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Reactivity of Substituted Aliphatic Nitro-compounds with Nucleophiles

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1 Introduction

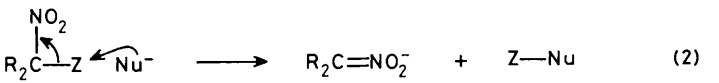
The chemistry of aliphatic nitro-compounds has become of considerable interest in recent years (a) because of the increasing importance of the nitro-group in synthesis, and (b) because of the variety of reactivity exhibited by the nitro-group, due to its strong $-I$ character, and to its facility to act as a strong electron acceptor.

This review will deal largely with the reactivity of α-substituted nitro-compounds with nucleophiles. Pertinent reactions of β-substituted and non-substituted aliphatic nitro-compounds will also be commented upon.

A. Mechanisms.—The reactions between substituted nitro-compounds and nucleophiles can be divided into reactions proceeding by single electron transfer (s.e.t.) or by polar reactions.

(i) *Single Electron Transfer Reactions.* The nitro-group is a good electron acceptor because of a low-energy π^* molecular orbital which allows the formation of a relatively stable radical-anion. Therefore, reaction between a nitro-compound and a nucleophile that is able to act as an electron donor, is likely to lead to electron transfer as shown in equation 1. Subsequent reactions follow from the nature of the radical-anion thus formed. The most common course of reaction is dissociation of the radical-anion to a radical and an anion, followed by further reaction of the radical. α-Substituted nitro-compounds commonly undergo substitution reactions, in particular, $S_{RN}1$ substitutions (substitution, radical-nucleophilic, unimolecular), while β-substituted compounds tend to undergo elimination.

$$RNO_2 + Nu^- \xrightarrow{\text{s.e.t.}} [RNO_2]^{-\bullet} + Nu^{\bullet} \qquad (1)$$



(ii) *Polar Reactions.* Polar attack by the nucleophile on the carbon atom of nitro-compounds to replace good nucleofuges such as halide anions is not as common as might be anticipated. Nitrite anions are poor nucleofuges but more importantly, the strong $-I$ effect of the nitro-group causes a lowering of electron density on α-substituents allowing attack by nucleophiles on the α-substituents with the displacement of nitro-anions as nucleofuges. These abstraction processes (equation 2) have been defined as X-philic reactions [1] or halogeno-philic reactions. In this

[1] N. S. Zefirov and D. I. Makhonkov, *Chem. Rev.*, 1982, **82**, 615.

review the term Z-philic will be used. This term has been suggested by Prof. C. J. M. Stirling,[2] to avoid confusion, because of the wide use of X as a general substituent.

The division of the reactions, between nitro-compounds and nucleophiles into two mechanistic areas needs to be treated with caution because of considerable overlap between s.e.t. and polar mechanisms. α-Substituted nitro-compounds which are most easily reduced are also those which have the most easily abstracted α-substituents. Similarly, nucleophiles which are good electron donors (reductants) are usually also good nucleophiles.

Our studies[3–6] in the area of s.e.t. and $S_{RN}1$ reactions started with an attempt to understand the mechanisms of the reactions between 2-substituted-2-nitropropanes and thiolates, reactions which also provide a good example of the overlap between s.e.t. and polar mechanisms. Both disulphides and α-nitrosulphides can be formed as products by a number of possible different mechanisms which are mainly separated by the nature of the initial reactions between the thiolates and the 2-substituted-2-nitropropanes (Scheme 1).

$$Me_2C(X)NO_2 + RS^- \longrightarrow Me_2C(SR)NO_2 + RSSR + X^-$$

Initiation:

s.e.t. $Me_2C(X)NO_2 + RS^- \longrightarrow [Me_2C(X)NO_2]^{-\bullet} + RS^\bullet$

Polar $Me_2C(X)NO_2 + RS^- \longrightarrow Me_2CNO_2^- + RSX$

Scheme 1

For the sake of convenience the review is divided into s.e.t. and polar reactions, and the overlap between mechanisms is discussed where relevant. Small sections on elimination and S_N1 reactions are included at the end. Aspects of the chemistry of substituted nitroalkanes have been recently reviewed.[7–9]

B. Synthetic Applications.—Many nitro-compounds are the synthetic target and various methods of preparation of a range of novel highly substituted compounds are detailed in Sections 2B and 2C and Table 1, *e.g.* radical *N*-alkylation of diazoles [Section 2C(iii), equation 12, Scheme 8], high density compounds (equation 19), and cyclopropyl rings [Section 2E(ii), equation 23].

The application of reactions of α-substituted nitroalkanes to new synthetic methods is detailed under respective sections. The main use is for forming C–C bonds [Section 2C(i)], especially in sterically hindered environments because of the low steric hindrance in radical reactions [Section 2D(v)]. The nitro-group is

[2] P. E. Pigou and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 2*, in press.
[3] W. R. Bowman and G. D. Richardson, *Tetrahedron Lett.*, 1981, **22**, 1551; *J. Chem. Soc., Perkin Trans. 1*, 1980, 1407.
[4] S. I. Al-Khalil and W. R. Bowman, *Tetrahedron Lett.*, 1984, **25**, 461.
[5] S. I. Al-Khalil and W. R. Bowman, *Tetrahedron Lett.*, 1983, **24**, 2517.
[6] W. R. Bowman, D. Rakshit, and M. Valmas, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2327.
[7] N. Kornblum in 'The Chemistry of the Functional Groups. Suppl. F. The Chemistry of the Amino, Nitroso, and Nitro Compounds, and their Derivatives', ed. S. Patai, Wiley, Chichester, 1983, p. 361.
[8] R. K. Norris in 'The Chemistry of the Functional Groups, Suppl. D, The Chemistry of the Halides, Pseudo-Halides, and Azides', ed. S. Patai and Z. Rappoport, Wiley, Chichester, 1983, p. 681.
[9] W. R. Bowman in 'Photoinduced Electron Transfer', ed. M. A. Fox and M. Chanon, Elsevier, The Hague, 1988.

often not required in the target molecule and can be removed by selective reduction (replacement of NO_2 by H) [Section 2E(iv)] or by elimination (Section 5, Schemes 7 and 20) to yield olefins (equations 9 and 13), nitro-olefins (equations 31—33), α,β-unsaturated ketones (Scheme 7, equations 8 and 32) and α,β-unsaturated esters, sulphones, and nitriles (Scheme 7 and equation 32).

2 Single Electron Transfer Reactions

The occurrence of single electron transfer has long been accepted in organic chemistry in redox reactions involving metal species, but the recognition that common nucleophiles can act as one-electron donors is much more recent. Various studies [7-14] have begun to define the parameters by which s.e.t. takes place in organic chemistry. The most important and widely studied group of s.e.t. reactions has been nucleophilic substitutions proceeding by the $S_{RN}1$ mechanism. Most of this section is therefore concerned with the scope and mechanistic parameters of $S_{RN}1$ reactions.

A. $S_{RN}1$ Substitution.—The first $S_{RN}1$ reactions of α-halogenonitroalkanes were observed by Hass and Siegle [15] as early as 1940 (equation 3). However, it was not

$$Me_2C(X)NO_2 + Me_2C{=}NO_2^- \longrightarrow Me_2C(NO_2)C(NO_2)Me_2 + X^-(X = I, Br, Cl) \quad (3)$$

until 1966 that the $S_{RN}1$ mechanism was postulated by Russell and Danen.[16] $S_{RN}1$ reactions have since been reported [9] for a wide variety of substrates which include substituted arenes and heterocycles, α-substituted *o*- and *p*-nitro -toluenes and -cumenes, *p*-nitrophenacyl halides, perfluoroalkyl halides, alkylmercury halides, and certain alkyl halides.

The $S_{RN}1$ mechanism for α-substituted aliphatic nitro-compounds as well as the variety of possible α-substituents is shown in Scheme 2. Pathway A shows the $S_{RN}1$ mechanism with loss of the α-substituent whereas pathway B shows loss of nitrite anions. Most of the α-substituted nitroalkanes that have been reported to undergo $S_{RN}1$ reactions are detailed in Table 1. The range of α-substituted nitroalkanes in $S_{RN}1$ substitutions are discussed in Section B and the nucleophiles participating in these $S_{RN}1$ reactions are discussed in Section C.

$$Me_2C(SCN)NO_2 + PhSO_2^- \xrightarrow[DMSO]{h\nu,\ 2h} Me_2C(SO_2Ph)NO_2 + {}^-SCN \quad (4)$$

(72%)

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Table 1 *α-Substituted nitroalkanes* [$R^1R^2C(X)NO_2$] *reported to undergo* $S_{RN}1$ *substitutions with nucleophiles*

X	*R*	*R*	*References*
Cl	Me	Me	3, 4, 6, 15—30
	Me	Et	26, 30
	Me	cyclopropyl, 4-pentenyl	28
	Me	CH_2O–THP	29
	cyclo-$(CH_2)_5$–		30
	cyclo-$(CH_2)OC(Me_2)OCH_2$		17
Br	Me	Me	3, 4, 6, 16, 17, 21, 23, 25, 30–36
	Me	Et	30, 31, 33
	Me	$CH_2OC(Me_2)OCH_2$	29
	cyclo-$(CH_2)_5$–		30, 31, 33
	cyclo-$(CH_2)_4$–		31
	cyclo-$CH_2OC(Me_2)OCH_2$		17
	cyclo-$CH_2OCH_2OCH_2$		25
I	Me	Me	3, 9, 15, 21, 35
	Me	Et	21
	cyclo-$(CH_2)_6$–		21
	cyclo-$(CH_2)_5$– and –$(CH_2)_4$		21, 36
SCN	Me	Me	4, 5
	cyclo-$(CH_2)_5$–		5
SO_2Ar	Me	Me	3, 18—20, 24, 26, 36—38
	Me	Et	26
SO_2Me	Me	Me	39
SAr	Me	Me	3, 6, 40
N-heterocyclic-S	Me	Me	3, 4, 6
S(O)R	Me	Me	3
NO_2	Me	Me	3—6, 18—22, 25, 31—33, 37, 41—45
	Me	Et	26, 31, 43
	cyclo-$(CH_2)_5$–		22, 31, 33, 41, 43
	cyclo-$(CH_2)_4$–		36, 43
	cyclo-$CH_2O(Me_2)OCH_2$		45
CN	Me	Me	32, 41, 42, 46
	Me	Et	42
	cyclo-$(CH_2)_{11}$–, –$(CH_2)_6$–, –$(CH_2)_5$–		46
	cyclo-$(CH_2)_4$–		42, 46
CO_2Et	Me	Me	32, 41, 42
COPh	Me	Me	41, 42
p-NO_2-C_6H_4–N=N–	Me	Me	32, 47
N_3	Me	Me	34, 35
	cyclo-$(CH_2)_5$–		35
R^1	Me	R^2	48—50
C_6F_{13}	Me	Me	51
p-NO_2-C_6H_4	Me	Me	7, 42, 52, 53
	Me	Pr^i, Et, Bu^tCH_2	54
	cyclo-$CH_2CH_2CH(Bu^t)CH_2CH(Me)$–		55
o-NO_2-C_6H_4	Me	Me	7
m-NO_2-C_6H_4	Me	Me	7,56
2,4-di-CN-C_6H_3	Me	Me	7
p-CN-C_6H_4	Me	Me	7
3,5-di-CF_3-C_6H_3	Me	Me	7
p-$PhSO_2$-C_6H_4	Me	Me	7
p-PhCO-C_6H_4	Me	Me	7
Ph	Me	Me	7
4-pyridyl	Me	Me	57
5-NO_2-thien-2-yl	Me	Me	58

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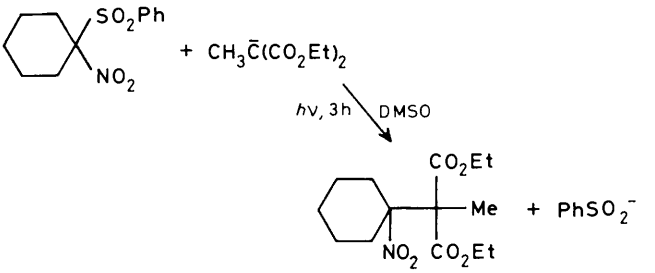


(5)

$$R_2C(X)NO_2 + Nu^- \xrightarrow{s.e.t.} [R_2C(X)NO_2]^{-\bullet} + Nu^{\bullet} \text{ (Initiation)}$$

Pathway A: $R_2C(X)NO_2 + Nu^- \longrightarrow R_2C(Nu)NO_2 + X^-$

X = I, Br, Cl, SCN, SR, S(O)R, SO_2R, N_3, NO_2, N-heterocyclic-S

Propagation steps:

$$[R_2C(X)NO_2]^{-\bullet} \longrightarrow R_2\dot{C}NO_2 + X^-$$

$$R_2\dot{C}NO_2 + Nu^- \longrightarrow [R_2C(Nu)NO_2]^{-\bullet}$$

$$[R_2C(Nu)NO_2]^{-\bullet} + R_2C(X)NO_2 \xrightarrow{s.e.t.} R_2C(Nu)NO_2 + [R_2C(X)NO_2]^{-\bullet}$$

Pathway B: $R_2C(X)NO_2 + Nu^- \longrightarrow R_2C(Nu)X + NO_2^-$

X = CN, COR, CO_2R, N_3, NO_2, *o*-, *m*-, and *p*-$NO_2C_6H_4$–, *p*-$PhSO_2$– and *p*-PhCO-C_6H_4–, 3,5-di-CF_3-C_6H_3–, *p*-NO_2-C_6H_4–N=N–, R, Ph, 5-nitrothien-2-yl

Propagation steps:

$$[R_2C(X)NO_2]^{-\bullet} \longrightarrow R_2\dot{C}X + NO_2^-$$

$$R_2\dot{C}X + Nu^- \longrightarrow [R_2C(Nu)X]^{-\bullet}$$

$$[R_2C(Nu)X]^{-\bullet} + R_2C(X)NO_2 \xrightarrow{s.e.t.} R_2C(Nu)X + [R_2C(X)NO_2]^{-\bullet}$$

Scheme 2 $S_{RN}1$ *Mechanisms for α-substituted nitroalkanes*

B. Examples of α-substituted nitroalkanes in $S_{RN}1$ reactions.—(i) *α-Halogeno- and α-Thiocyanato-nitroalkanes.* The α-chloro-, bromo-, and iodo-nitroalkanes are the commonly used substrates and have been shown to undergo $S_{RN}1$ substitution with a wide range of nucleophiles which include: nitronates, malonates, simple enolates, enolates of β-ketoesters, β-diketones, β-ketosulphones *etc.*, dialkylphosphites, sulphinates, and thiolates.

