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CHAPTER 10

Nucleophilic Aliphatic Substitution

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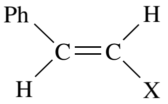
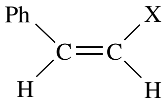
Vinylic Systems

Rappoport and co-workers' work has continued in a study of the substitution of (E)- and (Z)-β-bromo- or chloro-styrenes, (**1**) and (**2**), by MeS^- in DMSO-d_6 (sometimes in admixture with CD_3OD) as solvent.[1] Product studies indicated retention stereochemistry; rate measurements found only a small Br/Cl element effect, slower reactions of the p-OMe bromo compounds, and retardation by CD_3OD. These results are consistent with Tiecco's suggestion in 1983 that even this system, activated by only a single phenyl group, reacts through the nucleophilic addition–elimination multistep route.

Ochiai's group has continued work on the nucleophilic vinylic substitutions of alkenyl(phenyl)iodonium salts. (The leaving-group ability of the phenyliodonio group is about 10^6 times greater than that of triflate.)[2–4] Reactions of (Z)-(β-chloroalkenyl)- and (Z)-(β-bromoalkenyl)-iodonium tetrafluroroborates (**3**) with sodium benzenesulfinate in THF yielded the (Z)-1,2-bis(benzenesulfonyl)alkene (**4**) stereoselectively with retention of configuration.[2] Intermediate formation of (Z)-[β-(benzenesulfonyl)alkenyl]

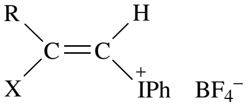


(**1**)



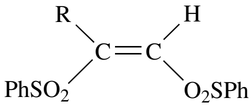
(**2**)

X = Br or Cl



(**3**)

R = n-C_8H_{17} X = Br or Cl



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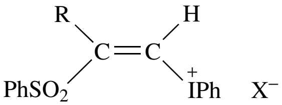

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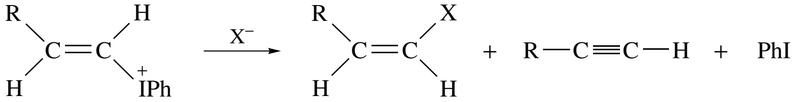


(**6a**) (**6b**) (**6c**) (**6d**)

R = n-C_8H_{17} X = Cl, Br, I, F

iodonium salt (**5**) was shown by PMR experiments in $CDCl_3$. The formation of (**5**) involves a hitherto unobserved Michael addition of benzenesulfinate anion to the alkenyliodonium salts at the β-C, followed by extrusion of halogen.

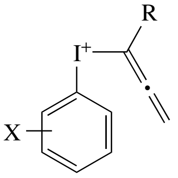
Reactions of (E)-1-decenyl(phenyl)iodonium salt (**6a**) with halide ions have been examined under various conditions.[3] The products are those of substitution and elimination, usually (Z)-1-halodec-1-ene (**6b**) and dec-1-yne (**6c**), as well as iodobenzene (**6d**), but F^- gives exclusively elimination. In kinetic studies of secondary kinetic isotope effects, leaving-group substituent effects, and pressure effects on the rate, the results are compatible with the in-plane vinylic mechanism for substitution with inversion. The reactions of four (E)-β-alkylvinyl(phenyl)iodonium salts with Cl^- in MeCN and other solvents at 25 °C have been examined.[4] Substitution with inversion is usually in competition with elimination to form the alk-1-yne.

Allylic and Other Unsaturated Systems

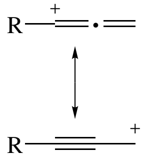
The work of Ochiai's group on nucleophilic vinylic substitution of phenyliodonium salts (see previous section) has been extended to examining the behaviour of allenyl (aryl)iodine(III).[5] Ratios of nucleophilic substitution to [3,3]-sigmatropic rearrangement for the collapse of allenyl(aryl)iodine(III), generated from the reactions of aryliodanes with propargylsilanes in the presence of BF_3–Et_2O in alcohols, have been determined. A suggested mechanism involves generation of propargyl cations (**8**), via a unimolecular pathway from the allenyl(aryl)iodonium ion (**7**).

The regio- and stereo-chemistry of the nucleophilic attack of (S)-*trans*-hex-3-en-2-ol and (S)-*trans*-hex-4-en-3-ol on the corresponding O-protonated or -methylated derivatives have been examined in the gas phase at 40 °C and 720 Torr.[6] Firm evidence of various kinds was obtained for the concerted S_N2' pathway accompanying the classical S_N2 mechanism. Competition between the two processes is essentially governed by the orienting properties of the oxonium intermediate towards the approaching nucleophile. Many other details were elucidated.

The substitution reaction of Cl^- with methyl chloride, 2-chloroethyl radical, and allyl chloride has been treated by several different *ab initio* theoretical models.[7] Depending on the method, the intrinsic barrier for the S_N2' process in allyl chloride is 7–11 kcal mol^{-1} higher than the barrier for the S_N2 reaction of methyl chloride. The reaction of Cl^- with the 2-chloroethyl radical involves an intermediate complex, which is best described as an ethylene fragment flanked by a resonating chloride anion–chloride radical pair. There are many other points of interest.



(**7**)



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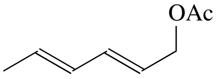

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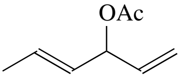

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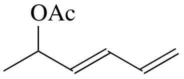

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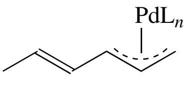
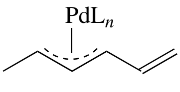


(**12**)



(**13**)

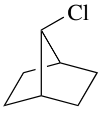
The effect of the nature of ion pairs as nucleophiles in a metal-catalysed substitution reaction has been investigated by determining product ratios for the Pd-catalysed allylic alkylations of substrates (**9**)–(**11**) under various conditions, particularly with respect to catalyst ligands, nucleophiles, and counterions.[8] Each dienyl acetate ionizes to form initially the vinyl (π-allyl)–Pd intermediate corresponding most closely to the leaving group, i.e. (**12**) from (**9**), (**13**) from (**11**), but (**12**) and (**13**) from (**10**). The initial intermediate can then either be trapped by the nucleophile or it can begin to equilibrate to some mixture of vinyl π-allyl intermediates. If nucleophilic addition occurs before full equilibration, the product ratio is different for each substrate; if equilibrium is reached from all three substrates prior to nucleophilic addition, then the product ratio is the same for each substrate. This unified mechanism provides the framework for interpreting the effects of ligands, nucleophiles, and counterions. Any role for S_N2' processes is at present discounted.

The specific acid-catalysed solvolysis of 1-methoxy-1,4-dihydronaphthalene or 2-methoxy-1,2-dihydronaphthalene has been subjected to kinetic and product studies.[9] The elimination product, naphthalene, predominates.

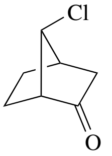
The *C*-glycosylation of pentose glycals with silylacetylenes or allylsilanes through oxocarbenium ion intermediates proceeds with high regio- and stereo-selectivity, giving the 1,4-*anti* compounds as the main products.[10]

Norbornyl and Closely Related Systems

The well-known low reactivity for the displacement of a nucleofuge from the C(7) position of norbornane has been illuminated by *ab initio* and natural bond orbital (NBO) calculations on the ground states of a series of 7-chloronorbornanes, e.g. (**14**)–(**16**).[11] MO calculations were also performed on the corresponding S_N2 transition states. The value of $\Delta H^{\ddagger}$ for the parent compound (**14**) is 22.4 kcal mol^{-1}, but it drops to 18.2 kcal mol^{-1} when a carbonyl group is present at C(2), and further to 10.1 kcal mol^{-1} when a second such group is present at C(3). The NBO analysis shows that this striking effect is due to the strong electric field of the substituent. Calculations for C−F and C=S gave similar results.



