; R = Ph) and *p*-nitrophenyl diethyl phosphate



(**252**)



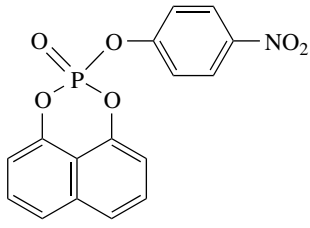
(**253**)



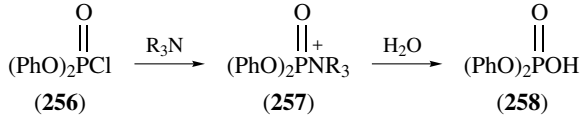
(**254**)

	R^1	R^2
(**a**)	$C_{12}H_{25}$	Me
(**b**)	Me	$C_{12}H_{25}$

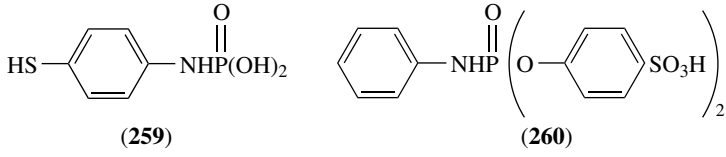
(**252**; R = Et) were hydrolysed in micellar solutions of the prepared ketoximes under pseudo-first-order reaction conditions.[128] In the alkaline hydrolysis of *p*-nitrophenyl ethyl chloromethylphosphonate (**254**), micellar catalysis by cetylpyridinium bromide is much reduced when KCl and KBr are present.[129]



(**255**)



(**256**) (**257**) (**258**)



(**259**) (**260**)

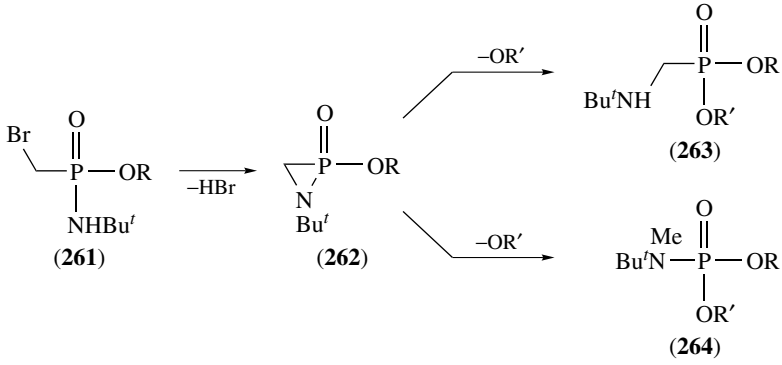
p-Nitrophenyl 1,8-naphthyl phosphate (**255**) is 1–2 orders of magnitude more reactive than *p*-nitrophenyl diphenyl phosphate (**252**; R = Ph) towards nucleophilic attack. An X-ray crystal structure of (**255**) revealed that the O(2)–P–O(3) bond angle is 105.8° and is therefore 'unstrained.' If a trigonal bipyramidal intermediate is formed, some strain will be engendered in attaining an O–P–O bond angle of 120°, but

the principal source of the higher reactivity of (**255**) over (**252**; R = Ph) is probably due to the easy access of the nucleophile to the phosphoryl centre.[130] Tertiary amines, pyridine, and imidazoles catalyse the hydrolysis, in aqueous acetonitrile, of diphenyl phosphochloridate (**256**) by attacking the phosphorus and displacing the chloro substituent to yield a cationic intermediate (**257**), which hydrolyses to diphenyl phosphate (**258**).[131]

Phosphorus–Nitrogen Centres

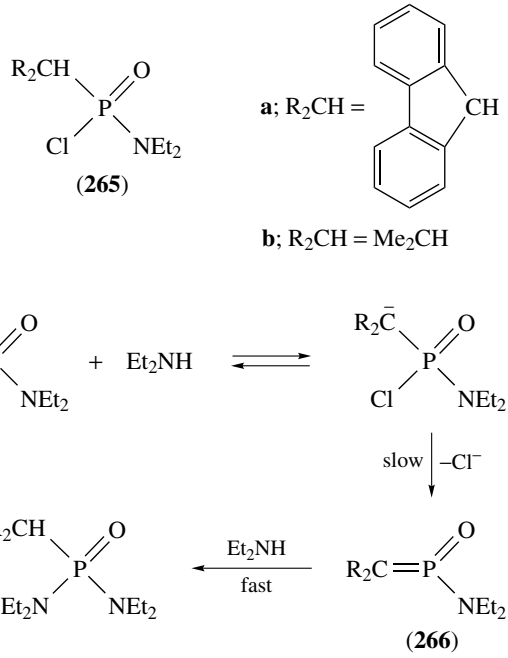
Kinetic studies have been reported of the acid hydrolysis of *N*-(*p*-sulfophenyl)phosphoramidic acid (**259**)[132] and of bis(*p*-sulfonyl) *N*-phenylphosphoramidate (**260**).[133]

Methyl *P*-bromomethyl *N*-*t*-butylphosphonamidate (**261**; R = Me) rearranges with methoxide, giving dimethyl-*t*-butylaminomethylphosphonate (**263**; R = R′ = Me) and dimethyl-*t*-butyl-*N*-methylphosphoramidate (**264**; R = R′ = Me) in comparable amounts. These products are derived from the (postulated) azaphosphiridine oxide intermediate (**262**; R = Me) by nucleophilic attack at phosphorus and cleavage at the P−N or P−C bond (Scheme 27). Increased bulk in the alkyl group of the alkoxy ligand (R = methyl < cyclohexyl < *t*-butyl < menthyl) or the alkoxide nucleophile (methoxide < *t*-butoxide) increases P−N bond cleavage at the expense of P−C cleavage.[134]

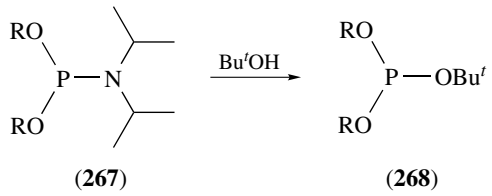


SCHEME 27

Compared with *N,N*-diethyl isopropylphosphonochloridate (**265b**), the corresponding fluorenyl compound (**265a**) shows remarkably high reactivity in nucleophilic substitution with Et_2NH. Substitution is catalysed by base {1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)} and shows little discrimination between competing Me_2NH and Et_2NH. These characteristics point to an elimination–addition (*EA*) mechanism with a reactive phosphene intermediate (**266**; Scheme 28). When Et_2ND is the nucleophile, H–D exchange at the α-carbon atom occurs much more quickly than substitution. This suggests that the elimination stage of the *EA* mechanism is reversible *E1cB*.[135]



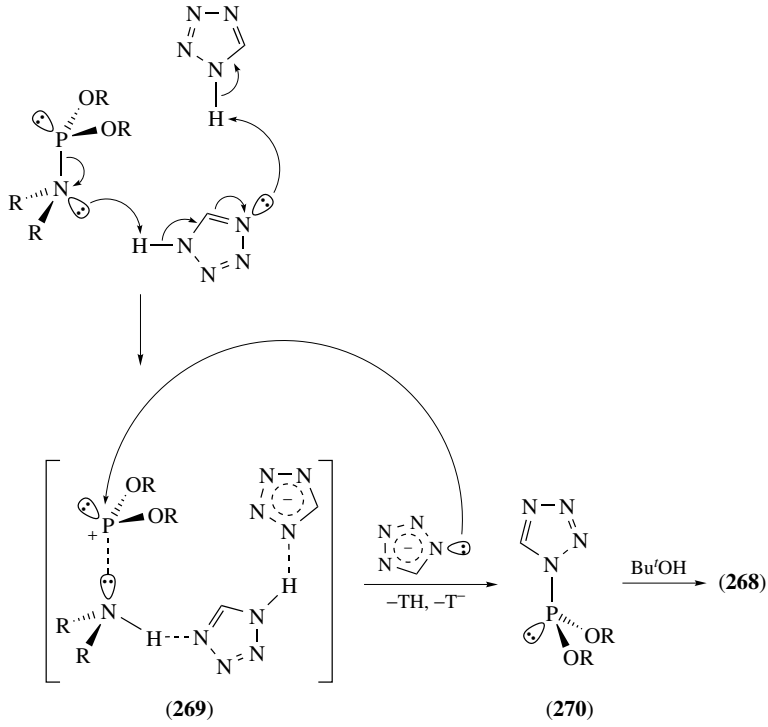
SCHEME 28



The tetrazole-catalysed alcoholysis of simple dialkylphosphoramidates (**267**) in THF to yield trialkylphosphites (**268**) occurs via nucleophilic catalysis (Scheme 29). The proposed mechanism sees tetrazole acting first as an acid catalyst to give the protonated intermediate (**269**), which then reacts with tetrazolide anion to yield the tetrazolylphosphite (**270**); alcoholysis of the latter (**270**) then yields the final product, the trialkylphosphite (**268**).[136]

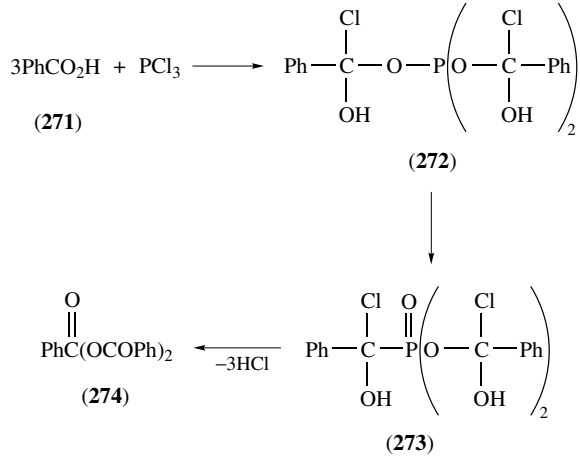
Phosphorus–Oxygen and Phosphorus–Sulfur Centres

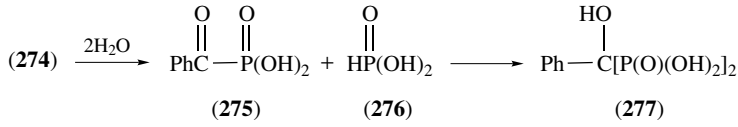
Benzoic acid (**271**) when reacted with PCl_3 yielded an adduct (**272**) which underwent an Arbuzov rearrangement to the phosphoryl compound (**273**), which eliminated 3HCl to give benzoylphosphonic anhydride (**274**). Addition of water to the reaction mixture converted the anhydride (**274**) into benzoylphosphonic acid (**275**), which underwent