The thiocyanato-derivatives[4,5] behave similarly to the halogeno-analogues and undergo $S_{RN}1$ substitutions with nitronates, benzene sulphinate, azide, and weakly nucleophilic thiolates such as *p*-chlorophenylthiolate (*e.g.* equation 4).

(ii) *α-Nitro-sulphones, -sulphoxides, and -thioethers.* α-Nitrosulphones were the first sulphur analogues reported[36–39] to undergo $S_{RN}1$ reactions (*e.g.* equation 5).

α-Nitrosulphides[3–6,40] also react with a variety of nucleophiles (nitronates, malonates, benzenesulphinate, and thiolates) to yield $S_{RN}1$ substitution products (*e.g.* equation 6). α-Nitrosulphides, $Me_2C(SR)NO_2$, of heterocyclic systems (R = 2-pyridyl, pyrimidin-2-yl, 1,3-benzothiazolin-2-yl, 1-methylimidazol-2-yl,

and 4,5-dihydro-1,3-thiazol-2-yl similarly undergo $S_{RN}1$ substitution[3,6] of the thiolate substituent by a range of nucleophiles.

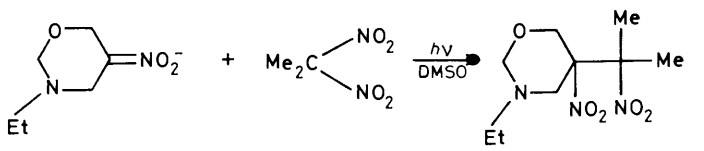
$$Me_2C(SR)NO_2 + Me_2CNO_2^- \xrightarrow[DMF]{h\nu, 4h} Me_2C(NO_2)C(NO_2)Me_2 + RS^- \qquad (6)$$

R = *o*-NO_2-C_6H_4 (13%)
= *p*-NO_2-C_6H_4 (71%)
= *p*-Cl-C_6H_4 (25%)

α-Nitrosulphoxides also undergo $S_{RN}1$ substitution with $Me_2CNO_2^-$ and $PhSO_2^-$.

(iii) *Geminal Dinitroalkanes.* The intermediate radical-anions, $[R_2C(NO_2)_2]^{-\bullet}$, need to lose nitrite in the dissociation step of the $S_{RN}1$ mechanism. Although nitrite is not normally regarded as a good nucleofuge in polar nucleophilic substitution reactions, it has enhanced nucleofugicity in radical-anions. The $S_{RN}1$ mechanism proceeding *via* loss of nitrite anions is shown in Scheme 2.

Geminal dinitroalkanes are readily prepared by oxidative addition[3–6,59,60] of nitrite to nitronate anions and have the advantage that '$^+NO_2$' is not easily abstracted by nucleophiles,[3,6] thereby favouring $S_{RN}1$ reactions (*e.g.* equation 7) rather than Z-philic abstractions.



(7)

(iv) α-*Nitro-ketones, -ethers, -cyanides, and -azides.* All of these compounds undergo $S_{RN}1$ substitution with loss of nitrite[32,41,42,46] when reacted with nitronates (Scheme 2, pathway B). Kornblum[7] suggested that the lack of $S_{RN}1$ reactivity with nucleophiles other than nitronates was because of the requirement of 'stable' radical-anion intermediates to carry the chain reaction. In the case when the α-substituent (X) is lost both radical-anion intermediates have the unpaired electron in a low energy nitro π* SOMO (see Scheme 2, pathway A). However, when nitrite is lost (Scheme 2, pathway B) the second radical-anion intermediate, $[R_2C(X)Nu]^{-\bullet}$, will only contain a nitro π* SOMO if the nucleophile has a nitro-group, *i.e.* with Nu = R_2CNO_2.

However, α-nitroazides react with azide, benzenesulphinate, and *p*-chlorophenylthiolate by the $S_{RN}1$ mechanism[34,35] *via* loss of nitrite (Scheme 3). The results suggest that α-nitroazides undergo s.e.t. with certain nucleophiles to form 'stable' radical-anions, $[R_2C(N_3)NO_2]^{-\bullet}$, which in turn dissociate to nitrite and α-azidoalkyl radicals ($R_2\dot{C}N_3$). The $R_2\dot{C}N_3$ radicals are stable enough to undergo

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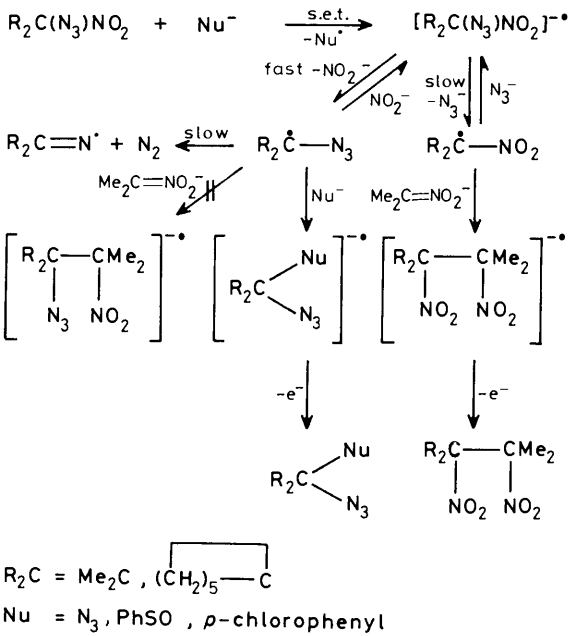


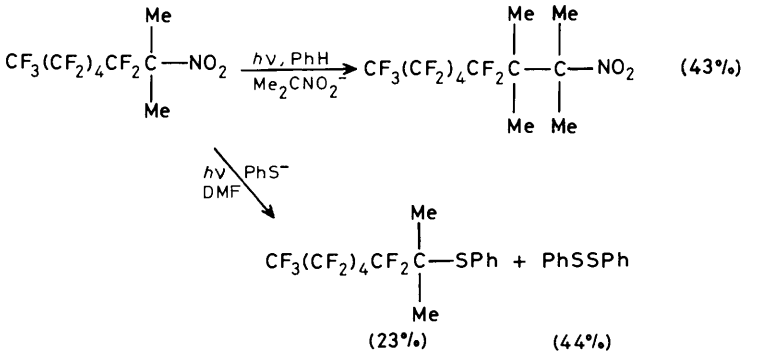
Scheme 3 *Mechanisms of the $S_{RN}1$ reactions of α-nitroazides*

rapid bimolecular reaction with nucleophiles to form new radical-anions, $[R_2C(N_3)Nu]^{-\bullet}$. These radical-anions do not appear to have a low energy SOMO but are obviously stable enough to allow rapid s.e.t. to the starting material to complete the $S_{RN}1$ chain. Only in the absence of a potential bimolecular reaction is nitrogen loss observed to yield σ-iminyl radicals.

α-Nitroazides are the only α-substituted nitroalkanes in which X or NO_2 is lost depending on the nature of the nucleophile. The reactions with nitronates surprisingly give loss of azide anions[14,35] by a much slower $S_{RN}1$ reaction (Scheme 3) or by oxidative dimerization. The addition of the nitronate anion to the intermediate α-azidoalkyl radical ($R_2\dot{C}N_3$) is unfavourable which allows a slower reaction *via* dissociation with loss of azide. These observations suggest that the relative nucleofugicities of N_3^- and NO_2^- from α-nitroazido radical-anions are similar.

A similar reluctance[32,47] to undergo $S_{RN}1$ substitution *via* addition of $Me_2CNO_2^-$ to the intermediate (p-NO_2-C_6H_4-N=N-$\dot{C}Me_2$) radical has been observed with 2-nitro-2-(p-nitrobenzeneazo)propane. The latter compound yields $S_{RN}1$ substitution and redox products with thiolates,[47] but only redox products with nitronates.[32,47]

(v) *Tertiary Nitroalkanes.* A number of $S_{RN}1$ substitutions of unsubstituted nitroalkanes have been reported.[48–50] Tertiary nitroalkanes form stable radical-anion intermediates $[R_3CNO_2]^{-\bullet}$ but the rate of dissociation to alkyl radicals



Scheme 4 $S_{RN}1$ *reactions of* 2-(*perfluorohexyl*)-2-*nitropropane*

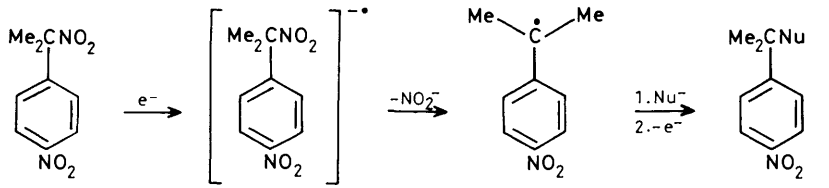
($R_3C^{\cdot}$) and nitrite anions is very slow. The 2-(perfluoroalkyl)-2-nitropropane, n-$C_6F_{13}C(Me_2)NO_2$, undergoes $S_{RN}1$ reactions[51] with $Me_2CNO_2^-$ and PhS^- (Scheme 4) due to stabilization of the intermediate radical-anions by the perfluoroalkyl group.

$$R_fC(Me)_2NO_2 + Nu^- \xrightarrow[h\nu]{s.e.t.} [R_fC(Me)_2NO_2]^{-\cdot} + Nu\cdot$$

$$[R_fC(Me)_2NO_2]^{-\cdot} \xrightarrow{-NO_2^-} R_f\dot{C}Me_2 \xrightarrow{Nu^-} [R_fC(Me)_2Nu]^{-\cdot}$$

$$[R_fC(Me)_2Nu]^{-\cdot} + R_fC(Me)_2NO_2 \xrightarrow{s.e.t.} R_fC(Me)_2Nu + [R_fC(Me)_2NO_2]^{-\cdot}$$

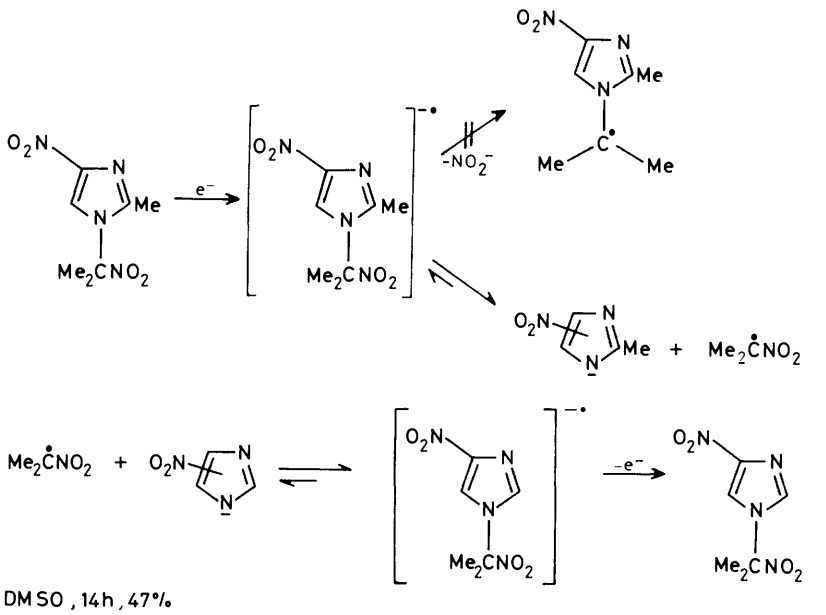
(vi) *Loss of Nitrite Anion from 'Benzylic' Nitro-compounds.* α,*p*-Dinitrocumenes are usually associated with reactivity pertaining to *p*-nitrocumyl free-radical chemistry[7] but can also be regarded as 2-nitropropanes which are substituted in the α-position by a *p*-nitrophenyl group. The $S_{RN}1$ chemistry of these compounds, as well as the *o*- and *m*-analogues, have been extensively investigated and fully reviewed by Kornblum[7,42,53] and is therefore, only briefly discussed (Scheme 5).



Nu^- = PhS^-, $Me_2CNO_2^-$, $PhSO_2^-$, $\bar{R}CH(CO_2Et)_2$, $^-NO_2$, ^-CN, $^-N_3$, R_2NH (*e.g.* pyrrolidine, quinuclidine, piperidine), R_3N (*e.g.* DABCO), 1-methyl-2-naphthoxide

Scheme 5 $S_{RN}1$ *Reactions of* α,*p-dinitrocumene*

Although loss of nitrite takes place, the resulting *p*-nitrocumyl radical is particularly well stabilized and the radical-anion resulting from addition of the nucleophile is of low-energy because the unpaired electron can reside in the nitrophenyl π* SOMO. However, when the nitro-group on the aryl ring is absent,[7]



Scheme 6 $S_{RN}1$ *Reactions of* 2-*methyl*-1-(1-*methyl*-1-*nitroethyl*)-4-*nitroimidazole*

similar behaviour to that of unsubstituted tertiary nitroalkanes is observed, *i.e.* $S_{RN}1$ reactions only take place when nitronates are used as the nucleophiles, and other nucleophiles lead to dimerization.

The analogous 2-(1-methyl-1-nitroethyl)-5-nitrothiopene,[58] and 2-nitro-2-(pyrid-4-yl)-propane[57] also undergo $S_{RN}1$ substitution with various anions. Although the 4-pyridyl group behaves more like the *p*-nitrophenyl group than the phenyl group in $PhC(Me_2)NO_2$, some nucleophiles such as azide still give products resulting from dimerization.