(**14**)



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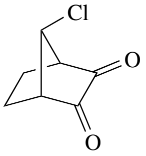


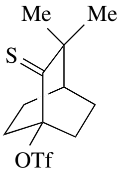
(**16**)

The rates of ethanolysis of 3,3-dimethyl-2-thioxobicyclo[2.2.2]oct-1-yl triflate (**17**) and 3,3-dimethyl-2-thioxobicyclo[3.2.2]non-1-yl triflate (**19**) relative to their corresponding parent compounds, (**18**) and (**20**), are $10^{-6.2}$ and $10^{-2.5}$, respectively, at 25 °C.[12] The smaller retarding effect of the thioxo group when introduced into the more flexible system supports the applicability of the authors' methodology to change the conjugative ability of bridgehead carbocations.

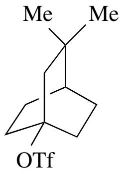
In the hydrolysis of the tosylate (**21a**) the predominance of *exo* isomers (**21b**) relative to *endo* isomers indicated the importance of steric hindrance of the C(1) Me group to *endo* attack by the nucleophile.[13] An analogous result was found for the products of bromination (**21d**) of the corresponding iodides (**21c**).

Epoxide Reactions

The ring opening of glycidic acids and their derivatives by reactants such as the sodium salt of malonic ester has been reviewed in Russian.[14]



(**17**)



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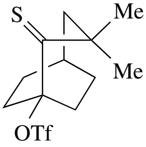

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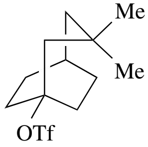

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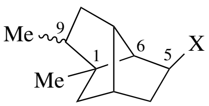


(**21**)

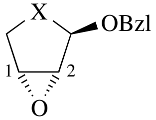
a; X = OTs
b; X = OH
c; X = I
d; X = Br

Crotti and co-workers' work on regiochemical control of ring opening of epoxides by means of chelating agents has continued.[15] Under standard conditions the regioisomeric C(1) derivatives are the sole products from the *trans* epoxides (**22a**) and (**22b**) and are the predominant products from the *cis* epoxides (**23a**) and (**23b**). Under chelating conditions the *cis* epoxides unexpectedly show a consistent increase in C(2) selectivity. The results are discussed in terms of electronic and steric effects.

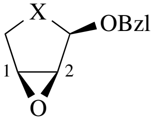
Mechanisms and stereochemistry have been investigated for the acid-induced ring opening of optically active 1, 2-propene oxides in gaseous CH_4 and CH_3F at 720 Torr and in the presence of H_2O or CH_3OH as nucleophile.[16] Two reaction pathways are possible, both proceeding through complete inversion of configuration at the reaction centre.

In the reactions of styrene oxide and butadiene monoxide with ester carbanions, attack takes place at both primary and secondary epoxy carbon atoms.[17] The findings provide evidence for the participation of the conjugative effect in the ring opening of these epoxides.

A model system consisting of methyloxirane, formate, and formic acid has been used to study the nucleophile-catalysed and nucleophile- and acid-catalysed opening of an epoxide ring by applying *ab initio* quantum mechanical calculations [up to the MP4(SDQ)/6−31+G**//MP2/6−31+G** level] and also density functional theory



(**22**)

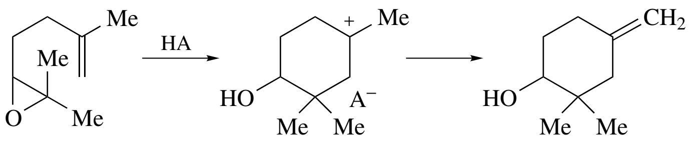


(**23**)

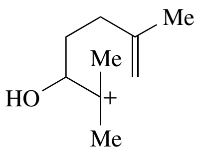
a; X = CH_2 *b*; X = O

calculations [Becke 3LYP/6–31 + G**).[18] This system is intended to serve as a model for the covalent binding of the epoxide inhibitor to the active site of glycosidase. Solvation effects were estimated by using the isodensity surface-polarized continuum model. The ring opening takes place preferentially between the epoxide oxygen and the less substituted carbon, and both the nucleophile and the acid–base catalyst are needed for the process to occur efficiently.

Theoretical evidence [Hartree–Fock (RHF) calculations and density functional theory] has been obtained for a concerted mechanism of oxirane cleavage and A-ring formation in oxidosqualene cyclization.[19] A common concerted mechanistic pathway has been demonstrated for the acid-catalysed cyclization of 5,6-unsaturated oxiranes in chemical and enzymic systems.[20] For example, the conversion of (**24**) into (**26**) proceeds via (**25**) and not via a discrete carbocation (**27**). Kinetic studies and other evidence are presented for various systems.



(**24**) (**25**) (**26**)

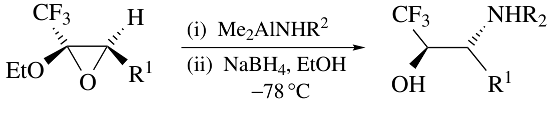


(**27**)

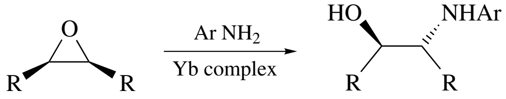
The transition structures for the intramolecular reactions of protonated *cis*- and *trans*-3,4-epoxypentan-1-ol, which result in the formation of protonated *cis*- and *trans*-2-methylfuran-3-ol with inversion and with retention, have been determined at the *ab initio* MP2/6–31G* and hybrid density functional B3LYP/6–31G* levels of theory.[21] Intramolecular attack with inversion occurs in concert with ring opening. The retention transition structures are too high in energy to afford credible reaction pathways. A further contribution from the same research group is a detailed kinetic study of general acid-catalysed benzo[*a*]pyrene diol epoxide hydrolysis.[22] Buffer solutions containing primary amines whose pK_a values span the range 5.4–10.7 were used, and a change in rate-limiting step was detected when amines of pK_a values in the neighbourhood of 8 were employed.

In the tetracyanoethylene-catalysed methanolysis of some steroidal hydroxyepoxides, an adjacent *cis*-5-hydroxy group changes the regio- and stereo-chemistry from *trans* diaxial to diequatorial cleavage.[23] The regioselective ring-opening halogenation of some epoxides by elementary iodine and bromine has been studied.[24] A series of new synthetic macrocyclic diamides and also dibenzo-18-crown-6, 18-crown-6, and aza-18-crown-6 acted as catalysts under mild reaction conditions in various aprotic solvents. Halohydrins were formed in high yields with more than 95% regioselectivity. The macrocyclic catalysts are considered to generate nucleophilic halogen species X_3^-.

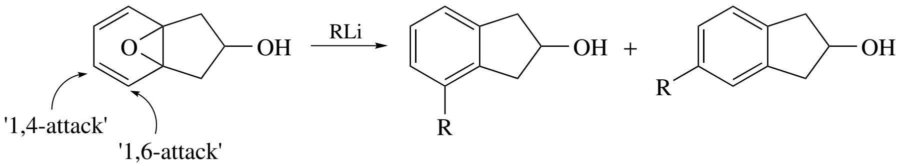
anti-(Trifluoromethyl) β-amino-alcohols (**29**) have been prepared in good yields and with 90% diastereoisomeric excess through a reaction of 1-(trifluoromethyl) epoxy ethers (**28**) with dimethylaluminium amide, followed by *in situ* chelation-controlled stereoselective reduction of the intermediate amino ketone.[25] Depending on R^1 the *anti:syn* ratio of the product ranged from 97:3 (Ph) to 73:27 (CH_2-cyclohexyl), for the reagent with R^2 = benzyl. Chiral β-amino alcohols (**31**) have been prepared by desymmetric ring opening of *meso*-epoxides (**30**) with anilines, the catalyst being a chiral Yb triflate complex.[26] Upto 80.1% *ee* was obtained, depending on R and Ar.



