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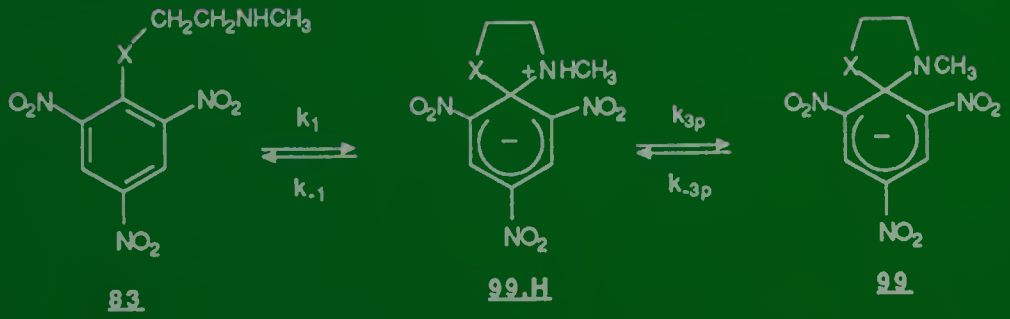
NUCLEOPHILIC AROMATIC DISPLACEMENT

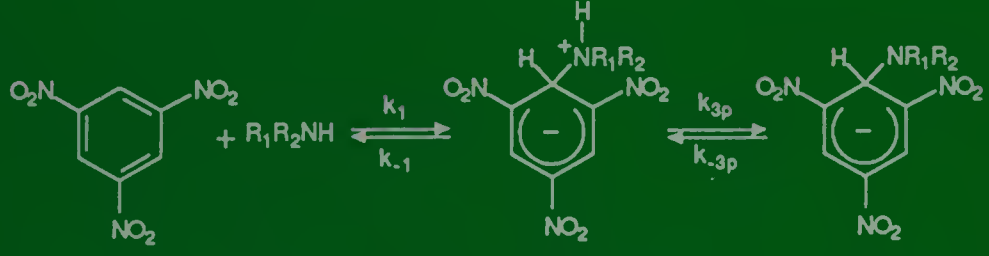
The Influence of the Nitro Group

François Terrier



83 99.H 99

X = NCH_3, O



100.H 100

R_1R_2NH=n-$C_4H_9NH_2$, CH_3NH_2, $C_6H_5CH_2NH_2$, $(CH_3)_2CHNH_2$, $CF_3CH_2NH_2$, $C_6H_5NH_2$, $C_5H_{11}N$, C_4H_9N, $(CH_3)_2NH$, $(C_2H_5)_2NH$

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THE INFLUENCE OF THE NITRO GROUP

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NUCLEOPHILIC AROMATIC DISPLACEMENT:

THE INFLUENCE OF THE NITRO GROUP

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Preface

A landmark in the field of nucleophilic aromatic substitutions was provided by the authoritative review and book published by J.F. Bunnett and J. Miller in 1951 and 1968, respectively. These emphasized the overwhelming importance of the nitro group in these reactions. At the time, however, the focus was essentially on those substitutions which proceeded via the simple two-step addition-elimination mechanism, known as the S_NAr mechanism.

Since 1968, much has happened in the field of nucleophilic aromatic substitutions of nitroactivated aromatic and heteroaromatic substrates. Besides the many developments in the mechanistic understanding and synthetic applicability of S_NAr processes, the discovery of new reaction pathways has considerably broadened the scope and importance of the chemistry of the nitro group in nucleophilic aromatic substitutions. The purpose of the present monograph is to provide a comprehensive account of this versatile field.

In understanding this project, I was aware of the difficulty in incorporating all the aspects that the nitro group plays in the substitutions into one monograph. Accordingly, the present book necessarily reflects some of my own tastes and interests in selecting the topics and their presentation. It is hoped, however, that my efforts to give a balanced presentation of mechanistic and synthetic features will be useful both to workers sharing my interests in the field and to colleagues and research students who may need access to a classified but well documented review of the entire subject area. Chapters 1-4 discuss the Chemistry of S_NAr substitutions and anionic σ-complexes. The latter species are the key intermediates in S_NAr reactions as well as in the large majority of the other nucleophilic aromatic substitutions considered in the subsequent chapters. Chapter 5 discusses for the first time the whole field of "Nucleophilic Aromatic Substitutions of Hydrogen", a subject which has received considerable attention in the last decade. The same is true for nucleophilic aromatic photosubstitutions which are considered in depth in Chapter 6. Chapter 7 discusses the possible role of electron transfer in some

substitution processes while the final chapter deals with the ANRORC reactions discovered by H. Van der Plas. The literature has been searched approximately up to the end of 1990.

I am indebted to Professor Henry Feuer for not only inviting me to write this book but also for his help in correcting my manuscript. I wish also to acknowledge fruitful discussions and encouragements from a number of colleagues: Claude Bernasconi, Erwin Buncel, Michel Chanon, Jean-Claude Hallé, Gerrit Lodder, Mieczyslaw Makosza, Cristina Paradisi, Robert Schaal, and Domenico Spinelli kindly read and commented on several of the Chapters. Receipt of unpublished work from Giuseppe Bartoli, Kiyoshi Mutai, Henk Van der Plas and Gene Wubbels was greatly appreciated. I express special thanks to Marie-France Boucher who typed the manuscript and to Taoufik Boubaker, Alain-Pierre Chatrousse and Patricio Mac Cormack who drew the numerous structures.

Finally I wish to thank my wife Christine, and my daughters Caroline, Sophie, and Barbara, for their invaluable support during the writing of this book.

Paris, April 1991

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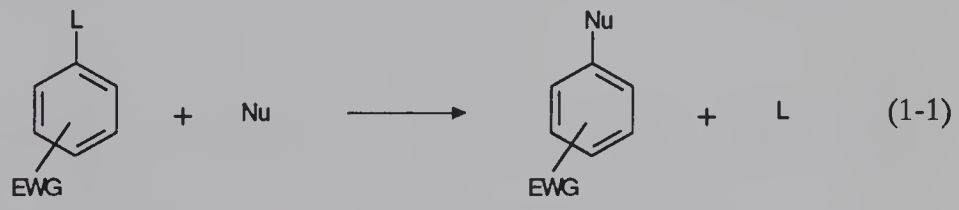
CHAPTER 1.
The S_NAr Reactions: Mechanistic Aspects

1.1 Introduction

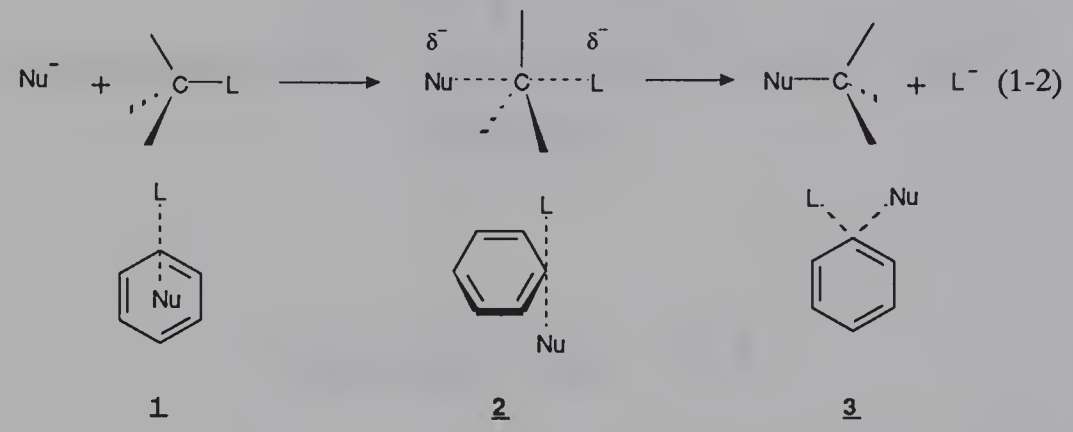
A general nucleophilic aromatic S_NAr substitution can be described by eq. 1-1, in which Nu represents an anionic or a neutral nucleophile and L a good leaving group or nucleofuge. A leaving group L can bear no charge (F, Cl, Br, I, NO_2, OR, OSO_2R, etc.), becoming negatively charged following displacement, or it can be positively or negatively charged (NR_3^+, SO_3^-), becoming uncharged or more negatively charged when displaced.[1–8] The symbol EWG is used to denote the presence of one or more electron-withdrawing groups (e.g., NO_2 in the aromatic ring). Because the presence of an EWG is very important, the S_NAr mechanism is referred to as an activated aromatic substitution process.[1–8]



(1-1)

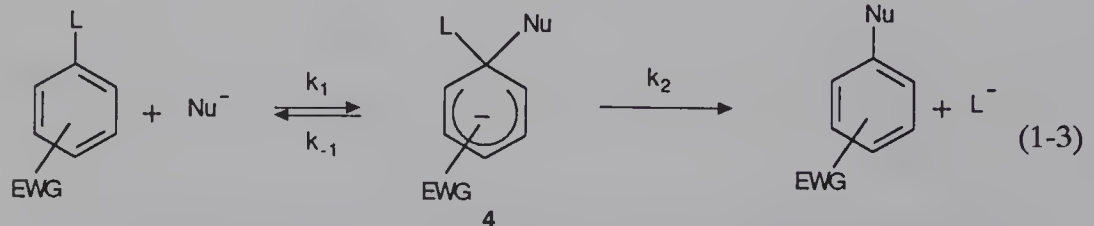
Major characteristics of S_NAr substitutions are that they occur without rearrangement and, when uncatalyzed, they display kinetics and response to structural and environmental factors that indicate a bimolecular mechanism.[1–8] In these respects, the S_NAr processes are formally similar to aliphatic nucleophilic S_N2 substitutions, but it was early recognized that the two dis-

placements cannot proceed along analogous reaction paths.[1–3] Assuming that aromatic substitutions go via a concerted mechanism of the type established for S_N2 reactions (eq. 1-2) would imply the formulation of transition state models in which the benzene resonance is retained, (e.g., **1**, **2**, or **3**). However, no model of this sort can be considered without violation of the Pauli principle and/or inconsistency with spatial requirements.[1,3,8]



1 **2** **3**

Therefore, an addition–elimination mechanism has been postulated by Bunnett for S_NAr processes.[1,2] As a first step, this involves addition of the nucleophile to the aromatic electrophile to form an intermediate cyclohexadienyl anion of some stability in which the carbon center undergoing the substitution becomes sp^3-hybridized—that is, the benzenoid resonance is broken. This intermediate, also known as a σ-complex intermediate, subsequently decomposes to give the substitution product. For anionic nucleophiles, the process is outlined in eq. 1-3 and illustrated by the potential energy diagrams of Fig. 1.1, which show that depending on the relative energies of the two transition states, either the formation or the decomposition of the anionic intermediate **4** may be rate limiting.



(1-3)

4

For neutral nucleophiles (e.g., water, alcohols, amines), the postulated mechanism is shown in eq. 1-4. In this case, the initially formed σ-adduct **5** is zwitterionic and in most cases contains an acidic proton, which can be removed

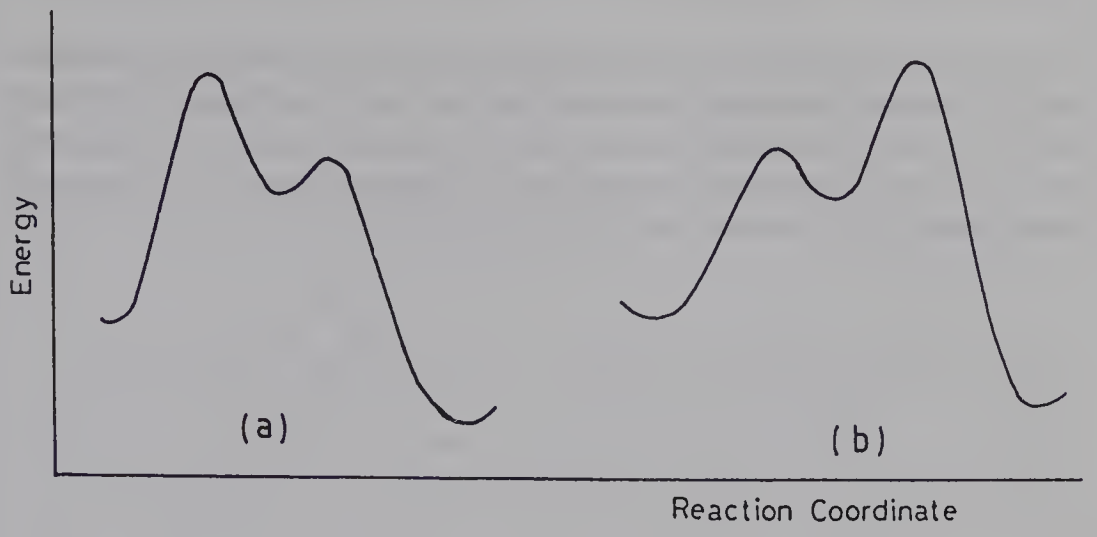
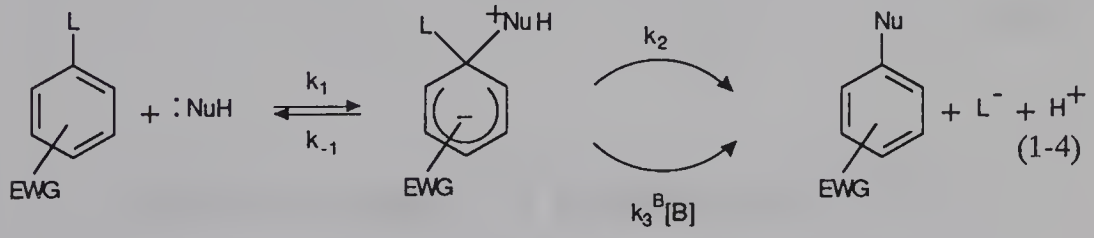


Figure 1.1. Energy diagrams for *S*NAr reactions of eqs. 1-3 and 1-4 (a) assuming rate-limiting formation or (b) rate-limiting decomposition of the intermediates 4 or 5.

by a base such as the nucleophile itself. Conversion of 5 to products can therefore occur via the uncatalyzed k_2 pathway or via the base-catalyzed k_3^B pathway. In the absence of base catalysis, energy profiles similar to those of Fig. 1.1 can be envisioned for reaction 1-4.



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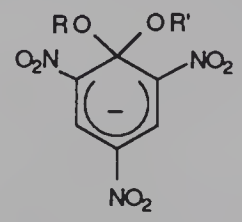
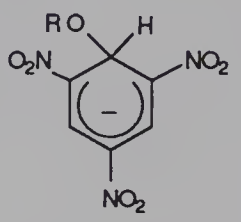
There is now much evidence that the mechanisms of eqs. 1-3 and 1-4 fit very well the great majority of intermolecular and intramolecular nucleophilic displacements involving nitro-activated aromatic and heteroaromatic substrates.[1–9] The matter has been the subject of so many reviews[1–9] that this chapter simply discusses some of the basic features that have together contributed to progress in our knowledge of these substitutions. Probably the most convincing evidence is the recent successful and unambiguous NMR identification of intermediates of type 4 along some substitution pathways of nitroaromatics.[10,11] For a long time, however, the evidence has come mainly from the structural analogy between the postulated reaction intermediates 4 and 5 and the stable σ-complexes of the type 6 and 7 identified by Jackson and Meisenheimer at the turn of the century, and described in Chapter 2.[12–18] Also, detailed kinetic studies of a great number of substitutions have revealed leaving

group and nucleophile effects as well as typical acid–base catalysis phenomena that can be understood only in terms of the intermediacy of the adducts **4** and **5**.[1–9,19–21] Finally, theoretical studies have appeared that strongly favor the formation of such structures, especially when the activation in the aromatic ring is provided by one or more NO_2 groups.[22–24]



6

R , R' = alkyl



7

Recent kinetic and theoretical studies have reinforced an early idea that the formation of the intermediates **4** or **5** may be preceded by the formation of molecular complexes—referred to as electron donor–acceptor (EDA), charge–transfer (CT), or π-complexes—which in some cases could be detectable.[3,25–34] This important question is briefly considered in this chapter in the context of medium effects, while a more comprehensive discussion is presented in Chapter 7.

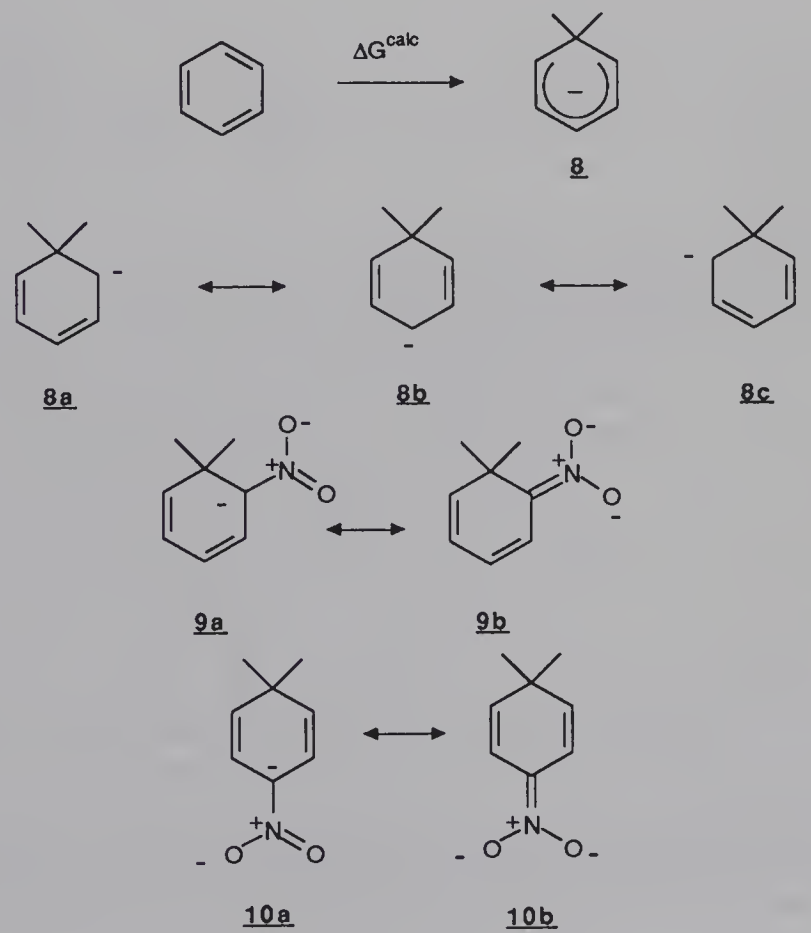
1.2 Activation of the Aromatic System by The NO_2 Group: Driving Force for S_NAr Reactions

1.2.1 Benzene and Related Arene Derivatives

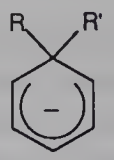
Non-electron-deficient benzene derivatives are intrinsically reluctant to participate in nucleophilic addition because of the evident repulsion between the π-electron system and the approaching nucleophile. On these grounds alone, it can be understood why the presence of electron-withdrawing groups is a primary requirement for the S_NAr reactions depicted in eqs. 1-3 and 1-4. Introduction of substituents such as NO_2 has the effect of reducing the electron

density of the benzenoid system, especially at the ortho and para carbons, thus favoring nucleophilic attack at these positions. According to Politzer and coworkers, a buildup of a positive electrostatic potential in the region of nitroaromatic C—NO_2 bonds also favors nucleophilic attack on nitroaromatic rings.[35,36] It remains therefore to be ascertained whether the process can result in the formation of relatively stable cyclohexadienyl intermediates like **4** and **5**.

In this regard, let us consider first the unsubstituted cyclohexadienyl anion **8** and the contributing resonance structures **8a**, **8b**, and **8c**. These structures do not violate any quantum mechanical principle, and they further suggest that the cyclohexadienyl anion can retain an appreciable amount of the resonance energy of the parent aromatic ring. More important, it appears that such structures will be more favored if the negative charge can be dispersed through electronegative atoms of substituents capable of conjugation in the positions ortho and para to the sp^3 carbon. In particular, introduction of a strong electron-withdrawing group such as NO_2 in these positions should lead to significant stabilization of **8**, as shown in structures **9a** ↔ **9b** and **10a** ↔ **10b**.