SCHEME 29

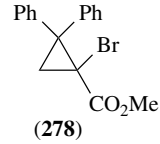
an addition reaction at its C=O group with the product of PCl_3 hydrolysis, phosphinic acid (**276**), to yield as the ultimate product phenylhydroxymethanediphosphinic acid (**277**). This pathway excludes the formation of benzoyl chloride, presumed hitherto to be the precursor which is phosphorylated to yield the diphosphinic acid (**277**).[137]

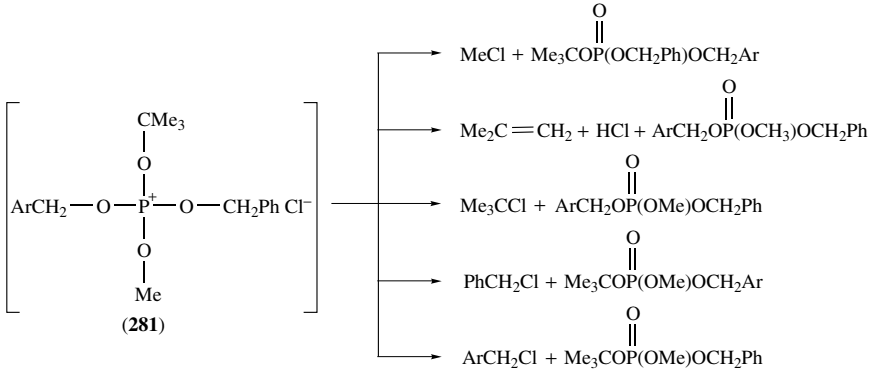




The reaction of $R_2P{-}O^-$ and $R_2P{-}S^-$ with methyl 1-bromo-2,2-diphenylcyclopropanecarboxylate (**278**) proceeds by the initial displacement of bromide ion, and thence gives rise to a complex mixture of products.[138]

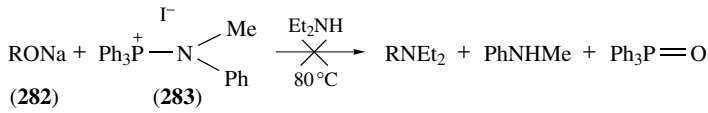
Benzyl methyl Y-substituted benzyl phosphites (**280**) react in CCl_4 at low temperature (−20 to 40 °C) with *t*-butyl hypochlorite (**279**) to give a complex mixture of products. Tetraalkoxyphosphonium chlorides (**281**; At = YC_6H_4) are the key intermediates, and it is proposed that they can undergo heterocyclic fragmentation in five different ways (Scheme 30).[139]



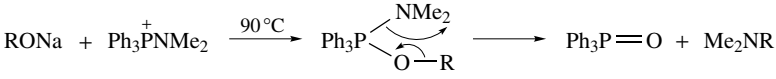


SCHEME 30

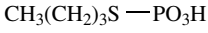
A thorough investigation has shown that the Tanigawa amination of alcohols, in which the corresponding alkoxide (**282**) is treated in DMF with *N*-methyl-*N*-phenylaminotriphenylphosphonium iodide (**283**) and a secondary amine at 80 °C, does not proceed at this temperature. *In situ* generation of the *N,N*-dimethylamino analogue (**284**) by reaction of (**283**) with dimethylamine, however, does lead to a smooth reaction at 90 °C. The proposed mechanism involves a pentacoordinated intermediate (**285**).[140]



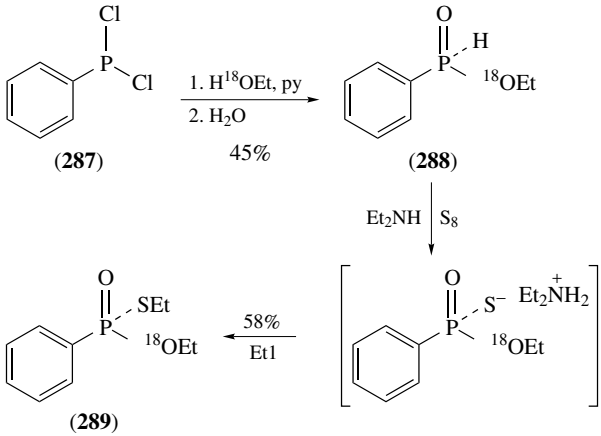
(**282**) (**283**)



(**284**) (**285**)

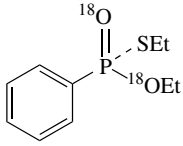


(**286**)



(**287**) (**288**) (**289**)

SCHEME 31



(**290**)

Mechanistic studies of the acid hydrolysis of *S*-butyl phosphorothioate (**286**) have been reported.[141]

The synthesis of ^{18}O-labelled phenylphosphonothioate (**289**) (Scheme 31) was achieved by reaction of dichlorophenylphosphine (**287**) with Et^{18}OH followed by addition of water to give (**288**). Oxidation with elemental sulfur in the presence of diethylamine then gave the salt of the *O*-ethylphenylphosphonothioate, which was alkylated with ethyl iodide to give the ^{18}O-labelled *O,S*-diethyl

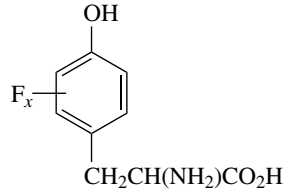
phenylphosphonothioate (**289**).[171] However, analysis by MS showed that some of the doubly labelled product (**290**) had also been formed. The authors suggest that it arose from the reaction of the dichlorophosphine (**287**) with $Et^{18}OH$, followed by partial hydrolysis of that product with $H_2{}^{18}O$ that had been formed concurrently by dehydration of the $Et^{18}OH$.[142]

Biologically Important Reactions

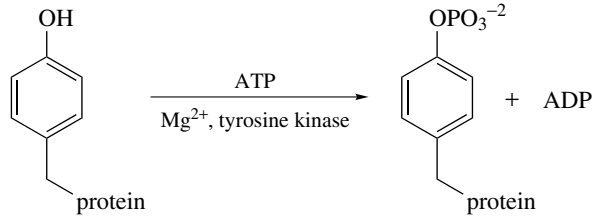
A series of synthetic fluorotyrosine-containing heptapeptides (**291**; X = fluorotyrosine) has been used to probe the nature of the transition state in a protein tyrosine kinase, a class of enzyme which catalyses the transfer of the γ-phosphoryl group from ATP to tyrosine residues in proteins (Scheme 32).[143] Indeed, both of the monofluoro, all four of the difluoro-, both of the trifluoro- and the tetrafluoro-tyrosines (**292**), which had been biosynthesized in gram quantities by incubating the corresponding fluorophenols with a recombinant enzyme tyrosine phenol-lyase in the presence of pyruvate and ammonia, were incorporated into the heptapeptides (**291**; X = fluorotyrosine) by automated solid-phase peptide synthesis. 2-Fluorotyrosine has $pK_a = 9.0$ and 2,3,5,6-tetrafluorotyrosine has $pK_a = 5.2$, with the di- and tri-fluoro analogues possessing values in between, and this range of substrates was used to show that (i) the substrate tyrosine phenol must be neutral to be enzymically active and (ii) a dissociative (path *b*), rather than associative (path *a*), transition state is indicated for phosphoryl transfer (Scheme 33).[143]

H_2N—Glu—Asp—Asn—Glu—X—Thr—Ala—CO_2H

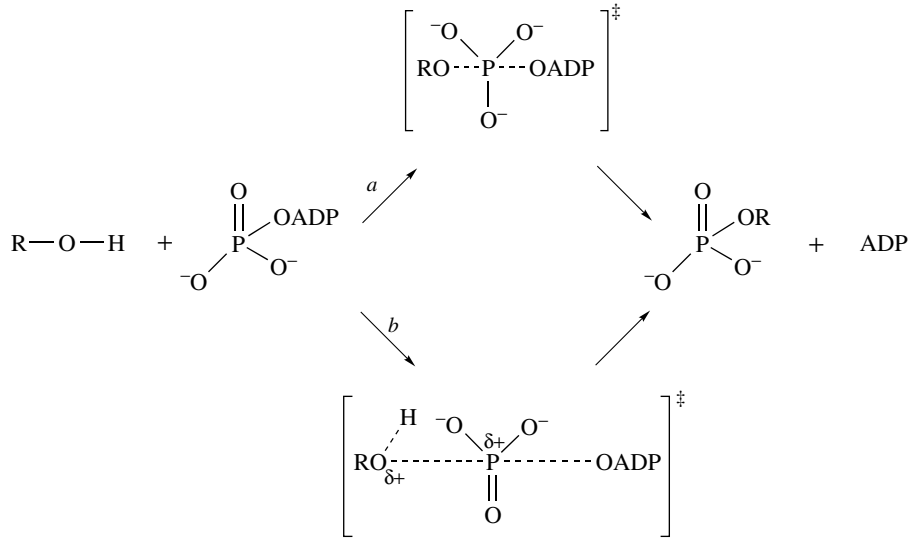
(**291**)



(**292**)

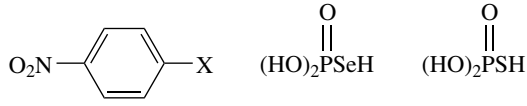


SCHEME 32



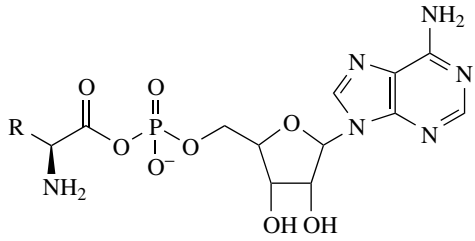
SCHEME 33

In a reverse micellar system prepared by dissolving sodium bis(2-ethylhexyl)sulfosuccinate in isooctane, the pK_a of 4-nitrophenol (**293**; X = OH) depends on the degree of hydration of the system. Such a system is claimed to be a good mimic of membrane-bound enzymes. Human placental alkaline phosphatase, known to be membrane-bound, has been deployed in this reverse micellar system with varying degrees of hydration, to study the enzymic hydrolysis of 4-nitrophenyl phosphate (**293**; X = OPO_3H). The pK_a of 4-nitrophenol (**293**; X = OH) was found to range between 9.2 and 10.8 for degrees of hydration ([H_2O]/[detergent]) between 40 and 4.44, and this allowed Brønsted constants to be determined for $k_{cat}(\beta_{lg} = -0.47)$ and for $k_{cat}/k_m(\beta_{lg} = -1.03)$. These model results were considered as support for phosphorylation being the rate-determining step in membrane-bound alkaline phosphatase, whereas in aqueous solution, dissociation of non-covalently bound phosphate is the rate-determining step.[144]