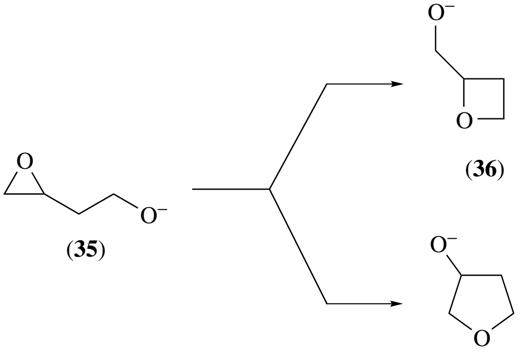
(**28**) (**29**)



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



(**32**) (**33**) (**34**)



(**35**) (**36**) (**37**)

The rare 4- and 5-alkylindan-2-ols (**33**) and (**34**) have been prepared in 62–72% yields by formal 1,6- and 1,4-nucleophilic ring opening of the 2-hydroxyindan-3a, 7a-oxide (**32**), respectively.[27] In a comparison of gas-phase and condensed-phase S_Ni reactions, the competitive four- and five-centre cyclizations [yielding (**36**) and (**37**), respectively] of the 3,4-epoxybutoxide anion (**35**) have been subjected to both experimental and theoretical study.[28] In the gas phase, the barriers to the transition states are comparable, but the tetrahydrofuran-3-ol product (**37**) is much more stable. Base treatment of (**35**) in two different solvent systems yielded the same two products as observed in the gas phase, but (**37**) is the kinetic product in both solvent systems.

Highly regioselective cyclizations of 3,4-, 4,5- and 5,6-unsaturated alcohols to yield tetrahydrofuranols and tetrahydropyranols have been carried out with the TS-1–H_2O_2 system[29] (this is a titanium silicate molecular sieve–H_2O_2 complex.) The reactions involve the intermediate formation of epoxides and their S_Ni ring opening.

Other Small Rings

In a long series on geminal substituent effects, the authors address the question: 'Do alkoxycarbonyl substituents stabilize small cycloalkane rings?'[30] This article is essentially thermochemical. It is concluded that *gem*-alkoxycarbonyl substituents provide only weak stabilization of small cycloalkane rings. Accordingly, high rates of S_Ni ring closure to *gem*-dialkoxycarbonyl cyclopropanes are not attributable to a stabilizing effect resulting from conjugation between alkoxycarbonyl substituents and the cyclopropane ring, as has been suggested. A Thorpe–Ingold or *gem*-dimethyl-type effect offers a more satisfactory interpretation.

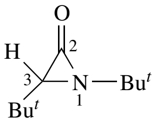
Reaction rates and product composition have been studied for the solvolysis of 1-[*trans*-2-(*m*- or *p*-substituted phenyl)cyclopropyl]-1-methylethyl *p*-nitrobenzoates in 80% aqueous acetone.[31] For the less reactive substrates (those with *m*-Br, *m*-Cl, or *m*-CF_3), the solvolysis products were the corresponding 2-(2-arylcyclopropyl)propan-2-ol, indicating a cyclopropylmethyl cation intermediate. The ring-opened products increased as the electron-donating ability of the substituents increased. Evidence is adduced that in such cases there is a homoallylic cation intermediate.

In the acid-catalysed ring opening of *N*-(3,4-dihydro-4-oxoquinazolin-3-yl)-substituted aziridines, participation by the quinazolinone carbonyl oxygen brings about ring opening with retention of configuration.[32] Monochiral *N*-diphenylphosphinylaziridines undergo ring-opening reactions with a variety of nucleophiles in good yield.[33]

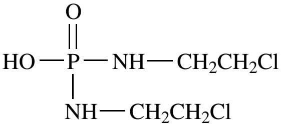
Competing modes of ring opening of 1,3-di-*t*-butylaziridinone (**38**) and similar aziridinones by a variety of *N, O, S*, and Hal nucleophiles do not give proportions of products in agreement with simple guidelines in the literature.[34] For example, (**38**) reacts with aromatic amines by 1,3-cleavage exclusively, as expected, but with aliphatic and saturated cyclic amines, various behaviour is found, including exclusive 1,2-cleavage.

The mechanism of bisalkylation by isophosphoramide mustard (**39**) has been studied.[35] The $\beta, \beta, \beta', \beta'$-$d_4$ derivative was used to demonstrate bisalkylation through sequential aziridinyl intermediates.

Novel S_N2 ring-opening reactions of 2- and 2,2-substituted thiiranes (**40**) with thiols, using as catalyst Na^+-exchanged X-type zeolite or triethylamine in methanol, have been examined;[36] (**40a**) and (**40b**) undergo ring opening regiospecifically at C(3), but for (**40c**) the reaction is not regiospecific, ring opening at both C(3) and C(2) occurring in various proportions, depending on catalyst and other conditions.

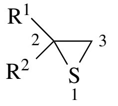


(**38**)



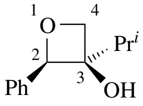
$$\mathrm{HO-\underset{\displaystyle \overset{|}{NH}-CH_2CH_2Cl}{\overset{\displaystyle O}{\overset{\|}{P}}}-NH-CH_2CH_2Cl}$$

(**39**)

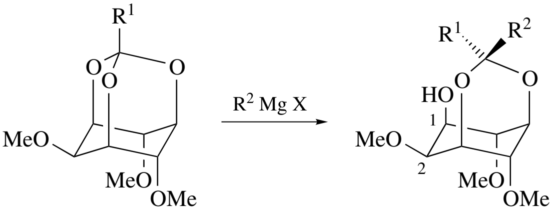


(**40**)

	R^1	R^2
a;	H	Me
b;	Me	Me
c;	H	Ph



(**41**)



(**42**)

R^1 = H or Ph

(**43**)

R^2 = Me

X = I or Br

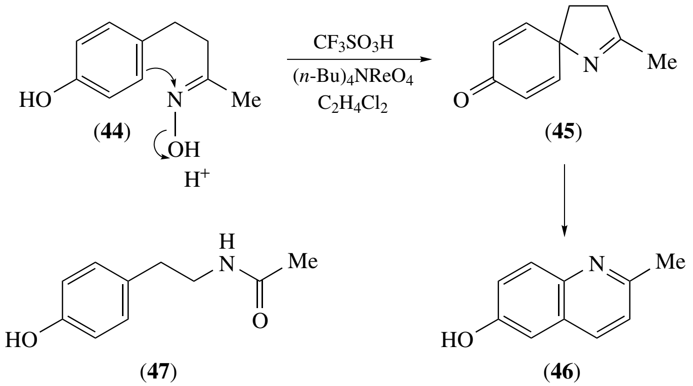
The ring opening of 3-isopropyl-2-phenyl-3-oxetanol (**41**) by different nucleophiles has been studied.[37] In the presence of BF_3–Et_2O, various nucleophiles RLi reacted regiospecifically at C(4), and the corresponding 1,2-diols were isolated in diastereomerically pure form. Other interesting details are provided.

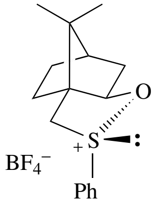
Reactions of orthoesters of *myo*-inositol (**42**) with 1–2 equiv. of Grignard reagent in benzene yield regio- and stereo-selectively ring-opened products (**43**) having a free hydroxy group at C(1).[38] The regioselectivity is attributed to the OMe at C(2) forming a chelation complex with magnesium.