(1-5)



(a) R = R' = H
(b) R = H , R' = CH_3
(c) R = R' = CH_3

11

These predictions agree well with recent theoretical calculations as well as with experimental data. Dewar has calculated that formation of a cyclohexadienylide ring from a benzene ring is associated with a decrease of only 41.80 kJ/mol (ΔG^{calc} in eq. 1-5) in resonance energy; that is, **8** retains a large portion of the original stabilization energy.[37] On the other hand, *ab initio* as well as MNDO/3 calculations have confirmed that **8** may be represented by valence structures **8a** ↔ **8b** ↔ **8c**, and have indicated a greatest π-population at the para position.[22–24,38] Analysis of ^1H and ^{13}C NMR data obtained in liquid ammonia for the cyclohexadienyl anions **11**, which were produced by proton abstraction from the corresponding 1,3-dienes or 1,4-dienes, have led to similar conclusions.[23] These studies have also demonstrated that the ring system of such anions is planar, with no homoaromatic overlap* occurring.[22–24,38]

12 **8** (1-6)

Calculations of the energies of various monosubstituted cyclohexadienyl anions **12** have been made and used to derive the stabilization energies of these anions relative to substituted benzenes.[22] These energies were defined as the energy changes for symmetrical exchange reactions of the type shown in eq. 1-6. Some data are presented in Table 1.1, in which a positive value indicates a greater stability of the substituted anion (**12**) compared to the unsubstituted anion (**8**). It can be seen that all electron-withdrawing groups have a stabilizing effect, but the calculated stabilization energies are much larger for NO_2 than for other groups (e.g., CN or CO_2H). The calculations also show that the stabilization increases in the order meta << ortho < para, confirming the primary role that resonance structures like **9b** or **10b** must play in determining the stabilities of nitrocyclohexadienyl anions. In contrast, most π-donor substituents (e.g., F, OCH_3, OH, NH_2) exert a destabilizing effect in the ortho and para positions.[22]

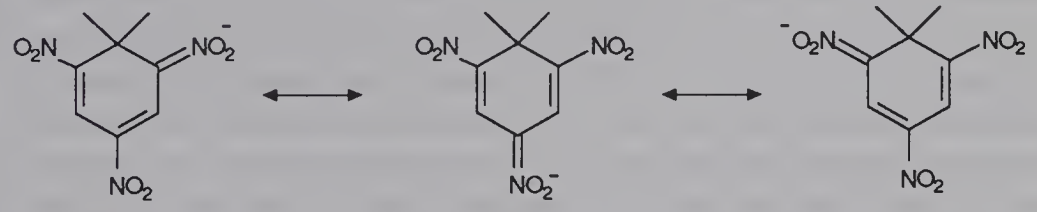
* Homoaromaticity has been found for cyclohexadienyl anions complexed by ligands such as $Cr(CO)_3$.[39]

Table 1.1. Stabilization Energies (kJ/mol) of Substituted Cyclohexadienyl Anions, as Defined by Equation 1-6[a]

	Position			
Substituent Z	1	2	3	4
H	0	0	0	0
CH_3	–5.3	–5.7	–4.6	–3.5
CN	54.1	125.8	69.6	148.6
CO_2H				120.2
NO_2	129.9	178.9	87.5	201.8
F	29	10.4	27.9	–6.6
OCH_3	43.3	–12.5	10	–31.2
OH	23.4	–13.3	16.5	–37.1
NH_2	15.8	–47,6	–9.5	–78.8

[a]Reproduced with permission from Birch, A. J.; Hinde, A. L.; Radom, L. *J. Am. Chem. Soc.* **1980**, *102*, 6430.

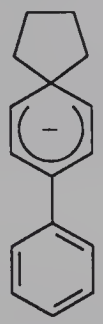
The stabilization energy brought about by the introduction of several activating groups in **8** has not yet been estimated via eq. 1-6. Other calculations have been carried out, however, which leave no doubt that the presence of a second and third NO_2 group in the ortho and/or para position(s) results in an increased stabilization of the anion[8,15,40–43] In the case of 2,4,6-trinitro derivatives, the calculations also predict that significantly more charge is located on the para-NO_2 group than on an ortho-NO_2 group; that is, the resonance structure **13b** is favored relative to **13a** and **13c**.[41–43]



13a **13b** **13c**

For structural reasons, to be discussed later in this chapter, many nitroarene–base interactions cannot proceed further than the addition step, providing opportunity for formation of potentially stable σ-adducts.[8,14–18] The trinitro adducts **6** and **7** are prototype examples, but many other trinitrobenzene

as well as dinitrobenzene adducts have been structurally characterized (Chapter 2). Because the stability of such adducts strongly decreases as the number of NO_2 groups in the benzene ring is reduced, no firm identification of simple mononitrobenzene adducts has been reported so far.[8,15–18] However, increasing the possibility of delocalization of the negative charge through an exocyclic phenyl ring has allowed the NMR characterization of the spiro adducts **14** and **15**, which contain no NO_2 groups. They are formed from the reaction of biphenylylchloroalkanes with alkali metals in tetrahydrofuran (THF) at −70°C.[44,45] Clearly, the existence and stability order of firmly identified σ-adducts reinforces the view provided by molecular orbital (MO) calculations, which refer to isolated molecules in the gas phase, that cyclohexadienyl intermediates can form in actual S_NAr reactions of nitrobenzenes.



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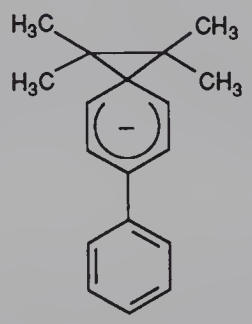


15

Regarding the rates of S_NAr reactions, Miller has suggested that in many substitutions the two transition states for nucleophilic addition and nucleofuge expulsion are probably more similar in energy to the intermediates (i.e., **4** or **5**) than to either reactants or products.[3] On these grounds, the overall rates of substitution should be reflected in the stabilities of the intermediates, and rate data for homogeneous sets of substitutions should be successfully interpreted by consideration of the effects of substituents on the stability of these intermediates.[3] In particular, the rates of substitutions involving rate-determining addition of the nucleophile should increase with increasing substituent constant. Figure 1.2 shows that such correlations have actually been observed in some systems in which the para substituent was varied.[3] A point of importance in Fig. 1.2 is that the Hammett correlation requires the use of the σ^--constant for such substituents such as NO_2, CO_2R, and COR, which interact conjugatively with the reaction center and thus serve to absorb the negative charge, as depicted in **10b**. Figure 1.2 also shows that except for NO and SO_2CF_3, NO_2 is the most activating para substituent in the reactions. The greater activating

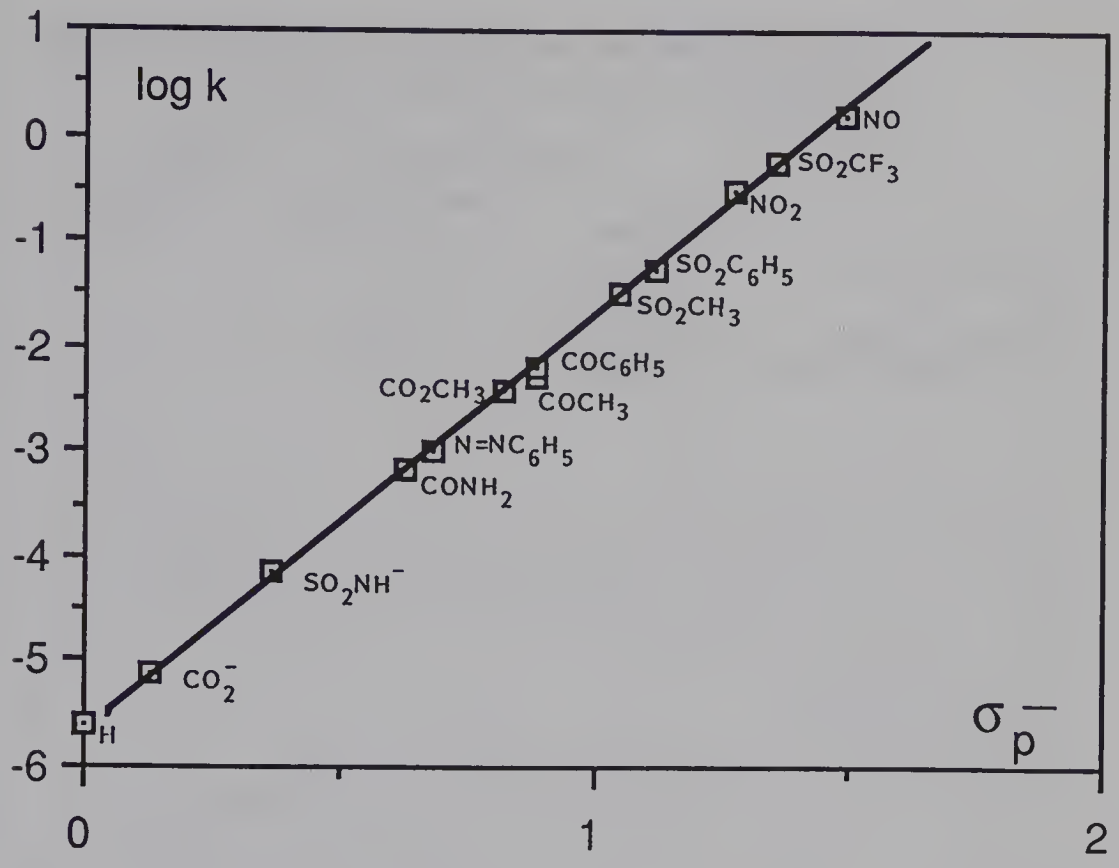


Figure 1.2. Hammett correlation for the reactions of 1-chloro-2-nitro-4-Z-substituted-benzenes with methoxide ion in methanol at 50°C ($\rho = 3.90$; k in liters per mole per second). (Data reproduced with permission from Miller, J. "*Aromatic Nucleophilic Substitution*", Elsevier: Amsterdam, 1968. The point for Z = SO_2CF_3 is taken from Shein, S. M.; Ignatov, V. A.; Kozorez, L. A.; Chervatyuk, L. F. *Zh. Obshch. Khim.* **1967**, *37*, 114.)

power of an SO_2CF_3 relative to an NO_2 group in the benzene series is now well substantiated.[8,17,46–49] Other work indicates that the positively charged N_2^+ group is more activating than NO_2.[3]

With the same reasoning, Table 1.1 predicts that substitutions involving *o*-nitro-activated benzenes should proceed at lower rates than those involving *p*-nitro isomers. Experimental data do not always fit this prediction, since there are many examples of a greater activation by an *o*-NO_2 than by a *p*-NO_2 group.[1,3,7] This occurs because the reactivity of *o*-nitro derivatives is a function of other variables such as steric factors, polarizability, field and electrostatic effects, and hydrogen bonding (Section 1.4).[1,3,7,8]

Neglecting all other influences such as steric factors associated with the presence of ortho substituents and assuming some additivity in the stabilization energies of the intermediates as listed in Table 1.1, the reactivity order:

Table 1.2. Effect of Position and Number of NO_2 Groups on the Rates of S_NAr Reactions in the Benzene Series

	Nucleophile, k ($l\ mol^{-1}\ s^{-1}$ at t = 25°C)		
Substrate	CH_3O^- in CH_3OH[a,b]	SO_3^{2-} in H_2O/ C_2H_5OH, 60:40[a,c]	Aniline in C_2H_5OH[d]
1-Fluoro-2-nitrobenzene	1.24×10^{-4}	1.04×10^{-5}	
1-Fluoro-4-nitrobenzene	1.79×10^{-4}	6.77×10^{-5}	
1-Fluoro-3,5-dinitrobenzene	2.57×10^{-4}	1.02×10^{-3}	
1-Fluoro-2,6-dinitrobenzene	5.53		2.35×10^{-3}
1-Fluoro-2,4-dinitrobenzene	15.40	3.21	7.20×10^{-3}
1-Fluoro-2,4,6-trinitrobenzene	$\sim 10^4$		188

[a]Bevan, C. W. L.; Foley, A. J.; Hirst, J.; Uwamu, W. O. *J. Chem. Soc. B,* **1970**, 794.

[b]Murto, J.; Nummela, L.; *26*, 1351.
Hyvönen, M. L.; Murto, M. L.
Acta Chem. Scand. **1972**

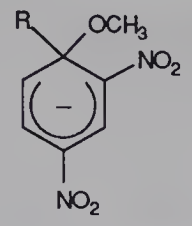
[c]Adeniran, M. A.; Bevan, C. W. L.; Hirst, J. *J. Chem. Soc.* **1963**, 5868.

[d]Calculated at t = 25°C from Parker, R. E.; Read, T. O. *J. Chem. Soc.* **1962**, 3149.

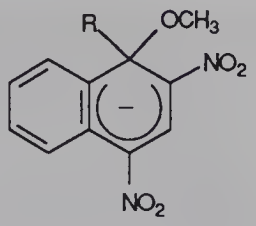
3-nitro < 3,5-dinitro ≈ 2- or 4-nitro < 2,4- or 2,6-dinitro < 2,4,6-trinitro

is expected in rate studies involving comparable systems. Data given in Table 1.2 show that qualitative agreement with experiment is found. Interestingly, activation by two *m*-NO_2 groups is in many cases sufficient to allow clean S_NAr processes to occur.[50] Contrasting with this behavior, compounds with only one meta-NO_2 group are in general too weakly activated for S_NAr processes, and they have a high tendency to react by alternative pathways.[1,3,8]

Extension of the aromatic system through benzoannelation enhances the stability of a cyclohexadienyl anion, mainly because of an increased delocalization capability of the negative charge.[8,15–17,37,51] Naphthalene σ-adducts like **17a** and **17b** are thermodynamically more stable than the benzene analogues **16a** and **16b**.[52,53] Accordingly, naphthalene derivatives are more prone to S_NAr substitution than similarly activated benzenes; for example, 1-chloro-2,4-dinitronaphthalene reacts 10–100 times faster than 1-chloro-2,4-dinitrobenzene with such common nucleophiles as CH_3O^- or aniline, even though there is evidence that the proximity of the peri position may sterically affect the reactions.[1] On the other hand, the activating effects of NO_2 groups located at the 5-, 6-, 7-, and 8-positions in the second aromatic ring are considerably less than those of NO_2 groups directly bonded to the ring in which nucleophilic substitution takes place.[54]



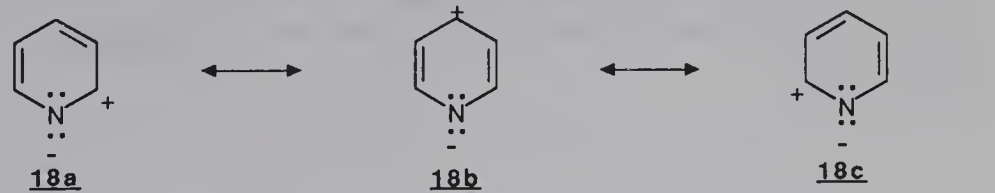
16 (a) R = H ; (b) R = OCH_3



17

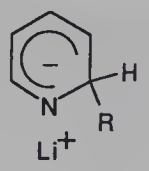
1.2.2 Pyridine and Related Aza-aromatics

Pyridine and other fully aromatic nitrogen heterocycles—often considered to be aza-substituted arenes—are π-deficient.[8,9] Replacement of a ring carbon in an arene system by a more electronegative nitrogen atom results in a greater electron density on that atom, with a concomitant reduction in electron density on the remaining carbon atoms. This deficiency favors nucleophilic attack, and therefore nucleophilic substitution of a suitable leaving group, especially at the α- and γ-positions to the heteroatom (resonance structures **18a–c**). Concomitantly, the formation of the corresponding aza-cyclohexadienyl intermediates **19** and **20** is facilitated by the somewhat lower aromaticity of the parent substrate and the ability of the nitrogen atom to stabilize such adducts by accommodating the negative charge, as shown in **19b** and **20b**. Contrasting with the failure to form **8** from benzene, the aza σ-adducts **21a** and **21b** have been directly obtained on treatment of pyridine with butyllithium in ether or in hexane and phenyllithium in *N,N,N′,N′*-tetramethylethylenediamine, respectively.[55–57] Both MNDO/3 calculations and NMR studies indicate that the ring systems of the 2-pyridyl anion **19** and the 4-pyridyl anion **20** are planar, showing that introduction of the aza functionality does not affect the geometry of the cyclohexadienyl anion.[58,59]



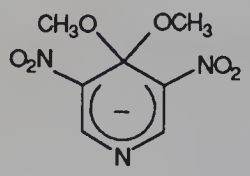
18a 18b 18c

19a 19b 20a 20b



21a R = n-C_4H_9

21b R = C_6H_5



22

The activating effect of the aza group at both the 2- and 4-positions lies not far below that of an NO_2 group.[9] This is demonstrated in Table 1-3, which compares some rate data obtained for a few typical pyridine substrates with those for the benzene analogues.

Because of the intrinsic activation by the aza group, introduction of one or two NO_2 groups in the 3- and/or 5- positions yields nitropyridines or dinitropyridines that are almost as reactive as the analogous dinitrobenzenes or trinitrobenzenes (Table 1.3).[66–70] A relevant observation is that stable σ-adducts of dinitropyridines (e.g., **22**) have a thermodynamic stability close to that of the trinitrobenzene analogues.[17,71]

Further evidence for the strong activating effect of the aza group is given by the observation that 1,3-diazines, such as 4-chloropyrimidine or 2-chloropyrimidine, show an S_NAr reactivity comparable to that of 2-chloro-5-nitropyridine and 2-chloro-3-nitropyridine.[9,69]

Activation at the α- and γ- positions in the pyridine ring is increased on conversion of the nitrogen atom into an N^+—R or an N^+—O^- group, both functionalities being much more activating than NO_2.[3,9,72] However, nitropyridines are so weakly basic ($pK_a < 0$) that quaternization of the aza group due to protonation does not commonly occur under the experimental conditions required to achieve most S_NAr substitutions of these derivatives.[9]

Treatment of nitropyridines or nitropyrimidines and related benzoannelated derivatives with strong bases may result in abnormal nucleophilic substitution pathways involving ring opening and ring closure reactions, that is, the S_N (ANRORC) mechanism.[73-76] These particular systems are considered in Chapter 8.

