Reaction mechanisms
Part (iii) Polar reactions

AnnMarie C. O'Donoghue and Chukwuemeka Isanbor

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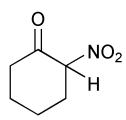
This review will focus on papers in 2008 reporting mechanistic studies of polar reactions predominantly in solution.

1. Hydrogen transfer

The papers reviewed in this section mainly consider polar reactions that involve a key proton transfer step. Two relevant examples of mechanistic studies involving hydride transfer and hydrogen bonding are also included. The rates of tautomerization of 2-nitrocyclohexanone **1** to enol **2** have been measured spectrophotometrically at 25 °C in several aprotic solvents and their binary mixtures.[1] The reaction was found to be catalyzed by bases, inhibited by acids and a "spontaneous" reaction, assigned as autocatalysis, was observed. The overall solvent effect on tautomerization could be accounted for by a Kamlet–Taft multiparameter equation.

A series of ruthenocene containing β-diketones **3** have been synthesised and apparent pK_a' values for ionisation at either the central carbon or an oxygen were determined by UV-Vis spectrophotometry.[2] Rate constants of interconversion of the keto and enol isomers, and corresponding equilibrium constants, were determined utilizing NMR spectroscopy, cyclic voltammetry or Osteryoung square wave voltammetry. The oxidation potential of the ruthenocene fragment was studied using cyclic voltammetry. The rate constants of ketonisation and enolisation, corresponding equilibrium constants, pK_a' values and ruthenocenyl oxidation potentials were all shown to be dependent on the electronegativity of the R-substituent.



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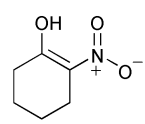

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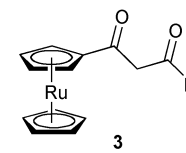
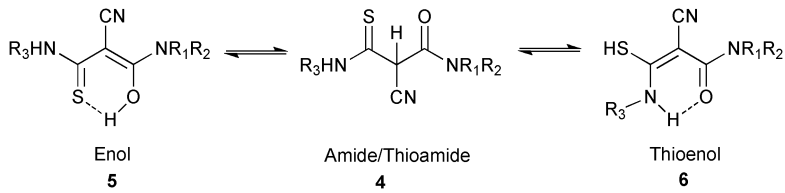


3

The equilibrium between thioamides RNHCSCHYY′ and their tautomeric thioenols RNHC(SH)=CYY′ in different aprotic solvents has been investigated by ^1H and ^{13}C NMR spectroscopy for substrates where Y and Y′ are electron withdrawing substituents.[3] In contrast to simple ketones and thioketones in which thioenolization is favoured over enolization by factors as large as 10^6, the effect of intramolecular competition by electron withdrawing ester groups Y and Y′ was to decrease this ratio. In a similar study, the equilibrium distribution of amide/thioamide **4**, enol **5** and thioenol **6** in different aprotic solvents has been determined (Scheme 1).[4] The $K_{Thioenol} + K_{Enol}$ in various solvents was found to follow the order $CCl_4 > CDCl_3 > C_6D_6 >$ THF-d_8 > $(CD_3)_2CO$ > CD_3CN > DMF-d_7 > DMSO-d_6. An intramolecular O–H···S hydrogen bond was found to lead to the preferred *Z*-configuration of the

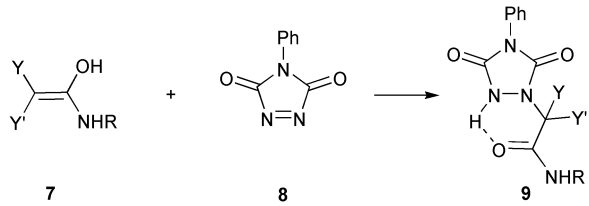
Department of Chemistry, University Science Laboratories, South Road, Durham, UK. E-mail: annmarie.odonoghue@durham.ac.uk; Fax: +44 191 384 4737; Tel: +44 191 3342 592



Scheme 1

enols whereas an N–H···O bond was found to stabilize the thioenol's preferred *E*-configuration with a non-bonded SH in solution.

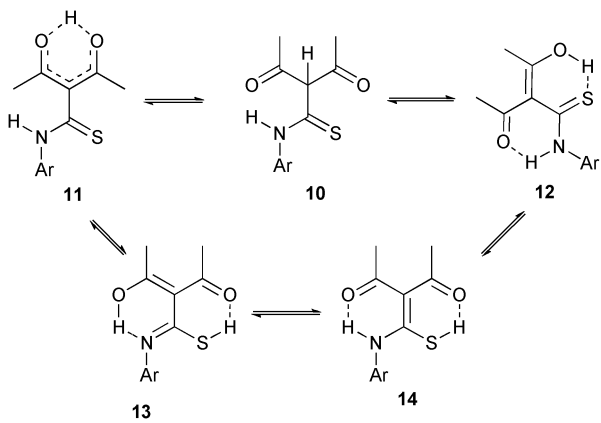
The reaction of 16 enols of amides **7** with 4-phenyl-1,2,4-triazoline-3,5-dione **8** has been found to give open chain adducts **9**, rather than [2 + 2] cycloadducts with a hemiaminal moiety, both in solid state and in solution (Scheme 2).[5] A formal oxa-ene mechanism was suggested which involves initial nucleophilic attack of $Y'YC^-$ of the enol at one of the nitrogens of dione **7** followed by, or coupled with, proton transfer to the other nitrogen.



Scheme 2

Keto form **10** and four enolic forms **11–14** have been detected in a study of the equilibrium between keto-enol tautomeric forms of *N*-aryl-diacetylthioacetamides **10** in several aprotic solvents, by use of ^1H and ^{13}C NMR spectroscopy (Scheme 3).[6] Enol **11** dominated in more polar solvents such as DMSO-d_6 whereas all other tautomeric forms contributed in similar proportions in less polar solvents such as chloroform and benzene. The implication of the tautomeric distribution in heterocylization reactions of ketone **10** was discussed.

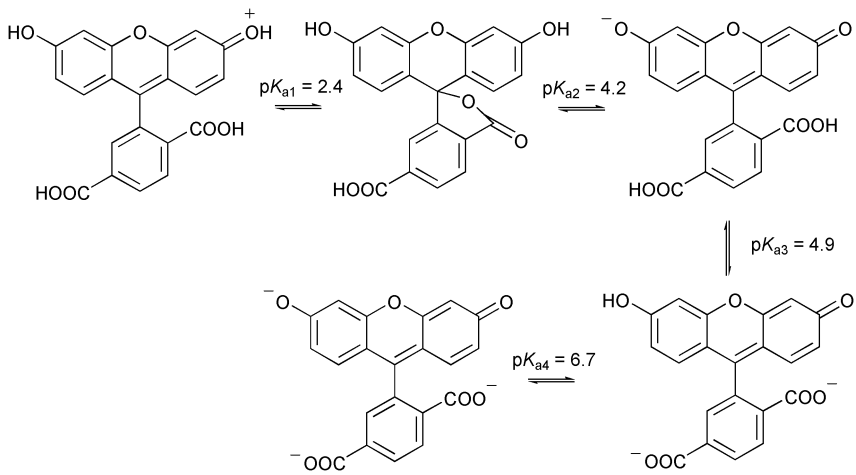
Rate constants of photolysis of 4-formylphenylacetic acid have been measured in a range of H_2O (and D_2O) solutions of different pH (pD) values.[7] The resulting rate



Scheme 3

profiles and solvent isotope effects were suggested to provide evidence for the formation of an elongated enol intermediate that is 2–3 pK units more acidic than simple non-elongated enols.

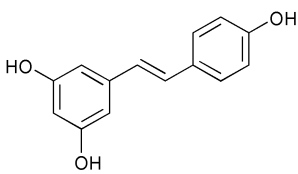
The four overlapping pK_a values of the fluorescent probe carboxyfluorescein (Scheme 4) have been experimentally determined by a UV-Vis spectroscopic method employing a combination of absorbance diagrams and chemometric analysis.[8]



Scheme 4

Differences among the absorbance, excitation and emission spectra of natural anti-oxidant (*E*)-resveratrol **15**, measured by absorbance and fluorescence spectroscopy, have permitted the determination of pK_a values of 8.8, 9.8 and 11.4 for the three phenolic hydroxyl groups, and also the aggregation state as a function of pH.[9] A general mass spectrometric method has been developed to determine the imidazolyl N1 pK_a value of histidine residues in proteins.[10] The method is based on the fact that the imidazole C2 undergoes H/D exchange at a rate that is a function of the ionisation state at N1. Values of pK_a in the range 24.7–27.2 have been determined for seven guanidine derivatives **16** (R_1, R_2 = $(CH_2)_2CH_3$ or $(CH_2)_3N(CH_3)_2$ or $(CH_2)_3OCH_3$) in acetonitrile using a UV-Vis spectrophotometric titration method.[11] The most basic among the guanidines was found to be 4 pK_a units more basic than well-known superbase N^1,N^2,N^3,N^4-tetramethylguanidine. Substituent effects on guanidine basicities in acetonitrile were assessed and compared with analogous effects in the gas phase.

Pentakis(trifluoromethyl)benzene **17** (X = H), -toluene **17** (X = CH_3), -phenol **17** (X = OH) and -aniline **17** (X = NH_2) have been synthesised by a pertrifluoromethylation route.[12] The gas phase acidities and pK_a values in different solvents (acetonitrile, DMSO, water) were measured for the title compounds **17** and a number of related molecules.



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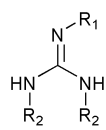

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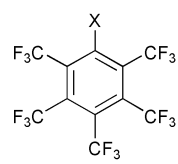
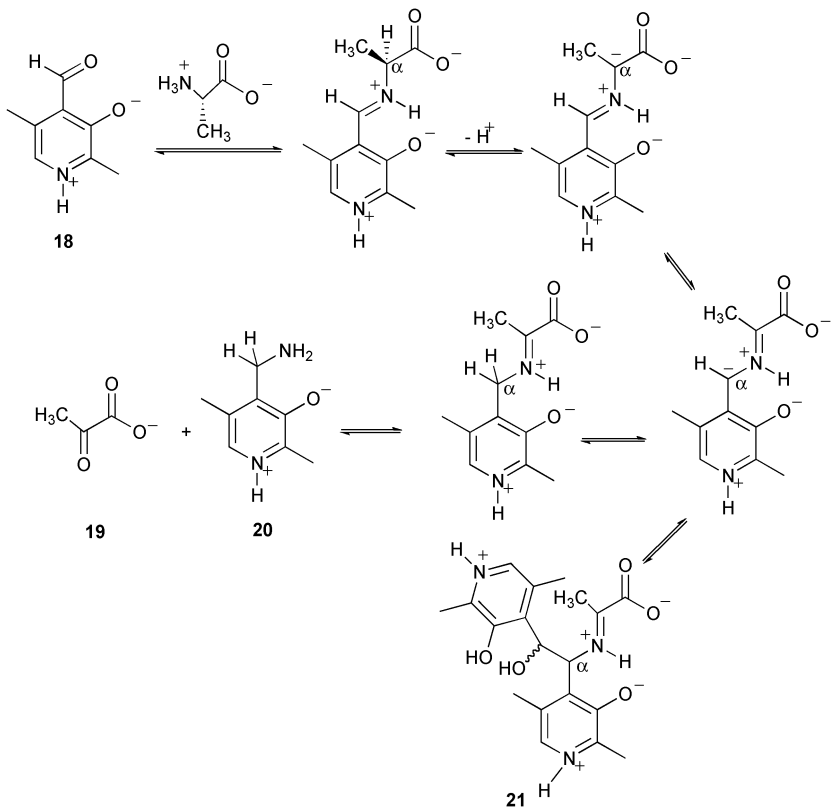


17

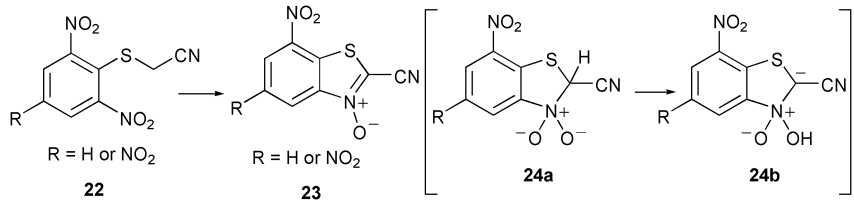
The non-enzymatic reaction of 5′-deoxypyridoxal **18** with L-alanine in water at 25 °C was found to give pyruvate **19**, pyridoxamine **20** and 'dimeric' species **21** at early reaction times where the latter is in chemical equilibrium with reactants (Scheme 5).[13] These products were suggested to be the result of the initial formation of an imine, from the reaction of 5′-deoxypyridoxal **18** with L-alanine, which undergoes deprotonation at the α-amino carbon of alanine to form a resonance delocalised carbanion. Reprotonation at the α-pyridyl carbon of this carbanion followed by hydrolysis yields products **19** and **20** whereas reaction of the α-pyridyl carbanionic centre with a second molecule of 5′-deoxypyridoxal **18** yields dimer **21**. No Claisen-type addition products were observed from the addition of the α-amino carbanionic centre to 5′-deoxypyridoxal **18** in contrast to the analogous reaction with glycine. In a related study, second order rate constants have been determined of deprotonation by DO^- and by Brønsted bases of the α-imino carbon of imines/iminium ions formed from the addition of glycine methyl ester to acetone and of glycine to phenylglyoxalate.[14] Formation of the iminium ions from acetone and glycine methyl ester and from phenylglyoxalate and glycine, was estimated to cause 7 and 15 pK unit decreases, respectively in the pK_a values relative to those for deprotonation of the parent carbon acids.