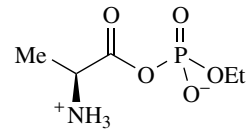
(**293**) (**294**) (**295**)

The hydrolysis, alcoholysis, and aminolysis of monoselenophosphate (**294**) have been reported for the first time; (**294**) is the labile selenium donor compound required for the synthesis of Se-dependent enzymes and seleno-tRNAs, and is formed from ATP and selenide, HSe^-. The rate of hydrolysis of monoselenophosphate (**294**) is



Aminoacyl adenylate

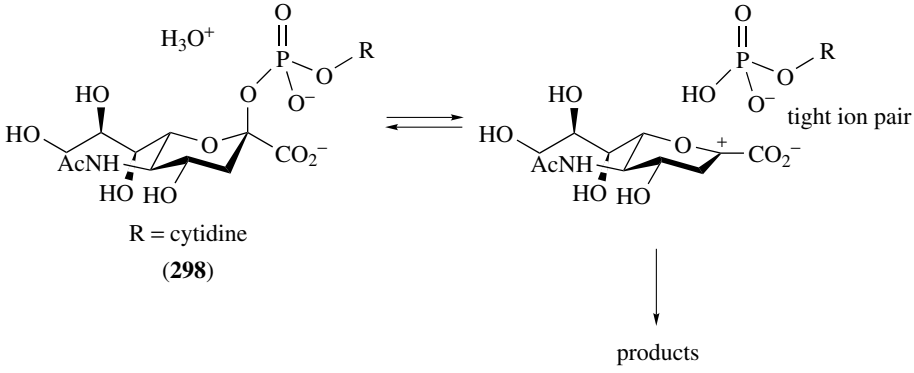
(**296**)



(**297**)

maximal at about pH 7, in contrast to that of monothiophosphate (**295**), which is maximal at pH 3. This suggests that the dianion of monoselenophosphate (**294**) is the species that reacts the fastest. From all the results obtained, the authors suggest that the mechanism of hydrolysis of monoselenophosphate (**294**) is dissociative in nature, involving a monomeric metaphosphate-like transition state.[145]

Aminoacyl adenylates (**296**), which are formed from protein amino acids and ATP, act as acylating agents towards t-RNAs, acylating their terminal 3′-hydroxy groups. These 'charged' tRNAs are then used in protein synthesis. Little is known about the reactivity of aminoacyl adenylates (**296**), and studies are now reported of a model compound, alanyl ethyl phosphate (**297**). As expected, hydrolysis in both acid and base involves attack at the C=O group of (**297**) with departure of ethyl phosphate. Metal ions (Cu^{2+}, Zn^{2+}) were found to act as catalysts of the hydrolysis.[146]



R = cytidine

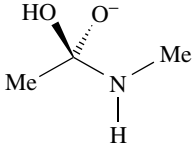
(**298**)

products

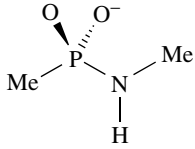
SCHEME 34

Cytidine 5′-phospho-*N*-acetylneuraminate (**298**), the coenzyme of sialyltransferases, is a sugar–nucleotide in which the leaving group is a nucleotidyl monophosphate that contains a carboxylate group directly attached to the anomeric centre. Studies of its hydrolysis reveal that at pH 5 specific acid catalysis occurs (Scheme 34) to yield a glycosyl carbocation as a tight ion pair, the lifetime of which was estimated

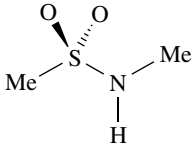
from trapping studies with azide ion to be $\geqslant 3 \times 10^{-11}$s. Generally, the carboxylate group was a spectator of the reaction, no evidence for its direct involvement being obtained.[147]



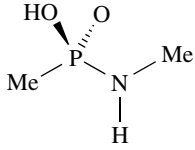
(**299**)



(**300**)



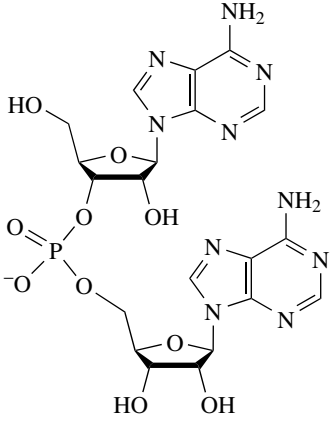
(**301**)



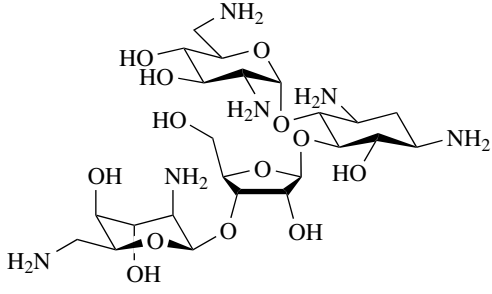
(**302**)

A theoretical investigation of *N*-methylmethanephosphonamidate (**300**), *N*-methylmethanephosphamide (**302**), and *N*-methylmethanesulfonamide (**301**) as protease transition-state isosteres has revealed that the anionic phosphonamidate (**300**) is the best mimic of the tetrahedral intermediate for base-catalysed *N*-methylacetamide (**299**) hydrolysis.[148]

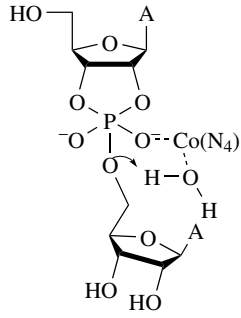
(**303**)



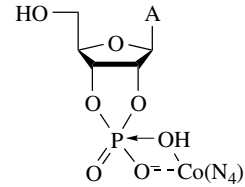
(**304**)



(**307**)



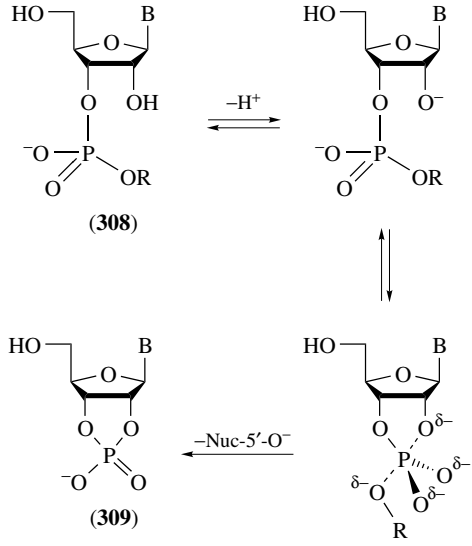
(**305**)



(**306**)

A series of diaquatetraaza cobalt(III) complexes accelerated the hydrolysis of adenylyl(3′–5′)adenosine (ApA) (**304**), an enhancement of 10^5-fold being observed with the triethylenetetramine complex (**303**) at pH 7. The pentacoordinated intermediate (**305**), which is formed with the complex initially acting as an electrophilic catalyst, then suffers general acid catalysis by the coordination water on the Co(III) ion to yield the complexed 1,2-cyclic phosphate (**306**), the hydrolysis of which occurs via intracomplex nucleophilic attack by the metal-bound hydroxide ion on the phosphorus atom.[149] Neomycin B (**307**) has also been shown to accelerate the phosphodiester hydrolysis of ApA (**304**) more effectively than a simple unstructured diamine.[150]

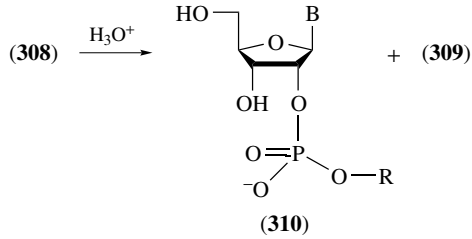
A series of uridine 3′-alkylphosphates (**308**) undergo in alkaline solution a hydroxide-ion catalysed reaction to give the 2′,3′-cyclic monophosphates (**309**) via phosphorane-type intermediates (Scheme 35). The alkyl groups ranged from ethyl



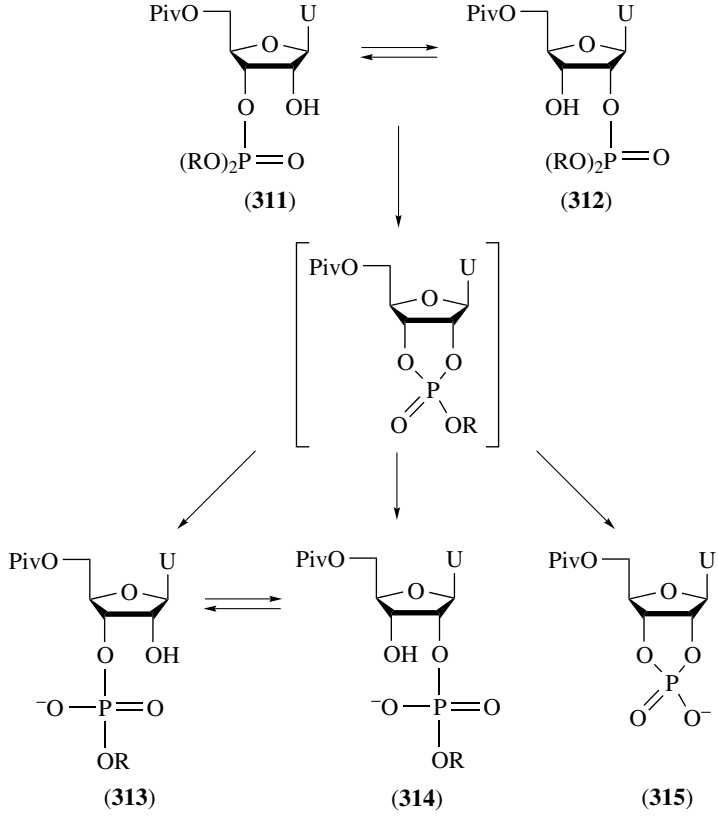
(**308**)