1.2.3 Five-Membered Ring Heterocycles

Five-membered ring heterocycles such as pyrrole, furan, thiophene, and selenophene possess a π-excessive character. This implies a low reactivity toward nucleophilic reagents, comparable to that of benzene. Accordingly,

Table 1.3. Comparison of the Activating Effects of the NO_2 and Aza Groups in S_NAr Reactions

Substrate	Nucleophile	t (°C)	Solvent	k ($l\ mol^{-1}\ s^{-1}$)	Ref.
4-Chloropyridine	CH_3O^-	50	CH_3OH	8.91×10^{-7}	3
4-Chloropyridine *N*-oxide				$1. \times 10^{-3}$	4
4-Chloro-1-methylpyridinium cation				5080.	3
1-Chloro-4-nitrobenzene				8.47×10^{-6}	3
2-Chloropyridine	CH_3O^-	50	CH_3OH	3.31×10^{-8}	3
2-Chloropyridine *N*-oxide				6.40×10^{-4}	3
1-Chloro-2-nitrobenzene				2.52×10^{-6}	3
4-Nitropyridine	CH_3O^-	25	CH_3OH	4.50×10^{-4}	66
4-Nitropyridine *N*-oxide				3.82×10^{-2}	67
1,4-Dinitrobenzene				3.70×10^{-4}	60
2-Nitropyridine	CH_3O^-	25	CH_3OH	1.05×10^{-5}	66
1,2-Dinitrobenzene				1.40×10^{-4}	60
2-Chloro-5-nitropyridine	CH_3O^-	20	CH_3OH	1.09×10^{-2}	61
	Piperidine	55	C_2H_5OH	2.82×10^{-2}	62
2-Chloro-3-nitropyridine	Piperidine	55	C_2H_5OH	1.84×10^{-2}	62
4-Chloropyrimidine	Piperidine	55	C_2H_5OH	9.55×10^{-3}	64
2-Chloropyrimidine	Piperidine	55	C_2H_5OH	3.14×10^{-3}	63
1-Chloro-2,4-dinitrobenzene	CH_3O^-	20	CH_3OH	1.89×10^{-2}	61
	Piperidine	55	C_2H_5OH	8×10^{-2}	3,65
2-Chloro-3,5-dinitropyridine	OH^-	25	H_2O	0.292	68
	Alanine	20		26.6	69
4-Chloro-3,5-dinitropyridine	Alanine	20		86.5	69
2-Chloro-5-nitropyrimidine	Alanine	20		5.43	69
1-Chloro-2,4,6-trinitrobenzene	OH^-	25		0.506	68

only substrates bearing suitably located electron-withdrawing groups such as NO_2 undergo facile S_NAr substitutions in these compounds. In accordance with simple theory, these substitutions proceed in general more readily at the α than at the β-position to the heteroatom.[9]

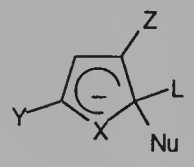
The effectiveness of S_NAr reactions at the α-position implies the formation

of hetarenide intermediates such as **X-23**, where Y and Z denote electron-withdrawing groups (e.g., NO_2). Compared to benzene systems, the lower aromaticity of the five-membered rings and the ability of heteroatoms such as O, S, and Se to accommodate the negative charge are two factors that favor the formation of **X-23**.[8] Another favorable factor is that attainment of the tetrahedral geometry at the reaction site in a σ-adduct involves much less bond strain in five-membered than in six-membered rings.[4,5,77,78] In agreement with these views, MNDO calculations suggest a much greater stability (about 50 kJ/mol) of the dinitrothiophene anion **X-23** (X = S, Y = Z = NO_2) than of the dinitrobenzene analogue **24**.[79]

The conclusions reached by MNDO calculations are confirmed by measurements of the stabilities of the firmly characterized dinitro adducts **X-25** and **X-26**.[17] For these substrates, the stability order is:

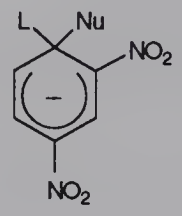
furan > selenophene > thiophene >> benzene ≥ pyrrole

in agreement with the expected influence of the heteroatom on the tendency to complexation of the heterocycles. Going from X = O to Se or S to N—R reduces the electron-withdrawing influence of the heteroatom and increases the aromatic character of the reactant molecules, thus decreasing the stability and the ease of formation of the adduct. The effect is especially important for the formation of the pyrrole adducts, which are considerably less stable than their furan, selenophene or thiophene analogues.[17]



X23

X = O , S , Se , N-CH_3



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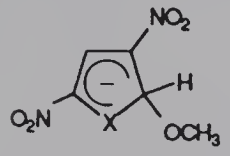
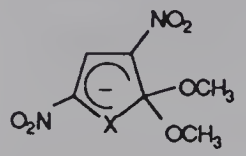


X25



X26

Table 1.4 shows that the S_NAr reactivities of these heterocycles parallel nicely the order of stability found for the corresponding σ-adducts. Thus, the rate constants for nucleophilic displacement of an NO_2 group from 2,5-

Table 1.4. Reactivity of Nitro-Activated Five-Membered Ring Heterocycles in S_NAr Reactions

Substrate	Nucleophile	t (°C)	Solvent	k (l mol^{-1} s^{-1})	Ref.
2,5-Dinitrofuran	Piperidine	25	CH_3CN	0.57	80
	4-CH_3-$C_6H_4S^-$		CH_3OH	4400	81
2,5-Dinitrothiophene	Piperidine		CH_3CN	1.06×10^{-3}	80
	4-CH_3-$C_6H_4S^-$		CH_3OH	420	81
2,5-Dinitro-1-methylpyrrole	Piperidine		CH_3CN	2.4×10^{-7}	80
	4-CH_3-$C_6H_4S^-$		CH_3OH	2.60	81
	CH_3O^-		CH_3OH	1.36×10^{-3}	82
1,4-Dinitrobenzene	Piperidine		CH_3CN	2.3×10^{-6}	80
	4-CH_3-$C_6H_4S^-$		CH_3OH	2.24×10^{-2}	81
	CH_3O^-		CH_3OH	1.7×10^{-4}	82
2-Chloro-5-nitro-1-methylpyrrole	CH_3O^-	25	CH_3OH	1.26×10^{-4}	83
2-Bromo-5-nitro-1-methylpyrrole				6.97×10^{-5}	83
1-Chloro-4-nitrobenzene				3.18×10^{-7}	83
1-Bromo-4-nitrobenzene				2.67×10^{-7}	83
2-Chloro-5-nitrothiophene	$C_6H_5S^-$	20	CH_3OH	0.126	95
		50	CH_3OH	1.31[a]	95
2-Bromo-5-nitrothiophene	Piperidine	20	C_2H_5OH	2.58×10^{-5}	87
	$C_6H_5S^-$		CH_3OH	0.136	95
2-Bromo-3-nitrothiophene	Piperidine	20	C_2H_5OH	1.29×10^{-4}	87
	$C_6H_5S^-$		CH_3OH	0.116	95
3-Bromo-2-nitrothiophene	$C_6H_5S^-$		CH_3OH	0.234	95
2-Bromo-3,5-dinitrothiophene	Piperidine	20	C_2H_5OH	2.95	84
2-Bromo-5-nitroselenophene	Piperidine	20	C_2H_5OH	1.21×10^{-4}	86
2-Bromo-3-nitroselenophene				1.16×10^{-3}	85
2-Bromo-3,5-dinitroselenophene				16.5	85
2-Chloro-5-nitrothiazole	$C_6H_5S^-$	50	CH_3OH	850	96

[a] Value calculated from data in ref. 95.

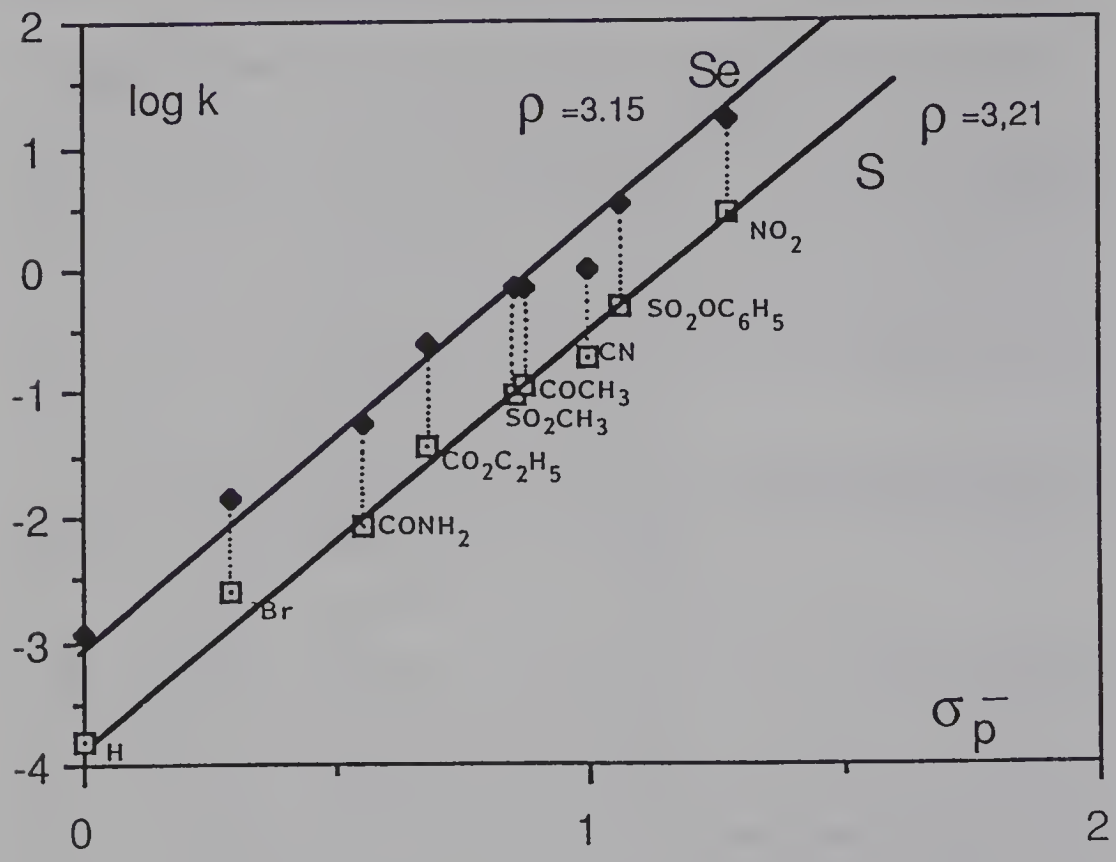


Figure 1.3. Hammett correlations for the reactions of various 2-bromo-3-nitro-5-Y-substituted thiophenes and selenophenes with piperidine in ethanol at 20°C (*k* in liters per mole per second). (Data reproduced with permission from Dell'Erba, C.; Spinelli, D. *Tetrahedron*, **1965**, *21*, 1061, and Dell'Erba, C.; Guareschi, A.; Spinelli, D. *J. Heterocycl. Chem.* **1967**, *4*, 438.)

dinitrofuran, 2,5-dinitrothiophene, and 2,5-dinitro-1-methylpyrrole by piperidine and *p*-toluenethiolate ion decrease in the order O > S >> N—R.[80,81] Depending upon the nucleophile, nitro-activated pyrroles react more rapidly or more slowly than the corresponding nitrobenzenes.[80–83] Also illustrated is the greater reactivity of nitroselenophenes compared to nitrothiophenes.[84–87]

Changes in reactivity caused by variations in the nature of the activating substituents have been in many cases successfully correlated by Hammett relationships.[85,88–91] Figure 1.3 shows the Hammett plots obtained in correlating the rates of piperidino-debromination of various 2-bromo-3-nitro-5-Y-thiophenes and 2-bromo-3-nitro-5-Y-selenophenes in ethanol (eqs. 1-7a and 1-7b).[84,85] The high positive ρ values (≈3.2) found for these reactions, together with the necessity of using σ_p^- instead of σ_p constants in the correlations, indicate that the transfer of the negative charge has made notable progress in the transition states, suggesting a complexlike structure.[90] Significantly, the Hammett equation was also found to fit changes in reactivity brought about by

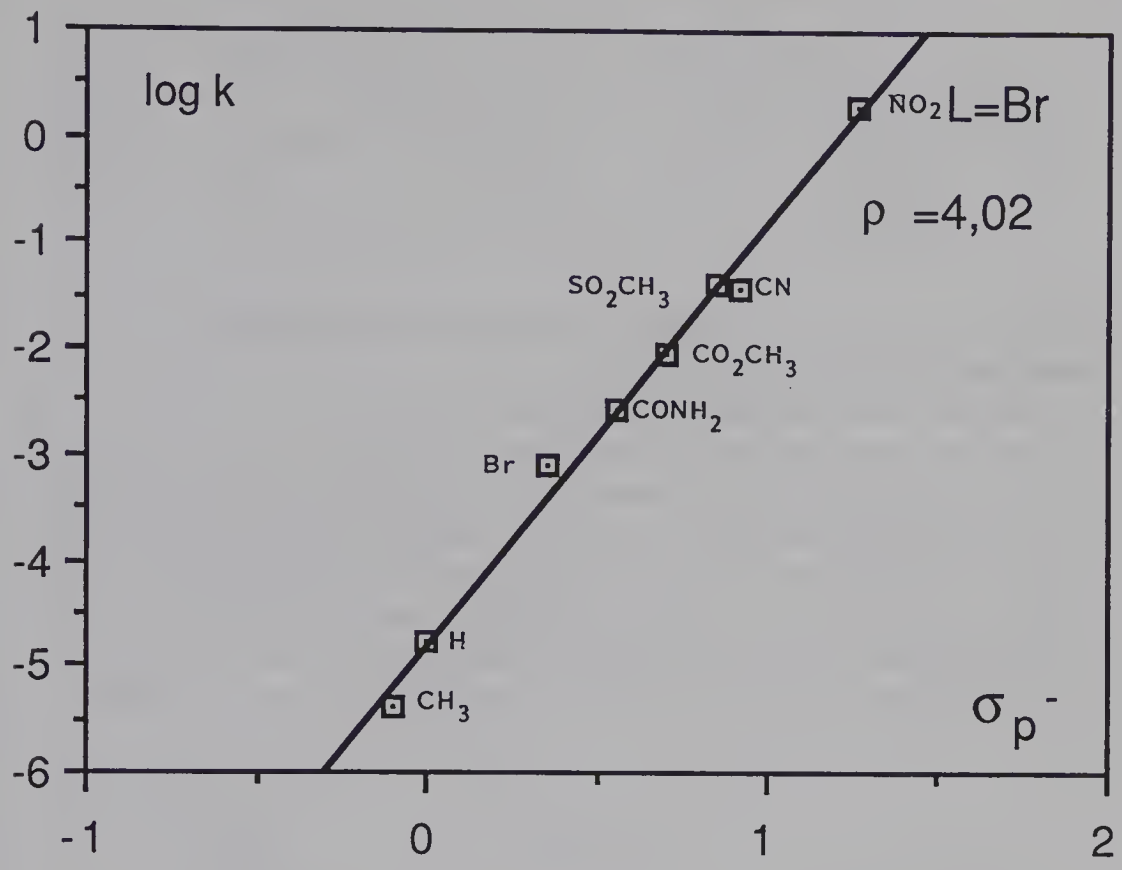
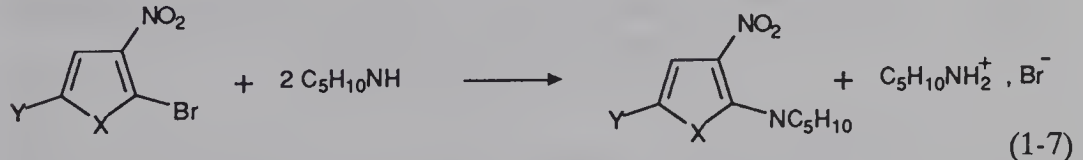


Figure 1.4. Hammett correlation for the reactions of various 2-bromo-3-Z-5-nitrothiophenes with piperidine in methanol at 20°C; *k* in liters per mole per second. (Data reproduced with permission from Spinelli, D.; Consiglio, G.; Noto, R.; Corrao, A. *J. Chem. Soc., Perkin Trans. 2,* **1975**, 620.)

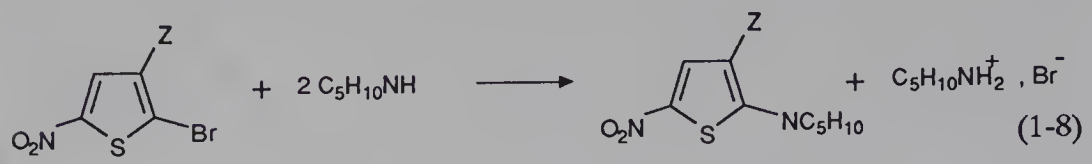
variations in the nature of the ortho-like Z substituents.[89,91] Figure 1.4 shows the Hammett plot for substitution of various 2-bromo-3-Z-5-nitrothiophenes with piperidine in methanol (eq. 1-8).[89,91] The existence of such linear free energy ortho correlations is peculiar to five-membered ring heterocycles, where steric effects of substituents ortho to the site of the nucleophilic attack are minimized. Of further interest is that the ρ values for the reactions shown in eq. 1-8 (~ 4.02) are higher than those for the reactions shown in eqs. 1-7a and 1-7b, indicating that substituents exert a higher electronic effect on the reaction center in the ortho-like rather than in the para-like position. This



(1-7)

(a) X = S ; (b) X = Se

Y = H, Br, $CONH_2$, $CO_2C_2H_5$, $COCH_3$, SO_2CH_3, CN, $SO_2OC_6H_5$, NO_2

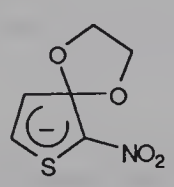


(1-8)

Z = CH_3, H, Br, $CONH_2$, CO_2CH_3, SO_2CH_3, CN, NO_2

behavior which has been termed the "hyperortho relationship," has been studied only in the thiophene series.[92]

Although the susceptibility to nucleophilic attack is weaker at the β- than at the α position to the heteroatom, identification of the stable σ-adducts **27** and **28** supports the idea that hetarenide intermediates of type **29** may form in nucleophilic substitutions of nitro-activated five-membered ring heterocycles bearing a leaving group in the 3-position.[93,94] Table 1.4 compares the reactivity of 2-nitro-3-bromothiophene with that of its 3-nitro-2-bromo and 5-nitro-2-bromo isomers toward benzenethiolate ion in methanol.[95] It is noteworthy that substitutions of 3,4-dinitrothiophenes often proceed abnormally (see Chapter 5, p. 306).



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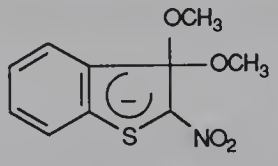

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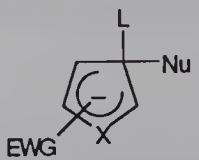


29

Introduction of a second electronegative heteroatom into five-membered ring systems may result in a large increase in the tendency toward nucleophilic substitution, especially if there is also activation by a suitably located NO_2 group.[3,96,97] Thus, it is shown in Table 1.4 that 2-chloro-5-nitrothiazole is about 650 times more reactive than 2-chloro-5-nitrothiophene toward benzenethiolate anion.[95,96] Nitropyrazoles and nitroimidazoles also have a high reactivity, but the reactions are often complicated by side processes.[98,99]

1.2.4 Nitrobenzofurazans, Nitrobenzofuroxans, and Related Systems

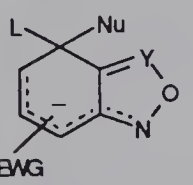
2,1,3-Benzoxadiazoles and related *N*-oxides, commonly known as benzofurazans and benzofuroxans, respectively,[100] are interesting 10- π- electron heteroaromatic ring systems which have a very high tendency toward S_NAr

Table 1.5. Reactivity of Some Nitrobenzofurazans in S_NAr Reactions[a]

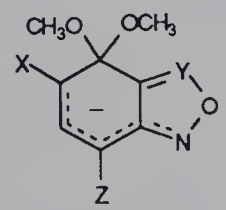
Substrate	Nucleophile	Solvent	k (l mol^{-1} s^{-1})	Ref.
4-Chlorobenzofurazan	CH_3O^-	CH_3OH	2×10^{-8}	102
4-Chloro-5-nitrobenzofurazan			10.5	102
5-Chloro-4-nitrobenzofurazan			66	102
7-Fluoro-4-nitrobenzofurazan	CH_3O^-	CH_3OH	3500	104a
7-Chloro-4-nitrobenzofurazan	CH_3O^-		7.7	104a
	$C_6H_5S^-$		87.4	104b
7-Bromo-4-nitrobenzofurazan	CH_3O^-		2	104a
7-Chloro-4,6-dinitrobenzofurazan	H_2O	H_2O	2.18×10^{-4} [b]	106
7-Methoxy-4,6-dinitrobenzofurazan	H_2O		1.46×10^{-2} [b]	106
1-Chloro-2,4,6-trinitrobenzene	CH_3O^-	CH_3OH	17	176b
	H_2O	H_2O	6.44×10^{-8} [b]	68
1-Methoxy-2,4,6-trinitrobenzene	H_2O	H_2O	1.99×10^{-6} [b]	68

[a] At 25°C.
[b] In reciprocal seconds (s^{-1}).

substitutions.[101,102] The feasibility of S_NAr processes at the 4- or 7-position via intermediates of type **30** is strongly supported by the successful identification of mononitro adducts of type **31** and **32**, which all have a stability comparable to that of trinitrobenzene analogues.[17,102–104a] In accordance with this result, rates of substitution of 7-L-4-nitrobenzofurazans and 4-L-5-nitrobenzofurazans, and of the analogous benzofuroxans with CH_3O^- ion are similar and compare well with those of the corresponding picryl derivatives (Table 1.5). 5-Halo-4-nitrobenzofurazans also exhibit a high susceptibility to S_NAr methoxydehalogenation.