(vii) 1-(1-*Methyl*-1-*nitroethyl*)-4-*nitroimidazoles*.[25] Two possible routes are possible for the $S_{RN}1$ reactions of 2-methyl-1-(1-methyl-1-nitroethyl)-4-nitroimidazole and 1-(1-methyl-1-nitroethyl)-4-nitroimidazole (Scheme 6). Products resulting from loss of the nitroimidazole moiety from the intermediate radical-anion were observed but products resulting from loss of NO_2^- were not seen. Reaction with $Me_2CNO_2^-$ gave 2,3-dimethyl-2,3-dinitrobutane for both compounds by an $S_{RN}1$ mechanism. Studies[61] using e.s.r. spectroscopy at low temperature indicated that the unpaired electron resides completely on the imidazole nitro-group with no overlap onto the aliphatic nitro-group. Therefore, rearrangement of MO's to

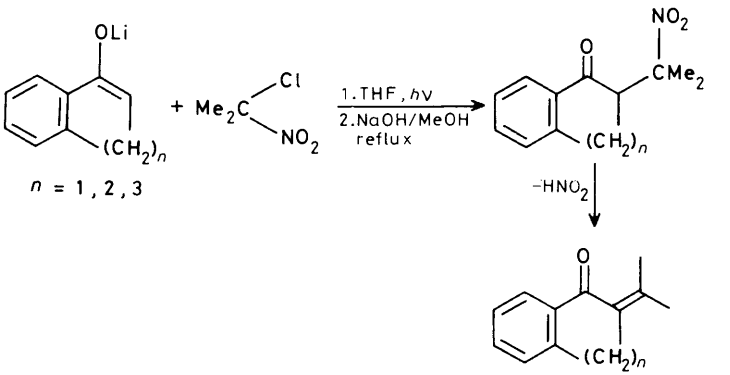
[61] M. C. R. Symons and W. R. Bowman, *J. Chem. Soc., Perkin Trans. 2*, 1988, 1077.

allow nitrite loss would be difficult and perhaps explains why the imidazole anion is lost rather than nitrite. The other obvious explanation is that the imidazole anion is a better nucleofuge than nitrite.

The potentially reversible reaction between 2-methyl-1-(1-methyl-1-nitroethyl)-4-nitroimidazole and the anion of 4(5)-nitroimidazole gave 1-(1-methyl-1-nitroethyl)-4-nitroimidazole (Scheme 6). This result is explained [25] on the basis that the anion of 2-methyl-4-nitroimidazole acts as a better nucleofuge than the anion of 4-nitroimidazole from the corresponding radical-anion, because of relief of steric strain.

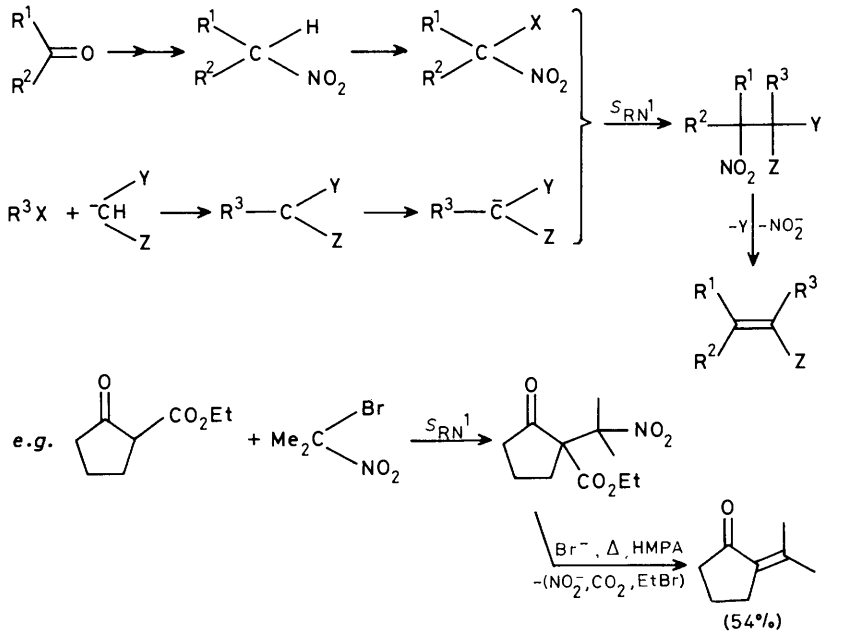
C. Nucleophiles Participating in $S_{RN}1$ Reactions with α-Substituted Nitroalkanes.— (i) *Carbon-centred Nucleophiles.* Nitronate anions have been the most commonly used nucleophiles for $S_{RN}1$ reactions of α-substituted nitroalkanes and are the anions of choice for study of potential $S_{RN}1$ substitutions. A wide range of secondary nitronates ($R^1R^2CNO_2^-$) have been used in which R^1 and R^2 are aliphatic, alicyclic (anions of nitro-cyclopentane, -cyclohexane, -cycloheptane, and -cyclododecane), and heteroalicyclic [44,45] (*e.g.* equation 7). The use of the anion of nitromethane [49] and the anions of primary nitroalkanes [7,9] has been reported.

Russell and co-workers [18,19,27,28] have shown that simple enolates readily participate in radical-nucleophilic substitution reactions with α-substituted nitroalkanes by an $S_{RN}2$, rather than a $S_{RN}1$ mechanism [see Section 2E(i)]. A wide range of enolates including those of $PhCOCH_2R$ (R = H, Me, and Pr^i), Me_3CCOCH_3, cyclohexanone, and its 3- and 4-methyl derivatives, cyclopentanone, indanone, and 1-tetralone, have been shown to undergo radical-nucleophilic substitution. Excess base in the reactions allows complete elimination of HNO_2 to yield α,β-unsaturated ketones. A representative example illustrating the synthetic potential is shown in equation 8.



(8)

Enolates exhibit low regioselectivity, *e.g.* the ratio of products for the 3-methylcyclohexanone reaction is 2-substitution: 6-substitution = 1:4. The low selectivity

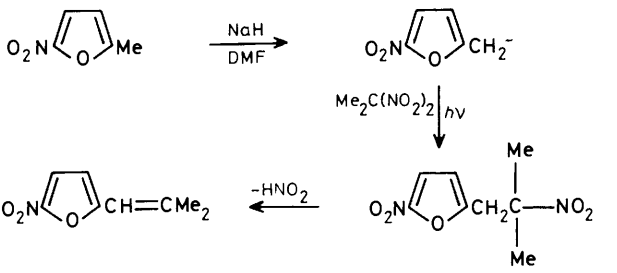


$R\bar{C}YZ$,
Y = CO_2Et; Z = CO_2Et,[38–30] COR,[28–30] CN,[30,33] SO_2Ar[30]
Y = COR; Z = CN, COR, CO_2R[30,31]
Y = COR^1; Z = COR^2 [28]
Y = H; Z = R^3 = COR;[22,29] Z = COR, R^3 = CO_2R[22]
Z = COR[19,28]

Scheme 7 *Synthetic applications of* $S_{RN}1$ *reactions between* $R_2C(X)NO_2$ *and* RCYZ

is explained by proton transfer to and from the intermediate β-nitroketone substitution product and the enolate.

The $S_{RN}1$ reactions between α-substituted nitroalkanes and disubstituted anions of the type $R\bar{C}YZ$ have proved particularly successful and have been developed as synthetic methods for α,β-unsaturated ketones, esters, nitriles, and sulphones. The methodology and some examples are shown in Scheme 7. A full list of the anions used is presented in reference 9. These reactions are a useful substitute for aldol-type reactions because the formation of the C–C bond is *via* radical coupling and is therefore much less sensitive to steric hindrance. These anions are weak nucleophiles, not easily oxidized, and therefore the $S_{RN}1$ mechanism is normally observed. Several methods have been used to convert the $S_{RN}1$ products into the α,β-unsaturated products: (*a*) elimination of HNO_2 when $\bar{C}H_2Z$ (Z = COR, CO_2R, NO_2) is used;[28,29] (*b*) ethoxydecarboxylation and loss of nitrite using Br^- in HMPA;[30,33] (*c*) reductive elimination [31] of NO_2^- and $ArSO_2^-$; and (*d*) reductive deacylation and loss of NO_2^-.[30]



(9)

Carbon-centred anions which are stabilized by heterocyclic rings (2-methyl-5-nitrofuran,[62] 4-isopropylpyridine,[57] and 4,4-dimethyl-2-isopropyl-4,5-dihydro-1,3-oxazole[63] have been reported to undergo nucleophilic substitutions with certain α-substituted nitroalkanes. The nitrofuran reaction (equation 9) is likely to proceed by an $S_{RN}1$ mechanism but the other two may proceed by redox dimerization mechanisms.

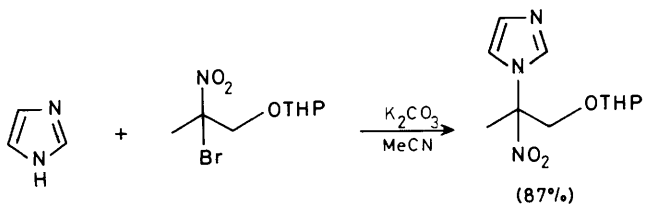
(ii) *Nitrogen- and oxygen-centred anions.* Amines appear to be poor nucleophiles for $S_{RN}1$ reactions. Piperidine has been reported to react very slowly (77% yield after 225 h) with α,*p*-dinitrocumene[53] but various amines react readily with the analogous *p*-nitrocumyl chloride.[53]

Azide and nitrite anions have also been reacted with α,*p*-dinitrocumene and *p*-nitrocumyl chloride in high yield[42,53] by $S_{RN}1$ mechanisms. The lack of $S_{RN}1$ reaction between nitrite and 2-halogeno-2-nitroalkanes is probably caused by poor initiation because nitrite adds readily to $Me_2\dot{C}NO_2$[59,60] and $[Me_2C(NO_2)_2]^{-\cdot}$ is an intermediate in several $S_{RN}1$ reactions.

Azide undergoes radical-nucleophilic substitution with $Me_2C(Br)NO_2$ to yield $Me_2C(N_3)NO_2$ (equation 10), but possibly by a non-chain mechanism.[35] The reaction between $Me_2C(N_3)NO_2$ and azide (equation 11) gave a 91% yield of $Me_2C(N_3)_2$ by an $S_{RN}1$ mechanism.

$$Me_2C(Br)NO_2 + N_3^- \xrightarrow[HMPA,\ 15\ h]{lab.\ h\nu} \underset{(25\%)}{Me_2(N_3)NO_2} \qquad (10)$$

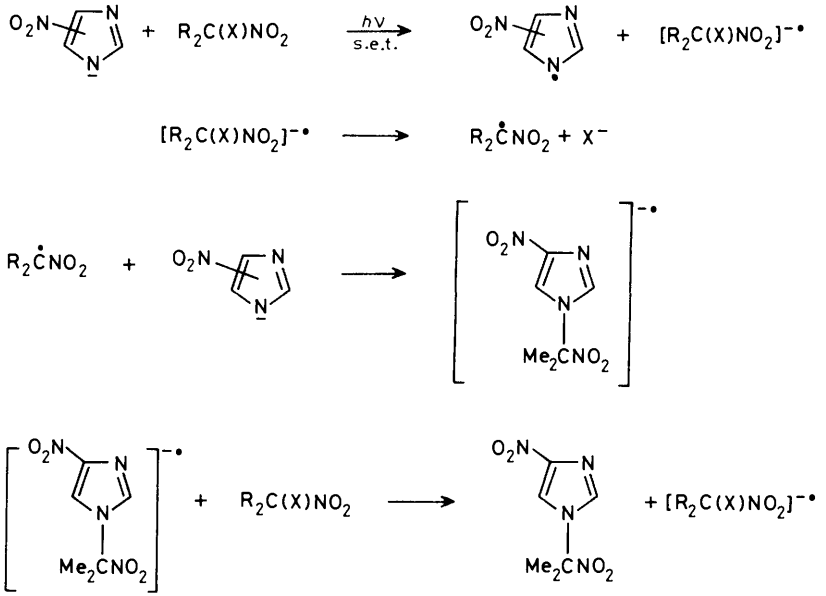
$$Me_2C(N_3)NO_2 + N_3^- \xrightarrow[CH_2Cl_2/H_2O,\ 40\ min]{lab.\ h\nu} \underset{(91\%)}{Me_2C(N_3)_2} \qquad (11)$$



(12)

[62] C. D. Beadle and W. R. Bowman, *J. Chem. Res.*, 1985, 150.
[63] H. Feuer, H. S. Bevinakatli, and X.-G. Luo, *J. Heterocycl. Chem.*, 1986, **23**, 825.

The *N*-anions of various diazoles undergo $S_{RN}1$ reactions with various α-substituted nitroalkanes,[17,25,64] *p*-nitrobenzyl chloride,[17,25,64] and 2-bromomethyl- and 2-chloromethyl-1-methyl-5-nitroimidazole.[25] The $S_{RN}1$ mechanism for the reaction between the anion of 4-nitroimidazole and $R_2C(X)NO_2$ is shown in Scheme 8. These $S_{RN}1$ reactions indicate a general route for the synthesis of



Scheme 8 $S_{RN}1$ *Mechanism for the reaction between the anion of* 4(5)*-nitroimidazole and* $R_2C(X)NO_2$

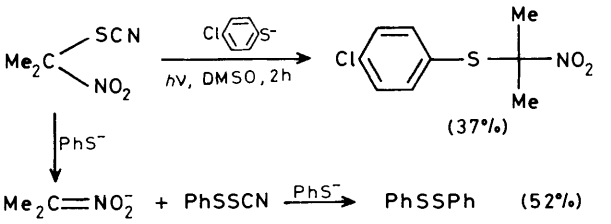
highly branched *N*-alkyl diazoles. The anions of the following diazoles have been used: imidazole,[17,64] pyrazole,[17] benzimidazole,[17,64] 5(6)-nitrobenzimidazole,[64] 5- and 6-nitroindazole,[64] and triazole.[17] An example is shown in equation 12. Only one oxygen-centred anion, 1-methyl-2-naphthoxide, has been reported in $S_{RN}1$ reactions, with α,*p*-dinitrocumene.[53]

(iii) *Sulphur-centred Nucleophiles.* Benzene- and *p*-toluene-sulphinate are commonly used nucleophiles and have been reacted with most α-substituted nitroalkanes in $S_{RN}1$ reactions, *e.g.* references 5, 7, 20, 21, 34—36, 38, 53, 56. Only one example of a $S_{RN}1$ reaction with alkylsulphinates has been reported[65] (equation 13).

$$Me_2C(Br)NO_2 + MeSO_2^- \xrightarrow[DMF]{h\nu} Me_2C(SO_2Me)NO_2 + Br^- \qquad (13)$$

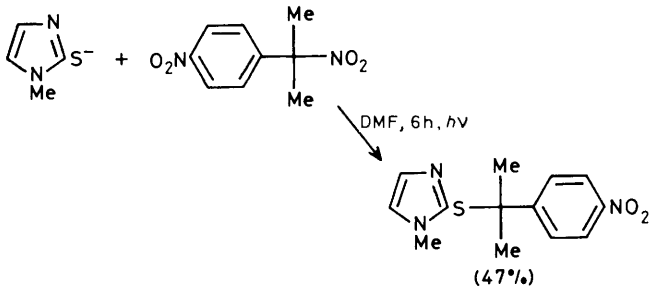
[64] A. T. O. M. Adebayo, W. R. Bowman, W. G. Salt, Abstracts of the 4th International Symposium of the Mechanisms of Reactions in Solution, University of Kent, Canterbury, July, 1986.