Scheme 5

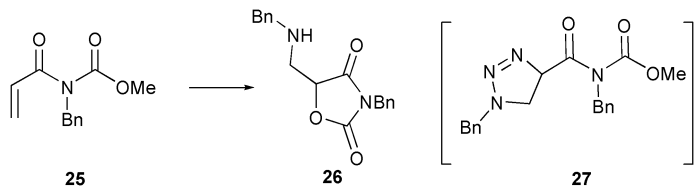
The kinetics and mechanism of cyclization of 2,6-dinitrophenyl- and 2,4,6-trinitrophenyl-sulfanylethane nitrile **22** to give 2-cyano-7-nitro- and 2-cyano-5,7-dinitrobenzo[*d*]thiazole-3-oxide **23** have been studied in methanolic *O*-buffers

at 25 °C (Scheme 6).[15] The reactions showed both general acid and base catalysis to an extent dependent on the pK_a of the buffer component and the ratio of both buffer components. In weakly basic buffers the rate-limiting step was shown to be C–H bond breaking at the cyclic intermediate **24a** while in strongly basic buffers general acid catalyzed elimination of hydroxide ion from intermediate **24b** was rate-limiting.



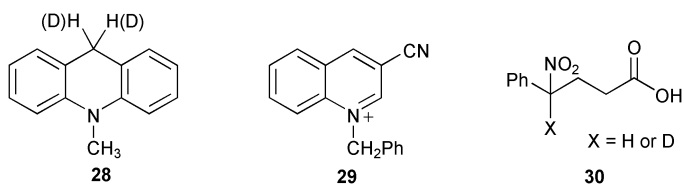
Scheme 6

The mechanism of reaction of phenylnitroso compounds with 2-(α-hydroxyalkyl)-3,4-dimethylthiazolium trifluoromethanesulfonate ('thiamine active aldehyde') to give *O*- and *N*-acyl-aryl hydroxylamines has been studied.[16] A primary kinetic isotope effect (KIE) of 4.9 obtained for the appropriate 2α-deuterated thiazolium salt was suggested to indicate that $C_{2\alpha}H$ bond cleavage is rate-limiting. The mechanism of the Brønsted acid-catalyzed conversion of olefin **25** to oxazolidine dione **26** in acetonitrile has been studied (Scheme 7).[17] Significant acceleration of the rate of addition of benzyl azide to the olefin **25** was caused by triflic acid, and under anhydrous conditions an intermediate triazoline **27** could be identified by *in situ* IR spectroscopy. It was suggested that the subsequent conversion of triazoline **27** to the oxazolidine dione **26** requires proton transfer from N3 to N1, which was shown to be facilitated by added water.



Scheme 7

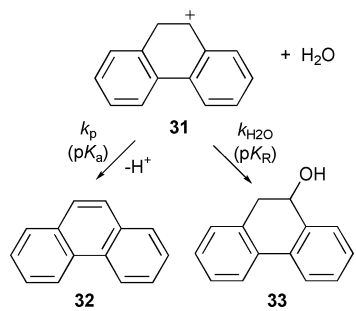
The intramolecular KIE for hydride transfer from 10-methyl-9,10-dihydroacridine **28** to the 1-benzyl-3-cyanoquinolinium ion **29** has been found to be in the range 5-6 by both ^{1}H NMR and mass spectrometry.[18] This isotope effect was suggested to be inconsistent with a two-step mechanism *via* a significant intermediate as it is similar to KIEs measured for other hydride transfers.



Rates of racemization of optically active 4-nitro-4-phenylbutanoic acid **30-H** have been measured in dimethoxyethane-water in the presence of triethylamine.[19] At greater than one equivalent of triethylamine, the racemization rates were independent of base concentration consistent with deprotonation of the nitroalkane by the intramolecular carboxylate group. Rates of exchange with D_2O were equal to the rates of racemization in dimethoxyethane: D_2O, which indicates that proton transfer is rate-limiting. An effective molarity of 13.7 for the carboxylate group was determined by comparison with the analogous reactions of the methyl ester. The KIE for racemization of acid **30-H** and the 4-deutero-analogue **30-D** was determined as $k_H/k_D = 5.78$ at 25 °C and for $20 < T < 50$ °C, $E_a^D - E_a^H = 5.2$ kJ mol^{-1} and $A_H/A_D = 0.63$. This data, it was suggested, indicates the absence of a major tunnelling contribution. The S_N2 reactivities of substituted alkoxides in the gas phase have been measured as part of a study of intramolecular solvation effects on nucleophilicity.[20] Application of Marcus theory to this data permitted the determination of the intrinsic nucleophilicities of the alkoxides. It was found that hydrogen bonding significantly decreases intrinsic nucleophilicity whereas substitution by polar groups has little effect.

2. Reactions involving carbocations

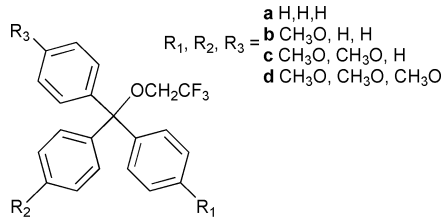
Using an 'azide clock' technique values of $k_p = 3.7 \times 10^{10}$ s^{-1} and $k_{H_2O} = 1.5 \times 10^8$ s^{-1} have been determined for deprotonation of the phenanthrenonium ion **31** to give phenanthrene **32** or by combination with water to give phenanthrene hydrate **33** (Scheme 8).[21] This data was used to estimate values of $pK_a = -20.9$ and $pK_R = -11.6$ for the phenanthrenonium ion **31**. This new data helped anchor a correlation between log k_p and pK_a for a range of aromatic molecules and enabled predictions of pK_a values for protonated benzene and naphthalene. Combining these pK_a values with available pK_{H_2O} values for the hydration of these arenes provided values of $pK_R = -2.3$ and -8.0 for the benzenonium and naphthalenonium ions, respectively and highlights the inherent stability of the benzenonium ion.



Scheme 8

The acid-catalyzed hydrolysis of methoxy-substituted trityl trifluoroethyl ethers **34** has been studied by UV-Vis spectrophotometry in dilute acidic aqueous solution at 25 °C (trityl = triphenylmethyl).[22] The reactivity of the parent trityl trifluoroethyl ether **34a** was found to be too low to quantify under these conditions. A computational study of the enthalpy and free energy for dissociation of $Ph_3C–O(H)CH_2CF_3 \cdot (H_2O)^+$ in the gas phase showed that it is not a stable bonded species. This, it was suggested, implies that acid-catalyzed fragmentations of methoxy analogues **34b–d** in aqueous solution are concerted with proton transfer. In a separate study, the

4,4′,4″-trimethoxytrityl cation ((4-$CH_3OPh)_3C^+$) has been observed to react with acetate ion in acetic acid reversibly to give the corresponding acetyl ester.[23] It was observed that the rate of reaction was independent of the concentration of sodium acetate over a 25 000 fold range. Similar results were observed in the presence of Bu_4N^+ in acetic acid as well as in acetic acid/acetonitrile mixtures. This data was interpreted to mean that the trityl carbocation–HOAc/AcO^- is an ion pair that forms during the time of mixing under stopped flow conditions, and that the process studied kinetically was the collapse of this ion pair to the ester product in two steps.



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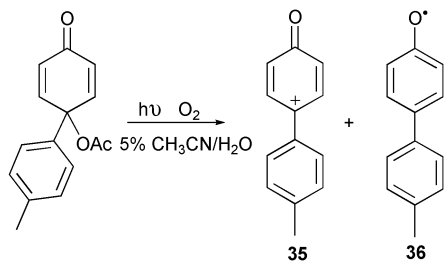
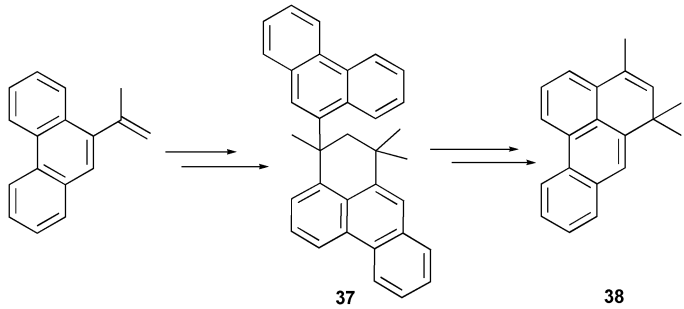
The oxenium ion **35** and aryloxy-radical **36**, reactive intermediates formed in the photolysis of 4-acetoxy-4-arylcyclohexadienones, have been characterized (Scheme 9).[24] Laser flash photolysis in water saturated with oxygen lead to the formation of both intermediates with λ_{max} values of 460 and 360 nm, respectively, whereas the analogous reaction in acetonitrile resulted only in the formation of the aryloxy radical **36**. Decay kinetics of the transients at 460 and 360 nm after photolysis, and identification of the resulting products of decay, permitted the assignment of these transients to oxenium ion **35** and aryloxyradical **36**. Further confirmation of the presence of oxenium ion **35** came from the agreement between calculated and experimental time-resolved Raman (TR^3) spectra.



35 **36**

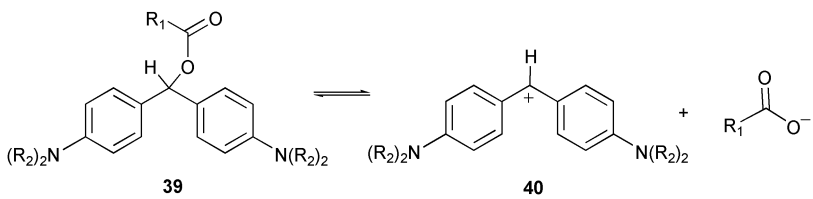
Scheme 9

The isopropenyl derivatives of a range of polycyclic aromatic hydrocarbons (PAHs) having four and five-membered fused ring systems were prepared by Wittig olefination of the corresponding acetyl PAHs.[25] In the presence of triflic acid these derivatives converted to PAH dimers **37** and/or phenalenes **38** (shown in Scheme 10 for the isoprenyl derivative of phenanthrene). The mechanism of formation of dimers and subsequently phenalenes was suggested to proceed *via* several carbocation intermediates. In the case of the isoprenyl derivatives of perylene, the stable carbocation intermediates could be studied directly by NMR spectroscopy in superacid solution.



Scheme 10

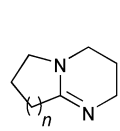
Rate and equilibrium constants of the first step of an S_N1 reaction could be measured by treatment of benzhydryl carboxylates **39** (R_1 = CH_3) with aqueous acetonitrile or acetone (Scheme 11).[26] This resulted in the formation of coloured benzhydrylium carbocations **40**, which do not undergo subsequent reaction with solvent, and permitted the determination of rate and equilibrium constants for carbocation formation spectrophotometrically. It was found that the relative rates of ionisation of esters **39** (R_1 = CH_3) do not correlate with the electrophilicity order of the carbocations **40**. Variable intrinsic barriers were given as the reason for the breakdown in this rate-equilibrium relationship. In a related study, the formation and subsequent decay of the benzhydrylium carbocation **40** (NR_2 = morpholino) from the ionization of benzhydryl esters **39** (R_1 = CH_3 or 4-nitrophenyl; NR_2 = morpholino) in aqueous acetonitrile or acetone could be measured directly in one kinetic run by UV-Vis spectrophotometry.[27] These data provided examples of S_N2C^+ reactions, which involve mechanisms in between the conventional S_N1 reaction, where carbocations appear as short-lived intermediates, and the formation of very stable carbocations where subsequent reactions of the carbocations do not occur.



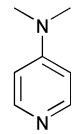
Scheme 11

The second order rate constants of the reaction of bicylic amidine bases DBU **41** and DBN **42** with a series of benzhydryl carbocations **40** have been measured in acetonitrile at 20 °C and could be compared with analogous values for DMAP **43** and DABCO **44**.[28] The rate constants were found to correlate linearly with the electrophilicity parameters of the benzhydryl carbocations, which enabled the determination of the nucleophilicity parameters N and s according to the linear free energy relationship $\log k_{2\ 20\ °C} = s(N + E)$. The order of nucleophilicity was found to increase in the series DMAP < DBU < DBN < DABCO. In a similar study, second order rate constants of the reaction of alkyl-substituted pyrroles with a series of benzhydryl carbocations have been determined in acetonitrile.[29] Nucleophilicity parameters N and s were determined for the pyrroles. It was found that highly

reactive pyrroles, *e.g.* *N*-(triisopropylsilyl)pyrrole, show similar nucleophilic reactivities to amines whereas less reactive pyrroles are comparable to allylsilanes or indoles. In a separate study, the stability of benzhydryl carbocation **40** ($R_2 = CH_3$) has been found to be significantly enhanced in aqueous solution by inclusion in the cucurbit[7]uril **45** host cavity.[30] The carbocation-host complex ($K_{CB[7]} = 2.0 \times 10^4\ M^{-1}$) shifted the carbinol-carbocation equilibrium towards the blue carbocation to a level of 90% at pH 5.2. The pK_R and pK_a values have been determined for diarylbenzhydryl carbocations in aqueous solution using an 'azide clock' method.[31] Elimination to xylylenes was observed to compete with reaction with solvent and azide ion in aqueous dioxane.