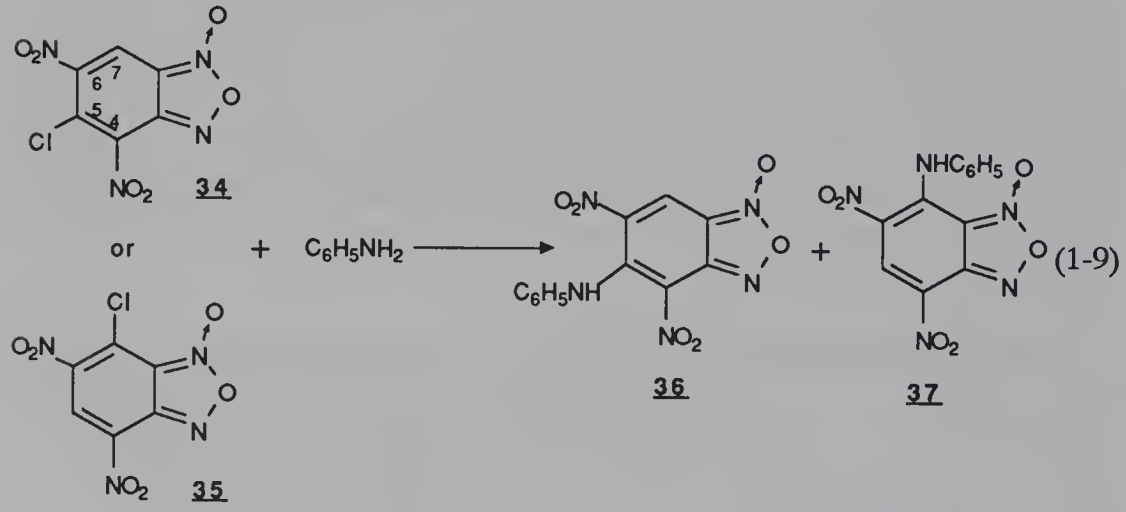
30 Y = N, N→O



31a X = H, Z = NO_2, Y = N
31b X = H, Z = NO_2, Y = N→O
32 X = NO_2, Z = H, Y = N
33 X = Z = NO_2, Y = N

Introduction of a second NO_2 group at a suitable position in the carbocyclic ring results in an enormous increase in the stability of the σ-adducts; for example, **33** is 10^{10} times more stable than **31** or **32**.[105] Not unexpectedly, there is a parallel increase in the S_NAr reactivity, as illustrated by the finding that 7-chloro-4,6-dinitrobenzofurazan and 7-methoxy-4,6-dinitrobenzofurazan hydrolyze very rapidly upon reaction with water in aqueous acid solutions: $kH_2O = 2.18 \times 10^{-4}\ s^{-1}$ and $kH_2O = 1.46 \times 10^{-2}\ s^{-1}$, respectively.[106] Such a reaction is negligible with mononitrobenzofurazan analogues and almost so with 1-chloro- and 1-methoxy-2,4,6-trinitrobenzenes.[68]

The high S_NAr reactivity of the above-mentioned compounds is a reflection of the relatively low aromaticity of the benzofurazan and benzofuroxan systems and the powerful electron-withdrawing effect of the annelated furazan and furoxan rings. The finding that 4-halobenzofurazans react with CH_3O^- at rates similar to those found for 1-L-4-nitrobenzenes is illustrative in this regard (Table 1.5). There are possible complications, however, since cine substitutions can in some instances compete with the S_NAr pathways.[107] The ability of nitrobenzofuroxans to undergo specific rearrangements is also a source of complications.[100,108,109] Their importance is illustrated in eq. 1-9, which shows that S_NAr substitutions of 5-chloro-4,6-dinitrobenzofuroxan (**34**) and 7-chloro-4,6-dinitrobenzofuroxan (**35**), with aniline give the same isomeric mixture of 5-phenylamino-4,6-dinitrobenzofuroxan (**36**) and 7-phenylamino-4,6-dinitrobenzofuroxan (**37**), respectively, and not **36** or **37**.[110] There is also a possibility of nucleophilic attack at the annelated moiety with destruction of the heterocyclic system.[111]



Substitution of O for S and Se in the heterocyclic moiety reduces the electron-withdrawing influence of the heteroatom and increases the aromatic

character of the molecules. Accordingly, 2,1,3-benzothiadiazoles and 2,1,3-benzoselenadiazoles have a lower S_NAr reactivity than analogous benzofurazans.[102,112]

1.3 Leaving Group and Nucleophile Effects

Understanding of the effect of changing the leaving group and the nature of the nucleophilic reagent on the reactivity of nitroaromatics has played a central role in the formulation of the S_NAr mechanism. An obvious relationship between these two variables notwithstanding, distinctive features pertaining to each of them are more appropriately emphasized in separate discussions.

1.3.1 The Influence of the Leaving Group

1.3.1.1 Halogen Nucleofugality in Nitroaryl Halides

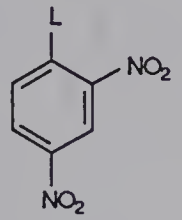
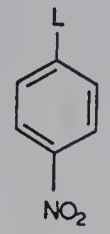
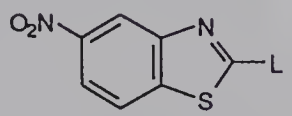
With most anionic and neutral reagents, fluorine in nitro-activated aromatic and heteroaromatic halides is a much better leaving group than other halogens, the order of reactivity being commonly F >> Cl ~ Br > I.[1,3,9] This is shown in Table 1.6, which summarizes data for reactions of different nitro-activated halides with various nucleophiles in different solvents. Relevant data are also presented in Tables 1.5 and 1.7. However, the mobility pattern is clearly dependent on the nature of the nucleophile, and the opposite reactivity order (viz., I > Br > Cl > F) is found to prevail in some instances. Typical examples are the reactions of 2,4-dinitrohalobenzenes with highly polarizable nucleophiles like SCN^-, I^-, or $C_6H_5NHCH_3$ (see Table 1.6).[3,8,113]

These variations in halogen nucleofugality are one of the observations that led initially to the formulation of the S_NAr substitutions in terms of eqs. 1-3 and 1-4. The order F > Cl ~ Br > I implies that C—L bond cleavage is not involved in the rate-limiting step.[1] This rules out a concerted mechanism but can be readily understood if the addition of the nucleophile is rate determining in the reactions shown in eqs. 1-3 and 1-4. On the other hand, these equations

Table 1.6. Halogen Nucleofugality in S_NAr Reactions of Halonitroaromatics and Halonitroheteroaromatics

Nitro compounds	L	Nu	t (°C)	Solvent	k (l mol^{-1} s^{-1})	Ref.
1-L-2,4-dinitrobenzenes	F	OH^-	25	H_2O	0.12	149
	Cl				1.2×10^{-4}	
	Br				9.9×10^{-5}	
	I				4.6×10^{-5}	
	F	$C_6H_5O^-$	25	H_2O	0.59	149
	Cl				1×10^{-3}	
	Br				1.5×10^{-3}	
	I				5×10^{-4}	
	F	Piperidine	25	H_2O	9.9	149
	Cl				4.1×10^{-2}	
	Br				4.7×10^{-2}	
	I				1.8×10^{-2}	
	F	Aniline	50	C_2H_5OH	1.68×10^{-2}	158
	Cl				2.69×10^{-4}	
	Br				4.05×10^{-4}	
	I				1.31×10^{-4}	
	F	*N*-Methylaniline	67	C_2H_5OH	1.02×10^{-4}	113
	Cl				1.03×10^{-4}	
	Br				2.49×10^{-4}	
1-L-4-Nitrobenzenes	F	$C_6H_5O^-$	25	DMSO	0.52	114b
	Cl				2.10^{-3}	
	Br				3.4×10^{-3}	
	I				9.5×10^{-4}	
	F	Phenothiazinide	25	DMSO	0.941	144
	Cl	anion			9.95×10^{-3}	
	Br				9.76×10^{-3}	
2-L-5-Nitrothiophenes	F	$C_6H_5S^-$	20	CH_3OH	10.1	92
	Cl				0.126	
	Br				0.136	
	I				0.088	
7-L-4-Nitrobenzofurazans	F	CH_3O^-	25	CH_3OH	3500	104
	Cl				7.7	
	Br				2	

Table 1.7. Comparison of the Reactivity of Thiophenoxide and Methoxide Anions in S_NAr Substitutions in Methanol[a,b]

Anion	L	$k^{CH_3O^-}$	$k_L^{CH_3O^-}/k_I^{CH_3O^-}$[c]	$k^{C_6H_5S^-}$	$k_L^{C_6H_5S^-}/k_I^{C_6H_5S^-}$[c]	$k^{C_6H_5S^-}/k^{CH_3O^-}$
	F	18	3100	780	27	43
	C_6H_5O	5.1×10^{-3}	0.88	0.29	0.01	56.9
	Cl	3×10^{-2}	5.20	21	0.7	700
	Br	2×10^{-2}	3.4	44	1.5	2200
	NO_2	15	2590	3.9×10^{4}	1345	2600
	S-C_6H_4-NO_2-4	2.6×10^{-3}	0.45	8.1	0.28	3110
	I	5.8×10^{-3}	1	29	1	5000
	F	1.7×10^{-4}	1300	2.2×10^{-4}	3.5	1.3
	Cl	3.8×10^{-7}	3	2.1×10^{-5}	0.3	55
	Br	2.6×10^{-7}	2	5.1×10^{-5}	0.8	200
	I	1.3×10^{-7}	1	6.3×10^{-5}	1	480
	F	140	4800	120	124	0.9
	Cl	0.27	9	1.7	1.7	6
	Br	0.15	5	2.5	2.5	17
	I	0.029	1	0.97	1	34

[a] Data at $t = 25°C$ reproduced with permission from Bartoli, G.; Todesco, P. E. *Acc. Chem. Res.* **1977**, *10*, 125.

[b] Values of k in liters per mole per second (l mol^{-1} s^{-1}).

[c] Ratios calculated by reference to the reactivity of the iodo derivative.

can also account for the order I > Br > Cl > F, provided the decomposition rather than the formation of the intermediates **4** or **5** be rate limiting. In this instance, there is extensive rupture of the bond of the leaving group in the transition state, so that a sequence similar to that encountered in saturated aliphatic S_N2 reactions may be expected on the basis of carbon–halogen bond strengths.[1,3,8]

The strong polarization of the $C^{\delta+}$—$F^{\delta-}$ bond compared to other carbon–halogen bonds is a major factor accounting for the frequently observed higher reactivity of nitroaryl fluorides compared with similarly activated halides.[1,3,114] Another important factor is the so-called α-substituent or *ipso* effect, which has been recognized by Miller and confirmed by MO calculations.[3,22] It is known that groups with strong –I effects stabilize the intermediate σ-complex when attached to the sp^3-hybridized carbon. Table 1.1 shows that this stabilization is relatively large for a fluorine atom. Since a transition state lies somewhere between reactants and products, this α-effect must contribute to some extent to stabilizing the transition state for bond formation to the nucleophile, thus enhancing the reactivity of nitroaryl fluorides relative to other halides.[3] A third factor is the low polarizability of F compared to Cl, Br, or I, which minimizes the repulsive interactions with the incoming nucleophile at least when the reagent is a small, "hard" anion with a localized negative charge.[114] For"soft", more polarizable anions, bond formation can occur at a larger distance from the electrophilic center, so that repulsion effects are less discriminating between the various halogens (see Section 1.3.2.2; Table 1.7).[114a]

The observation that the mobility order is reversed in some reactions shows that it is the balance between the factors contributing to the stabilization of the two transition states for formation and decomposition of the intermediates shown in eqs. 1-3 and 1-4 that ultimately determines the course of the overall substitutions. The situation has been visualized by Miller in a series of semiempirical theoretical calculations that have led to a description of the complete potential energy–reaction coordinate profiles for many substitutions of halonitroaromatics.[3,115] These energy profiles were mainly derived on the basis of electron affinities, of energies of bond and solvation, but specific effects like the aforementioned ipso effect were also considered. Despite the numerous assumptions involved in the method, the agreement between the predicted energy diagrams and the experimental results appears to be remarkably good. The examples given in Fig. 1.5 portray several typical situations: (a) rate-limiting formation of the intermediate, (b) rate-limiting decomposition of the intermediate, (c) a borderline process in which the intermediate is approximately equally partitioned between reactants and

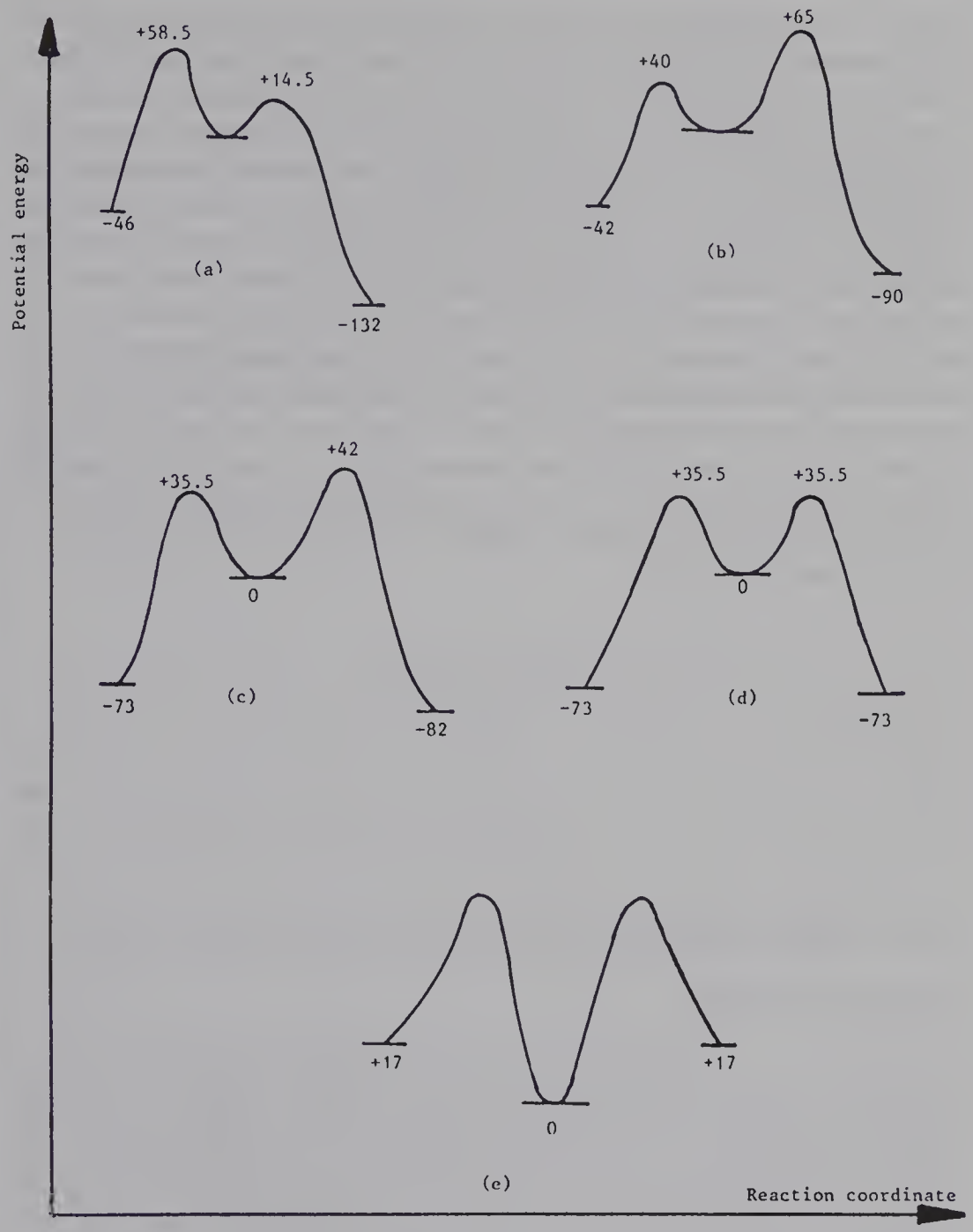
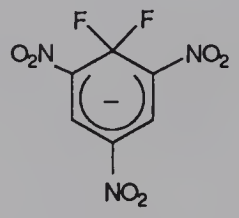


Figure 1.5. Potential energy-reaction coordinate diagrams for *S*NAr substitutions of nitroaryl halides, energies in kilojoules per mole:

(a) 1-Iodo-4-nitrobenzene and CH_3O^-/CH_3OH,
(b) 1-fluoro-2,4-dinitrobenzene and SCN^-/CH_3OH,
(c) 1-bromo-2,4-dinitrobenzene and I^-/CH_3OH,
(d) 1-Iodo-2,4-dinitrobenzene and I^-/CH_3OH, and
(e) 1-fluoro-2,4,6-trinitrobenzene and F^-/CH_3CN. (Curves a–d from ref. 3; curve e from ref. 119.)

products, so that the first step is highly reversible, and (d) and (e) exchange-type processes that involve identical entering and leaving halogens, so that a symmetrical intermediate is formed. Figure 1.5d exemplifies reactions in which the σ-complex is not detectable because it is too high in energy: for example, the chlorine–isotopic exchange reaction between lithium chloride [^{36}Cl] and 1-chloro-2,4-dinitrobenzene,[79,116] or the fluorine–isotopic exchange reactions between nitroaryl fluorides and rubidium fluoride [^{18}F], which represent an effective labeling technique.[117] Figure 1.5e is qualitative and suggests a reaction coordinate for the most interesting case of the reaction of F^- with picryl fluoride in acetonitrile or dimethyl sulfoxide (DMSO). In this system recently studied, the symmetrical σ-complex **38** is thermodynamically more stable than the initial state, in part because F^- has a very low stability in dipolar aprotic solvents.[118] This has allowed a full structural characterization of **38** by ^1H and ^{19}F NMR.[119] In view of the essentially complete formation of **38** in acetonitrile, an equilibrium constant of 1000 was used to calculate the energies given in Fig. 1.5e.



38

1.3.1.2 The Mobility of the Nitro Group and Other Leaving Groups

Because of the ipso effect, a number of electronegative (–I) substituents, which do not depart, or depart with difficulty in aliphatic systems, are readily displaced in S_NAr processes where bond formation to the nucleophile is rate limiting. The NO_2 group is certainly the most prominent example, since it has a mobility comparable to that of F in most S_NAr reactions (Table 1.7).[1,3] A strong polarization of the C—NO_2 bond together with a high ability to stabilize the cyclohexadienyl intermediate and the related transition state (Table 1.1) are the main reasons for the high nucleofugality of NO_2. However, because of its high polarizability, NO_2 departs more readily in reactions involving highly polarizable rather than nonpolarizable nucleophiles.[114] This point is considered in more detail in Section 1.3.2.2.

Other electronegative substituents that depart well in S_NAr processes are

the RO groups—a notable ipso effect has been calculated[22] for OCH_3—and the OC_6H_5, SO_2R, and SOR groups.[1–3,120] Positively charged substituents like NR_3^+ and $S(CH_3)_2^+$ have a high mobility. An exception is the diazonium group, which is subject to a specific mechanism.[121] A negatively charged substituent like SO_3^-, which is attached to the ring by the positive end of a dipole, is also readily displaced from very activated aromatic systems. 2,4,6-Trinitrobenzenesulfonate and 2,6-dinitro-4-trifluoromethylbenzenesulfonate react cleanly with primary and secondary amines and are useful as protein-modifying agents.[122,123]

Since the energetics of S_NAr reactions is also a function of the nucleophile and the solvent, no single order of leaving group ability can be proposed for these processes. Most experimental results, however, suggest the following approximate order for the reactions in which the addition of the nucleophile is rate limiting.[1–3,124]

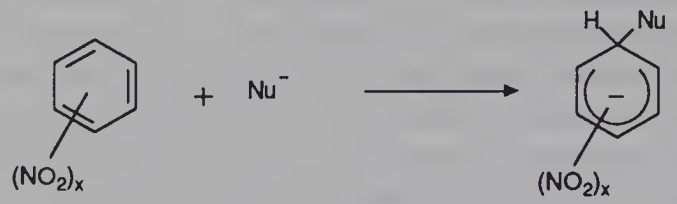
$$NR_3^+, S(CH_3)_2^+ > NO_2,F > OSO_2C_6H_5 > Cl,Br,I > SOR,SO_2R,N_3 > OR,$$

$$OC_6H_5, SR,SC_6H_5 > NR_2$$

The sequence above reveals some well-known features of S_NAr reactions.[1–3] Thus, within a polar category, the nucleofugality pattern is F > OR > NR_2, while for a given atom the order is L^+ (cation) > L^+Z^- (dipole) > L° (neutral group): for example, $N(CH_3)_3^+ > NO_2 > NR_2$ or $S(CH_3)_2^+ > SOR \sim SO_2R$. Also to be mentioned is the observation, within series of very similar groups, that leaving group ability correlates well with acid strength.[1] Good Hammett relationships have thus been obtained in plotting the log k values for methanolysis or hydrolysis of various 1-aryloxy-2,4-dinitrobenzenes or 2-aryloxy-5-nitropyridines against the pK_a values of the departing aryloxide anions.[1,76]

The absence of hydrogen in the reactivity sequence above is a very important feature. Because of the very low anionic stability of a departing H^- anion, ($pK_a \sim 36$),[125] it can be estimated that S_NAr displacements of hydrogen are very endothermic and have transition states for C—H bond breaking that are too high in energy to be kinetically accessible. Accordingly, nucleophilic additions to activated CH ring positions will normally stop at the intermediate σ-complex.[8] In these cases, the two-step process simplifies to the single equilibrium step of eq. 1-10 and the resulting unsymmetrical σ-complex **39** may then be stabilized sufficiently to be observable spectroscopically or even isolable as a crystalline alkali salt. Familiar examples in the benzene series are the adducts **40**, which arise from the addition of various nucleophiles to 1,3,5-trinitrobenzene and 1,3-dinitrobenzene.[8,14–18] Very stable adducts of this type have also been obtained in heterocyclic series (e.g., **X-25** and **41**).[126]

It is only via very specific mechanisms that nucleophilic displacement of hydrogen can occur in activated aromatic systems (Chapter 5).