Substitution at Elements Other than Carbon

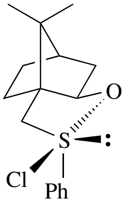
Experimental and theoretical evidence has been obtained for an S_N2-type mechanism in dissociation of B–N coordinate bonds in 2,6-bis[(dimethylamino)methyl]phenylborane derivatives.[39] *Ab initio* calculations were carried out for the system of NH_3 and BH_3.

An acid–rhenium catalyst mixture acts on (*E*)-4-(4-hydroxyphenyl)butan-2-one oxime (**44**) to produce a high yield of the spiro compound (**45**), which then rearranges to the substituted quinoline (**46**).[40] The Beckmann rearrangement product (**47**) is scarcely produced. The formation of (**45**) is essentially an intramolecular S_N2 process (the electron-rich aryl group being the nucleophile) on the sp^2 nitrogen of protonated oxime. Post-Hartree–Fock *ab initio* calculations indicate that the reaction pathways leading to (**45**) and (**47**) are of comparable energies and should be in effective competition. Experimental studies found considerable amounts of Beckmann product under various other conditions.





(**48**)



(**49**)

The isolation and stereochemical studies of a cyclic alkoxysulfonium salt (**48**) have been reported.[41] Such a species has previously been proposed as an intermediate in the hydrolysis of the chlorosulfurane (**49**).

Intramolecular Substitution

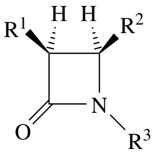
Three-membered ring-forming processes involving $^{-}X{-}CH_2{-}CH_2{-}F$ or $^{-}CH_2{-}C(Y){-}CH_2F$ ($X = CH_2$, O, or S and $Y = O$ or S) in the gas phase have been treated by the *ab initio* MO method with a 6–31+G* basis set.[42] When electron correlation effects were considered, the activation ($\Delta G^{\ddagger}$) and reaction (ΔG°) free energies were lowered by about 10 kcal mol^{-1}, indicating the importance of electron correlation in these reactions. The contribution of entropy of activation ($-T\Delta S^{\ddagger}$) at 298 K to $\Delta G^{\ddagger}$ is very small; the reactions are enthalpy controlled.

Ab initio calculations at the MP2/6–31+G(d,p)//MP2/6–31+G(d) level have been used to investigate the cyclizations of a series of stabilized 3-chlorocarbanions

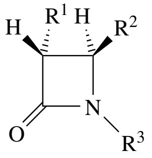
$ClCH_2CH_2CHZ^-$ [Z = C(O)H, CCH, or CN] to cyclopropane derivatives.[43] In each case the cyclization barrier is lower than the S_N2 barrier of an analogous acyclic system, despite the cyclization being over 25 kcal mol^{-1} less exothermic. The surprisingly small enthalpic barrier to the cyclizations is due to the nucleophile being held in close proximity to the electrophilic site in the substrate, and this destabilizes the ground state.

Density functional theory calculations (B3LYP/6–31G* level) have provided an explanation for the stereodivergent outcome of the Staudinger reaction between acyl chlorides and imines to form 2-azetidinones (β-lactams).[44] When ketene is formed prior to cycloaddition, preferential or exclusive formation of *cis*-β-lactam (**50**) is predicted. If, however, the imine reacts directly with the acid chloride, the step that determines the stereochemical outcome is an intramolecular S_N2 displacement, and preferential or exclusive formation of *trans* isomer (**51**) is predicted. These predictions agree well with the experimental evidence regarding the stereochemical outcome for various reactants and reaction conditions.

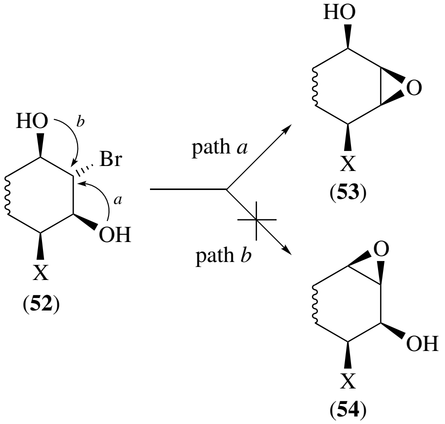
Bromocyclopentitols and amino(or amido)bromocyclopentitols having a C–Br bond *trans* to two vicinal hydroxy groups show selectivity in base-promoted epoxide formation, e.g. (**52**) gives (**53**) by path *a*, rather than (**54**) by path *b*.[45]



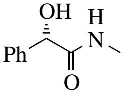
(**50**)



(**51**)



X = OH, NH_2 or

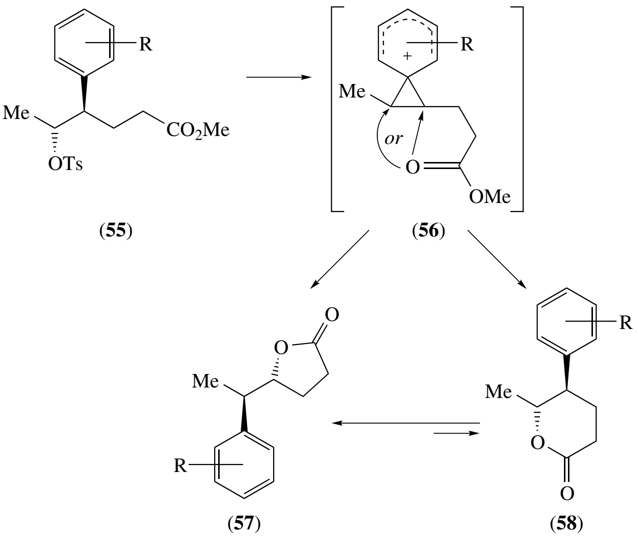


The hydrolysis of *o*-nitrobenzyl tosylate in 1:1 MeCN–H_2O gives *o*-nitrobenzyl alcohol and *o*-nitrosobenzaldehyde in a ratio of 1.8:1.[46] The formation of the aldehyde indicates that the nitro group participates in the expulsion of the tosylate group to give a cyclic intermediate, which then undergoes ring opening to *o*-nitrobenzaldehyde. *o*-Nitrosobenzaldehyde reacts with benzylamine to form 3-(*N*-benzylamino)anthranil (or its tautomer) as a major product.

Ab initio MO theory, mainly at the 3–21+G level, has been applied to intramolecular S_N2 methyl transfer between two oxygen atoms confined within a rigid template.[47] This is found to proceed exclusively by a high-energy retention mechanism when the oxygens are separated by three or four bonds, and by high-energy inversion when the oxygens are separated by six bonds. The mechanisms compete when the oxygen atoms are separated by five bonds. The CH_3/CD_3 kinetic isotope effects are normal (1.21–1.34) in retention and inverse (0.66–0.81) in inversion. The same group has pursued a further study of alkyl transfer with retention or inversion of configuration in re-examining the thermal rearrangement of 2-alkoxypyridine-1-oxides to 1-alkoxy-2-pyridones, a putative intramolecular [1s, 4s] sigmatropic migration of the alkyl group.[48] An alternative mechanism involving intermolecular alkyl transfer is now put forward.

It has been suggested that the Tanigawa reaction involves the decomposition of an intermediate by an intramolecular S_N2 process.[49]

The study of lactonization via an intermediate phenonium ion has been further pursued for several methyl 4-aryl-5-tosylhexanoates (**55**) as substrates.[50] The intermediate phenonium ion (**56**) has two possibilities for ring closure, yielding products (**57**) or (**58**). In all the substrates, Ar contained one or two methoxy groups and sometimes also a methyl group. The effects of reaction medium, temperature, and time on the product ratios were examined. It was concluded that substrates (**55**) give γ-lactone (**57**) selectively under thermodynamic conditions, but δ-lactone (**58**) under kinetic conditions. Substituents in Ar influence the selectivity through their electronic effects.