41 $n = 1$
42 $n = 3$



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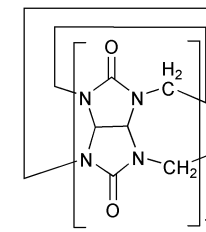

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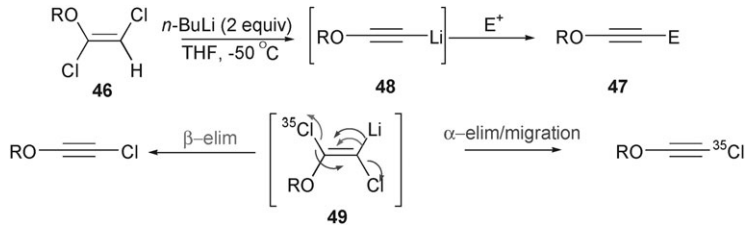
The rate constant ratio k_{ROH}/k_s has been determined of partitioning of the β-galactosidase-bound 2-deoxy-β-D-galactopyranosyl oxocarbenium ion intermediate between addition of trifluoroethanol (and eight other alkyl alcohols), and solvent water.[32] Absolute rate constants k_{ROH} ($M^{-1}\ s^{-1}$) were calculated from k_{ROH}/k_s and $k_s = 0.002\ s^{-1}$. A Brønsted β_{nuc} of 0.07 was determined as the slope of a logarithmic correlation of k_{ROH} against alcohol pK_a. The change from a 2-OH to a 2-H substituent at the intermediate was found to cause a 0.12 unit increase in β_{nuc} (as judged by comparison of this deoxy data with the previously determined value for the β-D-galactopyranosyl oxocarbenium ion), which constitutes an anti-Hammond effect. This was suggested to provide evidence that the general base catalyzed addition of alcohols to an enzyme-bound β-D-galactopyranosyl oxocarbenium ion proceeds along a reaction coordinate in which there is strong coupling between carbon–oxygen bond formation and proton transfer from the alcohol to a basic residue on the enzyme.

pK_a values have been reported for proton loss from the α-carbon of carbocations to form singlet methyl, dimethyl, phenyl, phenylmethyl, diphenyl, methoxy and methoxymethyl carbenes.[33] Equilibrium constants were evaluated for the isomerisation of the carbenes to alkenes or for their hydration to form alcohols (pK_{H_2O}) based on G3 calculations and estimates of free energies of transfer from gas to solution. Substituent effects on equilibrium data were discussed. The intrinsic gas phase acidities and electrophilicities of heterocations and carbocations relative to pyridine (Py) have been determined by mass spectrometry.[34] Ion/molecule reactions with pyridine of several gaseous silylium ions, carbocations and the dicoordinated boron cation $(MeO)_2B^+$ were investigated. Reaction was observed to occur in three competitive channels: electrophilic addition to a stable adduct, direct β-elimination that leads to proton transfer and α-elimination that leads to transfer of a substituent directly attached to a charge centre. The silylium ions all reacted mainly to give the adduct $[R_3SiPy]^+$ by electrophilic attack. Alkyl cations (tBu$^+$, iPr$^+$, Et$^+$) reacted mainly to give $[PyH]^+$ *via* β-elimination. The $(MeO)_2B^+$ ion gave three major products: the adduct $[(MeO)_2B\text{-}Py]^+$, $[PyH]^+$, and $[PyMe]^+$.

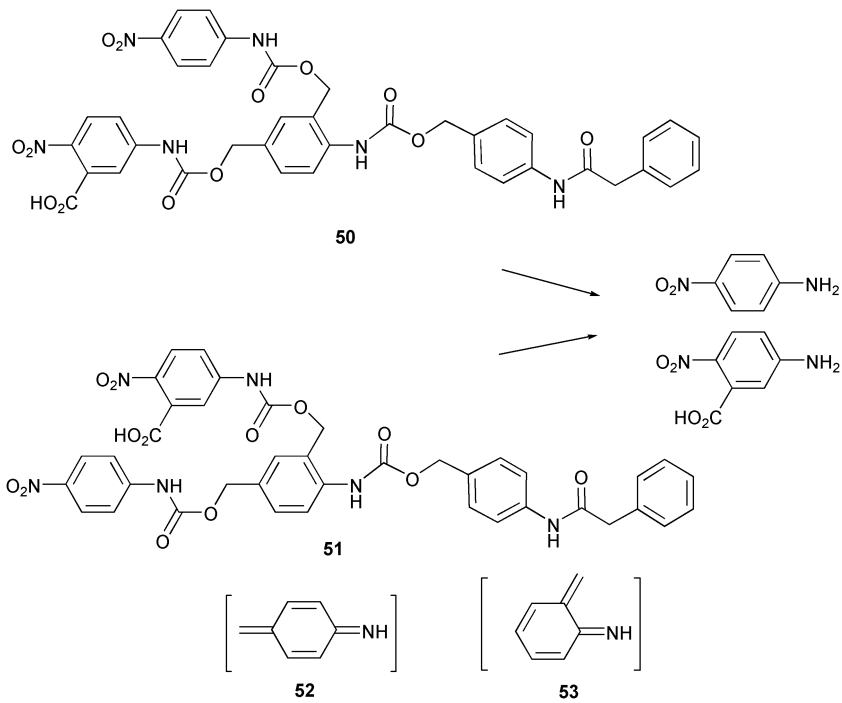
3. Elimination reactions

The mechanism of the reaction of dichloroenol ethers **46** with butyl lithium to give ynol ethers **47** has been investigated (Scheme 12).[35] It was known that the addition of two equivalents of *n*-butyl lithium to enol ether **46** leads to intermediate lithioacetylide **48** which can be subsequently trapped by an electrophile E^+. By a combination of isotopic ^{35}Cl labelling and product analysis, it was established that the mechanism of formation of lithioacetylide **48** involves *cis*-β-elimination *via* a lithium-chloro carbenoid intermediate **49** rather than α-elimination–migration (Scheme 12).



Scheme 12

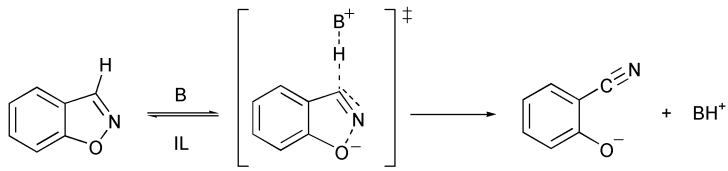
The disassembly of tripartate prodrug models **50** and **51** by azaquinonemethide elimination to give 5-amino-2-nitrobenzoic acid and 4-nitroaniline has been studied (Scheme 13).[36] Both compounds **50** and **51** were designed to contain a trigger group that could be removed through cleavage of the phenylacetamide by *penicillin-*G*-amidase*. Following enzymatic cleavage it was found that 1,4- and 1,6-double



Scheme 13

elimination, and decarboxylation, occurred. The results showed that 1,6-elimination through a *para*-azaquinonemethide **52** occurs faster than the 1,4-elimination through the *ortho*-azaquinonemethide species **53**.

The amine-induced E2 elimination of benzisoxazole **54** to *o*-cyanophenolate (Kemp elimination, Scheme 14) has been employed as a probe reaction to study the solvent properties of a range of ionic liquids (ILs).[37] An H-donor negative solvent effect was observed on the rate of reactions performed in methanol–[bmim][NTf_2] solvent mixture. A narrow range of activation parameters was calculated for the reaction induced by a range of primary, secondary and tertiary amines for [bmim][BF_4], and for pyrrolidine and piperidine in the presence of different ILs. These results were suggested to indicate a low degree of C–H bond breaking in the transition state.



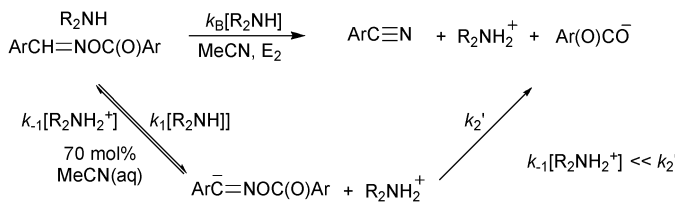
54

B = amine

IL = [bmim][BF_4]; [bmim][PF_6]; [bmim][NTf_2]; [bmim][NTf_2]; [bmpyrr][NTf_2]

Scheme 14

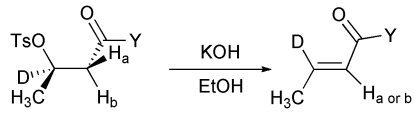
The elimination reactions of (*E*)-2,4-dinitrobenzaldehyde *O*-benzoyloximes promoted by $R_2NH/R_2NH_2^+$ have been studied kinetically (Scheme 15).[38] The reactions were found to be second order and yielded Brønsted parameters $\beta = 0.27–0.32$ and $|\beta_{lg}| = 0.28–0.32$. These results could be described by a negligible ρ_{xy} interaction coefficient, $\rho_{xy} = \delta\beta/\mathrm{p}K_{lg} = \delta\beta/\delta\mathrm{p}K_{BH} \approx 0$, which describes the interaction between the base catalyst and the leaving group, and were suggested to be consistent with an $(E1cb)_{irr}$ mechanism. By contrast, the analogous reactions in pure acetonitrile occur by a concerted E2 mechanism.



Scheme 15

The stereochemistry of the 1,2-elimination reactions of *tert*-butyl 3-tosyloxybutanoate **55** and thioester analogue **56** (Scheme 16) have been studied by ^1H and ^2H NMR spectroscopy after stereospecific deuteration of both esters to yield single diastereomers.[39] It was observed that activation by a carbonyl group has virtually no influence on the stereoselectivity. All substrates gave 5–6% syn elimination. Elimination of the (2*R**,3*R**) diastereomer of both the ester and thioester, **55** and **56** (H_a = H, H_b = D), yielded 21–21% of the (*Z*)-alkene, which is more than is observed with a

poorer nucleofuge. It was suggested that a relatively large amount of (*Z*)-alkene is an indication of an E2 pathway in which the transition state is E1cb-like rather than $(E1cb)_{irr}$.



55 Y = $OC(CH_3)_3$
56 Y = $SC(CH_3)_3$
H_a, H_b = H or D

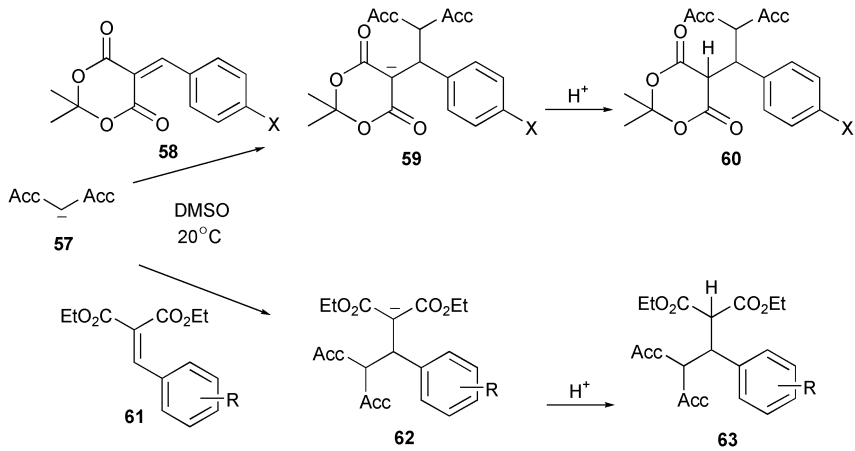
Scheme 16

Elimination mechanisms in the aminolysis of sulfamate esters $NH_2SO_2OC_6H_4X$ have been investigated in acetonitrile in the presence of a series of pyridines and alicyclic amines at various temperatures.[40] Brønsted plots were found to be biphasic for aminolysis with alicyclic amines giving an initial slope $\beta_1 = 0.53$ and a subsequent slope $\beta_2 = 0.19$. The reactions were considered to be dissociative involving E2- and E1cb-type mechanisms, with the formation of the phenylsulfamate anion $(NHSO_2OC_6H_4X)^-$ for reactions with pyridine and weaker alicyclic amines (β_1 segment) or the phenylsulfamate dianion $(NSO_2OC_6H_4X)^{2-}$ for stronger alicyclic amine bases (β_2 segment). The kinetics of the elimination of methanesulfonic acid from 1,2-diphenylethyl methanesulfonate and 1-(4-methylphenyl)- and 1-(4-chlorophenyl)-substituted derivatives have been studied.[41] The rate constants of the elimination reactions in the presence of the weak base pyridine were found to be independent of base concentration, indicative of a unimolecular E1 mechanism, whereas in the case of the stronger base piperidine upward curvature was observed due to the occurrence of a bimolecular component.