(**309**)

SCHEME 35



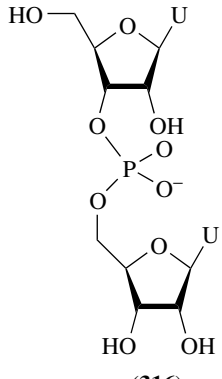
to 1,1,1-trichloroethyl, permitting the determination of a β_{lg} for the reaction of -1.28 ± 0.05, and this was interpreted as evidence for a mechanism lying on the borderline between a concerted and a stepwise mechanism. By contrast, in aqueous acid (**308**) undergo concurrent isomerization to 2′-alkylphosphates (**310**) and cleavage to 2′, 3′-cyclic phosphates (**309**) both processes being fairly insensitive to the electron-withdrawing ability of the alkyl group with β and β_{lg} values being -0.18 ± 0.02 and -0.12 ± 0.05, respectively.[151] The same group[152] has studied the acid hydrolysis of uridine 3′-dialkyl phosphates (**311**) (with protection of the 5′-hydroxyl group with a



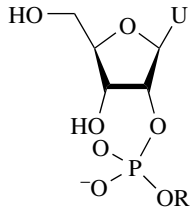
SCHEME 36

pivaloyl group), and they observed two parallel reactions: isomerization to 2′-dialkyl phosphates (**312**) and cleavage to a mixture of 2′- (**313**) and 3′-monalkyl phosphates (**314**) and a 2′, 3′-cyclic phosphate (**315**). The latter reaction presumably proceeded via the 2′, 3′-cyclic triester, which was too unstable to be detected (Scheme 36).[152]

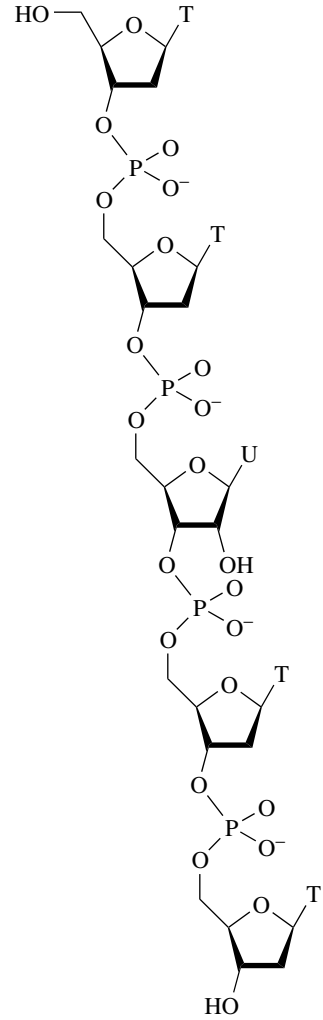
Measurements of medium and ionic strength effects on the rates of hydrolysis and isomerization of the dinucleoside monophosphate (3′, 5″-UpU) (**316**) in 0.1–0.7 M imidazole–imidazolium (Im/ImH$^+$) buffers have been reported.[153] The hydrolysis of (**316**) is catalysed both by Im and, less effectively, by ImH$^+$, whereas the isomerization to 2′, 5″-UpU (**317**; R = 5′-uridyl) is catalysed only by ImH$^+$. As a better model for RNA, the chimaeric oligonucleotide TTUTT (**318**), which undergoes the same



(**316**)

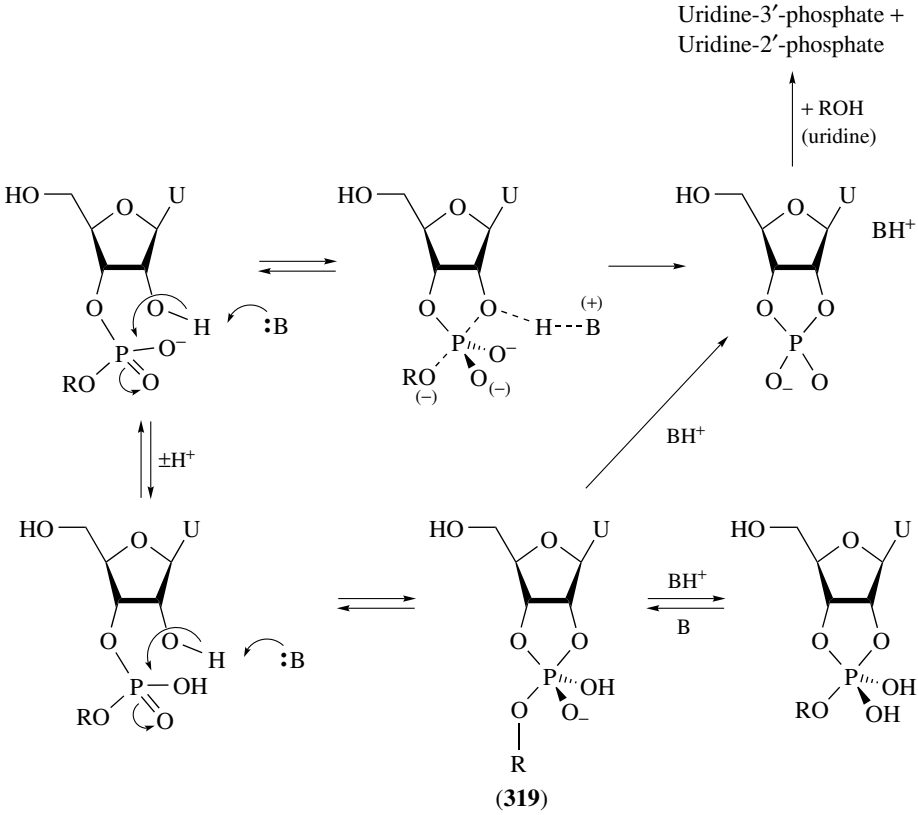


(**317**)



(**318**)

reactions at the unique in-chain uridylyl residue, was also studied. The isomerization reaction of TTUTT, was, like 3,5″-UpU, catalysed only by ImH^+, but the hydrolysis of TTUTT was catalysed more effectively by ImH^+ than by Im, in contradistinction to the results with 3′, 5″-UpU. From all the results obtained, it was concluded that the hydrolysis of the internucleoside bond in these phosphodiesters involves two parallel pathways: a more or less concerted general-base-catalysed reaction and a two-step process, involving the rate-determining general acid-catalysed breakdown of a phosphorane monoanion intermediate (**319**) (Scheme 37).[153]

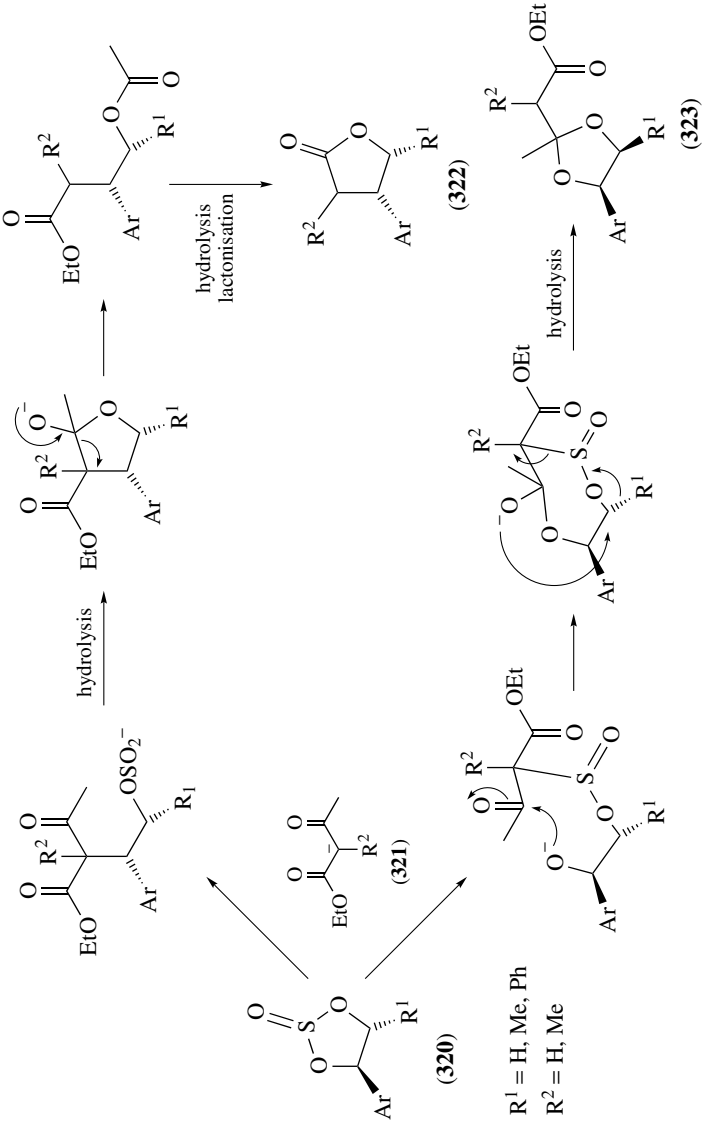


SCHEME 37

Sulfur-containing Acids

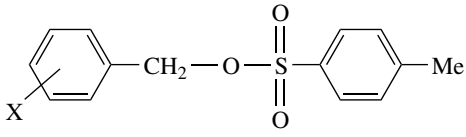
Sulfur–Oxygen Compounds

1,2-Cyclic sulfites (**320**) have been shown to react with sodium acetoacetate (**321**; $R^2 = H$) either by S_N2 attack at carbon to give γ-lactones (**322**) or by attack at the S=O group to give acetals (**323**) (Scheme 38).[154]

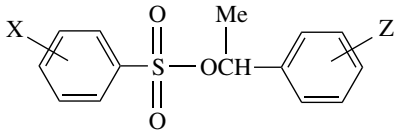

hydrolysis
hydrolysis
lactonisation
hydrolysis
(320)
(321)
(322)
(323)
R1 = H, Me, Ph
R2 = H, Me

SCHEME 38

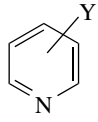
The specific rates of solvolysis of benzyl *p*-toluenesulfonate and nine benzylic-ring-substituted derivatives (**324**) have been satisfactorily correlated using N_T and Y_{OTs} scales within the extended Grunwald–Winstein equation.[155] The reactions of Z-phenylethyl X-benzenesulfonates (**325**) with Y-pyridines (**326**) in acetonitrile at 60 °C have been studied at high pressures. The results indicated that the mechanism of the reaction moves from a dissociative S_N2 to an early-type concerted S_N2 with increasing pressure.[156]