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

Ambident Nucleophiles

The structures of lithium and sodium cyanates and isocyanates and their related ion-pair S_N2 reactions have been examined by using quantum mechanics at the Hartree–Fock (HF)/6–31G**//HF/6–31G** level.[51] (The cyanate ion is NCO^-; the isocyanate ion is CNO^-.) The isocyanate ion pairs are the most stable monomeric forms; the lowest energy dimers are planar eight-membered rings. For the ionic S_N2 reaction of cyanate ion with MeF or MeCl, methyl isocyanate is the predicted major product. Predictions about the S_N2 reactions of the ion pairs were also made.

Alpha Effect

Second-order rate constants have been measured for the S_N2 reactions of benzyl bromide and *p*-nitrobenzyl bromide with hydroxy nucleophiles.[52] The values of $k(HOO^-)/k(HO^-)$ are very small (1.3 and 1.2, respectively) for the two substrates. Thus the α-effect is very small and it is suggested that this may be due to the lack of tight σ-bond formation at the transition state.

Isotope Effects

Westaway and co-workers' work on kinetic isotope effects (KIEs) has continued.[53–55]

In a long series on isotope effects in nucleophilic substitution reactions, the effect of changing the nucleophilic atom on ion pairing in an S_N2 reaction has been examined.[53] When the nucleophile is sodium thiophenoxide, ion pairing markedly alters the secondary α-deuterium KIE and the effect of changing the *p*-substituent on the nucleophile. In the case of sodium phenoxide, ion pairing does not significantly affect the secondary α-deuterium or the chlorine leaving-group KIEs or the effects of changing a *p*-substituent on the nucleophile or the substrate.

The $^{11}C/^{14}C$ incoming-group and secondary α-deuterium KIEs have been used to determine how a change in leaving group alters the structure of the transition state of the S_N2 reactions between *m*-chlorobenzyl *p*-substituted benzenesulfonates and cyanide ion.[54] The results suggest that the reactions occur by way of an unsymmetrical, product-like transition state.

Two methods were used to measure the chlorine leaving-group KIE for the S_N2 reduction of benzyl chloride to toluene by sodium borohydride in DMSO at 30 °C.[55] One procedure involved the classical IRMS technique. The second method was a new technique in which the ratio of the chlorine isotopes was obtained by fast atom bombardment mass spectrometry on silver chloride recovered from the reaction. The KIE values k^{35}/k^{37} found by the two methods were 1.007 and 1.008, respectively, identical within experimental error. This large KIE indicates considerable C–Cl bond rupture in the transition state.

Gas-phase Reactions

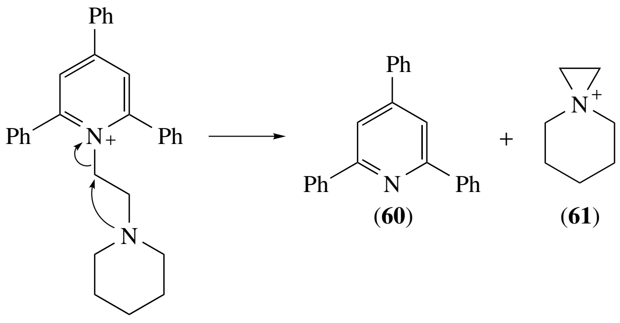
The dynamics and mechanism of nucleophilic displacements involving ions in the gas phase have been reviewed.[56] The article covers aspects of kinetics (especially the applicability of statistical reaction rate theory), the relation of structure and reactivity, and the effects on the reactions of introducing small numbers of solvent molecules. The behaviour of the ionic reaction in the gas phase is compared with that in solution.

In studies of ion–molecule reactions in the gas phase, the influence of collision energy on competitive S_N2 and S_Ni reactions has been examined for reactions of epimeric indan-1,2-diols with the NH_3–NH_4^+ system.[57] Stereospecific S_N2 and S_Ni pathways operate for the *cis* and *trans* derivatives, respectively.

Hase and co-workers' work has continued[58–60] with a review of computational and experimental studies of the dynamics of gas-phase S_N2 reactions of the type $X^- + RY \rightarrow XR + Y^-$, in particular for R = Me, X = Cl, and Y = Cl or Br.[58] The computational studies involve classical trajectory simulations on analytical potential energy functions derived from *ab initio* electronic structure calculations. *Ab initio* calculations at different levels of theory are considered. Among the topics studied are the dynamics of the $X^- + RY$ association process, a direct mechanism for $X^- + RY \rightarrow XR + Y^-$, and energy partitioning for the $XR + Y^-$ products. The series on trajectory studies of S_N2 processes has continued with an examination of the role of translational activation in the $Cl^- + CH_3Cl$ reaction[59] and in the $F^- + CH_3Cl$ reaction.[60] In the former the reactive trajectories are direct, with negligible trapping in the ion–dipole complexes, whereas in the latter there is evidence for the formation of ion–molecule complexes at lower energies.

Studies of gas-phase S_N2 reactions at sp^3 carbon have been made by Fourier transform ion cyclotron resonance mass spectrometry (FTICRMS) and complemented by both semiempirical and *ab initio* MO calculations.[61] The particular processes of interest involved intramolecular reactions in which neutral nucleophiles displace neutral leaving groups within cationic substrates, e.g. *N*-(2-piperidinoethyl)-2,4,6-triphenylpyridinium cation (**59**), in which the piperidino moiety is the nucleophile and 2,4,6-triphenylpyridine (**60**) is the leaving group. No evidence has been obtained for any intermolecular gas-phase S_N2 reaction involving a pyridine moiety as a leaving group. The quantum mechanical treatments account for the intramolecular preference.

An *ab initio* MO study has been carried out on a linear relationship between free energies of activation of Menshutkin reactions and the proton affinities of the nitrogen bases used as nucleophiles.[62] The relationship had been discovered some



(**60**) (**61**)

(**59**)

years ago. Different lines were obtained for sp^2 and sp^3 bases, and the calculations at the MP2/6–31+G*//RHF/6–31+G* level explain why this occurs. The relationship has now been extended to activation energies.

The $HO^- + CH_2F_2$ reaction has been studied by selected ion flow tube (SIFT) experiments and *ab initio* calculations.[63] SIFT experiments at 300 K showed that a bimolecular process [leading to $CHF_2{}^-$ (86%), F^- (11%), and $HF_2{}^-$ (3%)] competes with a three-body association leading to $HO^-.CH_2F_2$. The bimolecular rate coefficient has an upper limit of about $2.4 \times 10^{-12} cm^3 molecule^{-1} s^{-1}$ and shows a small negative temperature dependence, suggesting that reaction proceeds via an ion complex intermediate. The results were rationalized by the MO calculations.

The nature of the neutral or acidic hydrolysis of CH_2Cl_2 has been examined from ambient temperature to supercritical conditions (600 °C at 246 bar).[64] Rate measurements were made and the results show major deviations from the simple behaviour expressed by the Arrhenius equation. The rate decreases at higher temperatures and relatively little hydrolysis occurs under supercritical conditions. The observed behaviour is explained by a combination of Kirkwood dielectric theory and *ab initio* modelling.