4. Addition reactions

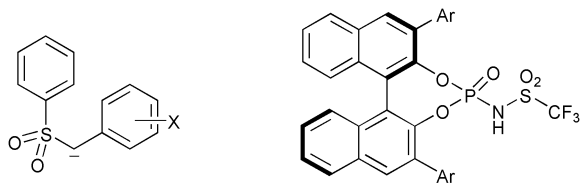
The kinetics of the addition of acceptor-substituted carbanions **57** to four benzylidene Meldrum's acids **58**, to give initial adduct carbanions **59** and ultimate addition product **60**, have been studied by UV-Vis spectrophotometry in DMSO at 20 °C (Scheme 17).[42] The reactions exhibited second-order kinetics and the resulting second order rate constants were found to follow the correlation $\log k_{2\ 20\ °C} = s(N + E)$, which was used to calculate electrophilicity parameters for Meldrum's acids **58**. Using Hammett correlations including this new data, electrophilicity parameters *E* could be estimated for a range of β,β-substituted styrenes, which in turn enables the prediction of absolute rate constants of many Michael additions. In a related study, the second order rate constants of the addition of carbanions **57** to diethyl benzylidene malonates **61** have been determined in DMSO at 20 °C.[43] Product studies revealed that the carbanions attack regioselectively at the electrophilic C=C bond of the Michael acceptors **61** to initially form the carbanion adducts **62** which may be protonated to give addition product **63**. Electrophilicity parameters *E* were calculated for diethyl benzylidene malonates **61**, which showed them to be ten orders of magnitude less reactive than Meldrum's acids **58**.

The kinetics of the reaction of four benzenesulfonyl-stabilized carbanions **64** with quinone methides, diaryl carbocations and a series of benzylidene Michael acceptors have been determined in DMSO at 20 °C in order to derive reactivity parameters *N* and *s*.[44] It was found that the additions of carbanions **64** to benzylidene Michael

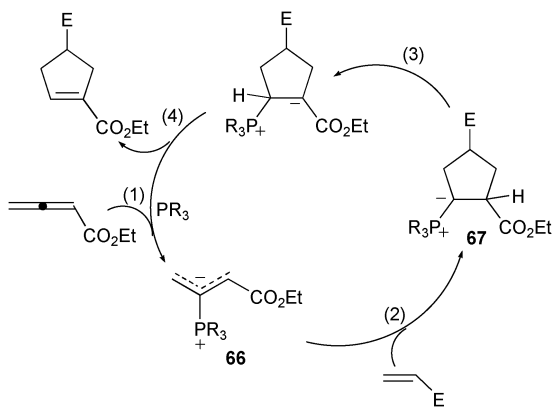


Scheme 17

acceptors were 5–24 times slower than predicted by the equation log $k_{2\ 20\ °C} = s(N + E)$. The *N*-triflylphosphoramide-catalyzed enantioselective Friedel–Crafts alkylation of indoles with α-keto esters, in addition to a highly enantioselective 1,4-addition have been reported.[45] A mechanism was suggested in which the *N*-triflylphosphoramides **65** act as Brønsted acid catalysts of both nucleophilic substitution and 1,4-addition to indoles.



The mechanism of the phosphine-catalyzed [3 + 2] cycloaddition reactions of allenoates and electron deficient alkenes has been studied.[46] It was found that this reaction occurs in four consecutive processes (Scheme 18): (1) rate-determining

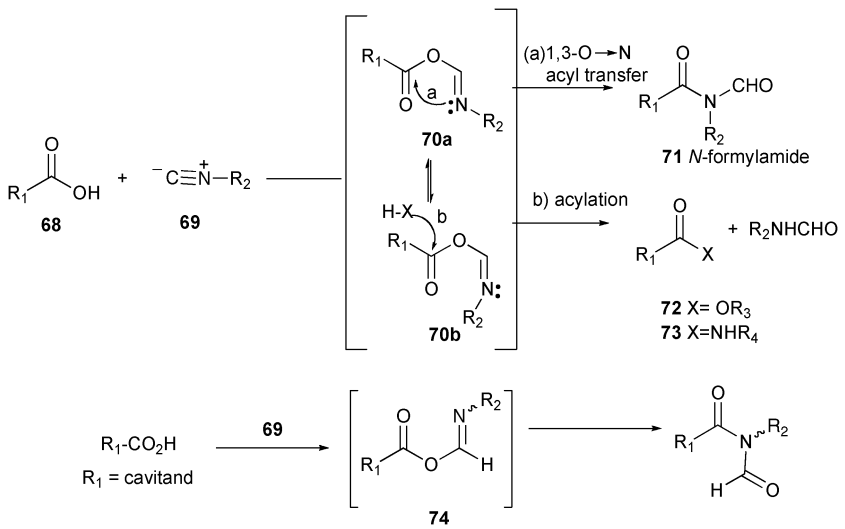


Scheme 18

generation of a 1,3-dipole **66** from allenoate and phosphine, (2) stepwise [3 + 2] cycloaddition to give another zwitterionic intermediate **67**, (3) a water-catalyzed [1,2]-hydrogen shift and (4) elimination of the phosphine catalyst. Isotopic labelling experiments combined with DFT calculations showed that the commonly accepted intramolecular [1,2]-proton shift should be corrected to a water-catalyzed [1,2]-proton shift.

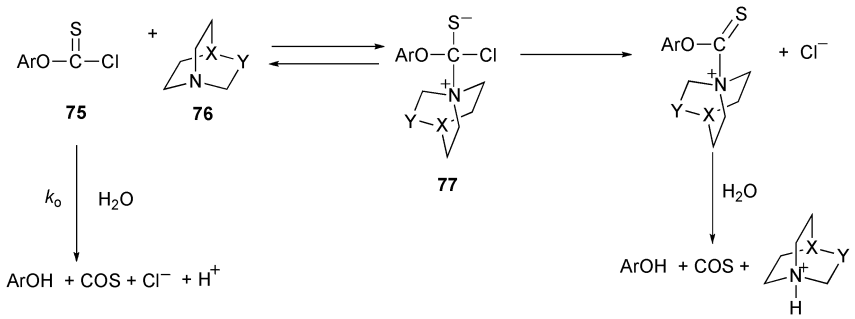
5. Acyl transfer at carbon

Mechanistic issues have been addressed in a novel thermolytic 'two component coupling' of carboxylic acids **68** and isonitriles **69** (Scheme 19).[47–49] B3LYP density functional calculations have been used to support a mechanism involving the formation of carboxylate mixed formimidic anhydride intermediate **70** which is either transformed to an *N*-formylamide **71** *via* a concerted pseudopericyclic [1,3] acyl shift or may be intercepted by nucleophilic trapping agents such as alcohols or amines to yield alternative products **72** or **73**. The scope of this new reaction towards the synthesis of novel peptides and peptide constructs was also explored. In a related study, the reactions of isonitriles **69** with carboxylic acids in a cavitand have been found to proceed *via* the *O*-acyl isoimide intermediate **74** followed by a 1,3-*O*–*N* acyl transfer to form *N*-acylformamide **71**.[50] The labile isoimide intermediate **74** was observed by ^{1}H NMR and IR spectroscopy.



Scheme 19

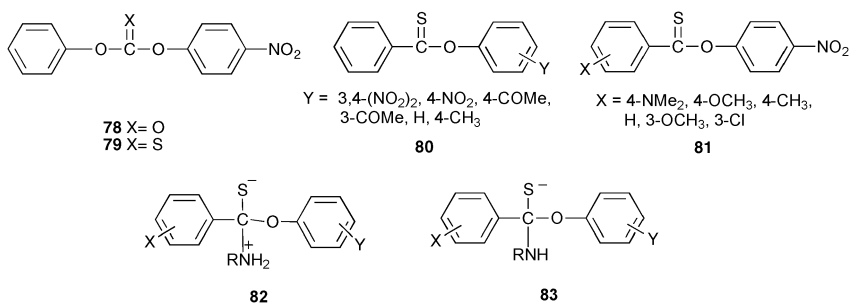
Kinetic studies have been reported for the reactions of aryl chlorothionoformates **75** with quinuclidines **76** in aqueous solution (Scheme 20).[51] First order rate constants k_{obs} of the release of the aryloxide anions were found to show a linear dependency on amine concentration with slope k_N. Brønsted-type plots (log k_N *vs.* pK_a of aminium ions) yielded β values ranging from 0.19–0.28 and a dual parametric equation with pK_a of the nucleophiles and non-leaving groups



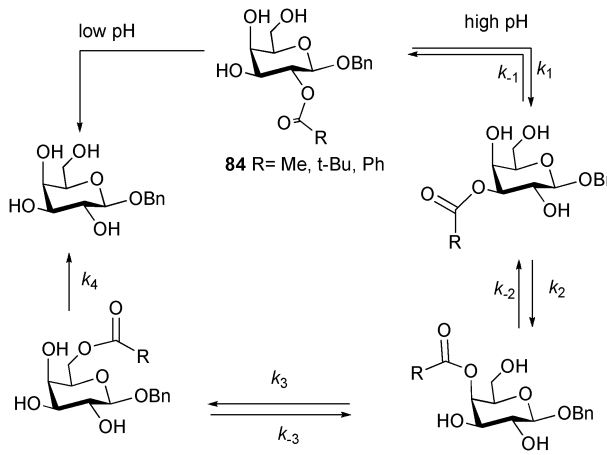
Scheme 20

showed $\beta_N = 0.26$ and $\beta_{nlg} = -0.16$. These data were used to propose a stepwise mechanism, with rate-determining formation of a zwitterionic tetrahedral intermediate **77**.

The aminolysis of 4-nitrophenyl phenyl carbonate **78**, thionocarbonate **79**, *O*-Y-substituted phenyl thionobenzoates **80** and *O*-4-nitrophenyl X-substituted thionobenzoates **81** with secondary amines has been investigated in 80% H_2O–20% DMSO at 25 °C.[52,53] The reaction of the thionobenzoates was suggested to proceed either through a zwitterionic tetrahedral intermediate **82** or its deprotonated form **83**, depending on the basicity difference between the entering amine and the leaving aryloxide. A similar zwitterionic intermediate mechanism was proposed for the aminolysis of carbonate **78** and thionocarbonate **79**. It was concluded that the amine basicity combines with modulation of the electronic nature of X and Y substituents to control the reaction mechanism.



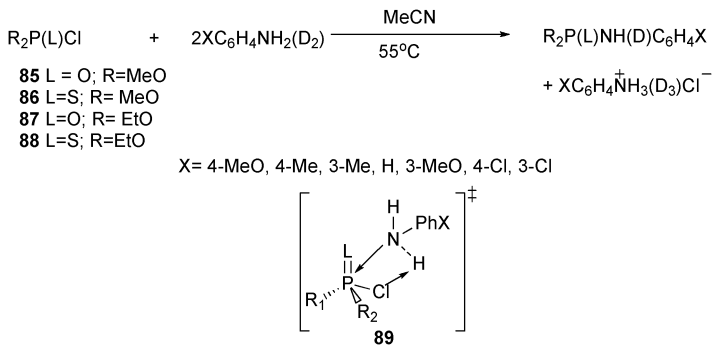
The stabilities of the different protecting groups and the migration kinetics of a series of benzyl 2-*O*-acyl-β-D-galactopyranosides **84** have been studied by NMR spectroscopy (Scheme 21).[54] A significant increase in the acyl group cleavage and migration rate constants to and from the axial 4-OH position (k_2 and k_{-2} in Scheme 21) relative to those for migration to and from the equatorial positions was observed. A slower migration of the larger ester group was observed which was suggested to be due to blocking of the nucleophilic attack of the neighbouring hydroxyl group on the ester carbonyl carbon.