(**324**)

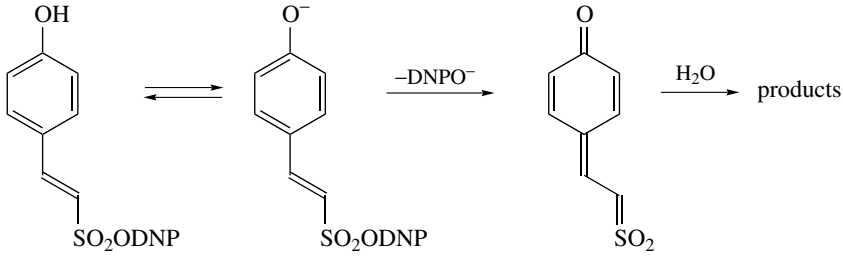


(**325**)



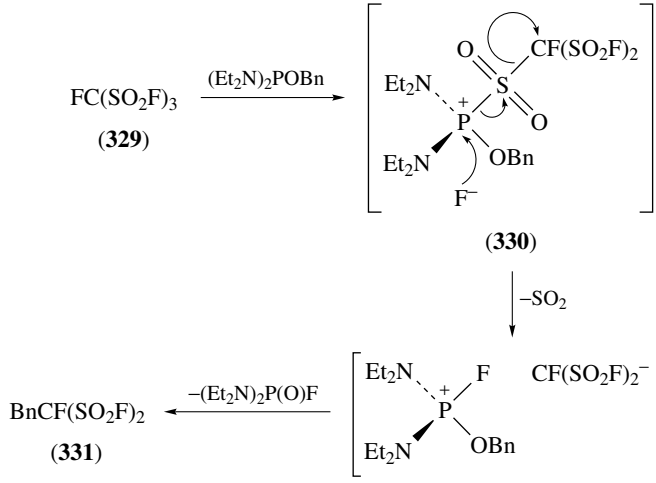
(**326**)

In strongly alkaline solution, 2,4-dinitrophenyl 4-hydroxy-β-styrenesulfonate (**327**) hydrolyses via a dissociation ($E1cB$) mechanism with the probable intervention of an extended 'sulfoquinone' intermediate (**328**).[157]

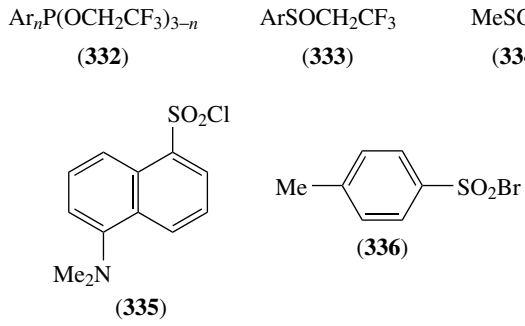


(**327**) (**328**)

Tris(fluorosulfuroyl)fluoromethane (**329**) reacted with bis(diethylamido)benzyl phosphite to yield an intermediate (**330**) which extruded a molecule of SO_2 to give as final product the bis(fluorosulfonyl) compound (**331**).[158] The kinetics and mechanism of the reaction of fluorinated tricoordinate phosphorus compounds (**332**) and aryl 2,2,2-trifluoroethyl sulfenates (**333**) have been reviewed.[159]

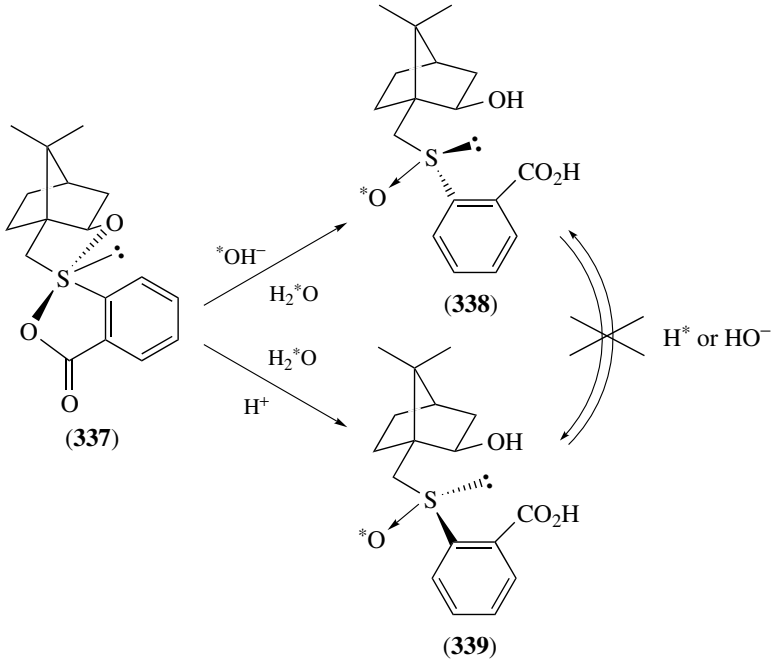


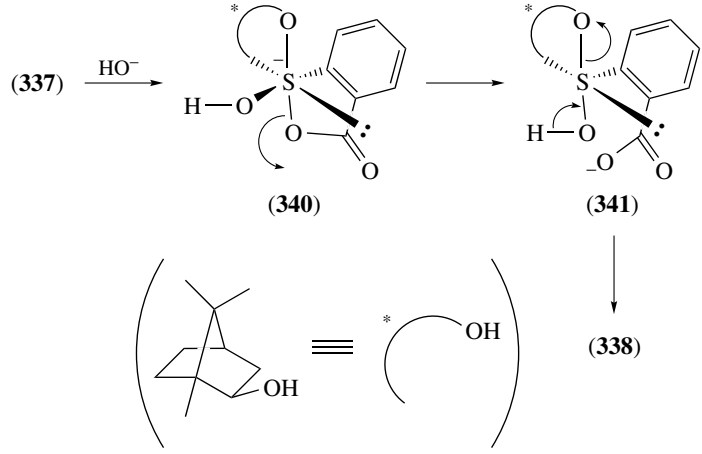
Ab initio SCRF/MO methods have been applied to the hydrolysis and methanolysis of methanesulfonyl chloride (**334**).[160] The aminolysis by aromatic amines of sulfonyl and acyl chlorides has been examined in terms of solvent parameters, the former being the more solvent-dependent process.[161] Solvent effects on the reactions of dansyl chloride (**335**) with substituted pyridines in MeOH–MeCN were studied using two parameters of Taft's solvatochromatic correlation and four parameters of the Kirkwood–Onsager, Parker, Marcus and Hildebrand equations. MeCN solvent molecules accelerate charge separation of the reactants and stabilize the transition state.[162]



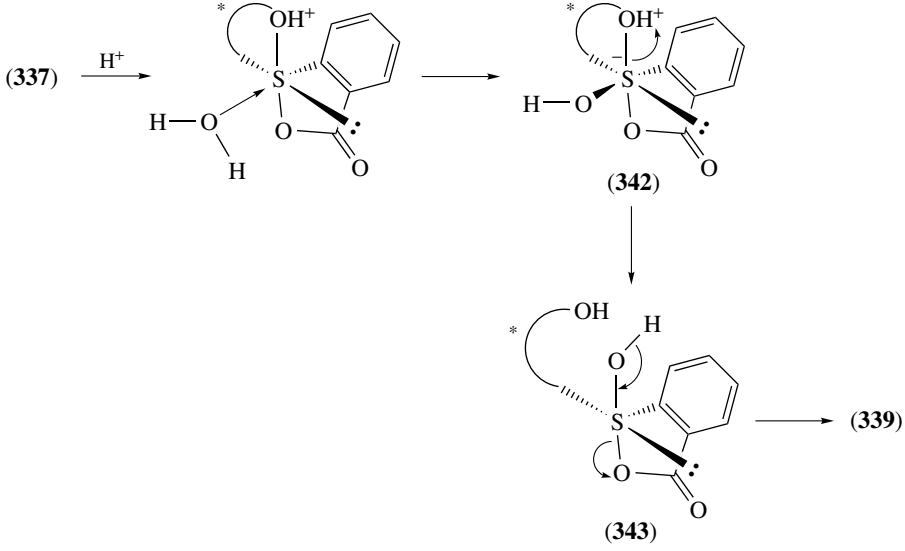
The activation parameters of the hydrolysis in aqueous dioxane of *p*-toluenesulfonyl bromide (**336**) pass through maxima at dioxane mole fractions of 0.01 and 0.12, which correspond to the range of stabilization of the solvent structure.[163]

The chiral spiro-λ_4-sulfurane (**337**) is easily hydrolysed under basic conditions (1 M NaOH) to give optically pure sulfoxide (**338**) as a single diastereomer. In contrast, hydrolysis of spiro sulfurane (**337**) under acidic conditions (1 M HCl) gave sulfoxide (**339**), also as a single diastereomer but with an opposite absolute configuration at the sulfur atom. The proposed mechanism of these reactions is as follows: hydrolysis under basic conditions may proceed through the attack of hydroxide ion on the central sulfur atom to give an intermediate (**340**) (Scheme 39). Cleavage of the S−O(acyloxy) bond and isomerization around the sulfur centre generates the pentacoordinate intermediate (**341**) with the hydroxyl group at the apical position. Then, deprotonation and tandem breaking of the S−O(alkoxy) bond takes place to give the highly diastereoselective formation of the sulfoxide (**338**) with *R* absolute configuration. Under the acidic conditions, the reaction may proceed through the initial protonation of the spirosulfurane at the oxygen of alkoxy, then attack by H_2O at the sulfur atom takes place and a hexacoordinate sulfur intermediate (**342**) is formed (Scheme 40). Cleavage of the S−O(alkoxy) bond of the intermediate (**342**) and isomerization around the sulfur centre produce an intermediate (**343**) with the hydroxyl group at the apical position. Final deprotonation and consecutive breaking of the S−O(acyloxy) bond gave sulfoxide (**339**) with *S* absolute configuration at the sulfur atom.[164]