Gas-phase nucleophilic substitution reactions of Y-benzyl chlorides and X-phenoxide or X-thiophenoxide nucleophiles have been investigated by using the PM3 semiempirical MO method.[65] The structure of the transition state was examined. The values of the gas-phase Hammett constants ρ_X and ρ_Y are much greater than for the solution reactions, but a theoretical cross-interaction constant ρ_{XY} (ca -0.60 for both phenoxides and thiophenoxides) agrees well with an experimental value of -0.62 for the thiophenoxide reactions in MeOH at 20 °C. Other work by the same group has involved theoretical studies of competitive gas-phase S_N2 and $E2$ reactions of $NCCH_2CH_2Cl$ with HO^- and HS^-.[66] An *ab initio* method at the 6–31+G* level was used, with electron correlation at the MP2 level. $E2$ is preferred to S_N2 for both HO^- and HS^-.

Ab initio MO calculations have been carried out for two carbocation-generating reactions: the S_N1 reaction of protonated 1-phenylethanol (H_2O leaving group) and the acid-catalysed hydration of styrene.[67] Optimizations were done at the MP2/6–31G* level. The S_N1 transition state lies half way between the reactant and the product with respect to the bond lengths, charge distribution, and secondary deuterium isotope effects.

An *ab initio* study of elimination and substitution has been done for the gas-phase reaction of F^- with chlorocyclopropane.[68] Among various findings it emerged that at the MP2/6–31(+)G*//HF/6–31(+)G* level, the S_N2 pathway has a lower activation barrier by 7.3 kcal mol^{-1} compared with the $E2$(*anti*) pathway.

The S_N2 reactions of the radical anions ($CHCl^{\cdot-}$ and $CHBr^{\cdot-}$) and the closed-shell anions (CH_2Cl^- and CH_2Br^-) with CH_3Cl and CH_3Br have been studied by using density functional theory.[69] The closed-shell anions were found to be more reactive than the radical anions, in agreement with experiment. Other details of the systems were also elucidated. *Ab initio* and semiempirical (AM1) methods were used to study the gas-phase S_N2 reactions between methyl nitrate and various nucleophiles.[70]

Radical Processes

The stereochemistry of the nucleophilic reaction of the enolate ion of 1,4-dihydro-4-methoxycarbonyl-1-methylpyridine with (*R*)-(−)- and (*S*)-(+)-2-bromobutane has been investigated.[71] The reaction proceeds with 99.7% inversion of configuration. Thus, even though the inner-sphere stabilization of this reaction is small, there is no sign of the outer-sphere electron-transfer (ET) process, which would lead to racemization.

By means of diastereomeric probes, it has been demonstrated that the vicinal nucleophilic displacement of a diethylphosphate group from a β-(phosphatoxy)alkyl radical may occur through backside or frontside attack, depending on steric constraints.[72]

The competition between ET and S_N2 processes in the reaction between radical anions of various aromatic compounds, e.g. anthracene, pyrene, (*E*)-stilbene, and *m*- and *p*-cyanotoluene, and substrates such as RHal (where R = Me, Et, Bu, 2-Bu, neopentyl, and 1-adamantyl) or various methanesulfonates has been studied in DMF as solvent.[73] The reaction mechanism could be characterized electrochemically in many of the systems indicated above. The presence of an S_N2 component is related not only to the steric requirements of the substrate, but also to the magnitude of the driving force for the ET process.

2,2,2-Trifluoroethyl chloride, bromide, and iodide (but not fluoride) react with thiolate ions in DMF under laboratory illumination at 30–50 °C to give high yields of 2,2,2-trifluoroethyl thiol derivatives.[74] Various features of the reactions show that they occur by the $S_{RN}1$ mechanism. The initiation may be spontaneous or thermal electron transfer between thiolate and halides, because the reactions can occur in the dark.

The two-electron reduction product of terephthalodinitrile reacts with alkyl halides in liquid ammonia to yield 4-alkylbenzonitriles and 2-alkylterephthalodinitriles.[75] The product ratio strongly depends on the alkyl halide and changes in favour of the *ipso* product, 4-alkylbenzonitrile, on going from tertiary alkyl to primary and from iodide to chloride. This change is the result of increased contribution of the S_N mechanism relative to the ET mechanism.

Medium Effects

Palm's group has continued to develop statistical procedures for treating solvent effects.[76] In a previous paper, a set of nine basic solvent parameter scales was proposed. Six of them were then 'purified' via subtraction of contributions dependent on other scales. This set of solvent parameters has now been applied to an extended compilation of experimental data for solvent effects on individual processes. Overall, the new procedure gives a significantly better fit than the well-known equations of Kamlet, Abboud, and Taft, or Koppel and Palm.

Kinetics of the solvolysis of acyl chlorides and alkyl chlorides in hydroxylic solvent mixtures have been measured conductimetrically at various temperatures and pressures.[77] The activation parameters $\Delta V^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ were calculated from the rate constants. The authors appear to have been interested mainly in acyl chlorides, but conclude that, whereas *p*-methylbenzoyl chloride reacts via a dissociative

S_N2 mechanism, *p*-methylbenzyl chloride reacts via an ion-pair mechanism of a unimolecular reaction.

Correlation analysis of solvent effects on the heterolysis of *p*-methoxyneophyl tosylate has been performed by using the Koppel–Palm and Kamlet–Taft equations.[78] The reaction rate is satisfactorily described by the electrophilicity and polarity parameters of solvents, but a possible role for polarizability or nucleophilicity parameters was also examined.

Heterolysis rates of *t*-butyl bromide, 1-bromo-1-methylcyclohexane, and 2-bromo-2-methyladamantane increase in the order of solvents MeCN $<$ γ-butyrolactone $<$ sulfolane, but heterolysis rates of 2-bromo-2-phenyladamantane decrease in the same order of solvents.[79] The observed effects are considered to be caused by superposition of dipolar and electrophilic solvations.

Studies of ‘dimensiosolvatic’ effects have continued with an attempt to quantify them for solvolyses of 2-bromoadamantane in water–alcohol mixtures.[80] Product selectivities $S = k(\text{ether})/k(\text{alcohol})$ were measured at various concentrations of water in an alcohol and at various temperatures. The reciprocals of the averages of S values for 1.0:0.8 alcohol–water mixtures at all the experimental temperatures (120–150 °C) were proposed ‘as measures D of dimensiosolvatic effects when a solvent molecule intervenes into contact ion pair to form solvent-separated ion pair.’ The scale runs from $D = 1.0$ (by definition) to $D = 10.0$ for *t*-butyl alcohol and is essentially a measure of the bulkiness of solvent molecules.

Kevill and co-workers’ work on solvolysis rates has continued.[81–83] The specific rates of solvolysis of the benzylmethylphenylsulfonium ion and five benzylic ring-substituted derivatives can be satisfactorily correlated using N_T solvent nucleophilicity scales.[81] Addition of a secondary term, governed by the aromatic ring parameter (I), shows the sensitivities towards changes in this parameter to fall and those towards changes in N_T to rise with increasing electron-withdrawing ability of the substituent. The specific rates of solvolysis of benzyl *p*-toluenesulfonate and nine benzylic-ring-substituted derivatives are satisfactorily correlated by using N_T and Y_{OTs} scales in the extended Grunwald–Winstein equation.[82] Addition of a third term involving the aromatic ring parameter I is statistically significant. Electron-withdrawing substituents increase the sensitivity towards changes in N_T, whereas they decrease the sensitivity towards changes in Y_{OTs} and I. The trend of sensitivities towards N_T can be very nicely shown, with very precise correlations, by using an internally generated scale of Y values. However, such a procedure has no overall advantage if it is desired ultimately to make a comparison with sensitivity values generated by using an external scale of Y values. Solvent effects on the rate coefficients of solvolysis of 4-chloro-2,2,4,6,6-pentamethylheptane and 3,3-dimethyl-1-neopentylbutyl mesylate (whose molecules are extremely crowded), previously analysed by using the extended Grunwald–Winstein equation incorporating N_T and Y_X values, are better correlated by using a combination of Y_X and I values.[83]