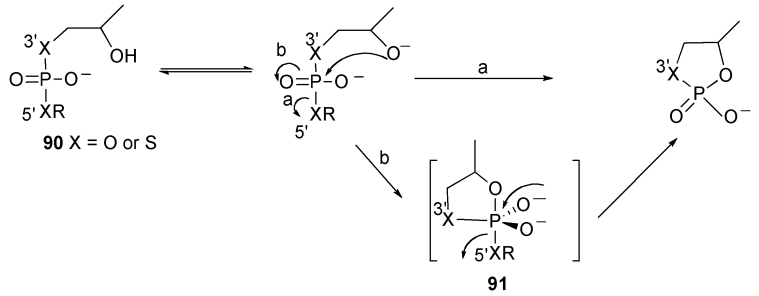
Scheme 21

6. Acyl transfer at phosphorus

Deuterium kinetic isotope effects (KIEs) have been reported for the aminolysis of dimethyl chlorophosphate **85**, dimethyl chlorothionophosphate **86**, diethyl chlorophosphate **87**, and diethyl chlorothionophosphate **88** with deuterated substituted anilines ($XC_6H_4ND_2$) in acetonitrile at 55 °C (Scheme 22).[55] Values of k_H/k_D of 0.798–0.979, 0.945–1.06, 0.714–0.919 and 1.01–1.10 obtained for **85**, **86**, **87** and **88**, respectively, were used to propose a concerted mechanism with dominant backside nucleophilic attack for the reactions of **85** and **87** and a concerted mechanism involving partial frontside attack through a hydrogen-bonded four-centre type transition state **89** for the reactions of **86** and **88**. An investigation of thiono-substitution effects on the cleavage of ribonucleoside analogue **90** has been reported (Scheme 23).[56] Sulfur substitution at either of the two bridging positions was found to result in a significant rate acceleration of diester cleavage when compared to the oxygen analogues. Kinetic isotope effects were used to propose an early transition state in a concerted reaction (a) when sulfur is in the 3′ position. With sulfur at the 5′ position the KIE data pointed to a highly associative transition state, however, it was not possible to distinguish between a concerted reaction with a phosphorane-like transition state and a stepwise mechanism (b) *via* intermediate **91**.

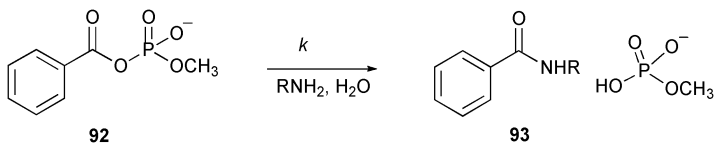


Scheme 22



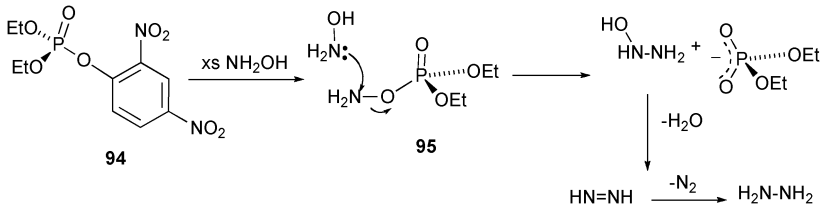
Scheme 23

The aminolysis of benzoyl methyl phosphate **92** in water to form the amide **93** has been reported (Scheme 24).[57] A plot of the second order rate constants of the reactions of the phosphate **92** with a series of primary amines was found to depend on the pK_a values of the conjugate acids of the amines. The Brønsted β_{nuc} values of 0.91 ± 0.02 obtained were found to be within the range of values (0.8–1.0) established for carboxyl substitution reactions where the rate-limiting step is decomposition of the tetrahedral addition intermediate, and were similar to a value of 0.83 reported for the aminolysis of acetyl phenyl phosphate. It was concluded that these reactions provide a simple and quantitative basis for regioselective acylation with the phosphates.



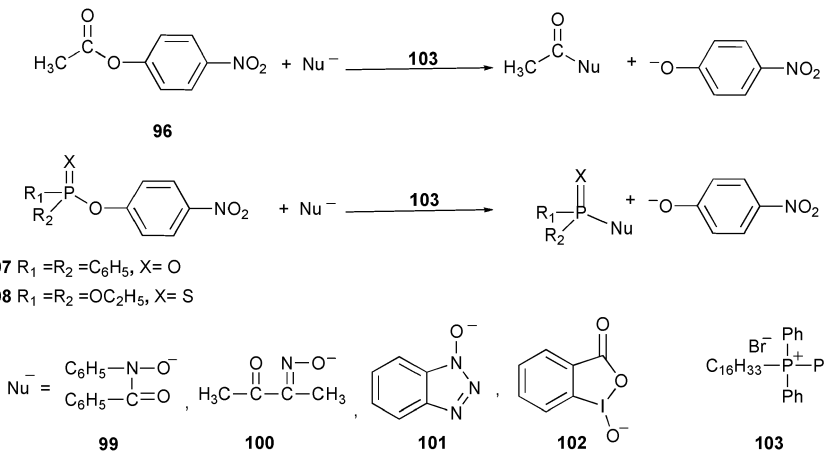
Scheme 24

The reactions of hydroxylamine with diethyl 2,4-dinitrophenylphosphate **94** have been found to give the *O*-phosphorylated product **95**, with subsequent release of hydrazine and nitrogen gas in the presence of an excess of hydroxylamine (Scheme 25).[58]



Scheme 25

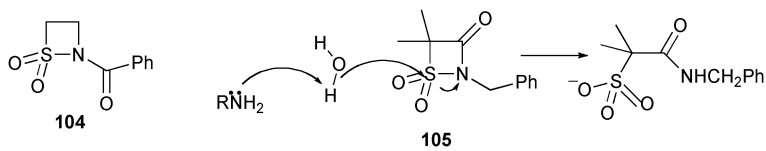
The kinetics of cleavage of carboxylate **96**, phosphinate **97** and thiophosphate **98** with different α–effect nucleophiles, *N*-phenylbenzohydroxamate **99**, butane-2,3-dione monoximate **100**, 1-hydrobenzotriazolate **101** and 2-iodosobenzoate **102**, have been investigated in the presence of cationic surfactant cetyltriphenylphosphonium bromide **103** (Scheme 26).[59] The reactivity order towards the α–nucleophiles was found to be **96** (C═O) > **97** (P═O) > **98** (P═S) which was attributed to a reduction in the electrophilicity of the central atom in the P═O and P═S esters.



Scheme 26

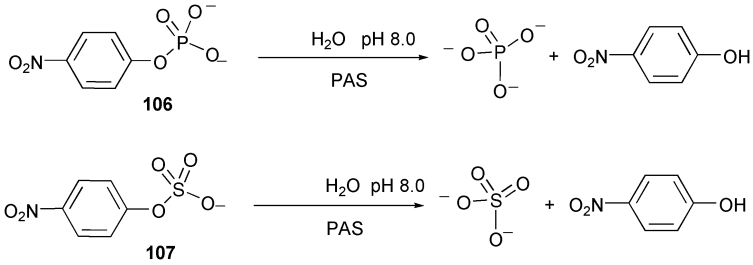
7. Acyl transfer at sulfur

The rate of aminolysis of *N*-benzoyl-β-sultam **104** in buffered amine solutions has been reported to show a first order dependence on amine concentration attributed to general base-catalysed hydrolysis by the amine (Scheme 27).[60] *N*-benzyl-4,4-dimethyl-3-oxo-β-sultam **105**, which is both a β-lactam and a β-sultam, preferentially undergoes hydrolysis at the sulfonyl rather than aminolysis at either the sulfonyl or acyl centres. The solvent kinetic isotope effects (SKIE), k^{H_2O}/k^{D_2O} of amine hydrolysis were found to be 1.4 and 1.9 for the hydrolysis of the sultams **104** and **105**, respectively, which was suggested to be compatible with a general base-catalyzed mechanism. A Brønsted β value of $+0.9$ was observed for both β-sultams, which was suggested to indicate that the general base amine is almost fully protonated in the transition state.



Scheme 27

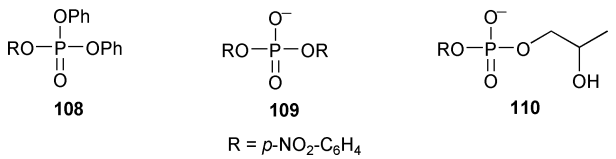
The promiscuous hydrolysis of phosphate monoester **106** catalysed by the enzyme, *pseudomonas aeruginosa arylsulfatase* (PAS) has been found to occur with multiple turnovers (>90) and values of $k_{cat} = 0.023\ s^{-1}$, $K_M = 29\ \mu M$, and $k_{cat}/K_M = 790\ M^{-1}\ s^{-1}$ at pH 8.0 (Scheme 28).[61] This corresponds to a remarkably high rate acceleration of 10^{13} relative to the non enzymatic phosphomonoester hydrolysis $[(k_{cat}/K_M)/k_w]$ and a transition-state binding constant K_{tx} of 3.4 pM. Promiscuous phosphatase activity and native sulfatase activity with sulfate monoesters **107** were observed to differ only by a factor of 620 (measured by k_{cat}) in both reactions. The magnitude and relative similarity of the kinetic parameters were used to suggest that a functional switch from sulfatase to phosphatase activities is feasible, either by gene duplication or by direct evolution *via* an intermediate enzyme with dual specificity.



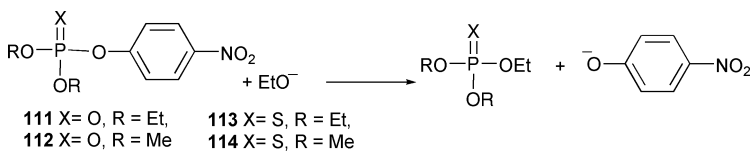
Scheme 28

8. Catalysis by metal ions

The speciation and kinetics of hydrolysis of 4-nitrophenyl diphenyl phosphate **108**, bis(4-nitrophenyl) phosphate **109**, and 2-hydroxypropyl-4-nitrophenyl phosphate **110** in the presence of Mg(II), Ca(II) and Sr(II) in 90% vol. DMSO at 37 °C have been reported.[62] Alkaline hydrolysis of the triester **108** was inhibited by all cations, but with both phosphodiesters **109** and **110**, strong catalytic effects were observed. Potentiometric titration of the metal perchlorates by $Bu_4N(OH)$ revealed formation of $M_2(OH)^{3+}$, $M(OH)^{+}$, $M(OH)_2$ and $M_2(OH)_5^{-}$. First-order rate constants of the cleavage of phosphodiesters **109** and **110** in the presence of 1–2 mM Mg(II) or Ca(II) in neutral or basic solution in 90% vol. DMSO were 10^8–10^{11} times higher than those of the background hydrolysis reactions at the same pH, while in water additions of up to 50 mM metal produced <100-fold acceleration. Results of DFT calculations modelled with Mg(II), of the possible structures of DMSO solvated catalyst-substrate complexes, were used to suggest that the increased catalytic activity in 90% DMSO is due to preferential solvation of cations by DMSO.



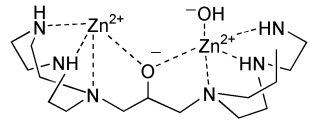
Um *et al.*[63] have reported a continuation of their work on the effect of alkali metal ethoxides on the ethanolysis of ethyl **111** and methyl **112** paraoxon and ethyl **113** and methyl **114** parathion (Scheme 29). Their studies revealed an unusual range of catalysis and inhibition as well as reactivity/selectivity patterns and contrasting behaviours of the ubiquitous alkali-metal cations towards P=O and P=S systems.



Scheme 29

The cyclization of 2-hydroxypropyl-4-nitrophenyl phosphate (HpPNP) **110** (attack of hydroxyl on phosphorous) catalysed by the dinuclear Zn(II) complex **115** has been found to proceed *via* a transition state that is different from that of the

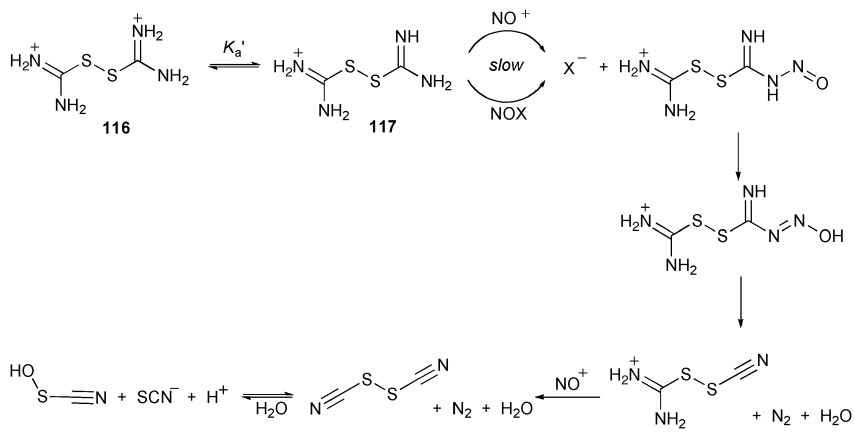
uncatalysed reaction.[64] Kinetic isotope effects (^{18}O and ^{15}N) were measured in the nucleophilic 2′ oxygen atom and in the oxygen and nitrogen of the leaving group (RO). These showed that the uncatalysed cyclization has a transition state with little phosphorous–oxygen bond fission to the leaving group ($^{18}k_{lg}$ = 1.0064 ± 0.0009, and ^{15}k = 1.0002 ± 0.0002) and that nucleophilic bond formation occurs in the rate determining step ($^{18}k_{nuc}$ = 1.0326 ± 0.0008). In the catalysed reaction, the authors cited larger leaving group isotope effects ($^{18}k_{lg}$ = 1.0113 ± 0.0005, and ^{15}k = 1.0015 ± 0.0005) and a smaller nucleophile isotope effect ($^{18}k_{nuc}$ = 1.0116 ± 0.0010) as indicating a later transition state with greater leaving group bond fission and greater nucleophilic bond formation. An equilibrium isotope effect (EIE) of 1.0245 for the deprotonation of the 2′-hydroxyl group of **110** was obtained computationally. The differences in the KIEs for the two reactions were used to suggest that effective catalysis by zinc dinuclear complex **115** is accompanied by selection for an altered transition state presumably arising from the preferential stabilization by the catalyst of charge away from the nucleophile and towards the leaving group.