SCHEME 39



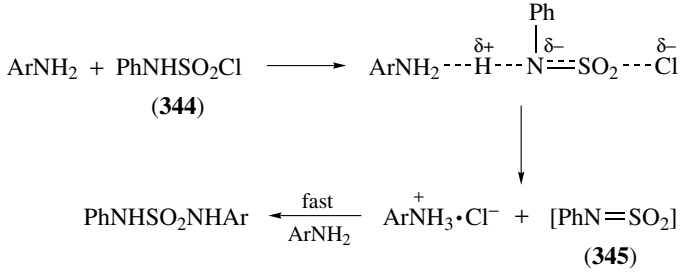
SCHEME 40

Sulfur–Nitrogen Compounds

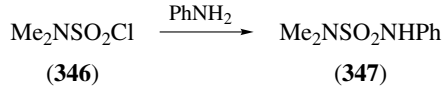
Detailed studies of the anilinolysis of *N*-phenylsulfamoyl chloride (**344**) (and related compounds) in chloroform support the operation of an *E2*-type mechanism in which an *N*-sulfonylamine (**345**) is formed in the rate-determining step (Scheme 41).[165] Lacking a proton on nitrogen, the corresponding *N,N*-dimethylsulfamoyl chloride (**346**) (and its congeners) cannot undergo an elimination of HCl, and instead attack by aniline occurs at the sulfur of the sulfamoyl group to yield *N,N*-dimethyl-*N′*-phenylsulfamide

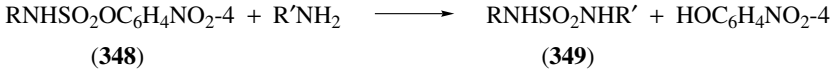
(**347**). This is a very much slower reaction and proceeds at rates 10^6-fold slower than the elimination pathway.[165] The same group has studied the aminolysis in chloroform of the corresponding *p*-nitrophenyl *N*-alkyl- or *N*-phenyl-sulfamates (**348**) which also yield sulfamides (**349**). Reaction with 2-substituted imidazoles, it was concluded,[166] probably proceeds via an *ElcB* mechanism (Scheme 42) involving extensive S−O bond cleavage with the formation of an *N*-sulfonylamine. Extending these aminolysis studies to a set of *p*-nitrophenyl *N*-*X*-phenyl sulfamates (**348**) using piperidine and a set of five pyridines, Brønsted β_{nuc} values have been determined which support *E2* mechanisms for these bases, although the data indicate that those reactants with the larger β_{nuc} values probably veer towards the *ElcB* pathway somewhat.[167]

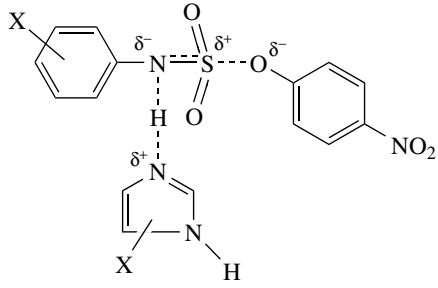
Kinetic studies of the hydrolysis of aryl *N*-(methoxycarbonyl)sulfamates (**350**) are reported for the first time.[168] The compounds are fairly strong acids with pK_a = 0.5–2.4, and in acid both S−O and C−O bond cleavages occur (Scheme 43). From an



SCHEME 41



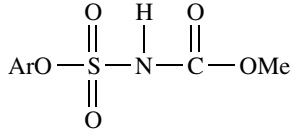




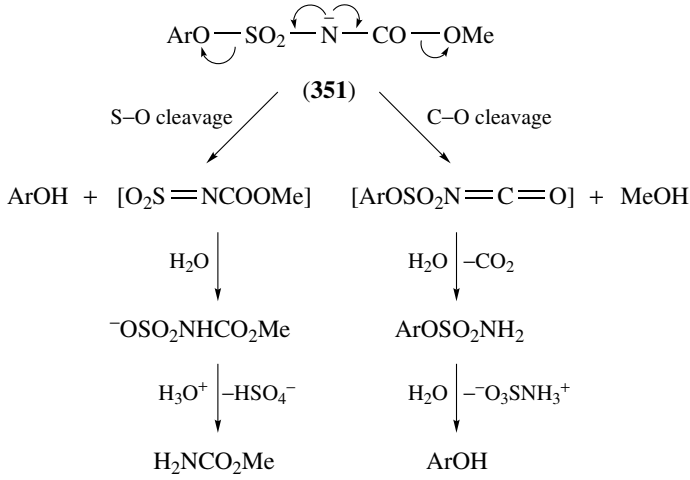
SCHEME 42

analysis of β_{lg}, solvent isotope effects, and solvent isotopic labelling of products, it was concluded that the S−O cleavage reaction involves either an intra- or inter-molecular general-acid-catalysed decomposition of the parent compound (**350**) or its ionized form (**351**) and the C−O cleavage reaction involves protonation of the leaving-group methanol and its expulsion from the dipolar intermediate (Scheme 43).[168]

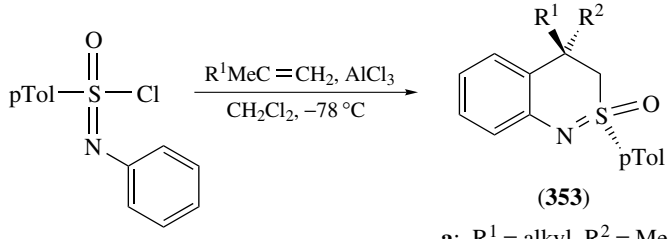
The Lewis acid-mediated reaction of *N*-phenyl-*S*-(4-methylphenyl)sulfonimidoyl chloride (**352**) with 1,1-disubstituted alkenes yields benzothiazines (**353**) with low stereoselectivity in moderate yields (33–57%).[169]



(**350**)



SCHEME 43

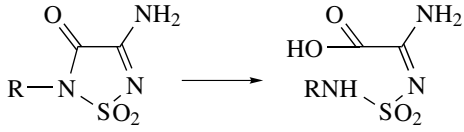


(**352**)

(**353**)

a; R^1 = alkyl, R^2 = Me

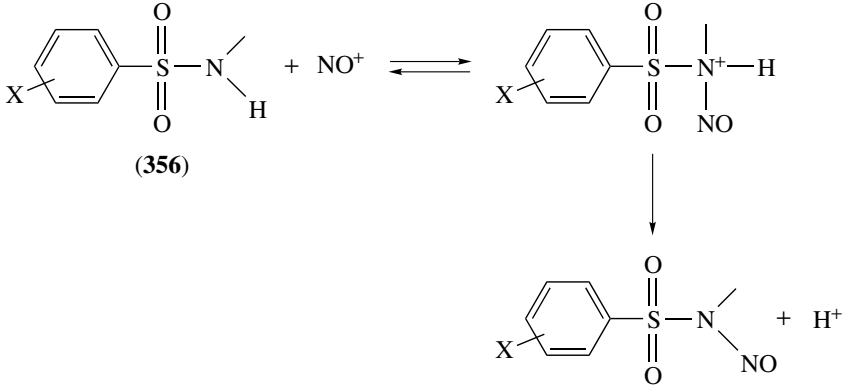
b; R^1 = Me, R^2 = alkyl



(**354**) (**355**)

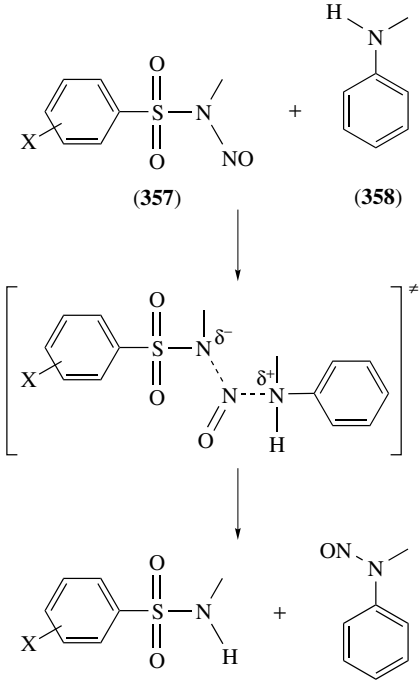
The kinetics of the hydrolysis reactions of 4-amino-2-phenethyl- (**354**; R = $PhCH_2CH_2$) and 4-amino-2-cyclohexyl-2,3-dihydro-3-oxo-1,2,5-thiadiazole 1,1-dioxide (**354**; R = C_6H_{11}) have been investigated in the pH range 1–10 at 24–73 °C. The products are the corresponding new compounds: 2-amino-2-[(*N*-substituted-sulfamoyl)imino]acetic acid salts (**355**; R = $PhCH_2CH_2$ or C_6H_{11}) which hydrolyse further, in a slow reaction, to the sulfamide and oxalic acid derivatives.[170]

Studies of the kinetics of the nitrosation of a series of 4-substituted *N*-methylbenzenesulfonamides (**356**) have revealed that electron-withdrawing groups retard the process. The mechanism probably involves a fast nitrosation pre-equilibrium followed by a slow proton transfer to the medium (Scheme 44).[171] The de-nitrosation reaction, which was also studied, is general acid catalysed and proceeds via a rate-determining proton transfer.[171] The same group determined the hydrolytic stability and efficiency as nitrosating agents of a small set of acyl-substituted *N*-methyl-*N*-nitrosobenzenesulfonamides (**357**; X = 2, 4, 6-Me_3, 4-OMe, 4-Cl and 4-NO_2). The nitrosating reactivity was measured by reaction of each with *N*-methylaniline (**358**), which reacts via a transition state with zwitterionic character (Scheme 45).[172] The acid and base hydrolysis of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (**357**; X = 4-Me) in micellar media have been reported.[173,174] 1-Methyl-1-nitroso-3-*p*-tolylsulfonylguanidine (**359**) undergoes a denitrosation reaction in acid medium which is probably concerted (Scheme 46).[84]



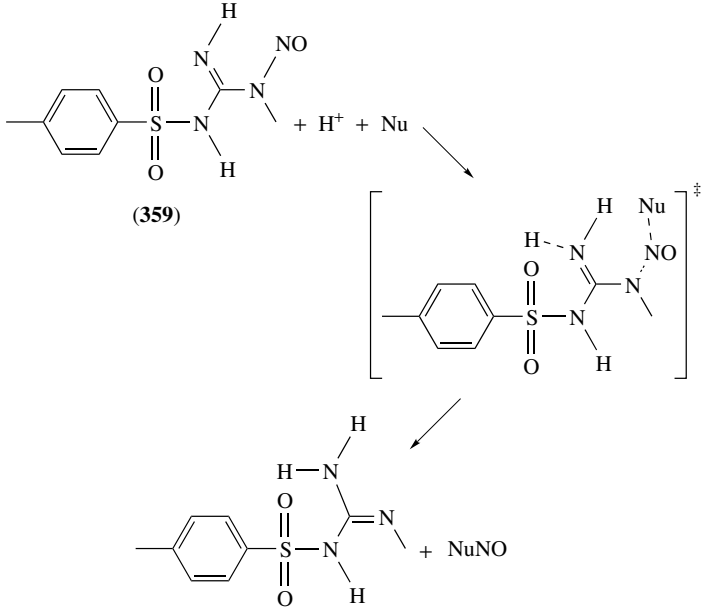
(**356**)