[65] W. R. Bowman and M. C. R. Symons, *J. Chem. Soc., Perkin Trans. 2*, 1983, 25; *Tetrahedron Lett.*, 1981, **22**, 4549.



(14)

Only weakly nucleophilic thiolates, (*e.g.* *p*-nitro- and *p*-chloro-phenylthiolate give substitution with α-substituted nitroalkanes,[3] whereas more nucleophilic thiolates such as phenylthiolate give Z-philic reactions (*e.g.* equation 14[5]). Only



(15)

Z-philic reactions are observed in protic solvents.[4,6] Phenylthiolate participates in $S_{RN}1$ reactions with 'benzylic' nitroalkanes when Z-philic abstraction is unlikely.[7,53,56] Methanethiolate undergoes $S_{RN}1$ substitution as well as a redox reaction with β-arylnitroalkanes.[66]

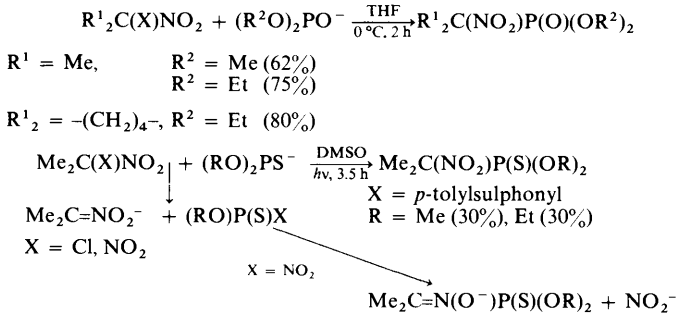
The anions of nitrogen-heterocyclic thiols (2- and 4-pyridinethiol, 2-mercapto-1,3-benzothiazole, 2-mercapto-1-methylimidazole 2-mercapto-4-methylthiazole, 2-pyrimidinethiol, and 4,5-dihydro-2-mercapto-1,3-thiazole) react with $Me_2C(X)NO_2$ (X = Br, Cl, NO_2)[3,6] and α,*p*-dinitrocumene[52] (equation 15) by the $S_{RN}1$ and other mechanisms. The nucleophiles are ambident, but react *via* the sulphur atom only and not *via* the nitrogen atom.

Thiocyanate anions react slowly with $Me_2C(I)NO_2$ only at high temperature[5,65] (equation 16) but do not react with $Me_2C(Br)NO_2$ even at 100 °C.[67] The lack of reactivity is probably due to poor initiation of the $S_{RN}1$ reaction [*i.e.* s.e.t. between ^-SCN and $Me_2C(X)NO_2$] because ^-SCN anions readily add to $Me_2\dot{C}NO_2$ radicals in oxidative addition reactions[5] to form the radical-anions, $[Me_2C(SCN)NO_2]^{-\bullet}$.

$$Me_2C(I)NO_2 + {}^-SCN \xrightarrow[50-100\,^\circ C]{h\nu,\ DMF} Me_2C(SCN)NO_2\ (10-40\%) \qquad (16)$$

[66] N. Kornblum, J. Widmer, and S. C. Carlson, *J. Am. Chem. Soc.*, 1979, **101**, 658.

(iv) *Phosphorus-centred Nucleophiles.* Dialkylphosphites undergo $S_{RN}1$ reactions[20,24,26] with a range of α-substituted nitroalkanes in reactions which are thermally initiated and only proceed to high yield in dry THF (Scheme 9). The analogous thiophosphites, however, only undergo $S_{RN}1$ substitution with $Me_2C(SO_2Ar)NO_2$, and undergo Z-philic reactions wtih $Me_2C(Cl)NO_2$ and $Me_2C(NO_2)_2$ (Scheme 9).



Scheme 9 *$S_{RN}1$ and Z-philic reactions of dialkyl phosphites and thiophosphites*

Some differences exist between the reactivity of nucleophiles and various substrates. The ratio of Z-philic to $S_{RN}1$ reactions tends to increase as the substituent Z becomes more easily abstracted, *i.e.* $R_2C(Z)NO_2 > p\text{-}NO_2\text{-}C_6H_4CR_2Z >$ ArZ. Dialkyl thiophosphites and phenylthiolate undergo $S_{RN}1$ substitution with aryl and *p*-nitrobenzyl/cumyl substrates but often undergo Z-philic reactions with $Me_2C(X)NO_2$. $PhSO_2^-$ only undergoes $S_{RN}1$ substitution with *p*-nitrobenzyl/cumyl substrates but undergoes Z-philic reaction with $R_2C(X)NO_2$ when Z is easily abstractable.

A number of nucleophiles undergo $S_{RN}1$ reactions with α-substituted nitroalkanes but not with aryl substrates, *e.g.* enolates of β-diketones and β-ketoesters, diazole anions, azide, and amines, whereas other nucleophiles have only been reported for aromatic $S_{RN}1$, *e.g.* amide ($^-NH_2$) and α-cyanoalkyl anions. A range of nucleophiles undergo $S_{RN}1$ substitution with all three types of substrates, *e.g.* enolates of ketones, nitronates, and thiolates.

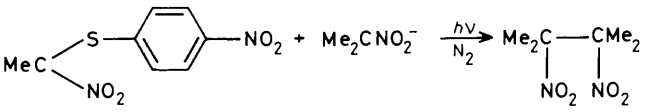
D. Mechanistic Features of $S_{RN}1$ Substitutions.—$S_{RN}1$ mechanisms are radical-nucleophilic chain reactions with initiation, propagation, and termination steps. Each step is discussed in detail, including mechanistic variations.

(i) *Initiation.* $S_{RN}1$ reactions can be initiated by generating any of the three reactive intermediates (see Scheme 2) $[R_2C(X)NO_2]^{-\bullet}$, $R_2\dot{C}NO_2$ or $R_2\dot{C}X$, and $[R_2C(Nu)NO_2]^{-\bullet}$ or $[R_2C(Nu)X]^{-\bullet}$. However, only generation of the initial radical-anion, $[R_2C(X)NO_2]^{-\bullet}$, has been reported.

Photoinduced s.e.t. between the nucleophile (donor) and substrate (acceptor) is used in almost all $S_{RN}1$ reactions of α-substituted nitroalkanes. The role of light catalysis is to energize the charge-transfer complex between substrate and

nucleophile, thereby enhancing the probability of s.e.t. In most $S_{RN}1$ reactions of $R_2C(X)NO_2$, neither the substrate nor the nucleophile absorb visible light, which suggests the presence of a CT-complex which does. Recent studies by Kornblum and co-workers[42,53] clearly illustrate this principle. Many $S_{RN}1$ reactions between $R_2C(X)NO_2$ and nucleophiles develop colours which disappear on completion of the reactions[25] indicating transient CT-complexes. Quantum yields range[7,42,53] from several hundred to 6 000 in those reactions studied.

Bordwell and co-workers[10,11] have shown for reactions with nucleophiles of low basicity that light catalysis is required for s.e.t., *i.e.* strongly basic nucleophiles undergo s.e.t., but weakly basic nucleophiles require photostimulation.

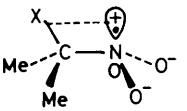


(17)

	% *Yield*
Standard reaction; DMF, 4 h	71
+ 6 mol% *p*-dinitrobenzene	9
+ 10 mol% galvinoxyl	3
O_2 in place of N_2	2
Dark	18

(ii) *Inhibition.* Evidence for light catalysis and inhibition by radical traps (*e.g.* di-t-butylnitroxide, oxygen, galvinoxyl) and strong electron acceptors (*e.g.* oxygen and *p*-dinitrobenzene) are the most common criteria used for assigning the $S_{RN}1$ mechanism. More comprehensive lists of criteria are detailed in references 7, 9, and 14. Inhibition studies are discussed in detail.[16,23,24,32,42,53] A typical example of inhibition results is shown in equation 17.[3]

(iii) *Use of e.s.r. Spectroscopy.* E.s.r. spectroscopy at low temperature[6,35,65,67] has been used to obtain evidence for the structures of the intermediates, and the mechanisms of various steps, for $S_{RN}1$ and related mechanisms of $R_2C(X)NO_2$ (see Scheme 2).



X = Br , Cl , NO_2 , PO_3Et_2 , COMe, SO_2Me , SO_2Ar , N_3 , SCN, 2-thiopyridine

Figure 1

Electron capture by $R_2C(X)NO_2$ to form stable radical anions, $[R_2C(X)NO_2]^{-\bullet}$, has been observed. The e.s.r. data indicate overlap of spin density from the nitro π^* MO's into the C–X σ^* MO's, and suggest that the structure shown in Figure 1 is favoured. The e.s.r. spectrum[68] of the radical-anions of α,*p*-dinitrocumene shows that the spin density resides largely on the aromatic nitro-group but is delocalized

[67] M. C. R. Symons and W. R. Bowman, *J. Chem. Res.*, 1984, 1433.
[68] M. C. R. Symons and W. R. Bowman, *J. Chem. Soc., Perkin Trans. 2*, 1988, 583; *J. Chem. Soc., Chem. Commun.*, 1984, 1445.

into the π-system of the aromatic ring and into the aliphatic C–NO_2 bond as shown in Figure 2.

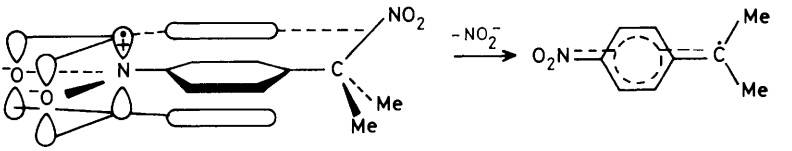


Figure 2

Dissociation of the radical-anions, $[Me_2C(X)NO_2]^{-\bullet}$, and the structures of the resulting radicals, $Me_2\dot{C}X$ and $Me_2\dot{C}NO_2$, has also been detected using e.s.r. spectroscopy.[35,65] The route of dissociation (*i.e.* loss of X^- or loss of NO_2^-) (see Scheme 2) is remarkably similar to that observed in solution $S_{RN}1$ substitutions. The rate and direction of dissociation is determined largely by bond strength and nucleofugicity, *e.g.* I > Br > Cl. The reaction between benzenesulphinate and $Me_2C(X)NO_2$ is a good example[21] of the effect of nucleofugicity. The chloro-derivative reacts very slowly to yield the corresponding sulphone (50% after 12 days in DMF at 25 °C), whereas the iodo-analogue gives a 93% yield after 4 h at −20 to −15 °C. The location of spin density could possibly be important if no overlap between NO_2 and X is present[61] (see Section 2Bvii) or when the nucleofugicities are similar, *e.g.* NO_2^- and N_3^-.

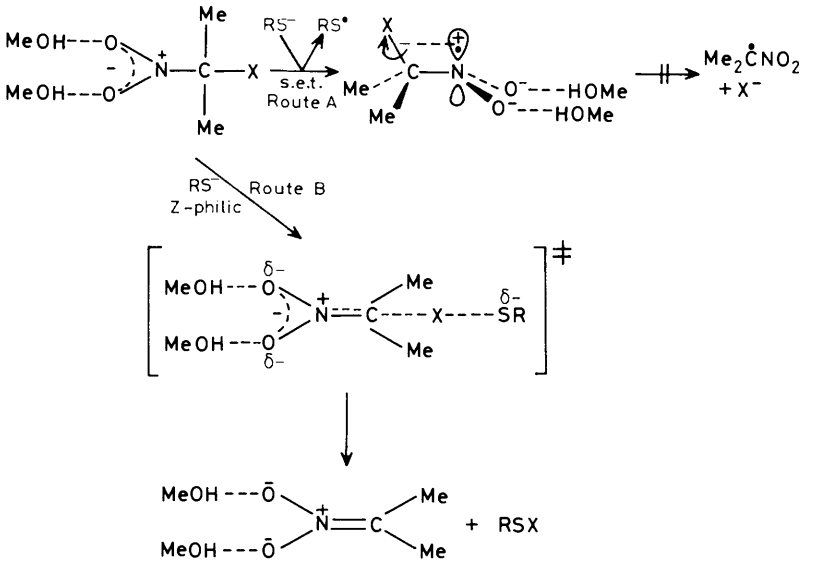
The dissociation of $[R_2C(X)NO_2]^{-\bullet}$ radical-anions proceeds with smooth reorganization of the π* and σ* molecular orbitals to the required transition state for loss or NO_2^- of X^- anions. Crossing between occupied and unoccupied MO's is unlikely. The radical-anion of α,*p*-dinitrocumene was also observed to dissociate to *p*-nitrocumyl radical by loss of NO_2^- (Figure 2).[68] The same process as described above almost certainly also applies to this dissociation, and that of analogous *p*-nitrobenzyl/cumyl[68] and heterocyclic (α-substituted 2-methyl-5-nitrofurans[69] and 1,2-dimethyl-5-nitroimidazoles[61]) radical-anions.

Evidence for the third step in the $S_{RN}1$ mechanism for $Me_2C(X)NO_2$ (Scheme 2, route A) has also been obtained using low temperature e.s.r. spectroscopy.[35,67] In the presence of an added nucleophile, electron capture initially gave the radical-anions, $[Me_2C(X)NO_2]^{-\bullet}$ and $Me_2\dot{C}NO_2$ radicals followed by new radical-anions, $[Me_2C(Nu)NO_2]^{-\bullet}$, resulting from addition of Nu^- to $Me_2\dot{C}NO_2$ radicals. $PhSO_2^-$ replaces Cl^-, Br^-, and NO_2^-; NO_2^- replaces Cl^- and Br^-; and Cl^- replaces Br^- from the respective $Me_2C(X)NO_2$. This technique[35] has also corroborated the unusual $S_{RN}1$ reactivity of $R_2C(N_3)NO_2$ (see Scheme 3), *e.g.* that $Me_2CNO_2^-$ will not add to $Me_2\dot{C}N_3$.