115

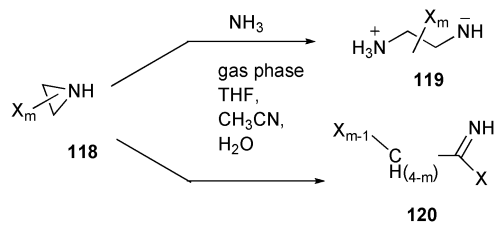
9. Bimolecular and vinylic nucleophilic substitution

The reaction kinetics for the acid nitrosation of formamidine disulfide **116** have been found to show autocatalysis arising from the catalytic activity of the thiocyanate ion formed as product (Scheme 30).[65] It was observed that in the presence of added nucleophiles, suppression of the autocatalytic route results from competition for nitrous acid between the added halides and the thiocyanate anion. Bimolecular rate constants k_{NO^+} = (3.2 ± 1.8) × 10^{10} M^{-1} s^{-1}; k_{NOSCN} = (2.1 ± 0.2) × 10^5 M^{-1} s^{-1}; k_{NOBr} = (9.4 ± 0.2) × 10^6 M^{-1} s^{-1} and k_{NOCl} = (4.0 ± 0.2) × 10^7 M^{-1} s^{-1} were obtained for the pathways catalysed by SCN$^-$, Br$^-$ and Cl$^-$, respectively. A mechanism was proposed involving the attack of the effective nitrosating species on the monoprotonated formamidine disulfide **117** as the rate-limiting step.



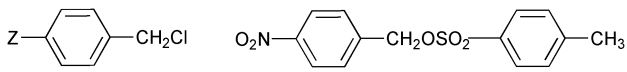
Scheme 30

A computational investigation of the reaction of ammonia with haloaziridines **118** conducted in polar and non polar solvents has been reported (Scheme 31).[66] The reaction is predicted to give to either 1,2-diaminohaloethane **119** or an imidoyl halide **120** depending on the halogen substituent X. Fluoroaziridines were found to react to give diaminoethane **119** at accelerated rates relative to aziridine exclusively by an S_N2 mechanism in each solvent tested, while the reactions of the chloro- and bromoaziridines **118** could be directed towards **119** in the highly nonpolar solvent or toward **120** in more polar solvents.



Scheme 31

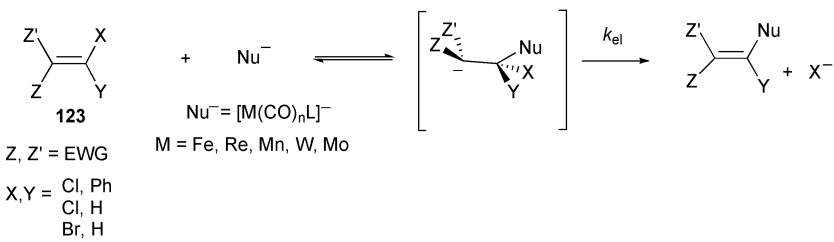
Ether and alcohol product selectivities have been used to support evidence that solvolyses of 4-substituted benzyl chlorides **121** are susceptible to mechanistic change from an S_N2 to an S_N1 mechanism over the range of reaction conditions from alcohol to water.[67] The solvolysis of 4-nitrobenzyl chloride **121** (Z = NO_2) or the tosylate **122** in alcohol–water mixtures were found to be an exception, and react exclusively by a classical S_N2 mechanism.



121 **122**

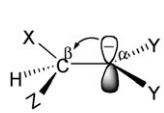
Nucleophilic reactions of metal carbonyl anions $[M(CO)_nL]^-$ with several vinyl halides **123** have been reported to follow the addition-elimination (Ad_NE) mechanism for the overall vinylic substitution (Scheme 32).[68] The nucleophilicity of the anions was also found to correlate better with anion one-electron oxidation potentials (E_{ox}) than with their basicity (pK_a of $[M(CO)_nL]H$).

The role of negative hyperconjugation and anomeric polar effects in stabilising the intermediate $XZHC^{\beta}C^{\alpha}YY'^-$ **124** (where substituents X, Y and Z are alkoxy, thioalkoxy or Meldrum's acid as in **125**) in nucleophilic vinylic substitution (S_NV) has been studied computationally by DFT methods.[69] Destabilizing steric effects on **124** were also discussed; these are larger when one or both substituents are



Scheme 32

methylthio groups in **124** and consequently affect the trends in the equilibrium constants of the S_NV reaction.



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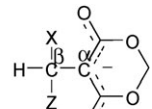
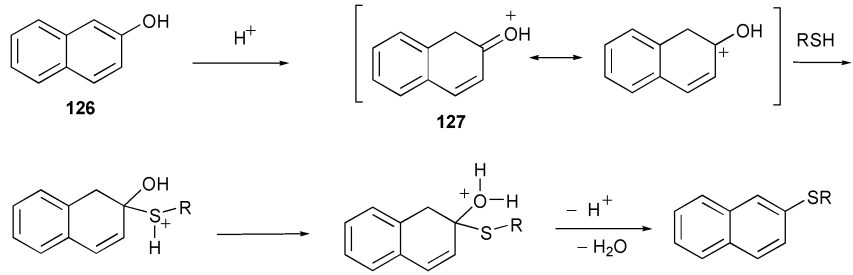


125

10. Nucleophilic aromatic substitution

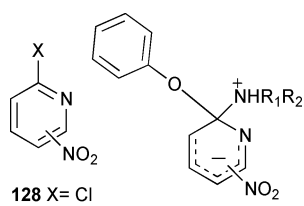
A combination of experimental and theoretical DFT methods have been used to study the mechanism of the acid catalysed nucleophilic substitution of 2-naphthol **126** with *n*-propanethiol in the presence *p*-toluenesulfonic acid.[70] The observed solvent effects on mechanism were used to propose a cationic mechanism *via* an oxocarbenium ion **127** for reactions in polar solvents (Scheme 33) and a multi-step mechanism for reactions in non-polar solvents in which the acid mediates the proton shuffling. DFT calculations identified a rate-determining transition state for reaction in non-polar solvents that involves protonation of the hydroxyl group of **126** to generate free water and a tight ion pair between a cationic protonated naphthalene and a tosylate anion. The similarities in the calculated and experimentally determined activation parameters for reaction in non-polar solvent ($\Delta H^{\neq}_{exp} = 105 \pm 9$, $\Delta H^{\neq}_{calcd} = 118$ kJ mol^{-1}; $\Delta G^{\neq}_{exp} = 112 \pm 18$, $\Delta G^{\neq}_{calcd} = 142$ kJ mol^{-1}) were quoted as evidence in support of the proposed mechanism.



126 **127**

Scheme 33

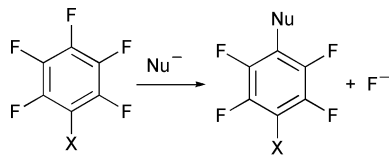
Rate constants have been reported of the reaction of 1-chloro-nitropyridines **128** and 1-phenoxy-nitropyridines **129** with *n*-butylamine, pyrrolidine and piperidine in DMSO as solvent.[71] Base catalysis detected in the phenoxy derivatives was attributed to rate limiting proton-transfer from the zwitterionic intermediates **130** to base. The results obtained were used to shed light on the fundamental aspects of activation, hydrogen bonding and steric effects associated with an aza or nitro group in the molecules as it affects the S_NAr reaction pathways.



128 X= Cl
129 X= OPh

130

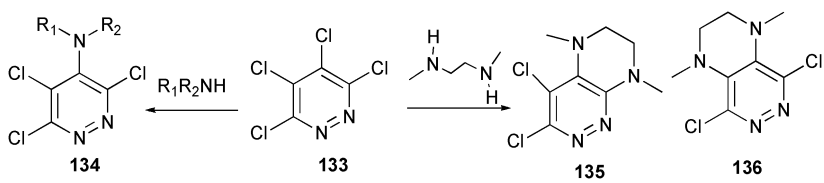
The gas phase nucleophilic aromatic substitution reaction that results from the one-photon ionization of the hexafluorobenzene $C_6F_6/NH_3/He$ mixture by vacuum UV light has been studied by mass spectrometry and IR spectroscopy. Initial ionisation was suggested to give $[C_6F_6]^+$ which then reacted with NH_3 to give cluster cation $[C_6F_6NH_3]^+$. Loss of HF from this cluster cation was found to give the substitution product $[C_6F_5NH_2]^+$.[72] This according to the authors is the first report on the identification of a stable intermediate $[C_6F_6NH_3]^+$ in an S_NAr reaction that occurs in the cationic state. A rationale for the variable effects of fluorine substitution on the S_NAr of **131** (X = F) to give substitution product **132** (Scheme 34) has been presented and evidence in support of polar influences by *ortho* fluorine has been advanced.[73] The influence of X = CN, CF_3, CF_2H and CFH_2 was also established by comparison of the appropriate measured rate constant for the nucleophilic aromatic substitution reactions of **131**, and these X-substituent effects were compared with the activation effects of ring nitrogen.



131 **132**

Scheme 34

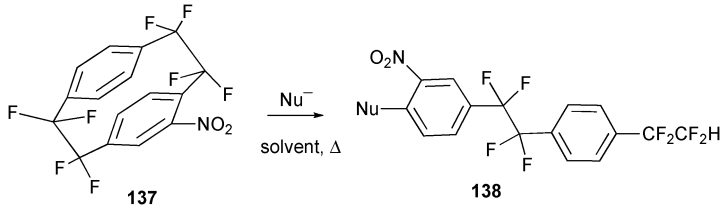
Reactions of tetrachloropyridazine **133** with aliphatic primary and secondary nitrogen nucleophiles have been reported to give selectively product **134** arising from replacement of chlorine at the 4-position (Scheme 35).[74] Substitution occurs at the most activated site *para* to ring nitrogen, despite the possible steric hindrance to substitution by adjacent chlorine atoms, reflecting the additional activating influence of ring nitrogen *meta* to the site of attack. When the nucleophile *N*,*N*-dimethyl-ethylene diamine was used, a mixture of [6,6] ring fused products **135** and **136** were formed following initial substitution at the 4-position.



134 **133** **135** **136**

Scheme 35

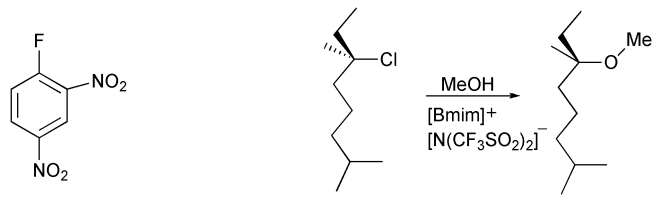
There has been a report that when paracyclophane **137** is treated with nucleophiles such as alkoxide or cyanide ions in alcohol–ether mixtures or acetonitrile, a novel ring-cleaving reaction occurs *via* an S_NAr mechanism in alcohol–ether mixtures or acetonitrile (Scheme 36). The nucleophile attacks at the bridgehead aryl carbon vicinal to the nitro group with subsequent aryl–CF_2 bond cleavage to give **138**.[75]



Scheme 36

11. Solvent effects

The kinetics of the S_NAr reactions of 1-fluoro-2,4-dinitrobenzene **139** and butylamine have been explored to design a new solvent media based on the molecular-microscopic properties of the binary mixtures of molecular solvent (acetonitrile (AN) or dimethylformamide) and ionic liquids [1-(1-butyl)-3-methylimidazolium tetrafluoroborate or 1-(1-butyl)-3-methylimidazolium hexafluorophosphate].[76] Kinetic synergistic effects were observed in AN + $([bmim]^+[BF_4]^-$ mixtures and were attributed to the particular basic solvating properties of this solvent mixture. Methanolysis of the chloride **140** to give the ether **141** has been studied in solutions containing 0%, 12% or 90% 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide $([bmim]^+[N(CF_3SO_2)_2]^-$ by volume over a range of temperatures (Scheme 37).[77] Results of the temperature dependent rate studies were used to demonstrate that there are enthalpic benefits and entropic costs associated with the change in the rate of a unimolecular substitution process on addition of a high proportion of an ionic liquid. The experimental results were supported by results from molecular dynamics simulations.