SCHEME 44



(**357**) (**358**)

SCHEME 45



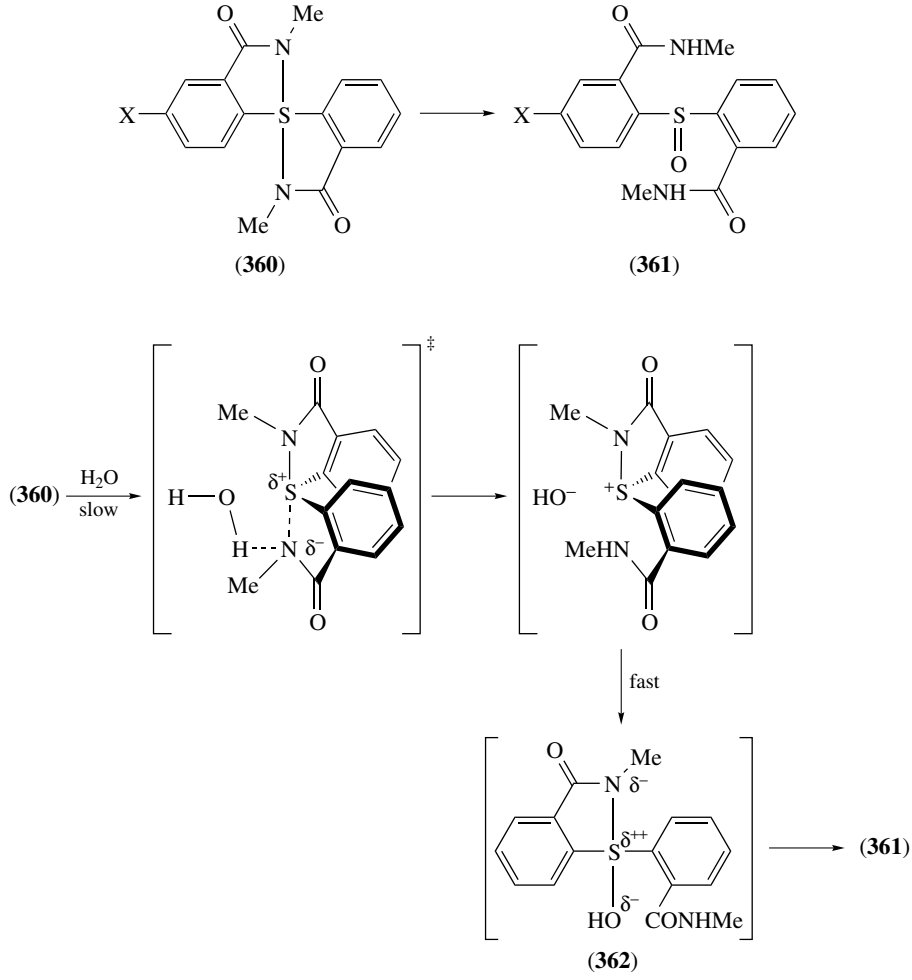
(**359**)

SCHEME 46

The parent compound and a set of monosubstituted bis(acylamino)diarylspiro-λ_4-sulfanes (**360**; X = H, Me, MeO, Cl, NO_2) undergo hydrolysis to the corresponding sulfoxides (**361**). The probable mechanism involves rate-determining cleavage of one of the S−N hypervalent bonds in the spiro ring with simultaneous proton transfer to the nitrogen atom. The hydroxide ion which is formed thereby then attacks the sulfur atom in a fast step to form a diaryl(acylamino)hydroxy-λ_4-sulfane (**362**), which is converted into the sulfoxide (**361**) (Scheme 47).[175]

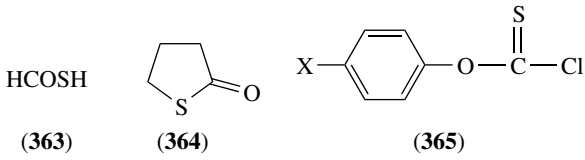
Sulfur–Carbon Compounds and Other Sulfur-containing Functionalities

An *ab initio* study of the unimolecular pyrolysis mechanisms of monothioformic acid (**363**) has yielded activation energies for dehydrogenation and dehydrosulfidation.[176]

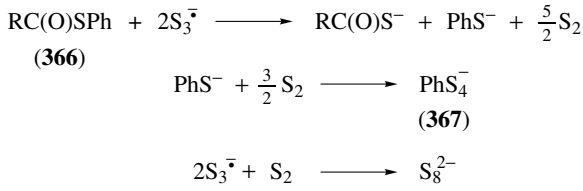


SCHEME 47

Enthalpy barriers for the decarbonylation and dethiocarboxylation of γ-thiobutyrolactone (**364**) have been calculated as 378 and 404 kJ mol^{-1}, respectively, which accords with the experimental results which saw CO as the major and COS as the minor thermal degradation products.[177] Phenyl and 4-nitrophenyl chlorothionoformates (**365**; X = H, NO_2) reacted with phenolates in aqueous dioxane with $\beta_{nuc} = 0.55$ and 0.47, respectively, from which it was concluded that a concerted mechanism prevailed.[178]



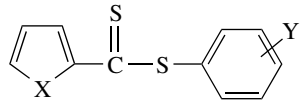
(**363**) (**364**) (**365**)



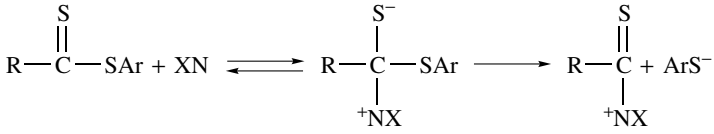
(**366**) (**367**)

SCHEME 48

S-Thiophenyl acetates (**366**; R = Me) and propionates (**366**; R = Et) react with electrogenerated polysulfide ions $S_3^{\bullet-}$ in DMF to yield thiocarboxylate ions, thiolate ions, and phenyl tetrasulfanide (**367**), the last deriving from the reaction of thiolate ions with sulfur (Scheme 48).[179] Studies of the aminolysis by a set of substituted anilines of Y-aryl dithio-2-thiophenates (**368**; X = S) and dithio-2-furoates (**368**; X = O) in acetonitrile have shown that the rate-determining step in these reactions is the departure of the thiophenolate ion from the zwitterionic tetrahedral intermediate $T^{\pm}$ (Scheme 49). Experiments with deuteriated anilines yielded k_H/k_D values of 1.7–1.9,

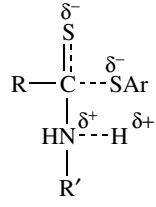


(**368**)



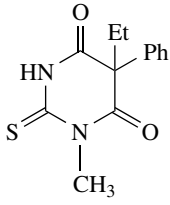
SCHEME 49

and these results are considered to favour a four-centre-type transition state (**369**).[180] Similar studies of the aminolysis of *O*-ethyl *S*-aryl dithiocarbonates point to an analogous mechanism (Scheme 49; R = EtO) involving a four-centre transition state (**369**; R = EtO).[181]

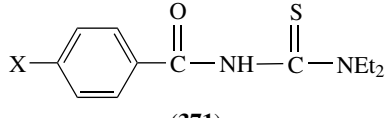


(**369**)

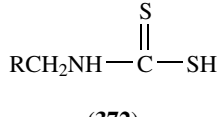
The kinetics of the alkaline hydrolysis of 5-ethyl-1-methyl-5-phenyl-2-thioxo-4,6-(*1H,3H,5H*)-pyrimidinedione (2-thioprominal) (**370**) have been reported.[182] Hammett plots of pK_a values were linear for a series of *N*-*X*-benzoyl *N*′, *N*′-diethylthioureas (**371**).[183]



(**370**)

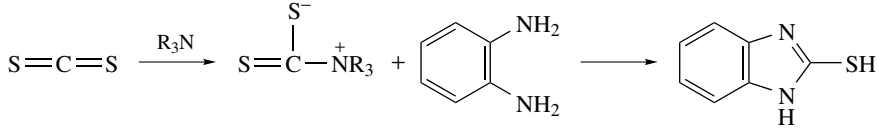


(**371**)



(**372**)

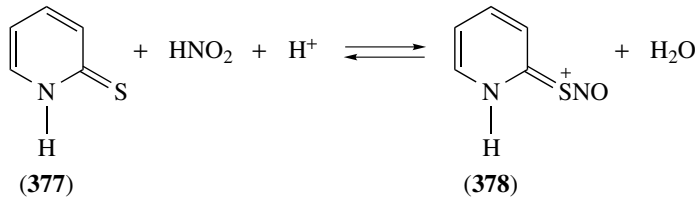
Kinetic studies of the acid hydrolysis of *N*-alkyl dithiocarbamates (**372**) have been reported.[184] The tertiary amine-catalysed addition of CS_2 (**373**) to 1,2-diaminobenzene (**375**) involves initial formation of the zwitterionic adduct (**374**), which then reacts with the diamine (**375**) to yield 2-mercaptobenzimidazole (**376**).[185]



(**373**) (**374**) (**375**) (**376**)

2-Mercaptopyridine (**377**) reacts rapidly with nitrous acid in mildly acid aqueous solution (via the thione tautomer) to give an unstable *S*-nitroso ion (**378**) in a reversible