(iv) *Effect of Solvent on the Dissociation of* $[Me_2C(X)NO_2]^{-\bullet}$ *Radical-anions.* No

[69] M. C. R. Symons and W. R. Bowman, *J. Chem. Soc., Perkin Trans. 2*, 1987, 1133.

studies have been carried out on the rates of dissociation of $[R_2C(X)NO_2]^{-\bullet}$. The effect of solvation on $[R_2C(X)NO_2]^{-\bullet}$ is difficult to study in $S_{RN}1$ reactions because of solvation of the nucleophile.[20] Thiolates, however, are poorly solvated in both protic and dipolar aprotic solvents, therefore allowing observation of the relative

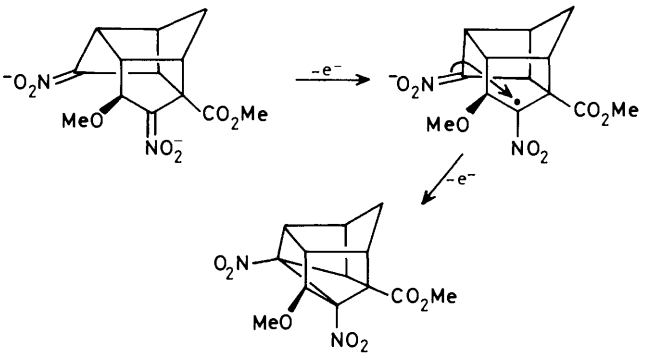


Scheme 10 *Effect of* MeOH *solvation on the reactions between* $Me_2C(X)NO_2$ *and thiolates*

rates of dissociation of $[Me_2C(X)NO_2]^{-\bullet}$, produced on s.e.t. from thiolate to $Me_2C(X)NO_2$. In dipolar aprotic solvents the reactions between $Me_2C(X)NO_2$ and RS^- proceed largely by the $S_{RN}1$ mechanism with a lesser amount of Z-philic attack.[3–6] However, the same reactions when carried out in MeOH or $MeOH/H_2O$ yield only disulphide products.[39]

These results have been explained[4,6] by initial solvation of $Me_2C(X)NO_2$ which leads to a solvated radical-anion after s.e.t. from the thiolate (Scheme 10, route A). Solvation of the nitro-group in the radical-anion shifts electron density away from the C–X bond which results in a higher requirement of energy to reorganize the MO's to a transition state for loss of X^-, and hence a much lower rate of $S_{RN}1$ reaction. At the same time, the increased solvation of $Me_2C(X)NO_2$ lowers the transition state energy of the Z-philic S_N2 reaction on X, causing a faster competing reaction (Scheme 10, route B). This effect is not observed in other $S_{RN}1$ reactions in MeOH, *e.g.* the reaction between 2-halogeno-2-nitropropanes and $Me_2CNO_2^-$ is much slower in MeOH than in DMF,[47] but very strong solvation of $Me_2CNO_2^-$ makes the Z-philic route much slower than the $S_{RN}1$ route. Therefore, solvation of $Me_2C(X)NO_2$ *decreases* the rate of dissociation of $[Me_2C(X)NO_2]^{-\bullet}$ but does not preclude it. Similar solvation effects have been observed for the reactions between 2-halogenomethyl-5-nitrofurans and thiolates.[70]

This solvation effect has been exploited [71] to develop a general synthetic method for reducing α-bromonitroalkanes to the corresponding nitronates using ethane-



(18)

thiolate in MeOH. Similarly, nitronates can be halogenated in MeOH with NBS and NCS without the resulting $R_2C(X)NO_2$ reacting by a $S_{RN}1$ reaction with $R_2CNO_2^-$.[71]

(v) *Addition of Nucleophiles to Radicals.* The addition of nucleophiles to radicals to form radical-anions (*e.g.* step 3 of the $S_{RN}1$ mechanism) is a new concept which has only gained acceptance in the last 20 years and in many cases is more likely to take place than combination of radical species (termination steps).

Evidence for this step of the $S_{RN}1$ mechanism comes from the oxidative addition of nucleophiles to $R_2\dot{C}NO_2$ radicals [59,60] as shown in Scheme 11. The second step of this procedure is the same as the $S_{RN}1$ mechanism but avoids initiation and Z-philic problems and in several cases [5,6,25,35] has proved a more reliable method for the synthesis of α-substituted nitroalkanes. The following nucleophiles have been used successfully in oxidative addition synthesis: NO_2^-,[6,59,60] ^-CN,[60] $R_2CNO_2^-$,[6,59,80] RS^-,[4,6,59] RSO_2^-,[59] *N*-heterocyclic thiolates, [6] N_3^-,[35] ^-SCN,[5] and diazole anions.[25] Competitive addition to $R_2\dot{C}NO_2$ radicals between the nucleophile and $R_2CNO_2^-$ is largely precluded because the oxidations are carried out in CH_2Cl_2/H_2O or Et_2O/H_2O solutions and strong protic solvation of $R_2CNO_2^-$ drastically lowers its nucleophilicity. A recent improvement [60] involves the use of a catalytic amount of ferricyanide which is recycled *in situ* with persulphate. The technique has been applied to cyclizations of a 1,4-dinitronate [72] (equation 18) and a 1,6-nitronate-phenolate.[73]

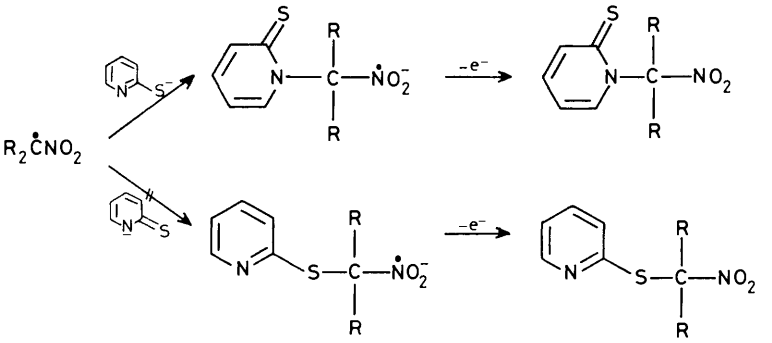
$$R_2C{=}NO_2^- + Fe^{III} \longrightarrow R_2\dot{C}NO_2 + Fe^{II}$$

$$R_2\dot{C}NO_2 + Nu^- \longrightarrow [R_2C(Nu)NO_2]^{-\bullet}$$

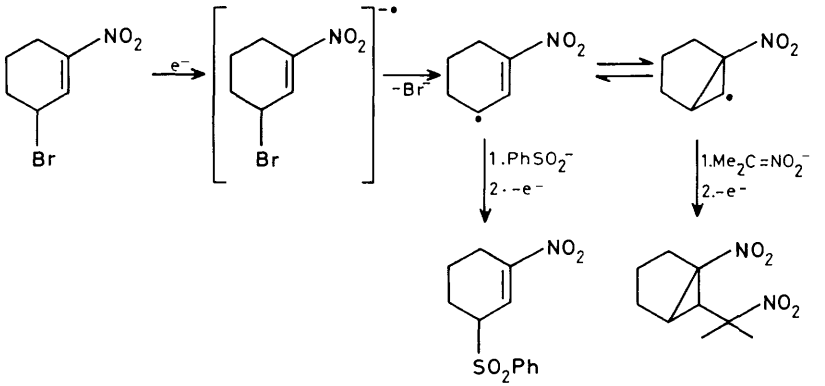
$$[R_2C(Nu)NO_2]^{-\bullet} + Fe^{III} \longrightarrow R_2C(Nu)NO_2 + Fe^{II}$$

Nu = CN, NO_2, SCN, RSO_2, RS, N-heterocyclic-8, diazoles (N-anions), $R_2C{=}NO_2^-$

Scheme 11 *Oxidative addition of nucleophiles to* $R_2\dot{C}NO_2$ *radicals using potassium ferricyanide as oxidant*



Scheme 12 *Kinetic control of the addition of ambident anions to* $R_2\dot{C}NO_2$ radicals

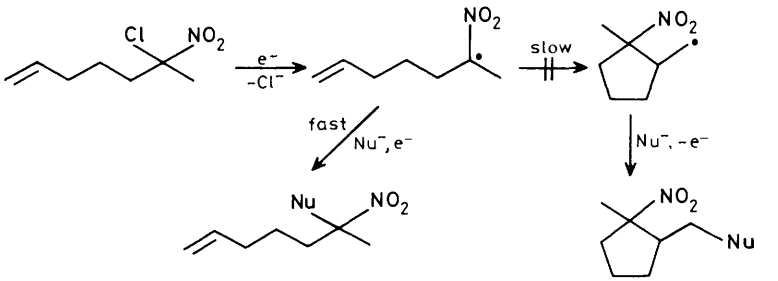


Scheme 13 $S_{RN}1$ *Reactions of 3-bromo-1-nitrocyclohex-1-ene*

The effect of basicity (or nucleophilicity) of the nucleophile is important in determining the rate of addition to radicals. The radical intermediates in $S_{RN}1$ reactions of $R_2C(X)NO_2$ are all strongly electrophilic, *i.e.* $Me_2\dot{C}NO_2$ or $Me_2\dot{C}X$ (X = a $-I$ group such as CO_2R, COR, CN, N_3 *etc.*), therefore the more nucleophilic the nucleophile the faster the addition, *e.g.* enolate anions react faster than nitronate anions with α-keto-radicals $R\dot{C}HCOR$).[18] Tolbert and Siddiqui[74] have proposed that the addition of nucleophiles to radicals is under kinetic and not thermodynamic control because the stability of the radical-anion intermediate is not achieved until well past the transition state. In the addition of nucleophiles to

[70] C. D. Beadle, W. R. Bowman, and J. Prousek, *Tetrahedron Lett.*, 1984, **25**, 4979.
[71] A. Amrollah-Madjdabadi, R. Beugelmans, and A. Lechevallier, *Synthesis*, 1986, 827 and 828.
[72] A. P. Marchand, P.-W. Jin, J. L. Flippen-Anderson, R. Gilardi, and C. George, *J. Chem. Soc., Chem. Commun.*, 1987, 1108.
[73] A. S. Kende and K. Koch, *Tetrahedron Lett.*, 1986, **27**, 6051.
[74] L. M. Tolbert and S. Siddiqui, *Tetrahedron*, 1982, **38**, 1079; *J. Org. Chem.*, 1984, **49**, 1744.

$R_2\dot{C}NO_2$,[6] the radical-anion $[R_2C(Nu)NO_2]^{-\cdot}$ stability is a function of the π^* MO of the nitro-group which is only achieved after relaxation and rearrangement of MO's from the higher energy σ^* $[R_2C(NO_2)\text{-}Nu]^-$ radical-anion. The transition state of the addition will precede this σ^* intermediate and not the lower energy π^* intermediate.



Nu^- = $Me_2C{=}NO_2^-$, c-$C_3H_6C(Me){=}NO_2^-$, $CH_2{=}CH(CH_2)_3C(Me){=}NO_2^-$, $(EtO_2C)_2^-$CMe, enolate of 2-methyl-1,3-cyclopentanedione, $Bu^t\text{–}C(O^-){=}CH_2$

Scheme 14 $S_{RN}1$ *Reactions of 2-chloro-2-nitrohept-6-ene*

This proposal has been applied to the addition of ambident anions to $R_2\dot{C}NO_2$ radicals,[6] which are generated either in $S_{RN}1$ substitutions or oxidative additions. All the nucleophiles react selectively *via* the most nucleophilic centre; *e.g. N*-heterocyclic thiolates (*S* not *N*),[6,52] aryl thiolates (*S* not *C*),[3] enolates (*C* not *O*),[18,20,27] thiocyanate (*S* not *N*),[5] dialkylphosphites (*P* not *O*),[24,26] dialkylthiophosphites (*P* not *S*),[24,26] sulphinates (*S* not *O*),[4,5,21] diazole anions (most nucleophilic *N*),[25] nitronates (*C* not *O*), and nitrite (*N* not *O*).

The addition of the anion of 2-pyridinethiol is of particular interest because the *N*-centred anion is *ca.* 10^4 times more basic than the *S*-centred anion, but selective nucleophilic attack by the *S*-centre is observed for S_N2 reactions on carbon. These anions only add *via* the *S*-centre to $R_2\dot{C}NO_2$[6] or *p*-nitrocumyl radicals[53] indicating that nucleophilicity and not basicity is rate determining[6] (Scheme 12). This proposal was further supported by showing that in the $S_{RN}1$ reactions between α,*p*-dinitrocumene and *N*-heterocyclic thiolates the *N*-substituted compounds are thermodynamically more stable than the *S*-substituted products.[53]

The addition of the ambident anions of 4(5)-nitroimidazoles[25] to $R_2\dot{C}NO_2$ further supports this theory (Scheme 12). The 4-nitro ambient anion is more nucleophilic (or basic) than the 5-nitro anion in which the closer proximity of the nitro-group lowers the electron density of the *N*-anionic centre. Addition of the 4-nitro anion is selectively observed (Scheme 8, step 3).

The addition of nucleophiles to radicals in these reactions is largely unaffected by steric hindrance. There is, however, a limit to the steric hindrance that is tolerated before alternative pathways begin to predominate. The reactions between *p*-NO_2-C_6H_4-$C(X)R^1R^2$ and $R^3\bar{C}(CN)_2$,[54] and between $Me_2C(X)NO_2$ and $R^1C(OLi)$-CHR^2,[27] have been studied to determine the effect of steric hindrance, For example,

in the former reaction, $S_{RN}1$ is only precluded when R^1 = Me, R^2 = Bu, and R^3 = Pr^i.