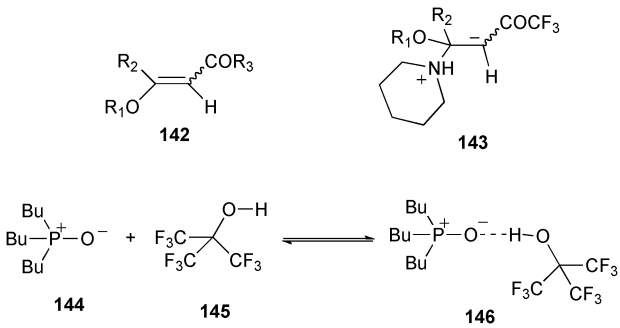


Scheme 37

Vdovenko *et al.*[78] have reported a multiple linear regression analysis of the effects of solvent on the S_NV reaction of β-substituted β-alkoxyvinyl trifluoromethyl ketones **142** (R_1, R_2 = alkyl, R_3 = CF_3) with piperidine in nine aprotic and six protic solvents. The largest solvent influence on the rate constants for the reaction was dipolarity/polarizability (π*) whereas the solvent's basicity had a negligible effect. Hydrogen bonds between protic solvents and the enones were found to aid departure of the alkoxide nucleofuge from zwitterionic intermediate **143**. A related infrared spectroscopic study of the enones **142** (R_1 = alkyl; R_2 = H, alkyl, aryl; R_3 = CF_3 or CH_3) has been used to conclude that the influences of the solvent dipolarity/polarizability (π*) and solvent acidity on the bathochromic ν(C=O) band shift are opposite to one another.[79]

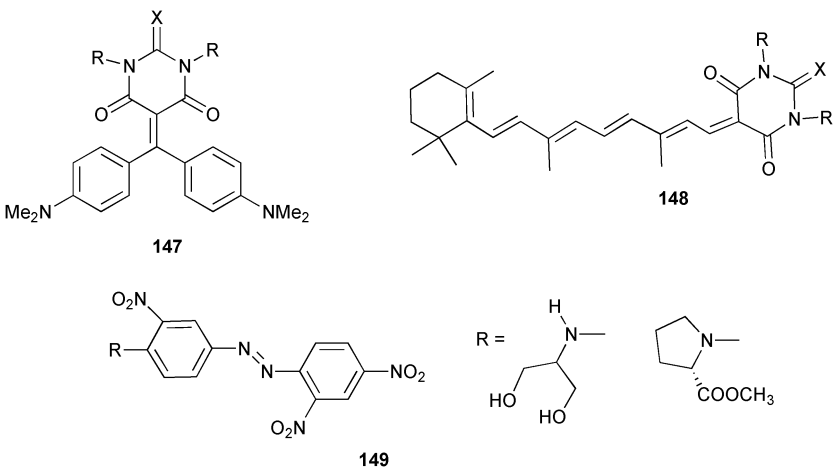
The 1 : 1 complex formed between tributylphosphine oxide **144** and perfluoro-*tert*-butanol **145** has been applied as a simple probe for solvent effects on molecular interactions in chloroform and tetrahydrofuran (THF) mixed solvent systems (Scheme 38).[80] The value of log K = 1.3 calculated for the stability of the complex **146** in the mixed solvents was found to be very close to the minimum experimental value

measured and was used to infer the unusually high polarity of the mixed solvent. In pure chloroform the hydrogen bond donor **145** is poorly solvated and in pure tetrahydrofuran the hydrogen bond acceptor **144** is poorly solvated however in the mixed solvent each interact strongly with the solvent which they select from the mixture.



Scheme 38

Solvatochromism of barbiturate dyes **147**, **148** (X, R = O, H; O, Me; S, H; S, Et) has been investigated in order to determine whether the free NH functions and those capped by alkyl groups have an effect on the chromophoric π-electron system.[81] It was shown that the effect of non-specific solvent interactions on the position of the UV/Vis absorption bands evaluated using the Kamlet–Taft and the Catalán equations depend mainly on the dipolarity and polarizability of the chromophoric system and are only slightly affected by substitution pattern of the barbiturate moiety. In contrast, specific interactions through hydrogen bonding expressed by solvent acidity and basicity can be attributed mainly to the barbiturate moiety and are hardly influenced by the nature of the chromophoric system. In a related study, the solvatochromism of aminodiol- and proline-methylester functionalised azo dye **149** have been evaluated using the Kamlet–Taft and Catalán equations.[82] The results of the multi linear correlation analyses led the authors to conclude that the influence of the polarizability of the solvent is the dominant effect on the UV/Vis absorption maxima of the dyes **149**.

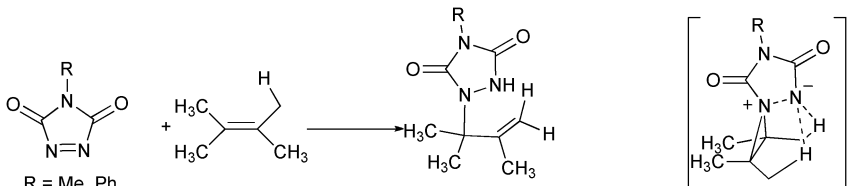


Rate constants for the rearrangement of *Z*-phenylhydrazones **150** (R = C_4H_9, C_6H_{13}, C_8H_{17}, $C_{10}H_{21}$, $C_{12}H_{25}$) into the relevant 4-acylamino-2,5-diphenyl-1,2,3-triazoles **151** have been measured in dioxane–water.[83] Analysis of the effect of an increase in alkyl chain length and substrate concentration on these rate constants provided evidence of a decrease in the polarity of the "actual" reaction medium and of the tendency of hydrazones **150** to self-assemble. Further evidence of self-assembly in solution was obtained from ^{1}H NMR spectroscopy and spcctro-fluorimetry and in the gas phase from ESI-MS (Scheme 39). In a related study the rearrangement of (*Z*)-phenylhydrazone **150** (R = Ph) has been studied in methanol in the presence of Cu(II) salts.[84] Evidence of Lewis acid bifunctional catalysis of this process was presented.

150 **151**

Scheme 39

The influence of solvent on the reaction of triazolinedione **152** with tetramethyl-ethylene **153** to form *N*-allylurazole **154** has been investigated (Scheme 40).[85] Both inter- and intramolecular kinetic isotope effects, obtained from the kinetic study of deuterated analogues of **154** and 2,2,2-(trideuterio)methyl-7-methyl-2,6-octadiene-d_3-1,1,1, were used to provide evidence for changes in mechanism of the reaction on going from non-protic to polar protic solvents. In non protic solvents, a polarized aziridinium imide **155** is irreversibly formed in the rate-determining step of the reaction which is followed by a fast hydrogen abstraction leading to the product **154** while in polar solvents, hydrogen abstraction is rate limiting.



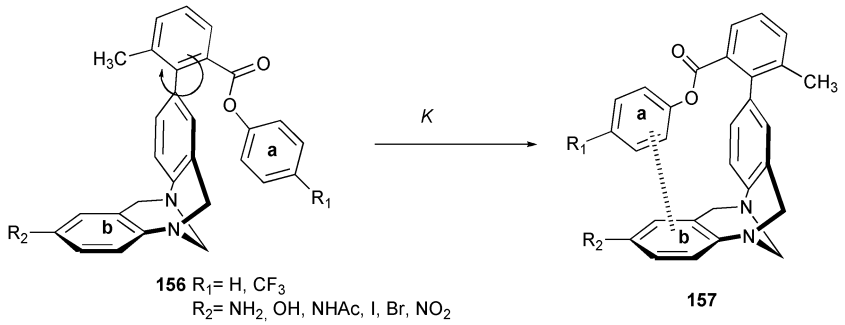
152 **153** **154** **155**

Scheme 40

12. Polar substituent effects

Substituent effects on the aromatic edge-to-face interaction in the esters **156**, bearing a phenyl or 4-(trifluoromethyl)phenyl ester moiety as the edge component (a), and a series of electron-donating and electron accepting substituents on the face aromatic ring (b), have been reported (Scheme 41).[86] The relative population at slow exchange between the unfolded and folded conformers **156** and **157** was monitored by ^{1}H NMR spectroscopy. Substituent effects on the folding equilibrium of the

molecular torsion balances between the conformers **156** and **157** were rationalised on the basis of changes in the electrostatic interactions, the exchange repulsion, and the dispersive contributions to the interaction free enthalpy.

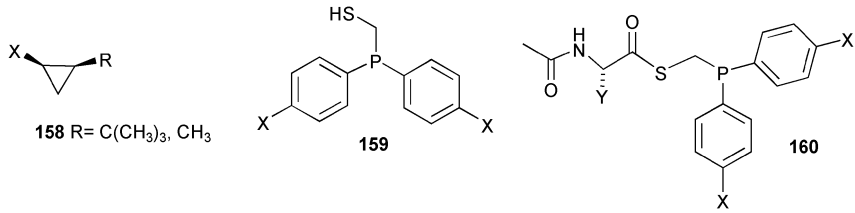


156 R_1= H, CF_3
R_2= NH_2, OH, NHAc, I, Br, NO_2

157

Scheme 41

Böhm and Exner have evaluated in terms of energies, by means of isodesmic reactions, the steric effects of polar and charged X-substituent groups on sterically crowded substituted cyclopropanes **158**.[87] Energies were calculated within the framework of the density functional theory at level B3LYP/6-311+G(d,p)//B3LYP/6-311+G(d,p) for 11 dipolar and 5 charged X-substituents and it was found that interaction of charged substituents is not only steric (destabilizing) but also inductive (stabilizing). The steric effects evaluated were found to differ distinctly from the standard steric constants derived from van der Waals radii of the substituents.



158 R= $C(CH_3)_3$, CH_3

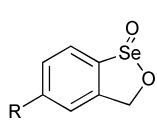
159

160

A survey of the peptide ligation rates mediated by a range of phosphinothiols **159** and phosphinothioesters **160** with varying degrees of electron-donating character imparted by *para* substituents (X) on their aryl rings have been performed.[88] Overall, electron-donating substituents provided higher rates of ligation and it was concluded that the interplay between electronic effects imparted by phosphinothiol substituents and steric effects imposed by amino acid reactants can affect the rate of the traceless Staudinger ligation of peptides in a predictable manner.

Substituent effects have been studied in a series of aromatic cyclic seleninate esters **161** and spirodioxyselenuranes **162** that function as mimetics of the antioxidant selenoenzyme glutathione peroxidase.[89] The methoxy-substituted selenurane **162** (R = MeO) was found to be the most efficacious catalyst for the reduction of hydrogen peroxide with benzoyl thiol, and the reaction rates were enhanced for both classes by electron-donating substituents. Hammett ρ values of -0.45 and -3.1

obtained for the seleninates **161** and selenuranes **162**, respectively, were used to suggest that oxidation at Se is the rate determining step in their catalytic cycles.



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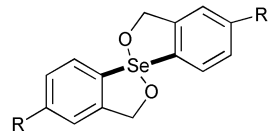
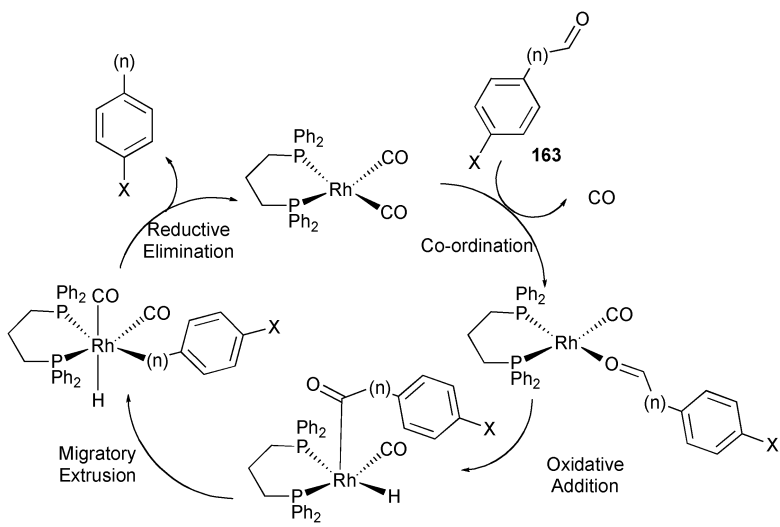


162

A combination of experimental and theoretical studies directed towards the elucidation of the mechanism of rhodium-catalysed decarbonylation of aldehydes **163** has been reported.[90] Linear Hammett plots with positive slopes $\rho = +0.79$ and $+0.43$ for decarbonylation of *para*-substituted benzaldehydes **163** ($n = 0$) and phenylacetaldehydes **163** ($n = 1$), respectively, were given as an indication of a build up of negative charge in the selectivity-determining step. The similarities in the values of kinetic isotope effects of 1.73 and 1.77 for decarbonylation of benzaldehydes **163** ($n = 0$) and phenylacetaldehydes **163** ($n = 1$), respectively, and the agreement of the computationally determined values with the experimental data were used to propose a mechanism involving a rapid oxidative addition into the C(O)–H bond followed by rate-limiting extrusion of CO and reductive elimination (Scheme 42).



Scheme 42

References

1 G. Siani, G. Angelini, P. De Maria, A. Fontana and M. Pierini, *Org. Biomol. Chem.*, 2008, **6**, 4236.
2 K. C. Kemp, E. Fourie, J. Conradie and J. C. Swarts, *Organometallics*, 2008, **27**, 353.
3 A. Basheer and Z. Rappoport, *J. Phys. Org. Chem.*, 2008, **21**, 483.
4 A. Basheer and Z. Rappoport, *Org. Biomol. Chem.*, 2008, **6**, 1071.
5 A. Basheer and Z. Rappoport, *J. Org. Chem.*, 2008, **73**, 184.