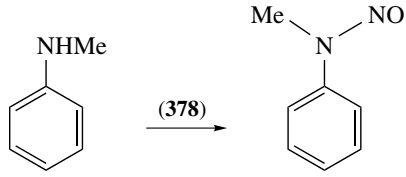
process with an equilibrium constant (K_N) of ca 1×10^5 dm^6mol^{-2}. SNO^+ is readily detected by two peaks in the UV spectrum at 295 and 240 nm with molar absorptivities of 9600 and 9300 $dm^3mol^{-1}cm^{-1}$, respectively; (**377**) is regenerated when the solution is made alkaline. In acidic solution, SNO^+ decomposed to the disulfide (2,2′-dipyridyl disulfide) and NO. There was clear evidence that SNO^+ can act as an efficient nitrosating species: addition of the thiol *N*-acetylcysteine (**379**) resulted in the almost instantaneous decomposition of SNO^+; addition of *N*-methylaniline (**380**) to an acidified solution of SNO^+ resulted in quantitative *N*-methyl-*N*-nitrosoaniline (**381**) formation.[186]



(**377**) (**378**)

$MeCONHCH(CO_2H)CH_2SH$

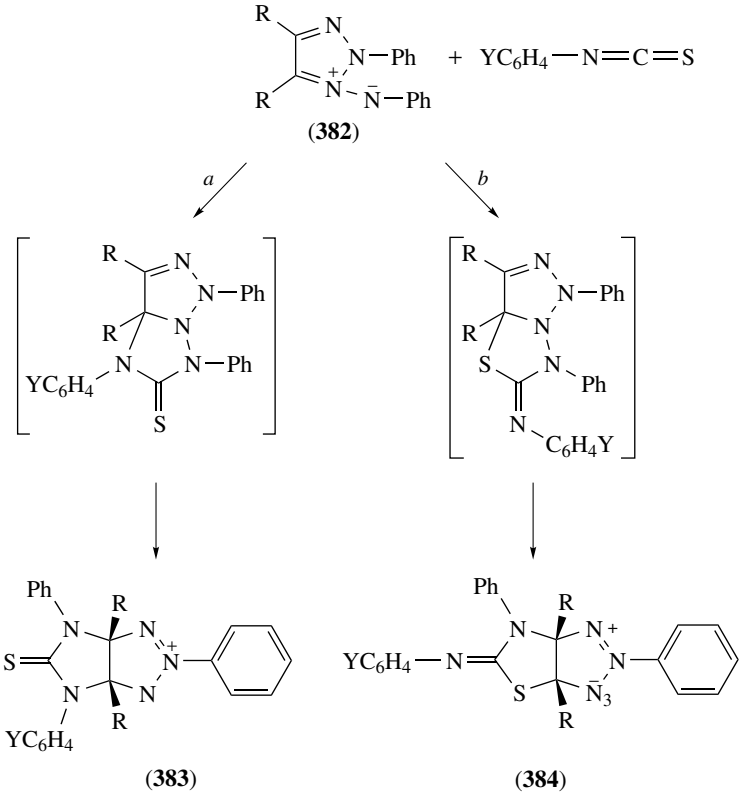
(**379**)



(**380**) (**381**)

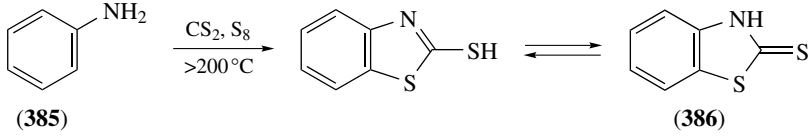
Substituted 1,2,3-triazolium-1-aminide 1,3-dipoles (**382**) react with aryl isothiocyanates at both the N=C (path *a*) and C=S (path *b*) sites to give mixtures of substituted imidazolo[4,5-*d*][1,2,3]triazoles (**383**) and new thiazolo[4,5-*d*][1,2,3]-triazoles (**384**) including tricyclic derivatives with the C(3a) and C(6a) bridgeheads linked via $(CH_2)_4$ and phenanthro groups (Scheme 50). The product distribution is controlled by the *para*-substituent of the aryl isothiocyanate. Theoretical calculations at the 3–21G* and 6–31G* levels suggest that linear triple-bonded canonical forms of the aryl isothiocyanate system play a key role in the ambident reactivity of these systems.[187]

The formation of benzothiazole-2-thiol (**386**) from aniline (**385**), carbon disulfide, and sulfur at 230 °C has been shown to occur by a sequence of three principal steps. Labelling experiments confirmed that both sulfur atoms originated from carbon disulfide. An initial polar reaction to form thiocarbanilide (**389**) via phenylcarbamic acid



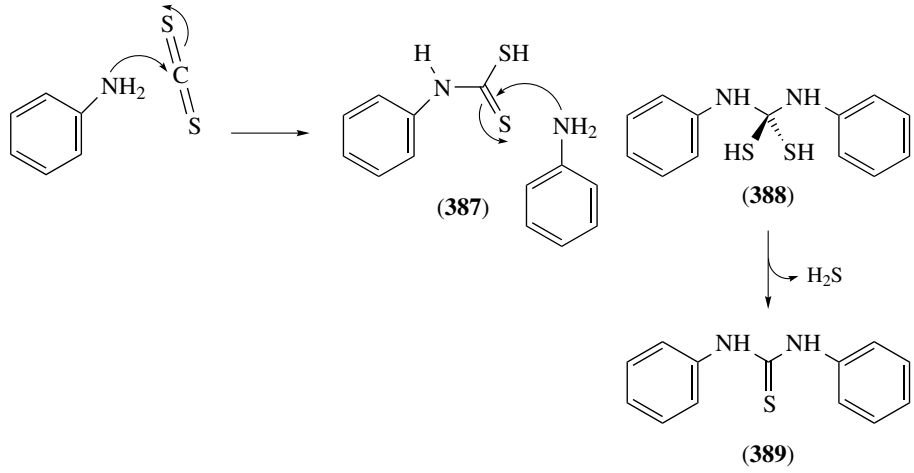
SCHEME 50

(**387**) and a tetrahedral intermediate (**388**) (Scheme 51) is followed by radical cyclization of these to benzothiazole (**386**) and 2-phenylaminobenzothiazole (**390**); the latter is converted into the desired product (**386**) by a polar displacement of aniline by H_2S (Scheme 52).[188]

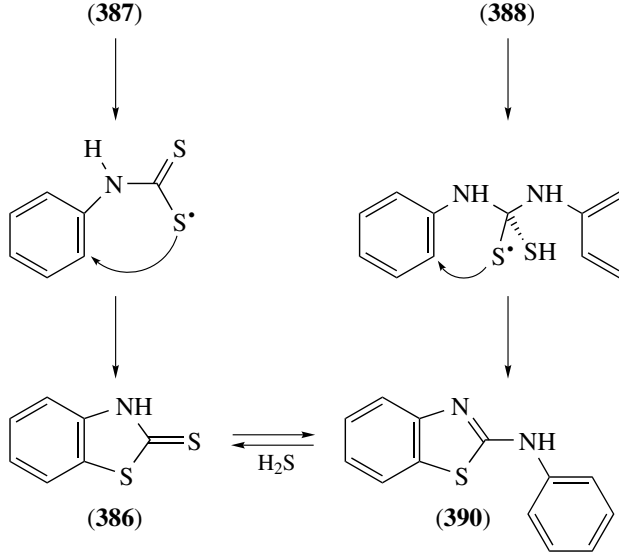


Other Acids

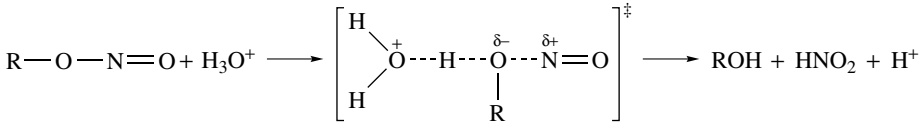
The acid hydrolysis of alkyl nitrites (Scheme 53) is inhibited by the presence of β-cyclodextrin (CD) owing to the formation of 1:1 inclusion complexes that are unreactive or much less reactive than the RONO not complexed. The degree of inhibition



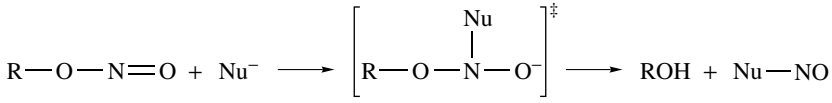
SCHEME 51



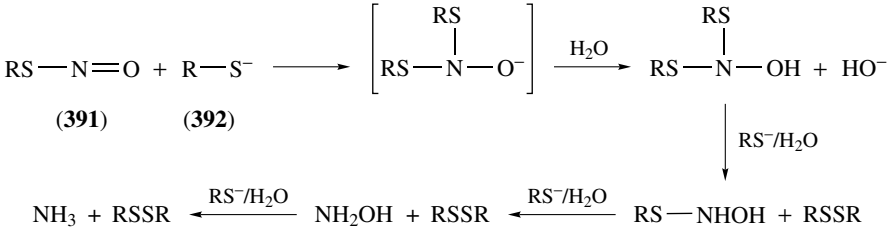
SCHEME 52



SCHEME 53



SCHEME 54



SCHEME 55

increases with increase in the association of the alkyl nitrite to CD: those with aromatic substituents interact more efficiently with the apolar CD cavity than do aliphatic alkyl nitrites. However, the basic hydrolysis of alkyl nitrites (Scheme 54) at pH values higher than the pK_a of β-cyclodextrin is powerfully catalysed by the presence of β-cyclodextrin because the nucleophilic reaction of alkyl nitrite by an ionized secondary hydroxy group of CD is faster than the reaction with HO^-, i.e. the reaction rate of the complex is faster than that of the RONO not complexed.[189]

Reactions of *S*-nitrosothiols (**391**) with their corresponding thiols (**392**) present in a large excess (>20-fold) proceed readily to give the disulfide. Ammonia is formed together with some nitrite anion, and these constitute >90% of the 'nitrogen' products. This is in marked contrast with the reaction at low thiol concentration, where nitric oxide is the major initial 'nitrogen' product, which is rapidly converted in the presence of oxygen in water into nitrite anion. The ammonia-forming reaction (Scheme 55) involves initial rate-determining attack of RS^- (**392**) at the nitrogen atom of the *S*-nitrosothiol (**391**), which is followed by other reactions of RS^- at the sulfur atom and various proton transfers, leading to the formation of hydroxylamine, then ammonia. For *S*-nitrosocysteine [**391**; R = $H_2NCH(CO_2)CH_2$], this pathway accounts for 80% of the total reaction at 25 mM cysteine [**392**; R = $H_2NCH(CO_2H)CH_2$]. The mechanism of the NO-producing reaction is to be the subject of a subsequent study, and could be either a homo- or hetero-lytic process.[190]

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