Liu and co-workers’ work on solvolysis rates has continued.[84–88] Rate coefficients of solvolysis of four 1-R-1-chloro-1-(4-methyl)phenylmethanes (R = Me, Et, Pr^i, or Bu^t) were measured in aqueous-acetone, -ethanol, and -methanol, and in ethanol-trifluoroethanol mixtures.[84] Grunwald–Winstein type correlation analysis using the

Y_{BnCl} scale suggests significant nucleophilic solvent intervention for the substrate with R = Me. Increasing bulkiness of R resulted in a gradual change to limiting S_N1 mechanisms. The superiority of employing the Y_{BnCl} scale over the combination of Y_{Cl} and I (aromatic ring parameter) scales in the mechanistic study was observed. Rate coefficients in various solvents have been measured for a series of 1-aryl-1-*t*-butylmethyl chlorides.[85] Correlation analysis with a single-parameter Grunwald–Winstein equation incorporating Y_{BnCl} was excellent in every case. Substituent effects were treated in terms of the Hammett equation (Brown–Okamoto σ^+ constants) and the Yukawa–Tsuno equation. Solvolysis rates have been measured for α-*t*-butyl(2-naphthyl)methyl chloride, 9-fluorenyl chloride, and a series of monosubstituted benzhydryl chlorides in a wide range of solvents.[86] These substrates were selected because the corresponding carbocations all show extended charge delocalization. The application of Y_{BnCl}, with or without the inclusion of a solvent nucleophilicity parameter, did not give fully satisfactory correlations, so a new scale of solvent ionizing power Y_{xBnCl} for the correlation of solvolytic reactivities of benzylic chlorides with extended charge delocalization was based on the results for α-*t*-butyl(2-naphthyl)methyl chloride. Applications of Y_{BnCl} or Y_{xBnCl} were held to give a better understanding of reaction mechanisms than those of Y_{Cl} combined with I. Further work from Liu's group has involved 'B-strain and solvolytic reactivity revisited. Nucleophilic solvent participation and abnormal rate ratios for tertiary chloroalkanes.'[87] The 'abnormal rate ratios' are those involving introducing Pr^i, and are considered due to competition between B strain and nucleophilic solvent participation. In presenting solvolytic studies of 4-methoxybenzyl chloride and bromide, and of 1-(4-methoxyphenyl)ethyl chloride, further opportunity was taken to criticize the introduction and use of the aromatic ring parameter I.[88]

Rate constants and products have been reported for solvolysis of benzhydryl chloride and *p*-methoxybenzyl chloride in 2,2,2-trifluoroethanol (TFE)–water and–ethanol, along with additional kinetic data for solvolysis of *t*-butyl and other alkyl halides in 97% TFE and 97% hexafluoropropan-2-ol.[89] The results are discussed in terms of solvent ionizing power Y and nucleophilicity N, and contributions from other solvation effects are considered. Comparisons with other S_N1 reactions show that the solvolyses of benzhydryl chloride in TFE mixtures are unexpectedly fast; an additional solvation effect influences solvolysis leading to delocalized cations.

Solvolysis rates of substituted 2-aryl-1, 1-dimethylethyl bromides have been determined in various binary solvent mixtures, particularly aqueous–organic mixtures.[90] Grunwald–Winstein treatments gave mixed results. They were reasonably successful for aryl = Ph or *p*-$\mathrm{MeC_6H_4}$, but aryl = *p*-$\mathrm{MeOC_6H_4}$ failed to give a single linear correlation against either Y or Y_{Cl}. It did, however, give fairly good linearity against Y_Δ, defined from the solvolysis of 4-methoxyneophyl tosylate.

Rates of solvolysis of 2-adamantyl azoxytosylate were measured over a range of temperatures in ethanoic acid, methanoic acid, and various mixed solvents.[91] For comparison solvolysis rates of 2-adamantyl tosylate were measured in several of the same solvents. The m value for 2-adamantyl azoxytosylate solvolysis is only 0.46, one of the lowest observed values for a reaction that is unambiguously S_N1.

Aqueous ethanolyses of adamantylideneadamantyl halides show Grunwald–Winstein sensitivity parameters (m) of 0.74 (±0.06), 0.90 (±0.01), and 0.88 (±0.03) for the chloride, bromide, and iodide compounds, respectively.[92] All reaction products are formed with retention of both the ring structure and the stereochemistry of the reaction centre. Observed common-ion rate depressions are consistent with a reaction pathway via a free solvated homoallylic carbenium ion.

Rate constants have been determined for solvolyses of 2-bromo- (or -chloro-) -2-methylbutane and 3-chloro-3-methylpentane in 10 diols at 298.15 K.[93] By combining kinetic data with thermodynamic data, transfer Gibbs energies of the reactants (initial state) and of the activated complex (transition state) were obtained, which allowed the solvent effects on both states to be quantitatively analysed.

The solvation and nucleophilic reactivity (towards ethyl iodide) of the 1,2,4-triazolate ion have been investigated in MeCN–MeOH mixtures.[94] Various correlations of thermodynamic and kinetic functions are presented.

The specific rates of hydrolysis of five organic halides in three water-based liquid mixtures near their respective equilibrium consolute points have been observed to be suppressed.[95] The systems studied included *t*-amyl chloride in isobutyric acid + water (upper consolute temperature), and 3-chloro-3-methylpentane in 2-butoxyethanol + water (lower consolute temperature). The slowing effect occurred within a few tenths of a degree on either side of the consolute temperature.

Ab initio MO calculations were carried out on the hydrolysis of CH_3Cl, with explicit consideration of up to 13 water solvent molecules.[96] The treatments were at the HF/3–21G, HF/6–31G, HF/6–31+G* or MP2/6–31+G* levels. For $n \geqslant 3$ three important stationary points were detected in the course of the reaction. Calculations for $n = 13$ at the HF/6–31+G* level reproduced the experimental activation enthalpy and the secondary deuterium KIE. The proton transfer from the attacking water to the water cluster occurs after the transition state, in which O–C is 1.975 Å and C–Cl is 2.500 Å.

The nature of salt effects in monomolecular heterolysis has been reviewed.[97] The experimental work of the same group on salt effects has continued with a study of the negative salt effect of lithium perchlorate on the heterolysis of 1-iodoadamantane in γ-butyrolactone.[98] It is assumed that the salt effect of lithium perchlorate is caused by the salt action on the solvent-separated ion pair of the substrate.

Extensive studies have been carried out on the concentrated salt effects on the solvolysis reaction rates of aliphatic halides and related compounds in acetone–water mixed solvents.[99] The main outcome of the complicated results presented appears to be that 'It is proposed that one could simply distinguish S_N1 from S_N2 reactions merely by observing a substantial increase in the solvolysis rate constant at 1.0 mol dm^{-3} $LiClO_4$ in aqueous mixed solvents.'

Phase-transfer Catalysis and Other Intermolecular Effects

Kinetic studies have been carried out for reactions of triphenylphosphine with substituted benzyl halides in various two-phase organic solvent–water media.[100] The effects of water, agitation, organic solvent, reactant and temperature were investigated. The order of relative reactivity for solvents was $CHCl_3 > CH_2Cl_2 \gg C_6H_6$.

Nucleophilic substitution on methyl *p*-nitrobenzenesulfonate in CH_2Cl_2 has been studied with a series of chloride salts with different structures and solvations: Bu_4NCl, PPNCl [bis(triphenylphosphoranylidene)ammonium chloride], KCl complexed by 18-crown-6 or Kryptofix 2,2,2, and for comparison PPNBr.[101] Rate constants and activation parameters are in accordance with an S_N2 mechanism. The results were treated by the Acree equation. There are two reaction paths: the first, involving the chloride ion, has the same rate for all the salts, whereas the second slower path, involving the ion pair, has a rate related to the dissociation constant of the salt.