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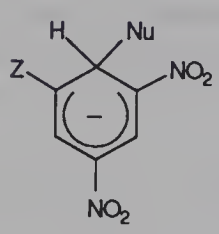

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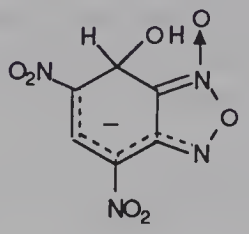

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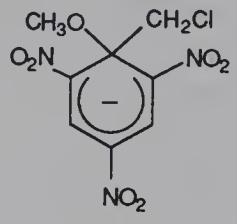


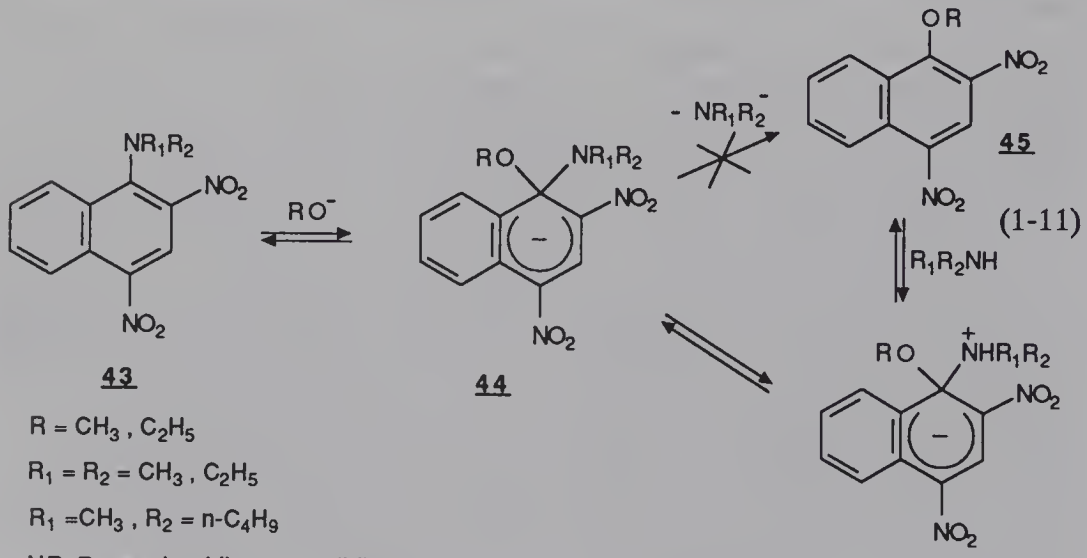
42

Z = H , NO_2

Nu = OH , OR , SR , NR_2 , CR_3

Like the hydrogen atom, alkyl groups are not displaced in S_NAr processes, and adducts like **42** have been identified.[127]

While amino groups depart very readily as amines when initially protonated,[17,19,20] they are not readily eliminated in the form of amide anions in basic media. Like H^-, such anions are highly unstable ($pK_a \sim 38$)[128] and their departure from the intermediate σ-complex is a highly endothermic process. Hence, nucleophilic additions to activated aromatic amines give stable unsymmetrical σ-adducts.[129,130] Illustrative reactions are the additions of alkoxide



(1-11)

43 **44** **45**

R = CH_3 , C_2H_5

$R_1 = R_2 = CH_3$, C_2H_5

$R_1 = CH_3$, R_2 = n-C_4H_9

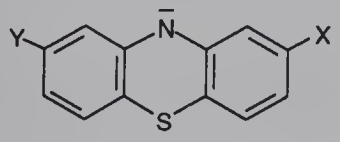
NR_1R_2 = piperidino, pyrrolidino

anions to the 1-dialkylamino-2,4-dinitronaphthalenes **43**, which afford the adducts **44**.[129] Interestingly, these complexes may also be formed in the reverse direction when secondary amines react with 2,4-dinitro-1-naphthyl alkyl ethers (**45**). However, the RO groups have a high mobility and the substitution process goes to completion in these instances, yielding the naphthylamines **43** as the final products (eq. 1-11).[131–134]

1.3.2 The Influence of the Nucleophile

1.3.2.1 Basicity and Polarizability

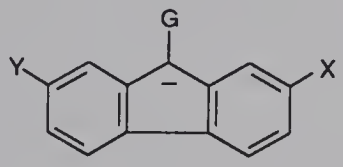
That nucleophilic reactivity depends on basicity is evidenced by the frequent observation that the rates of reaction of a nitroaromatic substrate with a series of structurally similar nucleophiles obey Brønsted or Hammett-type relationships satisfactorily.[135–139] This is illustrated in Fig. 1.6, which shows the Brønsted relationship obtained by Crampton on plotting the log values of the second-order rate constants for substitution of 1-chloro-2,4-dinitrobenzene by various meta- and para-substituted thiophenoxide ions versus the pK_a values for the corresponding thiols in 95% C_2H_5OH/5% H_2O.[139] The deviant point in Fig. 1.6 refers to the reaction with *o*-methylthiophenoxide ion in which steric effects are important.[139] Related correlations have been reported in substitutions of chloronitropyridines with meta- and para-substituted anilines.[140,141] In the thiophene series, it has been shown that a unique multiparameter free energy relationship accounts for the changes in reactivity observed in the reactions of 2-bromo-3,5-dinitrothiophene with para-, meta-, and ortho-substituted anilines in methanol.[142,143]



46

(a) X = Y =H; (b) X = Cl , Y = H

(c) X = Y = Br



47

G = CH_3, C_6H_5O, o-CH_3-C_6H_4- ,p-CH_3-C_6H_4, C_6H_5, m-ClC_6H_4 , $(CH_3)_2CHS$, C_6H_5S , p-BrC_6H_4S,

(a) X = Y = H; (b) X= Br, Y= H; (c) X =Y =Br

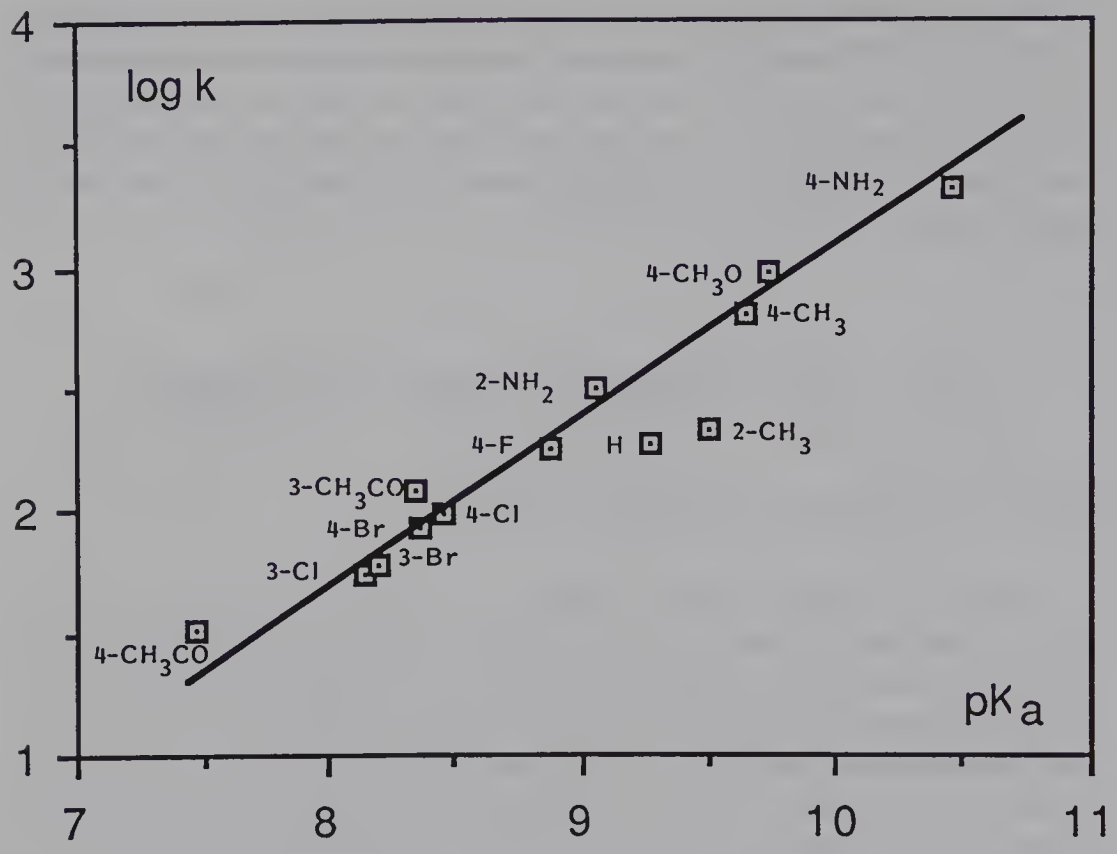


Figure 1.6. Brønsted correlation for the reactions of 1-chloro-2,4-dinitrobenzene with substituted thiophenoxide ions in 95% C_2H_5OH/5% H_2O at 25°C; *k* in liters per mole per second. (Data reproduced with permission from Crampton, M. R.; Willison, M. J. *J. Chem. Soc., Perkin Trans. 2*, **1974**, 238.)

All examples quoted above refer to the reactivity of oxygen, sulfur, and nitrogen nucleophiles in protic solvents; but it has been recently shown that reactions carried out in dipolar aprotic solvents obey similar free energy relationships.[144,145] Brønsted plots for substitutions of various 1-L-4-nitrobenzenes (L = F, Cl, Br, I, C_6H_5O) with substituted phenoxide anions, phenothiazinide nitranions (**46**) and fluorenide carbanions (**47**) in DMSO have been reported.[144,145] However, separate plots have been drawn for substituted 9-methyl, 9-aryl-, and 9-thiophenylfluorenide carbanions. This shows that the steric effect of the substituent at the 9-position of **47** is of importance in determining the reactivity of this family of nucleophiles.[144]

Bordwell has noted that Brønsted plots reported in the literature for reactions in which bond formation to the nucleophile is rate limiting have

Table 1.8. Brønsted β_{Nu} Values for S_NAr Reactions with Various Families of Nucleophiles in Hydroxylic Solvents and in DMSO[a]

Nucleophiles	Aromatic substrate	Solvent	β_{Nu}
9-Phenylfluorenides	4-Fluoronitrobenzene	DMSO[a,b]	0.58
	4-Chloronitrobenzene		0.65
	4-Bromonitrobenzene		0.71
9-Thiophenylfluorenides	4-Chloronitrobenzene		0.65
9-Methylfluorenides	4-Chloronitrobenzene		0.605
	4-Iodonitrobenzene		0.63
	4-Phenoxynitrobenzene		0.60
Phenothiazinides	4-Fluoronitrobenzene		0.51
	4-Chloronitrobenzene		0.70
	4-Bromonitrobenzene		0.70
Amines	1-Fluoro-2,4-dinitrobenzene	H_2O[c,d]	0.42
	1-Chloro-2,4-dinitrobenzene		0.52
	1-Iodo-2,4-dinitrobenzene		0.45
	1-Chloro-2,4,6-trinitrobenzene		0.64
Phenoxides	1-Fluoro-2,6-dimethyl-4-nitrobenzene	DMSO[e,f]	0.51
	1-Chloro-2,6-dimethyl-4-nitrobenzene		0.60
	1-Bromo-2,6-dimethyl-4-nitrobenzene		0.60
	1-Chloro-2,4-dinitrobenzene	CH_3OH[g,h]	0.91
Naphthoates	1-Bromo-2,4,6-trinitrobenzene	80% CH_3OH/ 20% H_2O[d,i]	0.56
Thiophenoxides	1-Fluoro-4-nitrobenzene	CH_3OH[h,j]	0.52
	1-Chloro-4-nitrobenzene		0.48
	1-Bromo-4-nitrobenzene		0.55
	1-Iodo-4-nitrobenzene		0.55

[a] Data reproduced with permission from Bordwell, F. G.; Hughes, D. L. *J. Am. Chem. Soc.* **1986**, *108*, 5991.
[b] t = 25°C.
[c] From Dixon, J. E.; Bruice, T. C. *J. Am. Chem. Soc.* **1972**, *94*, 2052.
[d] t = 30°C.
[e] From Bartoli, G.; Ciminale, F.; Todesco, P. E. *J. Org. Chem.* **1975**, *40*, 872.
[f] t = 60°C
[g] From Leahy, G. D.; Liverio, M.; Miller, J.; Parker, A. J. *Aust. J. Chem.* **1956**, *9*, 382.
[h] t = 50°C.
[i] From Nadar, P. A.; Gnanasekaran, C. *J. Chem. Soc., Perkin Trans. 2*, **1978**, 671.
[j] From Bartoli, G.; Di Nunno, L.; Forlani, L.; Todesco, P. E. *Int. J. Sulfur Chem., C*, **1971**, *6*, 77.

slopes β_{Nu} that range for the most part between 0.5 and 0.7.[144] This is shown in Table 1.8, which summarizes a large number of available β_{Nu} values for S_NAr reactions. In comparison, it is interesting to note that most β_{Nu} values reported for aliphatic S_N2 reactions are distinctly lower, being in the range 0.2–0.5.[144]

It is generally accepted that the position of the transition state along the reaction coordinate can be described in terms of the sensitivity of the reaction to changes in the basicity of the attacking nucleophile, as measured by the Brønsted β_{Nu} value. Thus, reactions exhibiting large β_{Nu} values would have transition states where bond formation and charge transfer have made considerable progress while reactions with small β_{Nu} values would have transition states where little bond formation and charge transfer have occurred. On these grounds, the β_{Nu} values for S_N2 and S_NAr reactions are indicative of a higher degree of bond formation and charge transfer in the S_NAr transition states than in the S_N2 transition states.[144]

Measures of intrinsic basicities of anions with different donor atoms toward carbon have been calculated from gas phase equilibrium data.[146] These calculations predict that at the same hydrogen basicity, the intrinsic basicity order toward carbon is $C^- > S^- > N^- > O$.[144] However, this order does not fit the experimental data, since the sequence commonly found in S_NAr reactions is $S^- >> C^- > O^- \geq N^-$.[144] The high polarizability of thioanions like $C_6H_5S^-$ or RS^- is the accepted explanation for the high nucleophilicity of sulfur bases.[114a] This effect is further demonstrated in Table 1.7, which compares the rate constants for substitution of some 1-L-2,4-dinitro- and 1-L-4-nitrobenzenes as well as of some 2-L-6-nitrobenzothiazoles with $C_6H_5S^-$ and CH_3O^- in methanol.[114a] As can be seen, the less basic thiophenoxide ion is the most nucleophilic reagent in all systems. That the ratio $k^{C_6H_5S^-}/k^{CH_3O^-}$ decreases on going from L = NO_2 or I to L = F or OC_6H_5 is the reflection of the decreasing polarizability of the leaving group (see Section 1.3.1.2).[114a] The ratio $k^{C_6H_5S^-}/k^{CH_3O^-}$ depends also on the substrate, being greater for 1-L-2,4-dinitrobenzenes than for 1-L-4-nitrobenzenes or for 2-L-6-nitrobenzothiazoles. Attempts to correlate changes in reactivity with basicity and polarizability effects through multiparameter relationships have been made by Todesco and coworkers.[114]

1.3.2.2 The N_+ Scale

Among other attempts to correlate nucleophilic reactivities in S_NAr reactions, a recent work by Ritchie is worth mentioning. This author studied the

reactions of quite different nucleophiles with many organic cations in various solvents and found that the relative reactivities of these nucleophiles are nearly invariant with respect to the identity and reactivity of the cation.[147,148] These invariances were expressed in terms of the equation:

$$\log k = \log k_0 + N_+ \qquad (1\text{-}12)$$

where k is the rate constant for reaction of a cation with a given nucleophile in a given solvent, k_0 is the reference rate constant that corresponds to the reaction of the same cation with H_2O in water, and N_+ *is a parameter characteristic of the given nucleophile in the given solvent and independent of the electrophile.*[147–149] From eq. 1-12, the N_+ values for many anionic and neutral nucleophiles were derived by setting $N_+ = 0$ for H_2O in water and by the use of *p*-nitro (Malachite Green) or analogous organic cations as the standard electrophiles.[147,149]

Although it has been established with cationic electrophiles, the N_+ scale of nucleophilic reactivity applies equally well to the S_NAr reactions of 1-L-2,4-dinitrobenzenes (L = F, Cl, Br, I) in which the attack of the nucleophile is rate determining. The plot of log k versus N_+ for the reactions of 1-fluoro-2,4-dinitrobenzene with various nucleophiles in water and methanol is shown in Fig. 1.7. Except for the N_3^- and RS^- ions, the correlation is quite satisfactory, as are those for the iodo, bromo, and chloro derivatives.[149] This is a very significant result since the nucleophiles showing behavior consistent with eq. 1-12 include a variety of anionic, neutral, "hard," "soft," and "α-effect" nucleophiles whose reactivities are not commonly accommodated by a single Brønsted relationship.[150] Another remarkable observation is the absence of selectivity–reactivity relationships in the S_NAr reactions studied.[149] This is shown by the data in Fig. 1.8, which compare directly the log k values for the fluoro and chloro derivatives. As can be seen, much of the scatter observed in Fig. 1.7 is removed and an excellent unit–slope linear relationship is obtained even though 1-fluoro-2,4-dinitrobenzene reacts about 1000 times faster than its chloro analogue with all nucleophiles.[149] The deviant behavior of RS^- ions shown in Fig. 1.7 is attributed to polarizability effects, as discussed above.[114,151] In contrast, the abnormally low reactivity of the N_3^- ion is not well understood.[149]

The independence of relative reactivities of the wide variety of nucleophiles on the nature of the electrophile has led Ritchie to the conclusion that the N_+ values are measures of some inherent property of the nucleophiles, most probably of the energy required to desolvate the nucleophile.[147–149] This suggests in turn that desolvation of the nucleophile is the dominant factor in determining correlations of relative rates by eq. 1-12. While it is now recog-