6 B. Zaleska, M. M. Burgiel and P. Serda, *Chem. Heterocycl. Compd.*, 2008, **44**, 349.
7 Y. Chiang, K. Kolmakov and A. J. Kresge, *Can. J. Chem.*, 2008, **86**, 101.
8 M. Aschi, A. A. D'Archivio, A. Fontana and A. Formiglio, *J. Org. Chem.*, 2008, **73**, 3411.
9 J. M. Lopez-Nicolas and F. Garcia-Carmona, *J. Agric. Food Chem.*, 2008, **56**, 7600.
10 M. Miyagi and T. Nakazawa, *Anal. Chem.*, 2008, **80**, 6481.
11 M. Eckert-Maksic, Z. Glasovac, P. Troselj, A. Kutt, T. Rodima, I. Koppel and I. A. Koppel, *Eur. J. Org. Chem.*, 2008, 5176.
12 A. Kuett, V. Movchun, T. Rodima, T. Dansauer, E. B. Rusanov, I. Leito, I. Kaljurand, J. Koppel, V. Pihl, I. Koppel, G. Ovsjannikov, L. Toom, M. Mishima, M. Medebielle, E. Lork, G. V. Roeschenthaler, I. A. Koppel and A. A. Kolomeitsev, *J. Org. Chem.*, 2008, **73**, 2607.
13 M. K. Go and J. P. Richard, *Bioorg. Chem.*, 2008, **36**, 295.
14 J. Crugeiras, A. Rios, E. Riveiros, T. L. Amyes and J. P. Richard, *J. Am. Chem. Soc.*, 2008, **130**, 2041.
15 J. Cerny, J. Hanusek and V. Machacek, *J. Phys. Org. Chem.*, 2008, **21**, 925.
16 L. M. Ferreira, M. M. B. Marques, P. M. C. Gloria, H. T. Chaves, J. P. P. Franco, I. Mourato, J. R. T. Antunes, H. S. Rzepa, A. M. Lobo and S. Prabhakar, *Tetrahedron*, 2008, **64**, 7759.
17 K. B. Hong, M. G. Donahue and J. N. Johnston, *J. Am. Chem. Soc.*, 2008, **130**, 2323.
18 C. L. Perrin and C. Zhao, *Org. Biomol. Chem.*, 2008, **6**, 3349.
19 N. Backstrom, N. A. Burton, S. Turega and C. I. F. Watt, *J. Phys. Org. Chem.*, 2008, **21**, 603.
20 X. Chen and J. I. Brauman, *J. Am. Chem. Soc.*, 2008, **130**, 15038.
21 D. A. Lawlor, R. A. M. O'Ferrall and S. N. Rao, *J. Am. Chem. Soc.*, 2008, **130**, 17997.
22 M. C. Lopez, I. Demirtas, H. Maskill and M. Mishima, *J. Phys. Org. Chem.*, 2008, **21**, 614.
23 W. F. Hao and V. D. Parker, *J. Org. Chem.*, 2008, **73**, 48.
24 Y. T. Wang, K. J. Jin, S. H. Leopold, J. Wang, H. L. Peng, M. S. Platz, J. D. Xue, D. L. Phillips, S. A. Glover and M. Novak, *J. Am. Chem. Soc.*, 2008, **130**, 16021.
25 C. Brule, F. Sultana, S. Hollenstein, T. Okazaki and K. K. Laali, *Eur. J. Org. Chem.*, 2008, 3700.
26 H. F. Schaller, A. A. Tishkov, X. L. Feng and H. Mayr, *J. Am. Chem. Soc.*, 2008, **130**, 3012.
27 H. F. Schaller and H. Mayr, *Angew. Chem., Int. Ed.*, 2008, **47**, 3958.
28 M. Baidya and H. Mayr, *Chem. Commun.*, 2008, 1792.
29 T. A. Nigst, M. Westermaier, A. R. Ofial and H. Mayr, *Eur. J. Org. Chem.*, 2008, 2369.
30 R. Wang and D. H. Macartney, *Tetrahedron Lett.*, 2008, **49**, 311.
31 A. F. Hegarty and V. E. Wolfe, *Arkivoc*, 2008, 161.
32 J. P. Richard, C. K. Heo and M. M. Toteva, *J. Phys. Org. Chem.*, 2008, **21**, 531.
33 J. R. Keeffe and R. A. M. O'Ferrall, *Arkivoc*, 2008, 183.
34 M. Benassi, P. V. Abdelnur, M. N. Eberlin, T. Okazaki and K. K. Laali, *Appl. Catal. A: Gen.*, 2008, **336**, 116.
35 B. Darses, A. Milet, C. Philouze, A. E. Greene and J. F. Poisson, *Org. Lett.*, 2008, **10**, 4445.
36 R. Erez and D. Shabat, *Org. Biomol. Chem.*, 2008, **6**, 2669.
37 F. D'Anna, S. La Marca and R. Noto, *J. Org. Chem.*, 2008, **73**, 3397.
38 S. Y. Pyun and B. R. Cho, *J. Org. Chem.*, 2008, **73**, 9451.
39 J. R. Mohrig, D. G. Alberg, C. H. Cartwright, M. K. H. Pflum, J. S. Aldrich, J. K. Anderson, S. R. Anderson, R. L. Fimmen and A. K. Snover, *Org. Biomol. Chem.*, 2008, **6**, 1641.
40 W. J. Spillane, A. O'Byrne and C. J. A. McCaw, *Eur. J. Org. Chem.*, 2008, 4200.
41 D. S. Kumar and S. Balachandran, *Int. J. Chem. Kinet.*, 2008, **40**, 481.
42 O. Kaumanns and H. Mayr, *J. Org. Chem.*, 2008, **73**, 2738.
43 O. Kaumanns, R. Lucius and H. Mayr, *Chem.–Eur. J.*, 2008, **14**, 9675.
44 F. Seeliger and H. Mayr, *Org. Biomol. Chem.*, 2008, **6**, 3052.
45 M. Rueping, B. J. Nachtsheim, S. A. Moreth and M. Bolte, *Angew. Chem., Int. Ed.*, 2008, **47**, 593.
46 Y. Liang, S. Liu, Y. Z. Xia, Y. H. Li and Z. X. Yu, *Chem.–Eur. J.*, 2008, **14**, 4361.
47 G. O. Jones, X. C. Li, A. E. Hayden, K. N. Houk and S. J. Danishefsky, *Org. Lett.*, 2008, **10**, 4093.
48 X. C. Li and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2008, **130**, 5446.
49 X. C. Li, Y. Yuan, C. Kan and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2008, **130**, 13225.
50 P. Restorp and J. Rebek, *J. Am. Chem. Soc.*, 2008, **130**, 11850.
51 E.A. Castro, M. Aliaga, P. R. Campodonico, J. R. Leis, L. Garcia-Rio and J. G. Santos, *J. Phys. Org. Chem.*, 2008, **21**, 102.

52 I. H. Um, S. J. Hwang, S. Yoon, S. E. Jeon and S. K. Bae, *J. Org. Chem.*, 2008, **73**, 7671.
53 I. H. Um, S. Yoon, H. R. Park and H. J. Han, *Org. Biomol. Chem.*, 2008, **6**, 1618.
54 M. U. Roslund, O. Aitio, J. Warna, H. Maaheimo, D. Y. Murzin and R. Leino, *J. Am. Chem. Soc.*, 2008, **130**, 8769.
55 N. K. Dey, M. E. U. Hoque, C. K. Kim, B. S. Lee and H. W. Lee, *J. Phys. Org. Chem.*, 2008, **21**, 544.
56 S. Iyer and A. C. Hengge, *J. Org. Chem.*, 2008, **73**, 4819.
57 J. Wodzinska and R. Kluger, *J. Org. Chem.*, 2008, **73**, 4753.
58 A. J. Kirby, B. S. Souza, M. Medeiros, J. P. Priebe, A. M. Manfredi and F. Nome, *Chem. Commun.*, 2008, 4428.
59 K. K. Ghosh, S. Bal, S. Kolay and A. Shrivastava, *J. Phys. Org. Chem.*, 2008, **21**, 492.
60 W. Y. Tsang, N. Ahmed, K. Hemming and M. I. Page, *J. Org. Chem.*, 2008, **73**, 4504.
61 L. F. Olguin, S. E. Askew, A. C. O'Donoghue and F. Hollfelder, *J. Am. Chem. Soc.*, 2008, **130**, 16547.
62 O. Taran, F. Medrano and A. K. Yatsimirsky, *Dalton Trans.*, 2008, 6609.
63 I. H. Um, Y. H. Shin, S. E. Lee, K. Yang and E. Buncel, *J. Org. Chem.*, 2008, **73**, 923.
64 T. Humphry, S. Iyer, O. Iranzo, J. R. Morrow, J. P. Richard, P. Paneth and A. C. Hengge, *J. Am. Chem. Soc.*, 2008, **130**, 17858.
65 V. Francisco, L. Garcia-Rio, J. A. Moreira and G. Stedman, *New J. Chem.*, 2008, **32**, 2292.
66 H. D. Banks, *J. Org. Chem.*, 2008, **73**, 2510.
67 T. W. Bentley, I. S. Koo, H. Choi and G. Llewellyn, *J. Phys. Org. Chem.*, 2008, **21**, 251.
68 P. K. Sazonov, G. A. Artamkina and I. P. Beletskaya, *J. Phys. Org. Chem.*, 2008, **21**, 198.
69 M. Karni, C. F. Bernasconi and Z. Rappoport, *J. Org. Chem.*, 2008, **73**, 2980.
70 M. Jacobsson, J. Oxgaard, C. O. Abrahamsson, P. O. Norrby, W. A. Goddard and U. Ellervik, *Chem.–Eur. J.*, 2008, **14**, 3954.
71 C. Isanbor and T. A. Emokpae, *Int. J. Chem. Kinet.*, 2008, **40**, 125.
72 H. Hasegawa, K. Mizuse, M. Hachiya, Y. Matsuda, N. Mikami and A. Fujii, *Angew. Chem., Int. Ed.*, 2008, **47**, 6008.
73 R. D. Chambers, P. A. Martin, G. Sandford and D. L. H. Williams, *J. Fluorine Chem.*, 2008, **129**, 998.
74 G. Pattison, G. Sandford, E. V. B. Wallace, D. S. Yufit, J. A. K. Howard, J. A. Christopher and D. D. Miller, *J. Heterocycl. Chem.*, 2008, **45**, 143.
75 W. R. Dolbier, Y. Zhai, W. Xu, W. Wheelus, F. Dulong, E. Goldberg, I. Ghiviriga and M. A. Battiste, *J. Fluorine Chem.*, 2008, **129**, 1133.
76 P. M. Mancini, G. G. Fortunato, C. G. Adam and L. R. Vottero, *J. Phys. Org. Chem.*, 2008, **21**, 87.
77 H. M. Yau, S. A. Barnes, J. M. Hook, T. G. A. Youngs, A. K. Croft and J. B. Harper, *Chem. Commun.*, 2008, 3576.
78 S. I. Vdovenko and I. I. Gerus, *J. Phys. Org. Chem.*, 2008, **21**, 279.
79 S. I. Vdovenko, I. I. Gerus and V. P. Kukhar, *Spectrochim. Acta: A*, 2008, **71**, 779.
80 J. L. Cook, C. A. Hunter, C. M. R. Low, A. Perez-Velasco and J. G. Vinter, *Angew. Chem., Int. Ed.*, 2008, **47**, 6275.
81 M. Bauer, A. Rollberg, A. Barth and S. Spange, *Eur. J. Org. Chem.*, 2008, 4475.
82 K. Hofmann, K. Schreiter, A. Seifert, T. Ruffer, H. Lang and S. Spange, *New J. Chem.*, 2008, **32**, 2180.
83 A. Fontana, S. Guernelli, P. Lo Meo, E. Mezzina, S. Morganti, R. Noto, E. Rizzato, D. Spinelli and R. Zappacosta, *Tetrahedron*, 2008, **64**, 733.
84 F. D'Anna, V. Frenna, S. Guernelli, G. Macaluso, S. Marullo and D. Spinelli, *J. Phys. Org. Chem.*, 2008, **21**, 306.
85 G. C. Vougioukalakis, M. M. Roubelakis, M. N. Alberti and M. Orfanopoulos, *Chem.–Eur. J.*, 2008, **14**, 9697.
86 F. R. Fischer, W. B. Schweizer and F. Diederich, *Chem. Commun.*, 2008, 4031.
87 S. Bohm and O. Exner, *Org. Biomol. Chem.*, 2008, **6**, 1092.
88 A. Tam, M. B. Soellner and R. T. Raines, *Org. Biomol. Chem.*, 2008, **6**, 1173.
89 D. J. Press, E. A. Mercier, D. Kuzma and T. G. Back, *J. Org. Chem.*, 2008, **73**, 4252.
90 P. Fristrup, M. Kreis, A. Palmelund, P. O. Norrby and R. Madsen, *J. Am. Chem. Soc.*, 2008, **130**, 5206.