The $S_{RN}1$ reactions between the anions of nitroimidazoles and $Me_2C(X)NO_2$ also show steric effects.[25] 4-Nitroimidazole reacts faster than 2-methyl-4-nitroimidazole, and 2-nitroimidazole does not react at all, indicating that substituents in the 2- and 5-positions hinder addition to $Me_2\dot{C}NO_2$. The addition of these nitroimidazole anions to the less hindered *p*-nitrobenzyl radical was much faster than to the sterically hindered $Me_2\dot{C}$ radical.[25]

The addition of nucleophiles to $R_2\dot{C}NO_2$ radicals is also strongly influenced by the nature of the counter-cation and the solvation of the nucleophiles,[20,24] as shown by competitive reactions (equations 19 and 20).

$$Me_2\dot{C}NO_2 + A^- \longrightarrow [Me_2C(A)NO_2]^{-\cdot} \xrightarrow{-e^-} Me_2C(A)NO_2 \qquad (19)$$

$$Me_2\dot{C}NO_2 + B^- \longrightarrow [Me_2C(B)NO_2]^{-\cdot} \xrightarrow{-e^-} Me_2C(B)NO_2 \qquad (20)$$

The most striking example from these studies[20] are the changes of the relative ratio B/A when A^- = $Me_2CNO_2^-$ and B^- = $MeC(CO_2Et)_2$, *e.g.* when the reactions were carried out with a solution of 0.2MLi^+ in THF, B/A = > 70, and in HMPA, B/A = 0.22, *i.e.* the malonate is strongly ion-paired in HMPA but not in the less polar THF.

(vi) *Behaviour of the Reactive Intermediates.* A number of processes have been observed to take place other than those directly defined by the $S_{RN}1$ mechanism

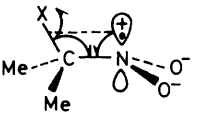
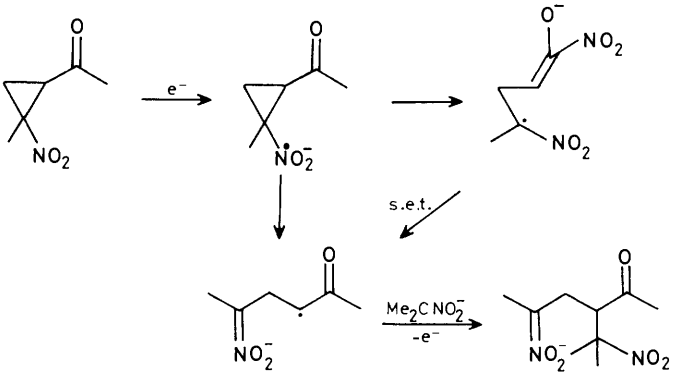


Figure 3



Scheme 15 $S_{RN}1$ *Reactions of* 2-*acetyl*-1-*methyl*-1-*nitrocyclopropane*

Valence tautomerism of the intermediate radical has been observed[75] in the $S_{RN}1$ reaction between the vinylogous bromonitro-compound, 3-bromo-1-nitrocyclohex-1-ene and $Me_2CNO_2^-$ (Scheme 13), whereas the reaction with $PhSO_2^-$ gives substitution as expected. Cyclization of alkenyl alkyl radicals in $S_{RN}1$ reactions has been observed[18] but fails to take place for $S_{RN}1$ substitutions of 2-chloro-2-nitrohept-6-ene[28] which proceed *via* radical intermediates (Scheme 14). Similarly, the expected ring-opening of nitrocyclopropylcarbinyl radical intermediates in the $S_{RN}1$ reactions of 1-chloro-1-cyclopropyl-1-nitroethane[28] was not observed. The rate of addition of the nucleophile to the first intermediate radical is clearly faster than the rate of rearrangement/cyclization of the intermediate radical.

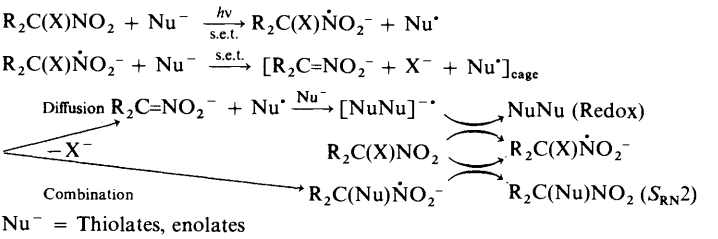
Ring opening has been shown to take place[50] in the $S_{RN}1$ reaction between 2-acetyl-1-methyl-1-nitrocyclopropane and $Me_2CNO_2^-$ (but not other anions) (Scheme 15). If the reaction proceeds by the normal $S_{RN}1$ dissociation of the intermediate radical-anion, *i.e.* to α-nitroalkyl radical and anion (Scheme 10, route A), then a rapid intramolecular s.e.t. must take place. Alternatively, the dissociation to nitronate and α-ketoalkyl radical must be feasible (Figure 3). These results suggest that dissociation (Scheme 10 and Figure 3) of the radical-anion intermediates in $S_{RN}1$ reactions may also be dependent on the relative stabilities of $X^{\cdot}$, X^-, $R_2\dot{C}NO_2$, and $R_2CNO_2^-$, as well as bond strength, nucleofugicity, and structure of the radical-anion.

E. Other s.e.t. Mechanisms.—The literature contains a number of s.e.t. mechanisms for the reactions between $R_2C(X)NO_2$ and nucleophiles which lead to substitution and/or redox which do not proceed by the $S_{RN}1$ mechanism.

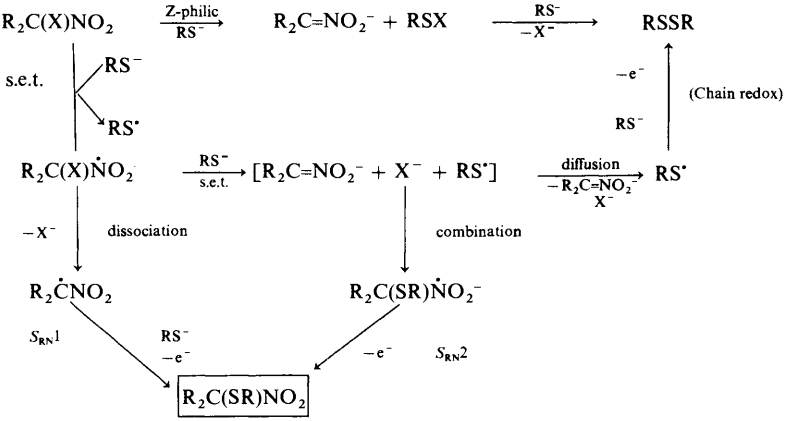
(i) *Chain Reactions involving s.e.t. between Radical-anions and Nucleophiles.* $S_{RN}1$ reactions involving competition between anions are independent of the nature of the leaving group because the anions compete for the intermediate radical ($R_2\dot{C}NO_2$).[18] Competition between Z-philic redox reactions and $S_{RN}1$ substitution (Schemes 1 and 10) is strongly dependent on the nature of the nucleofuge.[3–6] However, in certain reactions between $R_2C(X)NO_2$ and nucleophiles (*e.g.* enolates[18,27] and thiolates[4,6]) chain substitution and redox processes take place, in which competition between the mechanisms is nucleofuge-dependent and the intermediate radical-anion $[R_2C(X)NO_2]^{-\cdot}$, rather than $R_2C(X)NO_2$, has been shown to be the point of competition. The mechanisms for the nucleophilic substitution reaction (termed $S_{RN}2$)[18,27] and the chain redox reaction are shown in Scheme 16. Steps 2 and 3 of the $S_{RN}1$ mechanism (Scheme 2, route A) are combined in step 2 of the $S_{RN}2$ mechanism. The initiation steps and the steps regenerating the radical-anion, $[R_2C(X)\dot{N}O_2^-]$, (step 4: $S_{RN}1$ and step 3: $S_{RN}2$) are the same for both mechanisms. The second s.e.t. process must be dissociative to overcome coulombic repulsion between the two anionic species and requires easily oxidized nucleophiles.

Scheme 17 illustrates the possible mechanisms ($S_{RN}1$, $S_{RN}2$, chain redox, and Z-

[75] W. R. Bowman, D. S. Brown, C. T. W. Leung, and A. P. Stutchbury, *Tetrahedron Lett.*, 1985, **26**, 539.



Scheme 16 *$S_{RN}2$ And chain redox mechanisms*



Scheme 17 *$S_{RN}1$, $S_{RN}2$, Z-philic, and chain redox mechanisms*

philic abstraction) for the reactions between $R_2C(X)NO_2$ and thiolates. A number of trends can be discerned for the reactions of enolates and thiolates which influence the route followed:

(a) *Nucleofuge.* Substituents which are easily abstracted, *e.g.* Br, favour Z-philic abstraction, especially with thiolates. For enolates, $S_{RN}2$ is favoured over redox for Cl > NO_2, SO_2Ar, *i.e.* the poorer the nucleofuge the more likely Nu$^\bullet$ can diffuse from the solvent cage to yield redox processes.

(b) *Solvents.* For the enolate reactions, $S_{RN}2$/redox mechanisms are favoured over $S_{RN}1$ in THF, whereas DMSO favours redox or Z-philic abstraction over $S_{RN}2$. For thiolate reactions in MeOH Z-philic and chain redox reactions are favoured over $S_{RN}1$ and $S_{RN}2$ because protic solvation hinders the dissociation of $[R_2C(X)NO_2]^{-\bullet}$ in the $S_{RN}1$ route, and addition of RS$^\bullet$ to $R_2CNO_2^-$ in the solvent

cage in the $S_{RN}2$ route is hindered because of very strong solvation of $R_2CNO_2^-$, thereby allowing RS$^\bullet$ to diffuse out of the cage to yield the chain redox route.

(c) *Easily oxidized enolates, e.g.* simple enolates, favour a second s.e.t., whereas the less easily oxidized malonate ester anions favour $S_{RN}1$. In $S_{RN}2$ reactions the rate of the second s.e.t. is faster than the dissociation of $[R_2C(X)NO_2]^{-\bullet}$.

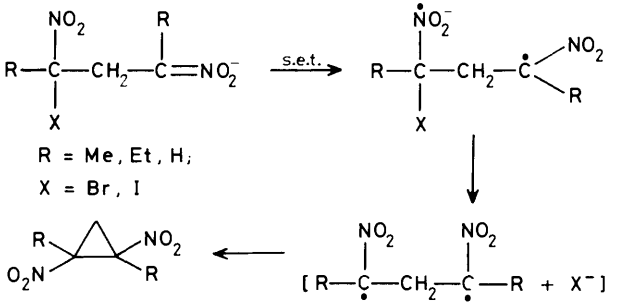
(d) *Steric hindrance or stabilization* of the keto-radical favours redox over $S_{RN}2$ in enolate reactions [PhC(O$^-$)=CHR: R = H, $S_{RN}2$ only; R = Me, Pr^i, mixed $S_{RN}2$ and redox; and R = Ph, only redox].

(e) *Inhibition* of the chain reactions or absence of light favours Z-philic abstraction.

(ii) *Non-chain Substitution Reactions.* S_N2 or S_N1 mechanisms are unlikely for reactions between $R_2C(X)NO_2$ and nucleophiles. Therefore, when reactions are not light-catalysed or inhibited, non-chain or short chain length, s.e.t. mechanisms, in which the radical intermediates are tightly held in a solvent cage, are possible. The term, $S_{ET}2$ (substitution, electron transfer, bimolecular) has been used to describe[76] the non-chain reaction shown in equation 21. Equivalent non-chain mechanisms ($S_{ET}i$)[77] have been proposed for several cyclizations forming cyclopropyl ring[77–79] (*e.g.* equation 22).[78]

$$Ph{\equiv}C^- + Me_2C(NO_2)_2 \xrightarrow{\text{s.e.t.}} \{PhC{\equiv}C^\bullet + [Me_2C(NO_2)_2]^{-\bullet}\} \longrightarrow$$

$$[PhC{\equiv}C^\bullet + Me_2\dot{C}NO_2 + NO_2^-] \longrightarrow PhC{\equiv}CC(Me_2)NO_2 + NO_2^- \quad (21)$$



(22)

(iii) *Non-chain Redox Reactions.* Redox reactions are observed when the $R_2\dot{C}NO_2$ radicals, formed from the initial s.e.t. and subsequent dissociation of the radical-

[76] G. A. Russell, M. Jawdosiuk, and M. Makosza, *J. Am. Chem. Soc.*, 1979, **101**, 2355.
[77] G. A. Russell, M. Makosza, and J. Hershberger, *J. Org. Chem.*, 1979, **44**, 1195.
[78] P. A. Wade, W. P. Dailey, and P. J. Carrol, *J. Am. Chem. Soc.*, 1987, **109**, 5452.
[79] N. Ono, T. Yanai, I. Hamamoto, A. Kamimura, and A. Kaji, *J. Org. Chem.*, 1985, **50**, 2807; A. Krief, L. Hevesi, G. Chaboteaux, P. Mathy, M. Sevrin, and M. J. De Vos, *J. Chem. Soc., Chem. Commun.*, 1985, 1693.

anions, $[R_2C(X)NO_2]^{-\bullet}$, undergo a further s.e.t. with the nucleophile rather than addition (Scheme 18). Redox is caused by three factors: easily oxidized anions leading to stabilised radicals,[10–12,17,18,76] steric hindrance,[18,27,34,35] and the absence of a low energy SOMO in the radical-anions formed by addition of the nucleophile to $R_2\dot{C}X$ radicals [see Section 2B(iv)].[7,57]

$$R_2C(X)NO_2 + Nu^- \xrightarrow{\text{s.e.t.}} [R_2C(X)NO_2]^{-\bullet} + Nu^\bullet \quad (1)$$

$$[R_2C(X)NO_2]^{-\bullet} \longrightarrow R_2\dot{C}NO_2 + X^- \quad (2)$$

$$R_2\dot{C}NO_2 + Nu^- \begin{cases} \longrightarrow [R_2C(Nu)NO_2]^{-\bullet} \\ \xrightarrow{\text{s.e.t.}} R_2C{=}NO_2^- + Nu^\bullet \end{cases} \quad (3)$$

$$R_2\dot{C}NO_2 + R_2C{=}NO_2^- \longrightarrow [R_2C(NO_2)C(NO_2)R_2]^{-\bullet} \quad (4)$$

$$[R_2C(NO_2)C(NO_2)R_2]^{-\bullet} + R_2C(X)NO_2 \xrightarrow{\text{s.e.t.}} R_2C(NO_2)C(NO_2)R_2 + [R_2C(X)NO_2]^{-\bullet} \quad (5)$$

$$Nu^\bullet + Nu^- \longrightarrow [Nu{-}Nu]^{-\bullet} \xrightarrow[-e]{} Nu{-}Nu \longleftarrow 2\,Nu: \quad (6)$$