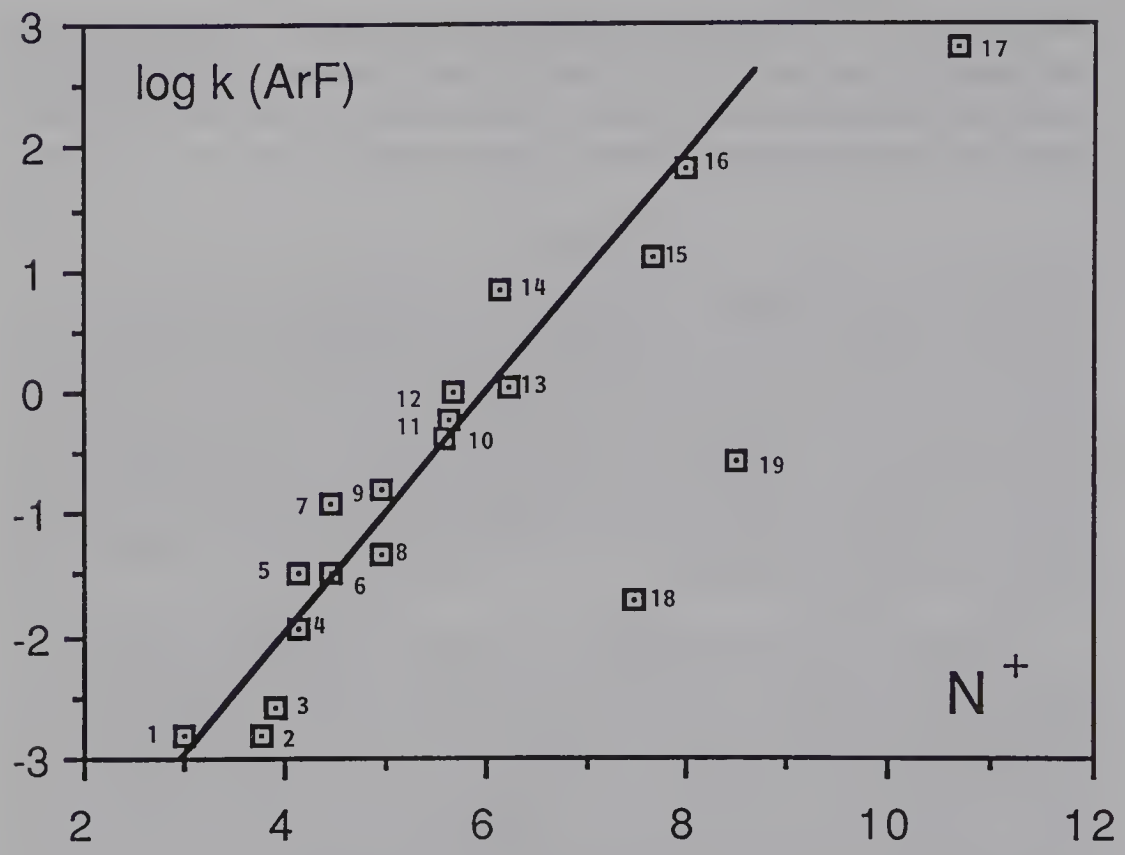


Figure 1.7. Correlation of the rates of S_NAr reactions of 1-fluoro-2,4-dinitrobenzene in water and methanol by eq. 1-12; *k* in liters per mole per second. Numbering is as follows. In water: (1) $CF_3CH_2NH_2$, (2) CN^-, (3) CH_3ONH_2; (5) $H_2NCH_2CO_2C_2H_5$, (6) $H_2NCH_2CONHCH_2CO_2^-$, (7) OH^-, (9) $H_2NCH_2CO_2^-$, (10) $H_2N\text{-}NH_2$, (11) $C_6H_5O^-$, (12) morpholine, (13) $CF_3CH_2O^-$, (14) piperidine, (16) HOO^-, (18) N_3^-. In methanol: (4) CH_3ONH_2, (8) $H_2NCH_2CO_2C_2H_5$, (15) CH_3O^-, (17) $C_6H_5S^-$, and (19) N_3^-. (Data reproduced with permission from Ritchie, C. D.; Sawada, M. *J. Am. Chem. Soc.* **1977**, *99*, 3754.)

nized that desolvation of the reagents is a preliminary requirement for many reactions,[152–154] it is important to note that Ritchie's idea implies that the transition states are characterized by rather large separations of the nucleophile and electrophile moieties. For S_NAr reactions involving rate-determining nucleophilic addition, this would mean that bond formation and charge transfer have made little progress in the transition states. These conclusions are in disagreement with those reached on the basis of the β_{Nu} values obtained from Brønsted plots[144] as well as with those deduced from the changes in reactivity caused by variations in the activation of the aromatic ring of the electrophile (p. 8).[1,3,8] A possible explanation of this conflicting situation is in terms of imbalanced transition states, with desolvation of the nucleophile being ahead of bond formation and charge transfer in the transition state. The situation is

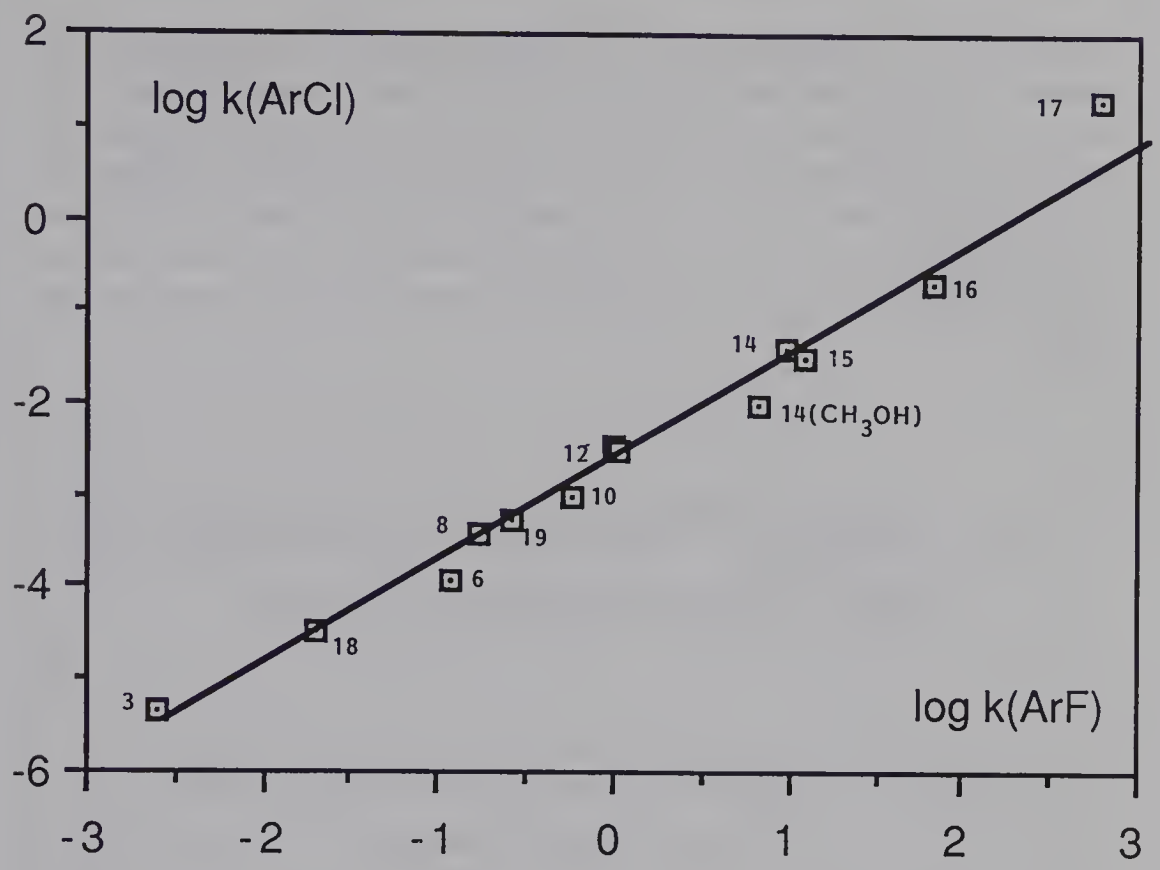


Figure 1.8. Linear free energy relation for reactions of 1-fluoro-2,4-dinitrobenzene (ArF) and of 1-chloro-2,4-dinitrobenzene (ArCl) in water or methanol; *k* in liters per mole per second. The numbering corresponds to that in Fig. 1.7. (Data reproduced with permission from Ritchie, C. D.; Sawada, M. *J. Am. Chem. Soc.* **1977**, *99*, 3754.)

reminiscent of that described for nucleophilic additions to esters or the ionization of carbon acids, and the reader is referred to original discussions in these areas for a more specific analysis.[152–156] Some indications that nucleophilic additions to aromatic sp^2 carbons are subject to imbalance effects have been obtained in studies of the formation of σ-adducts.[49] On the other hand, Bunton and coworkers have recently reconsidered the mechanism of some S_NAr substitutions, suggesting that they involve single electron transfer steps (see Chapter 7). This hypothesis is also consistent with Ritchie's evidence that nucleophilic additions to halonitroarenes do not follow the reactivity–selectivity principle.[27]

Notwithstanding some variations due to changes in the nature of the leaving group and the solvent, common nucleophiles exhibit a relatively regular reactivity in S_NAr processes in which the formation of the intermediate σ-complex is rate limiting. An approximate sequence, at least in protic solvents, is[8,124]

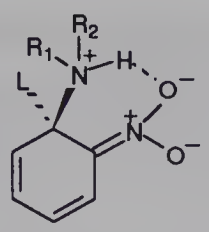
$$SO_3^{2-} > C_6H_5S^- > R_3C^- > RO^- > RR'NH, RNH_2 > C_6H_5O^-, OH^- > C_6H_5NH_2 > NH_3 > I^- > Br^- > Cl^- > H_2O > ROH$$

Noted in this series the absence of CN^-, which adds very readily to activated aromatic rings but gives rise to reactions that do not usually proceed via the S_NAr mechanism (see Chapter 5).[1,8] The low reactivity of OH^-—a much stronger but much more solvated base than $C_6H_5O^-$—is also noteworthy, since it apparently acts as a general base in many S_NAr reactions in aqueous solution.[126,157] When the reactions are carried out in dipolar aprotic solvents, which poorly solvate anions with a localized negative charge, OH^- is a much more reactive species than $C_6H_5O^-$.

1.4 Effect of Specific Variations in the Nitroaromatic Moiety

1.4.1. ortho Versus para Activation by an NO_2 Group

It is very important in S_NAr processes to be able to determine the circumstances under which an NO_2 group is more activating in the ortho than in the para position to the leaving group.[1,3,7] The prevailing view is that in the absence of other influences, an NO_2 group in the ortho position is inherently more activating than one in the para position, presumably as a result of the stronger inductive effect of the former.[50] For substitutions by anionic nucleophiles, however, this rate-enhancing effect is counterbalanced by electrostatic repulsion between the highly polarizable ortho-NO_2 group and the incoming nucleophile.[1,3,114] On the other hand, MO calculations predict less capacity for resonance stabilization of an intermediate cyclohexadienyl anion by an ortho-NO_2 than by a para-NO_2 group, and hence a somewhat higher energy for the transition states of the substitutions of ortho-nitro derivatives.[22] When important, steric effects in both the aromatic substrate and the intermediate σ-complex will also tend to decrease the reactivity of ortho derivatives.[1–8] As a matter of fact, the ortho/para ratio is usually less than unity in reactions of halonitrobenzenes (L = F, Cl, Br, I) and dinitrobenzenes (L = NO_2) with anionic reagents.[1–8,50] For example, Table 1.9 shows that the k^o/k^p ratios of the rate constants for substitution of ortho- and para-chloronitrobenzenes with CH_3O^- and $C_6H_5S^-$ are 0.15 and 0.33 respectively, in methanol.



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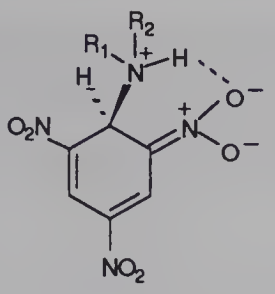

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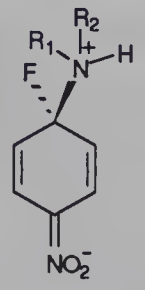

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The reactivity pattern above is not encountered, however, in reactions with many primary and secondary amines.[1–8] Thus, inspection of Table 1.9 reveals that *o*-halonitrobenzenes react more rapidly than their para isomers with piperidine in various solvents: the corresponding k^o/k^p ratios are 1.58 for L = F in DMSO and 2.20 for L = Cl in methanol. This inversion in reactivity has received considerable attention[1–7,159–161] Enhanced stabilization of the zwitterionic intermediate through intramolecular hydrogen bonding between the ammonio proton and the ortho-NO_2 group—a phenomenon visualized in structure **48** and known[162] as "built-in solvation"—is the commonly suggested explanation for the greater reactivity of *o*-nitro derivatives with amines. This proposal has been criticized, but independent evidence that such intramolecular hydrogen bonding indeed occurs, even in aqueous solution, has been obtained from a proton transfer rate study.[163] This suggests a hydrogen bond strength of about 9.6 kJ/mol in aqueous solution for a 2,4,6-trinitrobenzene derivative like **49**.[163] In a less polar solvent, and with a smaller number of NO_2 groups sharing the negative charge, this hydrogen bond is likely to be appreciably stronger; in fact, it has been suggested that full proton transfer to the *o*-NO_2 group occurs in benzene.[164] Support for such hydrogen bonding has also been recently provided by new theoretical calculations.[165]

Under specific experimental conditions, k^o/k^p ratios greater than 1 have also been observed in reactions with anionic nucleophiles. In the reactions of ortho- and para-halonitrobenzenes with alkoxide ions, the ortho/para ratio increases when going from CH_3O^- ($k^o/k^p < 0.5$) to $C_2H_5O^-$ ($k^o/k^p \sim 1.1$) to $(CH_3)_2CHO^-$ ($k^o/k^p \sim 15$) to $(CH_3)_3C{-}O^-$ ($k^o/k^p \sim 360$) in the corresponding alcohols.[50,166a] The situation appears to be largely governed by the nature of the cation. For example, substitution of K^+ by benzyltrimethylammonium cation lowers the k^o/k^p ratio from 360 to 26 in the case of the fluoronitrobenzenes in *t*-butyl alcohol.[166] This trend has been attributed to a specific stabilization of the transition state in *o*-nitro-substituted substrates by a potassium bridge between the oxygen of the nucleophile and the nitro group. This would be facilitated by the low ability of alkali alkoxides to give free ions in alcoholic solutions.[167–169] In this respect, it is noteworthy that *o*-halonitrobenzenes

Table 1.9. Influence of the Nucleophile on the Relative Reactivities of ortho- and para-L-Substituted Nitrobenzenes

Nucleophile/solvent	t (°C)	L	1-L-2-nitro-	1-L-4-nitro	k^o/k^p	Ref.
CH_3O^-/CH_3OH	25	F	1.24×10^{-4}	1.79×10^{-4}	0.70	50
$C_2H_5O^-/C_2H_5OH$	25		7.40×10^{-4}	6.67×10^{-4}	1.11	
$(CH_3)_2CHO^-/(CH_3)_2CHOH$	25		5.45×10^{-3}	3.35×10^{-4}	16.28	
$(CH_3)_3CO^-/(CH_3)_3COH$	29.5[a]		5.4×10^{-3}	1.5×10^{-5}	360	166a
	28[b]		8.5×10^{-3}	3.3×10^{-4}	26	
$C_6H_5O^-/CH_3OH$	25		5.25×10^{-7}	1.26×10^{-6}	0.4	
Piperidine/DMSO	25		1.60×10^{-2}	1.01×10^{-2}[c]	1.58	166b
$C_3H_7NH_2$/DMSO	45		3.13×10^{-3}	2.05×10^{-4}	15.3	171
$C_3H_7NH_2$/Toluene	45		2.4×10^{-5}	5.4×10^{-8}	444	
$(CH_3)_2CHNH_2$/DMSO	45		6.43×10^{-4}	4×10^{-4}[c]	1.61	
$(CH_3)_2CHNH_2$/Toluene	45		5.4×10^{-6}	5×10^{-10}	$\sim 10^4$	
CH_3O^-/CH_3OH	25	Cl	6.17×10^{-8}	4.27×10^{-7}	0.15	166a
$C_2H_5O^-/C_2H_5OH$	25		2.63×10^{-7}	1.66×10^{-6}	0.16	
$C_6H_5S^-/CH_3OH$	50		1.10×10^{-4}	3.3×10^{-4}	0.33	159b
Piperidine/CH_3OH	60		2.33×10^{-6}	1.06×10^{-6}	2.20	159a
Piperidine/C_6H_6	60		1.05×10^{-5}	1.77×10^{-7}	59	
CH_3O^-/CH_3OH	25	NO_2	1.40×10^{-4}	3.70×10^{-4}	0.38	75

[a] $(CH_3)_3COK$.

[b] Benzyltrimethylammonium *t*-butoxide.

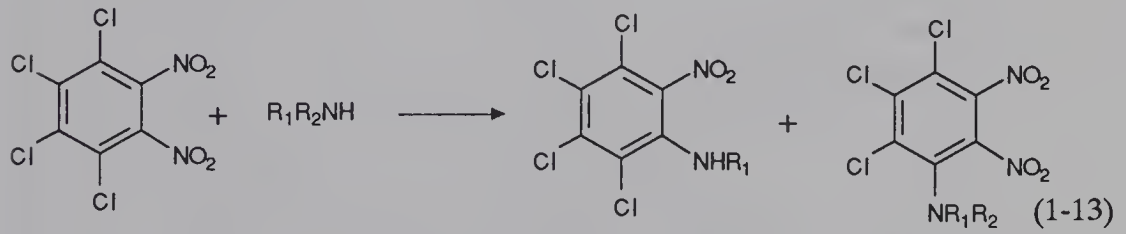
[c] $t = 50$°C.

become more reactive than their para isomers towards CH_3O^- when the reactions are carried out in very concentrated rather than dilute solutions of $KOCH_3$ or $NaOCH_3$ in methanol.[170]

Because of the formation of species like **48**, it may well be that substitutions of ortho derivatives do not always involve the same rate-determining step as those of para isomers. For example, it has been demonstrated that the formation of **48** (L = F; R_1 = *n*-C_3H_7, *i*-C_3H_7; R_2 = H) is rate limiting in the reactions of *n*-propylamine and isopropylamine with *o*-fluoronitrobenzene in toluene, while it is the decomposition of the corresponding zwitterionic intermediate **50** that is rate determining in the same reactions with *p*-fluoronitrobenzene.[171] Such differences in the mechanisms of the reactions must be kept in mind in the analysis of the activation of S_NAr reactions by ortho- and para-NO_2 groups.

1.4.2 Competing S_NAr Reactions: Reactivity at Unsubstituted Versus Substituted Ring Carbon Atoms

Nitroaromatic rings can possess several electrophilic positions susceptible to nucleophilic attack, so that competitive S_NAr processes may occur. The relative possibilities of the different substitutions are then determined by the degree of activation of the various positions, the nature of the leaving group, and the nature of the nucleophile. Steric factors at the reaction centers have also a prominent role, being often responsible for the observation of a remarkable regioselectivity. Nucleophilic substitutions of most 3-L-substituted-1,2-dinitrobenzenes (L = Cl, OR) thus occur exclusively at C-2 because of steric inhibition of resonance for the NO_2 group at this position.[1,3,7] No displacement of the 3-L-group and the NO_2 at C-1 is observed. Nucleophilic substitutions of polyhalonitrobenzenes like 1,2,3,4-tetrachloro-5,6-dinitrobenzene are interesting examples of reactions in which steric factors in both the electrophile and the nucleophile determine the course of the processes.[172] Primary amines thus react preferentially by displacing the NO_2 group from the most activated but also most sterically hindered 5(6)-position to give compound **51**. In contrast, more bulky nucleophiles like secondary amines react by replacing a chlorine atom from a less hindered position ortho to an NO_2 group to give compound **52** (eq. 1-13).[172]



(1-13)