A new transition-state-searching algorithm was used to determine the mechanism for methanol condensation to form dimethyl ether within the microporous environment of the zeolite, chabazite, using periodic boundary conditions and density functional theory.[102] An acid site in the zeolite produces $MeOH_2^+$ for nucleophilic attack by a second adsorbed MeOH molecule.

Structural Effects

The number of references for this section has fallen greatly, and it now seems unnecessary to use sub-headings.

A methodology that can classify reactions by using similarity measures has recently been introduced and has now been extended to include a steric similarity index.[103] Both substitution and elimination reactions are included.

The rate constants for methanolysis of alkyl *p*-toluenesulfonates conform to a two-parameter equation of the Hammett–Taft type, the governing structural factor being steric hindrance.[104] However, the alcoholysis rates of alkenyl and alkynyl *p*-toluenesulfonates do not obey this relation, probably because the multiple bonds stabilize the reaction intermediate.

Solvolysis of 1-(X-phenyl)-1-cyclohexyl chlorides in MeOH–MeCN mixtures was studied at 30.0 and 40.0 °C.[105] The ρ_X^+ values, −4.67 to −4.81 at 30.0 °C, are within the range for secondary and tertiary compounds which are believed to react by an S_N1 mechanism. The Grunwald–Winstein *m* values (plots using $Y_{1-\mathrm{AdOTs}}$) are $\geqslant 1.0$, and these relatively large values suggest that the positive charge developed in the transition state is considerable and is delocalized on to the aromatic ring. The kinetics and mechanism of nucleophilic substitution reactions of *exo*- and *endo*-2-norbornyl arenesulfonates with anilines have been investigated in MeOH–MeCN mixtures at 60.0 °C.[106] Rate constants for three distinct competing processes were separately determined: solvolysis k_s, unimolecular k_1, and bimolecular k_2. The Hammett equation with cross-terms was applied to the effects of substituents X in the nucleophile and Z in the leaving group on the analysed rate constants, but in most cases the ρ_{XZ} term was negligible. The Hammett equation with cross-terms has also been applied to the reactions of Z-substituted benzyl X-benzenesulfonates with Y-substituted thiobenzamides in acetone at 45 °C.[107] The findings $\rho_Z < 0$ and $\rho_{YZ} > \rho_{XZ}$ indicate that this reaction proceeds by a dissociative S_N2 mechanism.

Isoparametricity has been experimentally verified as occurring in the reactions of Y-substituted benzyl bromides with X-substituted anilines in dioxane and in 2, 3, and 5 M DMSO solutions in dioxane at 40 °C.[108] The phenomenon is interpreted on the basis of structural variation of the transition state of the S_N2 reaction. The same author studied the kinetics of the reactions of benzyl bromides with imidazoles and pyridines in nitrobenzene at 40 °C.[109,110] Cross-correlation analysis was applied.[109] The reactivities of imidazoles towards benzyl bromides are considerably less than those of pyridines of equal basicity.

Solvolysis rates of 2,2,2,-trifluoro-1-(3-chlorophenyl)-1-(substituted phenyl)ethyl and 2,2,2-trifluoro-1-(3,5-dichlorophenyl)-1-(substituted phenyl)ethyl tosylates or bromides have been measured conductimetrically at 25.0 °C in 80% aqueous ethanol.[111] The former reaction series showed a bilinear Yukawa–Tsuno correlation with $\rho = -4.81$ and $r = 1.41$ for substituents more deactivating than 3,5-dimethyl, and with $\rho = -6.19$ and $r = 1.57$ for the substituent range more activating than 4-methyl. The bilinear correlation was interpreted in terms of the changing coplanarity of the two aryl rings. The 3,5-dichlorophenyl-fixed substrates showed an excellent Yukawa–Tsuno correlation for the substituent range 4-MeO to 4-Cl, with $\rho = -5.95$ and $r = 1.69$. The variable aryl rings in this series show the largest extent of resonance interaction in the transition state with a carbenium ion centre that is highly deactivated by α-CF_3 and α-(3,5-dichlorophenyl).

Rate data for the Menshutkin reaction between strongly activated Z-substituted benzyl *p*-toluenesulfonates and Y-substituted *N,N*-dimethylanilines in MeCN at 35 °C fit the equation $k_{obs} = k_1 + k_2$ [DMA], which is consistent with concurrent first- and second-order processes.[112] The S_N1 constant k_1 is unaffected by changing the nucleophile and conforms to Yukawa–Tsuno treatment with $\rho = -5.2$ and $r = 1.3$. The S_N2 constant k_2 was increased by electron-donating substituents in the nucleophile and showed upward curvature when subjected to the Brown σ^+ treatment.

Studies on the reactions of MeBr and EtBr with KOH in absolute or aqueous MeOH showed that the main products are Me_2O and EtOMe, respectively.[113] The rates are the same whether KOH or KOMe is used to provide the nucleophile because the equilibrium $HO^- + MeOH \leftrightarrows MeO^- + H_2O$ lies very much to the right.

Miscellaneous S_N2 Reactions

In studies of onio-assisted S_N2 reactions, the behaviour of substrates such as $[Ph_3AsCH_2OTf]^+TfO^-$ has been examined.[114] This contains a 1,1-biselectrophilic sp^3 carbon centre. With neutral nucleophiles (Nu^1) under mild conditions a series of 1,1-bis-onium salts $[Ph_3AsCH_2Nu^1]^{2+}2TfO^-$ was obtained in good yields. Under more stringent conditions the triphenylarsonio function can act as a nucleofuge in a subsequent reaction with a second nucleophile Nu^2, yielding a series of unsymmetrical 1,1-bis-onium salts $[Nu^2CH_2Nu^1]^{2+}2TfO^-$.

The reaction of 1-alkoxypolyfluoroalkyl sulfonates with lithium tetraalkyl aluminates yields stereospecifically alkylated products with a high degree of inversion.[115] However, the reaction with trialkylaluminium reagents is considerably less stereospecific.

A series of imidate esters derived from secondary alcohols has been found to react with potassium benzoate or potassium phthalimide to give products of S_N2 substitution in excellent yields and with clean inversion of stereochemistry.[116]

Molecular dynamics simulations of ground and transition states have been carried out for the S_N2 displacement of chloride ion from 1,2-dichloroethane by the Asp 124–CO_2^- at the active site of *Xanthobacter autotrophicus* haloalkane dehalogenase.[117]

Detailed theoretical studies have been made for the S_N2 reaction of methyl bromide with $Me_2CuLi.LiCl$, with particular attention to solvent and cluster effects.[118]

A long series on stereochemistry has continued in a study of the acetolysis of triterpenoid *p*-toluenesulfonates in the presence of NaOAc.[119] Both substitution and elimination products were formed. Substitution could be accounted for by bimolecular processes (S_N2 on carbon, S_AN on sulfur). Some confirmation of this was obtained by kinetic studies.

Miscellaneous Kinetic Studies

Kinetic studies of various systems have been carried out as follows: the reaction of 2,2′-dichlorodiethyl sulfide and of 2-chloroethyl ethyl sulfide with diethylenetriamine and triethylamine in 2-methoxyethanol;[120] the catalysed reactions of substituted phenols with epichlorohydrin;[121] the reactions of *para*-substituted benzyl bromides with isoquinoline under high pressure;[122] the reactions of *O*-alkylisoureas with OH-acidic compounds [the actual system was *N*,*N*′-dicyclohexyl-*O*-(1-methylheptyl)isourea with acetic acid];[123] and the ring opening of isatin in aqueous binary mixtures of methanol and acetonitrile cosolvents.[124]

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