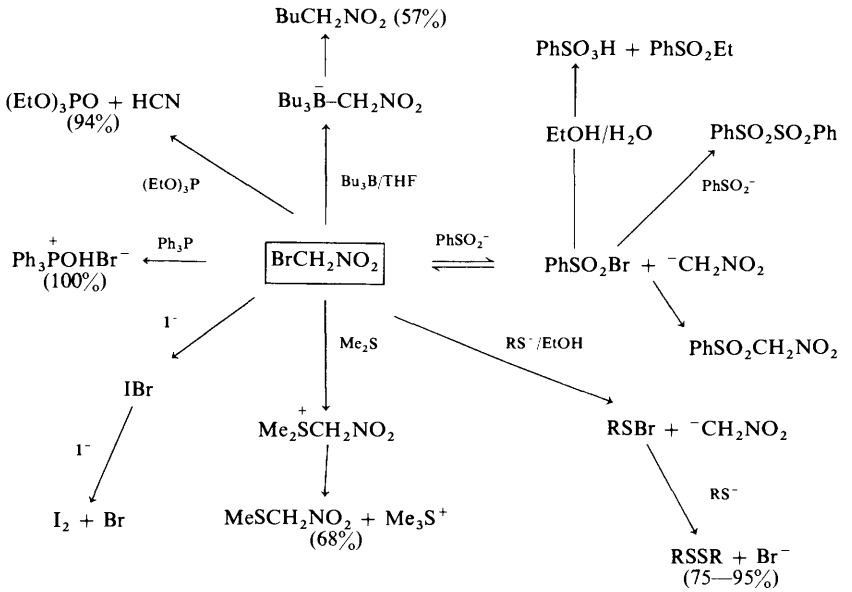
Scheme 18 *Non-chain redox mechanisms for reactions between* $R_2C(X)NO_2$ *and nucleophiles*

Intermediate radicals are stabilized[18,27] by the following substituents: aryl (*e.g.* 9-fluorenide, $Ph_2\bar{C}$–CN), vinyl, thioethers (*e.g.* 2-methyl or phenyl-1,3-dithiane), ethers, and amines, whereas relatively low stabilization results from nitro, ester, ketone, and sulphono substituents.

The redox reactions between 9-arylfluorenide anions and $R_2C(NO_2)_2$ have been extensively studied.[10–12] The initial s.e.t. (step 1 in Scheme 18) gives second-order rate constants which can be correlated with the reduction potentials of the electron acceptors, over a 20 pK_{HA} range for the 9-arylfluorenide anions.[12] This step is endergonic ($\Delta G° \simeq 5.5$—13 kcal mole^{-1}) and the reverse s.e.t. is near diffusion control.[10] The dissociation of the $[R_2C(NO_2)_2]^{-\bullet}$ radical-anions is rate determining (step 2 in Scheme 18).[10] The s.e.t. in step 3 is near diffusion control and exergonic ($\Delta G° = -16$ kcal mole^{-1}),[10] *i.e.* any $R_2\dot{C}NO_2$ formed is immediately scavenged by fluorenide anions. However, as the concentration of $R_2CNO_2^-$ builds up, it competes (step 4) with the fluorenide anions for $R_2\dot{C}NO_2$, setting up a chain reaction (steps 1—5) and changes the kinetic order.[10] The fluorenide radicals dimerize in step 6.

Reactions of $R_2C(X)NO_2$ which lose nitrite from the intermediate radical-anion can lead to dimers[7,51,57] from both $R_2C(X)NO_2$ [see Section 2B(iv) and equation 10] and nucleophile because $R_2\dot{C}X$ can readily dimerize whereas there is no evidence of dimerization of $R_2\dot{C}NO_2$.

(iv) *Reduction of* $R_2C(X)NO_2$. α-Substituted nitroalkanes can be reduced in s.e.t. chain reactions by a variety of reagents (*e.g.* Bu_3SnH, NaHTe, 1-benzyl-1,4-dihydronicotinamide, CH_3S^-, $NaBH_4$, $LiAlH_4$). The mechanisms, scope, and synthetic potential of these reactions have been extensively investigated and recently



RS = PhS, EtS, *o*-NO_2-C_6H_4-S, EtOC(S)S, $H_2N{=}C(NH_2)S$

Scheme 19 *Reactions between* $BrCH_2NO_2$ *and nucleophiles*

reviewed.[80] These chain reactions are similar to $S_{RN}1$ substitutions, *i.e.* an initial s.e.t. from the reductant intermediate [*e.g.* $Bu_3Sn^{\bullet}$, $(CH_2S)^{-\bullet}$] to $R_2C(X)NO_2$ to yield a radical-anion, $[R_2C(X)NO_2]^{-\bullet}$, which dissociates with loss of X^- or NO_2^- to give a radical, $R_2\dot{C}NO_2$, $R_2\dot{C}X$, or $R_3C^{\bullet}$. At this point the mechanisms diverge and in the reduction reactions the radical abstracts hydrogen ($H^{\bullet}$) from the reductant to yield R_2CHNO_2, R_2CHX, or R_3CH and regenerates the reductant intermediate which carries the chain.

3 Polar Reactions

A. S_N2 on Carbon Reactions.—Competition between $S_{RN}1$ and S_N2 (on carbon) substitutions has been extensively investigated for the reactions between $Me_2CNO_2^-$ and *p*-nitrobenzyl derivatives.[7,23] $Me_2CNO_2^-$ is a weak nucleophile and a good electron donor. Therefore, in the reactions with *p*-NO_2-$C_6H_4CH_2X$, the rate of s.e.t. is relatively constant, but the rate of S_N2 substitution is higher for better nucleofuges (X^-). When X = I, only S_N2 substitution is observed *via* the oxygen centre of the ambident $Me_2CNO_2^-$ anion, but with poor nucleofuges, *e.g.* $X = {}^+NMe_3$, mainly $S_{RN}1$ substitution, *via* the carbon centre of $Me_2CNO_2^-$, is

[80] N. Ono and A. Kaji, *Synthesis*, 1986, 693.

observed. Similar results have been observed for the reactions between $Me_2CNO_2^-$ and α-substituted 2-methyl-5-nitrofurans.[62]

The reactions between thiolates and 2-bromo- and 2-iodomethyl-5-nitrofuran proceed by both S_N2 on carbon and Z-philic substitution,[70] and not by $S_{RN}1$, mechanisms, showing that competition between S_N2 and Z-philic reactions depends on nucleophilicity, Z-abstractability, and nucleofugicity of X, and the solvent.

When the halogeno- and nitro-groups are geminal, *e.g.* $BrCH_2NO_2$, Z-philic effects are much more pronounced because of the lower electron density on the substituent due to the proximity of the nitro-group.[81] For example, all the thiolates, and even $PhSO_2^-$, and I^-, reacted with $BrCH_2NO_2$ to give Z-philic reactions (Scheme 19). The reactions between a wide variety of nucleophiles and $BrCH_2NO_2$ are shown in Scheme 19. The 'hard' nucleophiles, MeO^-, ^-OH, and $^-BH_4$ attack the 'hard' H^+ electrophilic centre, phosphorus nucleophiles attack the oxygen 'electrophilic' centre, and only Me_2S attacks the carbon electrophilic centre. There is a rapid equilibrium between $Me_2C(X)NO_2$ (X = I, Br) and $PhSO_2^-$, and $Me_2CNO_2^-$ and $PhSO_2X$, and only a slow $S_{RN}1$ reaction to $Me_2C(SO_2Ph)NO_2$,[2] in both DMF and MeOH, indicating that Z-philic abstraction is strongly favoured over s.e.t. and hence $S_{RN}1$ substitution. $Me_2C(Cl)NO_2$ was inert to $PhSO_2^-$ for either Z-philic or $S_{RN}1$ reactions.[2]

B. Z-Philic Nucleophilic Substitutions.—(i) *Polynitro-compounds.* α-Substituents are readily abstracted by nucleophiles when more than one nitro-group is present [*e.g.* $ZC(NO_2)_3$ and $RC(NO_2)_2Z$]. The resulting di- and tri-nitro anions are very stable and are good nucleofuges, and the α-substituents are strongly electropositive, thereby strongly favouring Z-philic reactions. However, each extra nitro-group increases the oxidizing power[82] which increases the likelihood of s.e.t. The competition between Z-philic (Scheme 1) and s.e.t. redox mechanisms (Scheme 18) for the reactions between 1,1,1-trinitroethane and n-butylthiolate,[32] and between tetranitromethane and various anions[83] has been discussed. Some reactions of tetranitromethane clearly proceed by s.e.t. mechanisms because certain products can only be formed *via* radical reactions, *e.g.* the reaction between tetranitromethane and the anion of *p*-cresol yields Pummerers' ketone (30%), a known radical-dimer. The *o*-nitro-*p*-cresol formed (30%) could arise by either polar or s.e.t. mechanisms.

(ii) *α-Substituted Mono-nitroalkanes.* Deprotonation of nitroalkanes with an α-hydrogen can be regarded as the simplest form of Z-philic attack, and is thermodynamically favourable (hence the acidity), but the rate of deprotonation is slow as a result of the change of hybridization from sp^3 *to* sp^2 [as with all the Z-philic reactions of $R_2C(X)NO_2$]. This phenomenon is called the 'nitro-anomaly'.

[81] B. R. Fishwick, D. K. Rowles, and C. J. M. Stirling, *J. Chem. Soc., Chem. Commun.*, 1983, 834 and 835; *J. Chem. Soc., Perkin Trans. 1*, 1986, 1171.

[82] J. Armand, *Bull. Soc. Chim. Fr.*, 1965, 543; N. Sayo, Y. Tsukitani, and M. Masui, *Tetrahedron*, 1967, **24**, 1717; R. Glicksman and K. Morehouse, *J. Electrochem. Soc.*, 1959, **104**, 288.

[83] S. L. Walters and T. C. Bruice, *J. Am. Chem. Soc.*, 1971, **93**, 2269 and references therein.

Z-Philic and s.e.t. mechanisms ($S_{RN}1$, $S_{RN}2$, chain and non-chain redox) are in competition in many reactions between nucleophiles and $R_2C(X)NO_2$. The Z-philic reactions have often been ignored because the aim has been to investigate $S_{RN}1$ or other s.e.t. processes. The effect of the nitro-group is crucial, but falls off rapidly with distance, and Z-philic reactions are not observed when the substituent is on the β-carbon or further away.

Z-Philic abstraction can proceed by either polar or s.e.t. mechanisms as shown in equations 23 and 24 respectively.[4,6,70] The s.e.t. mechanism requires a S_H2 type Z-philic substitution in which a radical ($Nu^{\bullet}$) displaces a $R_2CNO_2^-$ anion, and that all intermediates are tightly held in a solvent cage. Evidence suggests[4,6,70] that the polar mechanism is more probable.

$$R_2C(Z)NO_2 + Nu^- \longrightarrow [Nu^{\delta-} \cdots Z \cdots C(R_2)NO_2^{\delta-}] \longrightarrow Nu\text{–}Z + R_2CNO_2^- \quad (23)$$

$$\xrightarrow{\text{s.e.t.}} [R_2C(Z)\dot{N}O_2^- + Nu^{\bullet}] \longrightarrow \lceil Nu^{\delta\bullet} \cdots Z \cdots {}^{\delta\bullet}C(R_2)NO_2^- \rceil \quad (24)$$

The factors which favour Z-philic abstractions[84] also favour s.e.t. For example, increased basicity of the nucleophile favours s.e.t.[11] but also improves nucleophilicity and hence Z-philic abstraction. Similarly, as $R_2C(Z)NO_2$ improves as an electron acceptor[82] (Z = I > Br > Cl > CN > CO_2Et > CH_2OH > H > Me), the abstractability of Z also increases. Although the differences in reduction potential are markedly different, the rate of Z-philic abstraction appears to increase more rapidly, and dominates with easily abstracted groups, *e.g.* I and Br.

The factors which favour Z-philic abstraction for $R_2C(Z)NO_2$ are: (*a*) easily abstracted Z, *e.g.* I > Br > SCN > Cl, NO_2 > SO_2Ar; (*b*) high nucleophilicity (see equation 14 for an example); (*c*) protic solvation [see Section 2D(iv) and Scheme 10]; (*d*) similar polarizability of Nu^- and Z, *e.g.* I and RS^- are both polarizable or 'soft'; (*e*) radical scavengers or strong electron acceptors to inhibit competing s.e.t., *e.g.* the reaction between $Me_2C(NO_2)_2$ and *p*-Cl-$C_6H_4S^-$ yields the $S_{RN}1$ product, $Me_2C(SR)NO_2$ (69%), but is totally inhibited by oxygen and yields RSSR (60%) *via* Z-philic abstraction.[3]

Z-Philic mechanisms are easily assigned when the direct products (as shown in equation 23) are isolated, *e.g.* for $Me_2C(X)NO_2$: Z = Br, Nu^- = $^-CH(CO_2Et)_2$,[32] $CH_3COCHCO_2Et$,[32] Ph_2CCN,[12] ^-CN; Z = Cl, Nu^- = $PhC(O^-)$=CR^1R^2 with R^1 = H, R^2 = Bu^t, Pr^i, and R^1 = R^2 = Me;[18,27] Z = NO_2, Nu^- = $PhC(O^-)$=CHMe,[27] Bu^t$C(O^-)$=CH_2;[18] Z = CN, Nu^- = PhC≡C^-;[76] Z = SO_2Ar, Nu^- = $PhC(O^-)$=CHMe;[27] Z = Cl, Nu^- = $(EtO)_2PS^-$ (Scheme 9).[24]

Z-Philic mechanisms are also easily assigned when an unambiguous product, which derives from the direct product (Nu–Z), is isolated. For example, the reactions[2,81] between $ArSO_2^-$ and $BrCH_2NO_2$, $Me_2C(I)NO_2$, and $Me_2C(Br)NO_2$ in $MeOH/H_2O$ yield sulphonyl halides, $ArSO_2Z$, which react with MeOH or H_2O to give $ArSO_3Me$ and $ArSO_3H$ respectively. Similarly, the reactions between

[84] A. Foucaud in 'The Chemistry of the Functional Groups, Suppl. D. The Chemistry of Halides, Psuedo-Halides, and Azides', ed. S. Patai and Z. Rappoport, Wiley, Chichester. 1983. p. 441.