51

$R_1 = C_2H_5$, n-C_3H_7, i-C_3H_7, n-C_4H_9

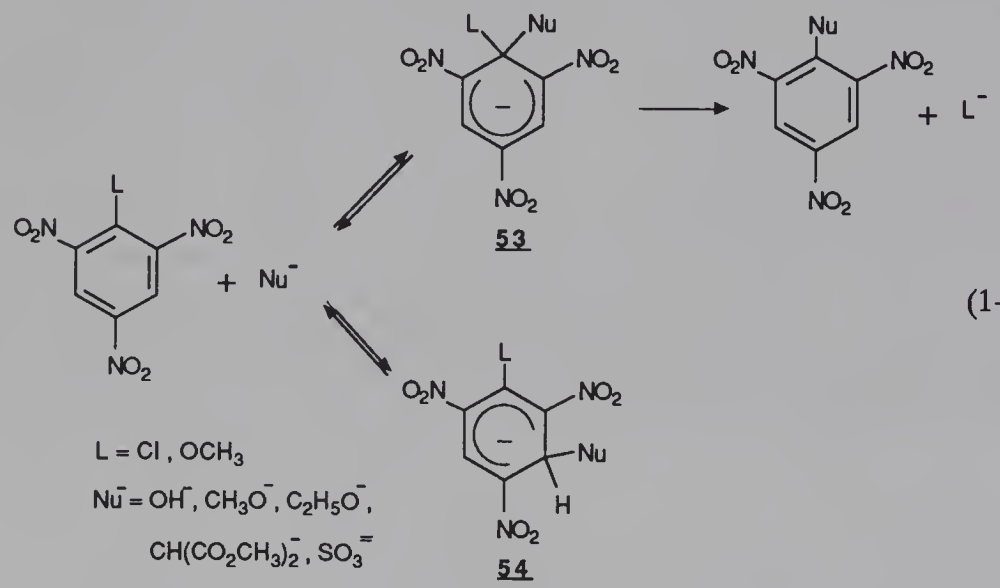
$R_2 = H$

52

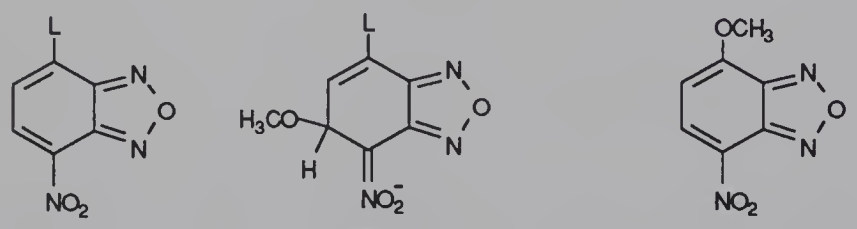
$R_1 = R_2 = CH_3$, n-C_3H_7, n-C_4H_9

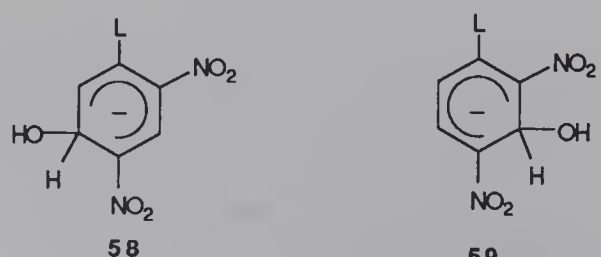
A significant feature is that nucleophilic attack at an activated unsubstituted ring position is, in general, kinetically favored compared to that at an activated substituted position.[8,15–18] As a result, formation of transient σ-adducts not subject to further conversion by a classical S_NAr process can occur in side-equilibrium reactions that are achieved prior to the actual substitution pathways. Under suitable experimental conditions, such intermediates can be

of sufficient stability to be observable spectroscopically.[8,15–18] Representative examples are the reactions of picryl halides or 2,4,6-trinitroanisole with oxyanions like OH^- or RO^- or with carbanions like $^-CH(OR)_2$, where the formation of the adducts **54** precedes that of the substitution products via the intermediates **53** (eq. 1-14).[173-177] Similarly, the adducts **56** are formed initially in the substitutions of 7-halo-4-nitrobenzofurazans (**55**) with CH_3O^- to give the ether **57**.[104] More complicated situations can occur when the nitroaromatic ring has two different activated CH positions. For example, both the adducts **58** and **59** form in side equilibria in the substitutions of 1-L-2,4-dinitrobenzenes with OH^- to give 2,4-dinitrophenol in aqueous DMSO.[68,178] Reasons for the more rapid addition of the nucleophiles to CH rather than to CL positions include the absence of electrostatic repulsion between the hydrogen atom and



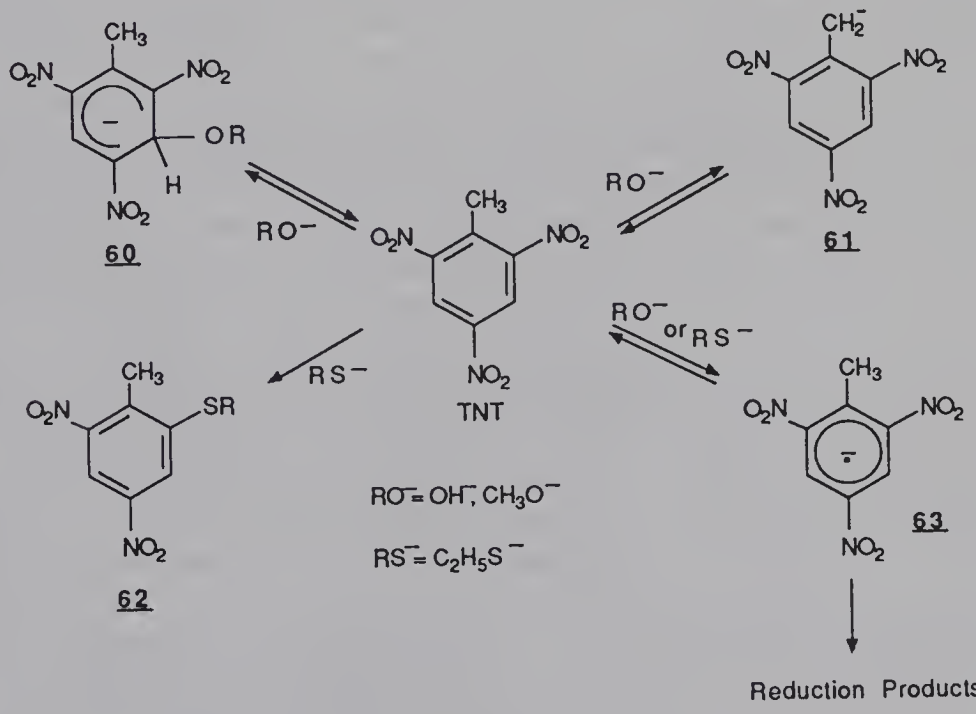
(1-14)





the incoming nucleophile and the lower steric requirements at an unsubstituted compared to a substituted position.[8,17] There are other reasons as well, and the problem is discussed more extensively in Chapter 2.

Depending on the structure of the aromatic compound, a variety of other processes can occur under conditions favorable for a nucleophilic aromatic substitution. In particular, many electrophiles may transfer a proton or an electron, and competition between hydrogen abstraction, electron transfer, side σ-complex formation, and an S_NAr process may result.[8,179] Such a competition is exemplified for nitrobenzyl arenes like 2,4,6-trinitrotoluene (TNT) in Scheme 1.1. With nucleophiles like OH^- or RO^-, parallel processes leading to the σ-complex **60** and the carbanion **61** are favored.[8,17,180,181] But S_NAr displacement of the 2-NO_2 group occurs preferentially with formation of **62** when TNT reacts with RS^- ions in DMSO or hexamethylphosphoramide (HMPA).[182] In this latter case, the activation provided by the two other meta-NO_2 groups is clearly sufficient to promote the substitution.[182] Electron transfer occurs as well, as shown by the observation of the radical anion **63**, which decomposes slowly with the formation of reduction products.[182] Conclusive evidence for the formation of **63** has been obtained through electron spin resonance (ESR) spectroscopy.[182] However, so far it has not been possible to isolate the electron transfer process and to study it separately from the other



Scheme 1.1.

competing processes in the TNT system. The role of radical anions as possible intermediates in some nucleophilic aromatic displacements is considered in Chapter 7.

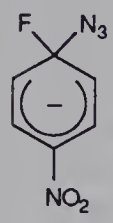
Nuclear hydrogen abstraction is another possible competing process in nitroaromatic–base interactions.[8,183]

1.5 Spectral Evidence for the Intermediacy of σ-Complexes in S_NAr Reactions

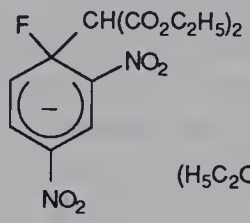
The structural characterization of numerous stable σ-complexes provides strong but not definitive evidence for the formation of the cyclohexadienyl intermediates in the S_NAr reactions shown in eqs. 1-3 and 1-4.[8] Therefore, much effort has been devoted to a successful detection of these species during actual substitution reactions of various nitroaromatics.

Structural assignments based on UV–visible spectroscopy have not been altogether successful for two main reasons. First, the σ-complex intermediates involved in S_NAr reactions usually have very short lifetimes and do not accumulate under common reaction conditions. Second, as pointed out in Section 1.4.2, nucleophilic attack occurs in general at a much higher rate at an unsubstituted than at a substituted ring carbon.[17] Therefore formation of a σ-complex not subject to further conversion can in many cases occur in a side-equilibrium process that is established prior to the actual substitution pathway; very often, it is this adduct rather than the expected isomeric intermediate that is the most readily observable.[8] These difficulties involved with structural assignments based on UV–visible spectroscopy are exemplified by the reaction of picryl chloride with hydroxide ion. In this system, the transient colored species observed at high base concentrations in aqueous solutions was first claimed to be the intermediate complex **53** (L = Cl, Nu = OH).[184] However, it was subsequently shown by Crampton and coworkers, using NMR spectroscopy that the σ-complex formed was in fact the 1,3-complex **54** (L = Cl, Nu = OH).[185, 186] The corresponding reactions have been described in eq. 1-14. Other reports of intermediates that have been shown to be erroneous are those of the adduct **64** of 1-fluoro-4-nitrobenzene and azide ion in dry dimethylformamide (DMF) and of the adduct **65** of 1-fluoro-2,4-

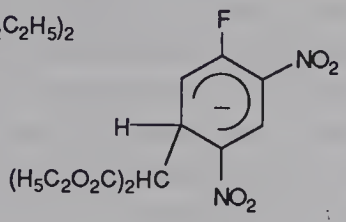
dinitrobenzene and diethyl malonate anion.[8,118,144,187] A most plausible structure for the species observed in the latter case is either **66** or **67**.[8]



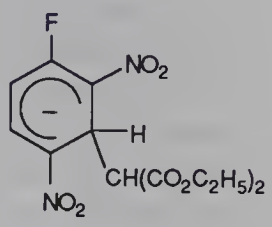
64



65

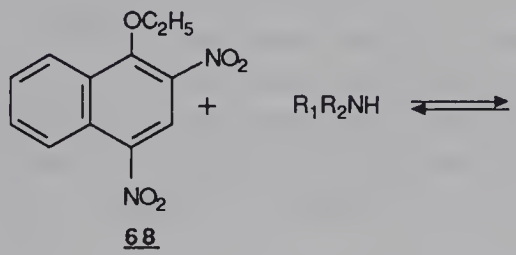


66

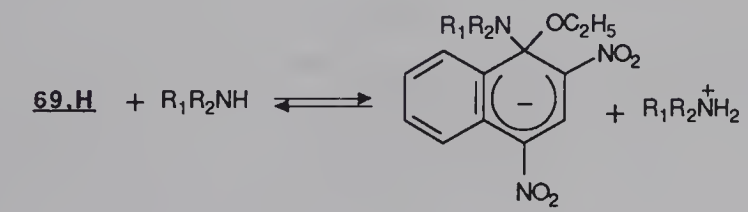


67

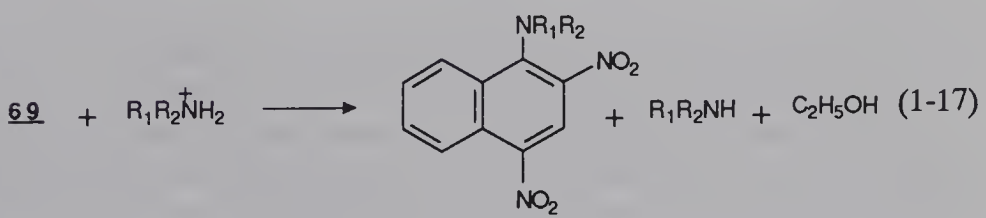
The best authenticated report of intermediate σ-complexes during actual substitution reactions is the work of Orvik and Bunnett, who found in 1970 that the reactions of 2,4-dinitro-1-naphthyl ethyl ether (**68**) with *n*-butyl- and *t*-butylamines to give the expected 2,4-dinitro-1-naphthylbutylamines **70a** and **70b** proceed in two distinct stages in DMSO (Scheme 1.2).[21] They identified



68 **69,H** (1-15)



69 (1-16)

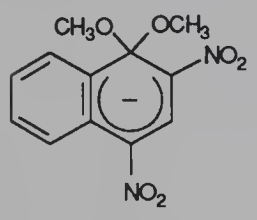


70 (= **43**) (1-17)

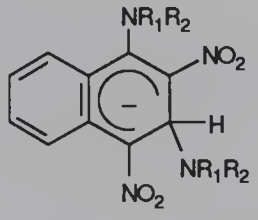
(a) $R_1 = H$; $R_2 = n\text{-}C_4H_9$; (b) $R_1 = H$; $R_2 = t\text{-}C_4H_9$; (c) NR_1R_2 = piperidino ; (d) NR_1R_2 = pyrrolidino

Scheme 1.2.

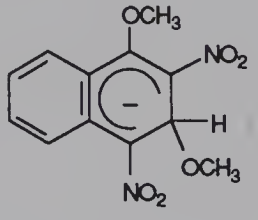
the intermediates formed in the first stage as being the conjugate bases **69** of the zwitterionic σ-adducts **69,H**, which are the species initially formed on the reaction pathways. The identification was based on the striking similarity of the UV–visible spectra recorded for **69** to that of the 1,1-dimethoxy complex **17b** of 2,4-dinitro-1-naphthyl methyl ether.[8,52] Formation of the 1,3-adducts **71** was not considered, but subsequent stopped-flow kinetic studies have shown that such naphthalenic species have markedly different absorption spectra: **72**, but not **17b**, has a notable absorption at wavelengths of approximately 550 nm.[53,129,188] Also, 1,3-adducts like **72** have a very low stability and are hardly detectable even in DMSO. More important, the structure of the intermediate σ-adduct **69a** has been unambiguously characterized in an elegant study by Fyfe and coworkers, who used a flow NMR technique at low temperature in 75% DMSO/25% CH_3OH.[10,189] Recently, Bunnett and Sekiguchi investigated the reactions of **68** with piperidine and pyrrolidine and reported the formation of the intermediates **69c** and **69d** in DMSO.[132,134] The structure of the piperidino adduct **69c** was confirmed by NMR spectroscopy,[133] and it is of interest that the spectrum obtained compares well with that recorded in generating this adduct by reaction of ethoxide ion with 2,4-dinitro-1-naphthylpiperidine.[190] As commented in Section 1.3.1, amide anions are such bad leaving groups that the substitutions of arylamines with alkoxide ions do not proceed further than the unsymmetrical σ-adducts. Many other adducts of type **69** have been characterized in this way.[129,130,133,190]



17b

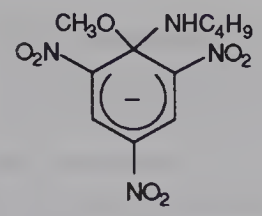


71

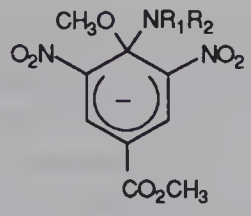


72

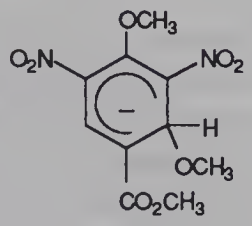
Compelling evidence for intermediates analogous to **69** has been obtained in S_NAr substitutions in the benzene series.[11] Using the flow NMR technique at –40°C, Fyfe and coworkers identified the short-lived adduct **73**, which is the expected intermediate in the reaction of 2,4,6-trinitroanisole with *n*-butylamine in 50:50 DMSO/CH_3OH.[11] Similarly, Hasegawa has reported the observation, by UV–visible spectroscopy, of the adducts **74a** and **74b** in the substitutions of methyl 4-methoxy-3,5-dinitrobenzoate with piperidine and pyrrolidine in DMSO.[191,192] A possible confusion with a side formation of isomeric 1,3-adducts was ruled out by the finding that **74a** and **74b** have absorption spectra markedly different from those recorded for a species such as **75**.[191]



73



74

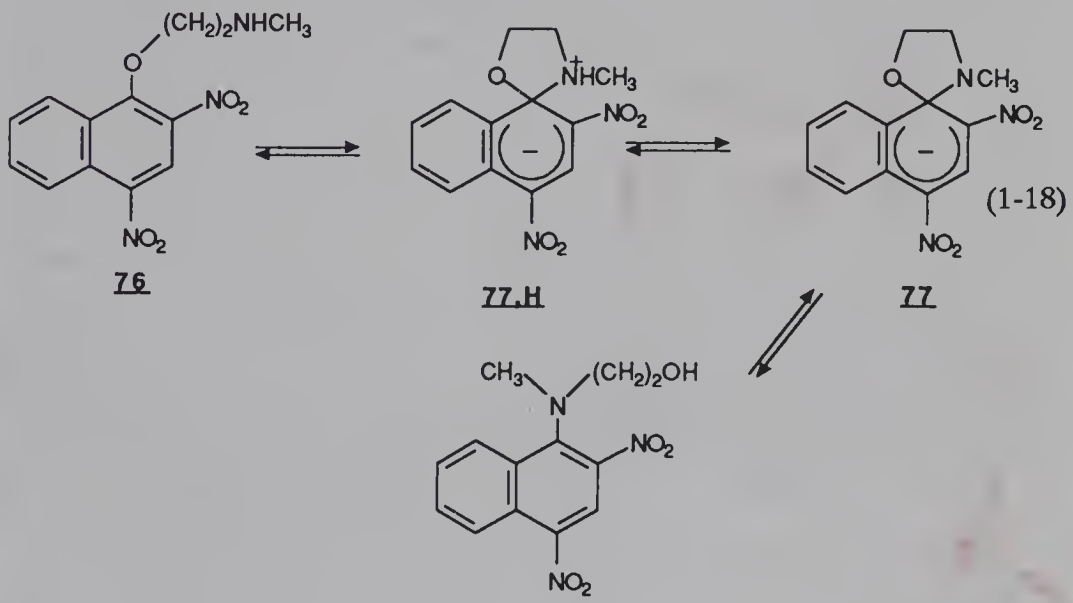


75

(a) NR_1R_2 = piperidino

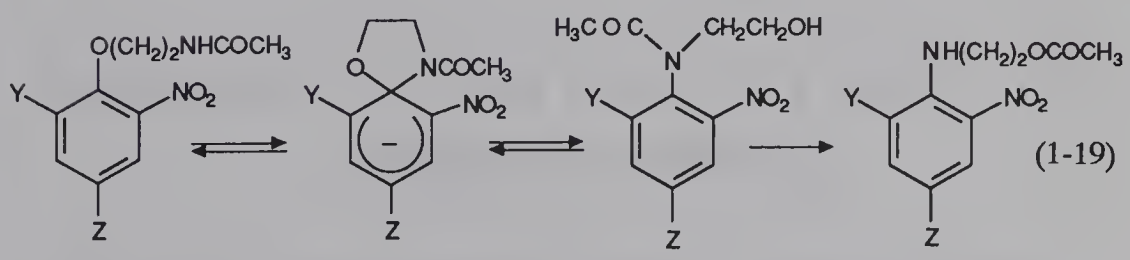
(b) NR_1R_2 = pyrrolidino

Intramolecular S_NAr reactions proceed through the formation of intermediate spiro adducts, which have been unambiguously characterized in several instances.[8,17,193] An interesting example is the adduct **77**, which has been identified by NMR and UV–visible spectroscopy as a relatively stable intermediate in the conversion of the ether **76** into the naphthylamine **78** (eq. 1-18).[194,195] Note that this reaction is representative of an intramolecular S_NAr displacement of an alkoxide anion by an amino group and is therefore the



(1-18)

76 **77.H** **77** **78**



(1-19)

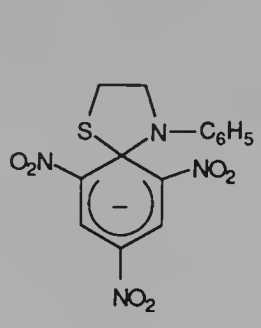
(a) Z = NO_2 ; Y = H

(b) Z = H ; Y = NO_2

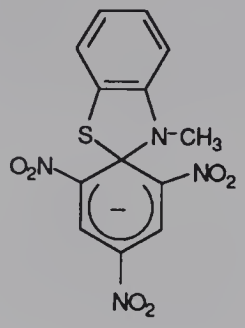
79

intramolecular counterpart of Scheme 1.2. Although they are less stable than **77**, the oxazolidine adducts **79** have been detected by NMR techniques in effecting the rearrangements depicted in eq. 1-19 in DMSO.[196–198]

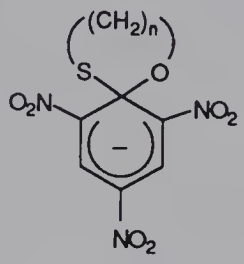
Intramolecular displacements of a thioalkoxide anion by an amino group have been observed.[199,200] They involve the intermediate formation of thiazolidine adducts, as demonstrated by the NMR identification of **80** and **81**. Oxathiolane adducts like **82a** and **82b** form in displacements of thioalkoxide anions by alkoxide anions. Such intermediates have a short lifetime, and only the visible spectra have been reported.[201–203] Recently, the adducts **84a** and **84b** have been firmly characterized as intermediates in the rearrangements of *N,N'*-dimethyl-*N*-(2,4,6-trinitrophenyl) glycinamide (**83a**) and the related alanine derivative **83b** into the acetamide and propanamide compounds **85a** and **85b**, respectively (eq. 1-20).[204,205]