$Me_2C(NO_2)_2$ and $(RO)_2PY^-$ (Y = S, O) yield $Me_2C{=}N(O^-)P(Y)(OR)_2$ which derives from reactions between the Z-philic products $(RO)_2P(Y)NO_2$ and $Me_2CNO_2^-$ (Scheme 9).[24]

The reactions between $BrCH_2NO_2$ and nucleophiles illustrate the HSAB polarizability factors, *i.e.* hard nucleophiles attack the hard H^+, soft nucleophiles attack the soft Br^+, and the *O*-philic phosphorus nucleophiles attack the nitro-oxygens.[2,81] The *O*-philicity of *P*-nucleophiles is also illustrated by the attack of $(RO)_2PO^-$ on a nitro-group of $Me_2C(NO_2)_2$, but not on the Cl or $ArSO_2$ groups of $Me_2C(Cl)NO_2$ or $Me_2(SO_2Ar)NO_2$.[24]

The effect of abstractability (I > Br > Cl, NO_2 is illustrated by several reactions, *e.g.*

$Me_2C(X)NO_2$ and $^-CH(CO_2Et)_2$: Z-philic abstraction for X = Br, but $S_{RN}1$ for X = Cl and NO_2;[32]

$Me_2C(X)NO_2$ and $ArSO_2^-$: I > Br > (Cl, no abstraction);[81]

$R^1_2C(X)NO_2$ and $R^2_2CNO_2^-$: I > Br > (Cl and NO_2, low abstraction);[7]

$Me_2C(X)NO_2$ and *p*-Cl-$C_6H_4S^-$: I > Br > SCN > Cl, NO_2 > SO_2Ph.[3,4,6]

(iii) *Competition between Z-Philic and s.e.t. Mechanisms.* Chain reactions ($S_{RN}1$, $S_{RN}2$, chain redox) can be readily assigned from inhibition studies [Section 2E(i)]. The difficulty is in determining whether dimeric (redox) products [$R_2C(NO_2)C(NO_2)R_2$ and Nu–Nu] arise from (*a*) Z-philic abstraction to yield $R_2CNO_2^-$ and Nu–Z, followed by $S_{RN}1$ reaction between $R_2CNO_2^-$ and unreacted $R_2C(Z)NO_2$ to yield $R_2C(NO_2)C(NO_2)R_2$, and reaction of Nu–Z with excess Nu^- to yield Nu–Nu (as shown in equations 25 and 26), or (*b*) a non-chain redox mechanism as shown in Scheme 18 and Section 2E(iii).

$$R_2C(Z)NO_2 + Nu^- \longrightarrow R_2CNO_2^- + Nu{-}Z \xrightarrow{Nu^-} Nu{-}Nu + Z^- \quad (25)$$

$$R_2C(Z)NO_2 + R_2C{=}NO_2^- \longrightarrow R_2C(NO_2)C(NO_2)R_2 + Z^- \quad (26)$$

In the $S_{RN}1$ reactions between $R^1_2C(X)NO_2$(X = I, Br) and $R^2_2C{=}NO_2^-$, the products resulting from Z-philic reaction, $R^2_2C(X)NO_2$ and $R^1_2C{=}NO_2^-$, undergo further $S_{RN}1$ reactions with possible substrates (equations 27 and 28), but can be isolated if the $S_{RN}1$ reactions are inhibited.[7,47] The mixture of products is avoided if less easily abstracted groups such as Cl or NO_2 are used, which indicates that the origin of the jumbling is unlikely to be due to a s.e.t. between $R^1_2\dot{C}NO_2$ and $R^2_2CNO_2^-$ (equation 29) in the middle of a normal $S_{RN}1$ reaction.

$$S^{RN1} \quad R^1_2C(Z)NO_2 + R^2_2C{=}NO_2^- \rightleftharpoons R^1_2C{=}NO_2^- + R^2_2C(Z)NO_2 \quad (27)$$

$$\longrightarrow R^1_2C(NO_2)C(NO_2)R^2_2 + R^1_2C(NO_2)C(NO_2)R^1_2 + R^2_2C(NO_2)C(NO_2)R^2_2 \quad (28)$$

$$R^1_2\dot{C}NO_2 + R^2C{=}NO_2^- \overset{s.e.t.}{\rightleftharpoons} R^1_2C{=}NO_2^- + R^2_2\dot{C}NO_2 \quad (29)$$

The mechanisms of the redox reactions between $R_2C(X)NO_2$ and thiolates (see Scheme 17) are difficult to ascertain because the sulphenyl intermediates (RS–Z) resulting from abstraction are very reactive and rapidly react with further thiolate to yield RSSR.[2,3,4,6,71,81] Most evidence[2,3,4,6,81] suggests that the reaction proceeds by the Z-philic route and not the non-chain redox route: *e.g.* (*a*) the formation of $R_2C(NO_2)C(NO_2)R_2$ is strongly inhibited by radical and radical-

anion inhibitors in dipolar aprotic solvents; (*b*) $R_2CNO_2^-$ is isolated in protic solvents because $S_{RN}1$ substitution is hindered; (*c*) the stoicheiometry of $R^1_2C(X)NO_2:RS^-$ is 2:1 in MeOH; (*d*) thiyl radicals cannot be trapped; (*e*) sulphenyl halides can be trapped by reaction with $PhSO_2^-$ (yielding $RSSO_2Ph$), or by reaction of $R_2C(Cl)NO_2$ with a hindered thiolate (Ph_3CS^-), which allows the sulphenyl intermediate Ph_3CSCl to be isolated; (*f*) no inhibition of RSSR by inhibitors.

The reactions between 5-bromo-5-nitro-1,3-dioxane and EtS^- give high yields of respective dimers but are subject to inhibition and light catalysis.[85] A Z-philic reaction would be expected because Br^+ is easily abstracted and EtS^- is a strong nucleophile. It is possible that these reactions proceed by chain dimerization and not non-chain redox processes. Extensive studies[17] of the reactions between 5-bromo-2,2-dimethyl-5-nitro-1,3-dioxane and Bu^tS^- also suggest that some s.e.t. must be taking place and that the radical-anion stability of the bromonitro-substrate is enhanced by the β-oxygens.

4 Lewis Acid-induced Nucleophilic Substitution of Nitroalkanes

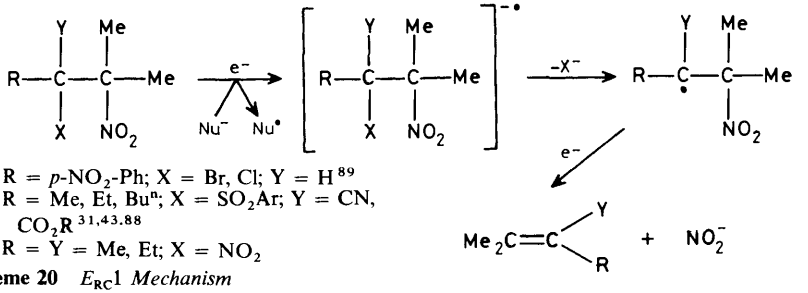
Tertiary, cumyl, and allylic nitro-compounds (R_3CNO_2, $PhC(Me_2)NO_2$, and $CH_2{=}CHCH_2C(Me)(R)NO_2$) undergo nucleophilic substitution with various silyl-nucleophiles ($Me_3Si{-}Nu$, Nu = CN, N_3, enolate, SPh, $CH_2CH{=}CH_2$) in the presence of a Lewis acid, $SnCl_4$.[86] No mechanism was proposed for these reactions but they would appear to be S_N1 substitutions. An example is shown in equation 30. $SnCl_4$ also catalyses the aromatic electrophilic substitution between benzene and RNO_2.[86]

5 Eliminations

Vicinal dinitroalkanes,[7,46,87] β-nitro-sulphones and sulphides,[31,43,88] and β-bromo- and β-chloro-nitroalkanes,[89] undergo s.e.t from various nucleophiles (Na_2S, PhS^-, $Me_2CNO_2^-$, NaHTe, and Bu^n_3SnH, *via* reductive elimination of the nitro-group and β-substituents, to yield the respective olefins (Scheme 20). Norris and co-workers[90] proposed the $R_{RC}1$ mechanism (elimination, radical-chain, unimolecular) to explain the reaction between $Me_2CNO_2^-$ and p-NO_2-C_6H_4-$CH(Br)C(NO_2)Me_2$. They also suggest that all these eliminations proceed by the $E_{RC}1$, or closely related, mechanisms.

A large number of eliminations resulting from the reactions between various substituted nitroalkanes and nucleophiles proceed by polar mechanisms. Loss of HX from α-substituted nitroalkanes (equation 31) does not take place because of the reduced electron density on the α-substituent due to the $-I$ effect of the nitro-group. However, *cis* elimination of PhS–OH to yield nitro-olefins from α- and β-

[85] Z. V. Todres, *Tetrahedron*, 1985, **41**, 2771.
[86] N. Ono, T. Yanai, A. Kamimura, and A. Kaji, *J. Chem. Soc., Chem. Commun.*, 1986, 1283; N. Ono, T. Yanai, and A. Kaji, *ibid.*, 1040.
[87] N. Kornblum and L. Cheng, *J. Org. Chem.*, 1977, **42**, 2944.
[88] N. Ono, H. Miyaka, and A. Kamimura, *Tetrahedron Lett.*, 1985, **41**, 4013; N. Ono and A. Kaji, *Synthesis*, 1986, 693.
[89] D. J. Freeman, R. K. Norris, and S. K. Woolfenden, *Aust. J. Chem.*, 1978, **31**, 2477.
[90] T. Sakakibara, I. Takai, and R. Sudoh, *Synthesis*, 1982, 261; T. Hayami, S. Tomoda, Y. Takehuchi, and N. Nomura, *Tetrahedron Lett.*, 1982, **23**, 4733.



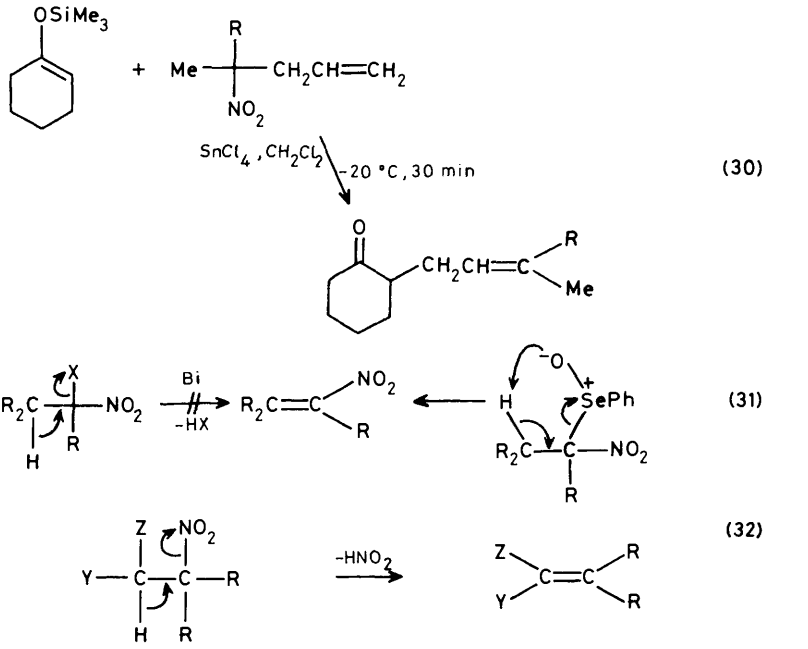
e.g. R = *p*-NO_2-Ph; X = Br, Cl; Y = H[89]
R = Me, Et, Bu^n; X = SO_2Ar; Y = CN, CO_2R[31,43,88]
R = Y = Me, Et; X = NO_2

Scheme 20 $E_{RC}1$ *Mechanism*

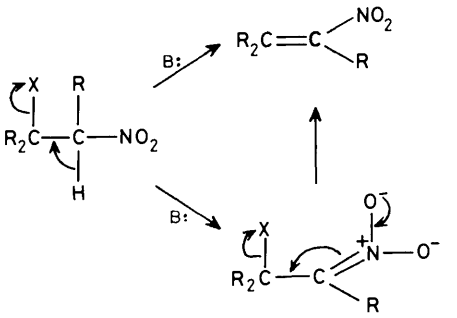
phenylselenyl nitroalkanes takes place readily on treatment with peroxide (equation 31).[90]

E_2-Eliminations of nitrous acid proceed in the presence of base from β-substituted-nitroalkanes with a β-H (equation 32) to yield conjugated olefins, *i.e.* eliminations of an acidic β-hydrogen and the formation of thermodynamically stable olefins. Synchronous elimination of nitro-and β-ester groups using bromide in HMPA also leads to α,β-unsaturated esters and ketones (Scheme 7).[30]

Elimination of HX from β-substituted primary and secondary nitroalkanes with an α-hydrogen is widely used in various procedures for the preparation of nitro-



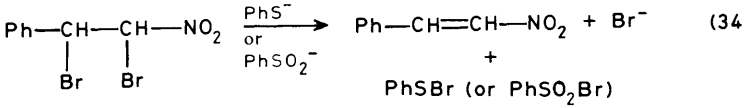
Y = H; Z = NO_2,[29] COR,[19,28] *p*-nitrophenyl,[45] 5-nitro-2-furyl (equation 10),[62] 1-methyl-5-nitroimidazol-2-yl
Y = COR; Z = COR′, CO_2Et



(33)

olefins (equation 33). Leaving groups include halides, OH, OAc, HgCl, OMs, OTs, $C(NO_2)_3$, ONO, and $R_2CNO_2^-$. Elimination possibly proceeds by deprotonation to an intermediate nitronate which then eliminates X^-.

Interestingly, Z-philic elimination is preferred over loss of HX in the reactions between phenylthiolate and *p*-toluenesulphinate, and 1,2-dibromo-2-nitro-1-phenylethane in MeOH and DMF (equation 34).[2] *E*-β-Nitrostyrene is formed in good yield in the reactions with both nucleophiles as well as products arising from the intermediates, PhSBr and $ArSO_2Br$ [PhSSPh, $ArSO_2SO_2Ar$, and $ArSO_3Me$ (MeOH reaction)].



(34)

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