80

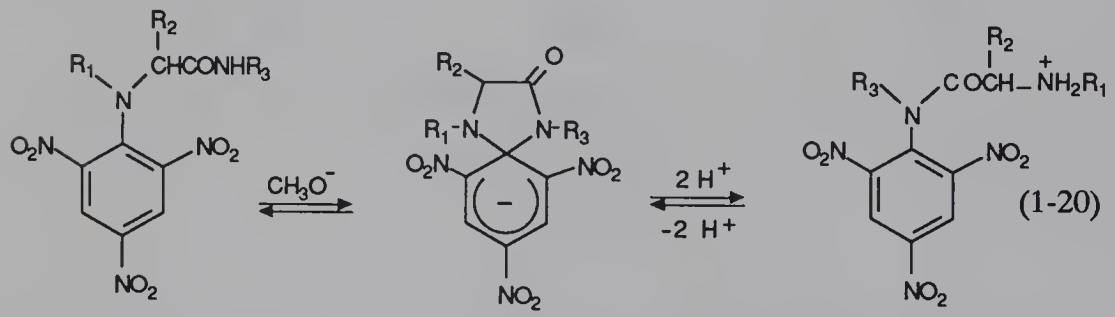


81



82

(a) n=2 ; (b) n=3



(1-20)

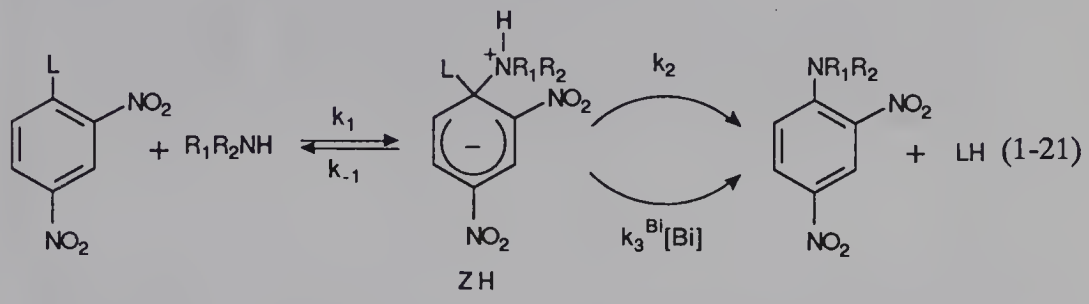
83 **84** **85**

(a) $R_1 = R_3 = CH_3$; $R_2 = H$; (b) $R_1 = H$; $R_2 = R_3 = CH_3$

1.6 Base Catalysis in S_NAr Reactions of Nitroaromatics

Compelling evidence for the S_NAr mechanism comes from kinetic studies of systems that have the property of undergoing changes in the rate-limiting

step or have at least marked variations in relative rates of intermediate complex formation and decomposition either by addition of external agents or more simply by varying the concentration of the nucleophilic reagent.[7,8] Reactions of some nitro-activated aromatics with primary and secondary amines have played a central role in this regard.[7,8,19–21] This is most easily seen with reference to the reaction shown in eq. 1-21, which is representative of the most frequently studied type of aromatic substrate.



(1-21)

As is apparent from eq. 1-21, the initially formed zwitterionic adduct (ZH) contains a labile NH proton, which can be removed by a base. The system thus lends itself to the influence of Brønsted base catalysis, and the intermediate can proceed to products either spontaneously (k_2) or via the alternative pathway(s) afforded through removal of the NH proton (the k_3^{Bi} steps). Since the latter process is expected to have low activation energy, the alternative decomposition pathway(s) should be relatively favored. Hence, the addition of base to the reaction mixtures should sometimes considerably affect the relative rates of product formation versus reversion to reactants of the intermediate, and thus affect the overall rate-controlling step. In typical experiments, the base may be the amine used as the nucleophilic reagent, but it may also be a lyate ion (OH^-, RO^-) or any other base that is specifically added to the reaction mixture.[7,8,19,20]

Assuming for simplicity that only a particular base B is an effective catalyst in eq. 1-21, the situation is expressed quantitatively by the rate expression shown in eq. 1-22, which is derived by applying the steady-state approximation to the reaction shown in eq. 1-21; k_A is the measured second-order rate constant at a given concentration of B, while the other rate constants are defined as shown in eq. 1-21.

$$\frac{\text{rate}}{[\text{Ar–L}][\text{R}_1\text{R}_2\text{NH}]} = k_A = \frac{k_1k_2 + k_1k_3^B[\text{B}]}{k_{-1} + k_2 + k_3^B[\text{B}]} \qquad (1\text{-}22)$$

Equation 1-22 suggests three main situations of interest with respect to the reaction shown in eq. 1-21.

1. $k_2 + k_3^B [B] >> k_{-1}$. In this case, the formation of the intermediate is rate limiting. Equation 1-22 simplifies to:

$$k_A = k_1 \tag{1-23}$$

and there is no possibility for base catalysis. The reactions show energy profiles of the type depicted in Fig. 1.1a.

2. $k_2 + k_3^B [B] << k_{-1}$. This situation corresponds to formation of the intermediate ZH in a rapidly established preequilibrium, and the decomposition of ZH is the rate-determining step. Equation 1-22 reduces to eq. 1-24, which predicts base catalysis with a linear dependence of k_A on the base concentration.

$$k_A = \frac{k_1 k_2}{k_{-1}} + \frac{k_1 k_3^B [B]}{k_{-1}} \tag{1-24}$$

3. $k_2 + k_3^B [B] \sim k_{-1}$. In this intermediate situation, eq. 1-22 indicates that base catalysis should be also observed, with k_A depending on base concentration in curvilinear fashion; approximate linear dependence at low [B] will change to a plateau at high [B] where formation of the intermediate becomes rate limiting ($k_A = k_1$).

All three situations have been recognized in the numerous kinetic studies devoted to the reactions shown in eq. 1-21.[6,7,19,20,206–208] These studies have also shown that the occurrence or absence of base catalysis, as well as the efficiency of this catalysis, depends on the identity of the amine, the leaving group, the base, and the solvent.[7,29,31,134,206,207] In general, base catalysis is more often observed with secondary than with primary amines, with poor leaving groups, and in less polar solvents.[7] The incidence and form of the base catalysis is presented in Table 1.10 for some selected reactions shown in eq. 1-21. Most data pertaining to systems studied prior to 1973 have been classified by Bernasconi.[7] Recent works on substitutions of nitrothiophene derivatives have shown that reactions presented in eq. 1-21 are applicable to heterocyclic systems.[209–211]

Among the several factors, the influence of the leaving group appears to be the most straightforward, since it can be readily anticipated that the condition $k_{-1} >> k_2 + k_3^B [B]$ required for the observation of base catalysis will be more easily fulfilled with sluggish (F, OR, SR) than with good or moderately good (Cl, Br, I) leaving groups. Table 1.10 shows that the k_2/k_{-1} ratios are commonly much greater than 1 for L = Cl but often much less than 1 or of the order of 1 for L = F, OCH_3, and OC_6H_5. Also noteworthy is that the k_3^B/k_2 ratios, which can be used as a measure of the efficiency of the catalysis,

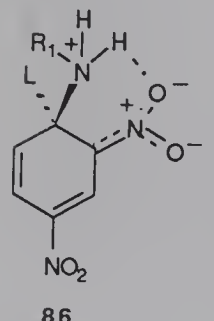
Table 1.10. Occurrence and Form of Base Catalysis in S_NAr Reactions of 1-L-2,4-Dinitrobenzenes by Amines in Various Solvents[a]

Entry	Solvent	L	Amine	t (°C)	Base catalysis	k_1 ($l\ mol^{-1}\ s^{-1}$)	k_2/k_{-1}	k_3^B/k_{-1}	k_3^B/k_2
1	10% Dioxane/90% H_2O	F	$(CH_3)_3CNH_2$	20	No	5.9×10^{-3}	>>1		
2		OCH_3	Piperidine	29.4	OH^-	3.77×10^{-3}	$\sim 10^{-4}$	25.7	$\sim 2.5 \times 10^5$
					Piperidine			0.15	1500
3		OC_6H_5	Piperidine	29.4	OH^-	3.10×10^{-2}	0.069	121	1750
					Piperidine			7.86	112
4		SC_6H_5	Piperidine	29.4	OH^-	8.4×10^{-4}	0.15	6.55	43.6
5	50% Dioxane/50% H_2O	Cl	$C_4H_9NH_2$	24.8	No	2.2×10^{-3}	>>1		
6		Cl	Piperidine	0	No	1.4×10^{-2}	>>1		
7	Methanol	F	Piperidine	25	No	6.46	>>1		
8		OCH_3	Piperidine	67.9	CH_3O^-		<<1		α[b]
9	Benzene	F	$C_4H_9NH_2$	25	$C_4H_9NH_2$	0.71	0.24	50	210
10		F	$(CH_3)_3CNH_2$	25	$(CH_3)_3CNH_2$	0.01	0.19	20.9	108
11		F	Piperidine	25	Piperidine		<<1		1230
					DABCO[c]				64.5
12		F	Morpholine	25	DABCO[c]		<<1		444
13		F	*p*-Anisidine	25	*p*-Anisidine		<<1		>22
					DABCO[c]				>5500
14		Cl	$C_4H_9NH_2$	25	No	3.9×10^{-4}	>>1		
15		Cl	Piperidine	25	No	8.5×10^{-2}	>>1		
16		Cl	*p*-Anisidine	25	*p*-Anisidine		<<1		7.2
					DABCO[c]				99

[a] Data taken from Bernasconi, C. F., *Int. Rev. Sci., Org. Chem. Ser. 1*, **1973**, *3*, 33, by permission of the publishers, Butterworth Heinemann (Publishers) Ltd.
[b] Noncatalyzed contribution could not be detected.
[c] DABCO = 1,4-diazabicyclo[2.2.2]octane

increase with decrease of the leaving group ability (entries 2–4 in Table 1.10). On the other hand, since the reversion of the zwitterionic intermediate to reactants leads to a charge neutralization, k_{-1} is expected to increase strongly in nonpolar solvents, thus favoring $k_{-1} >> k_{-2} + k_3^B$ [B] and the occurrence of base catalysis.[7,29,31] This expectation is borne out by experimental data: the reaction of 1-fluoro-2,4-dinitrobenzene with *t*-butylamine is not base catalyzed in 10% dioxane/90% H_2O ($k_2/k_{-1} >> 1$) but is base catalyzed in benzene ($k_2/k_{-1} = 0.19$).[7,208] Similarly, the reaction of a heterocyclic derivative like 2-phenylsulfonyl-5-nitrothiophene with piperidine shows no appreciable catalysis in methanol but is strongly subject to catalysis by piperidine in benzene.[212]

The role of an ortho-NO_2 group appears to be responsible for the greater difficulty in detecting base catalysis with primary ($k_2/k_{-1} >> 1$) compared with secondary ($k_2/k_{-1} < 1$) amines in reactions presented in eq. 1-21. As discussed in Section 1.4.1, there is evidence for stabilization of zwitterionic intermediates of ortho-nitro derivatives through intramolecular hydrogen bonding between an ammonio proton and the ortho-NO_2 group.[163] Such stabilization is expected to reduce the k_{-1} value for reversion to the reactants at about the same extent for primary and secondary amines because in both structures **86** and **87** the process requires initial breaking of the hydrogen bond.[7] In contrast, the influence should be different on k_2, since the spontaneous decomposition of the zwitterion is commonly viewed as involving an intramolecular transfer of an ammonio proton to the leaving group, either via the transition state **88** in aprotic solvents like benzene[213] or the transition state **89** in hydroxylic solvents.[7] In the intermediate **86** for primary amines, there is a non-hydrogen-bonded proton available, so that the possibility for spontaneous decomposition is not much affected by the hydrogen bonding. In **87**, on the other hand, there is only one proton available for the transfer and it is tied up in a hydrogen bond. This should reduce the susceptibility to spontaneous decomposition, hence decreasing the ratio k_2/k_{-1} for secondary amines compared with that for primary amines. The effect should be especially large in nonpolar solvents like benzene, which reinforce the hydrogen bonding and, in fact, drastically dif-



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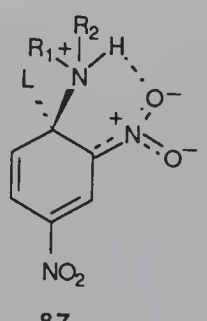
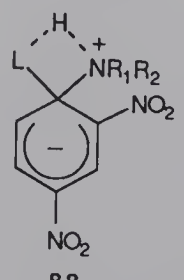
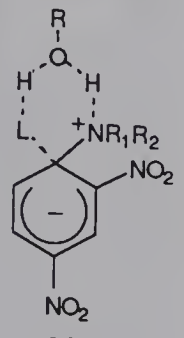


87



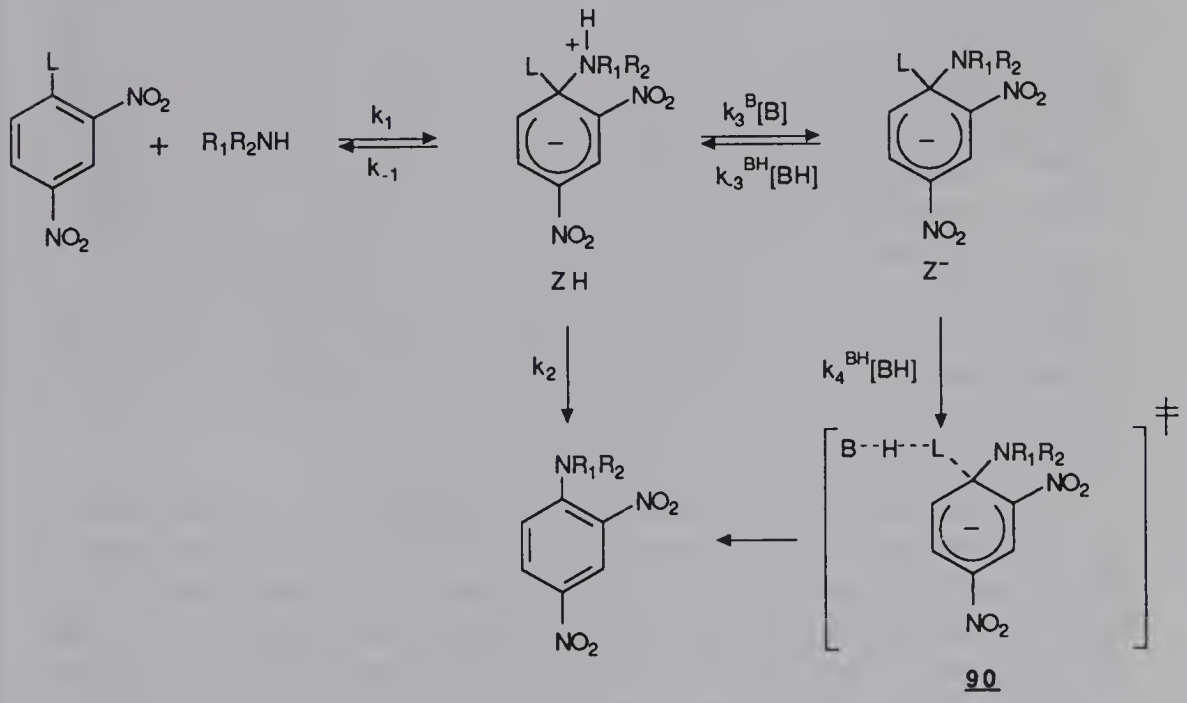
88



89

ferent k_2/k_{-1} values are found for the reactions of 1-fluoro-2,4-dinitrobenzene with *n*-butylamine (k_2/k_{-1} = 0.24) and with morpholine or piperidine (k_2/k_{-1} << 1) in this solvent.[7] Of interest is that reactions of both 1-fluoro-2,4-dinitrobenzene and 1-chloro-2,4-dinitrobenzene with weakly basic primary amines (e.g., *p*-anisidine) are base catalyzed in benzene (see entries 13 and 16 in Table 1.10).

Understanding of how the base catalysis is operative in reactions in which the decomposition of the zwitterionic intermediate is, at least partially, rate limiting has considerably improved in recent years.[8,19–21,131,132] Two major mechanisms, which are known as the specific base–general acid (SB-GA) and the rate-limiting proton transfer (RLPT) mechanisms, are now well substantiated.[7,8] Both these mechanisms can be discussed usefully in relation to the detailed formulation in Scheme 1.3. In all cases, the effect of the base is to deprotonate the initially formed zwitterion ZH, yielding the anionic σ-complex Z^-, which subsequently decomposes to products. Scheme 1.3 does include the afore-discussed uncatalyzed decomposition step (k_2), which corresponds to the energy profile of Fig. 1.1b. However, this pathway often contributes negligibly to the overall process and, for simplicity, it is sometimes omitted in the forthcoming discussion.



Scheme 1.3.

1.6.1 The Specific Base–General Acid Mechanism

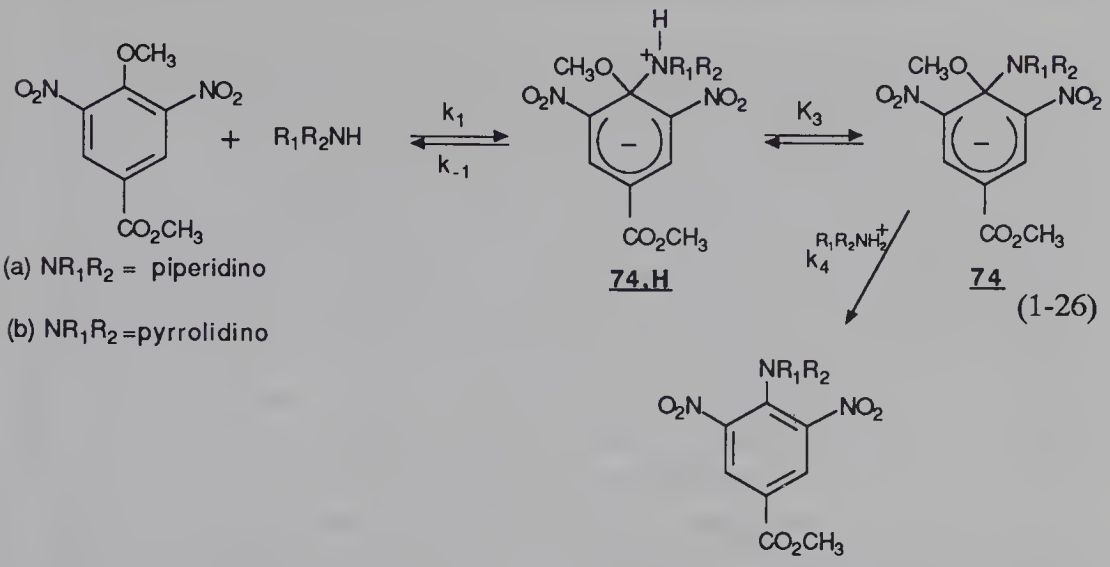
The SBGA mechanism consists of a rapid equilibrium deprotonation of the zwitterionic σ-complex ZH, followed by rate-limiting, general acid catalyzed leaving group departure from the anionic σ-complex Z^- via the concerted transition state **90**. It is a mechanism that satisfies the overall requirements of the phenomenological rate law in eq. 1-22, since the derived expression for the reaction on the basis of Scheme 1.3 is

$$k_A = \frac{k_1k_2 + k_1k_4^{BH}K_3[B]}{k_{-1} + k_2 + k_4^{BH}K_3[B]} \qquad (1\text{-}25)$$

where k_4^{BH} is the rate coefficient for acid-catalyzed expulsion of L from Z^- and K_3 is the equilibrium constant for the reaction $ZH + B \rightleftharpoons Z^- + BH$.

The SB-GA mechanism was suggested in the 1960s and generally accepted in 1970 after a study of Orvik and Bunnett of the reaction of 2,4-dinitro-1-naphthyl ethyl ether (**68**) with *n*-butylamine and *t*-butylamine in DMSO (Scheme 1.2).[21,214] In this kinetic study, the authors presented evidence that these S_NAr reactions proceed in two distinct stages. They identified the first stage as being the sum of eqs. 1-15 and 1-16: that is, nucleophilic addition of the amine occurs to give **69a,H** or **69b,H** which is rapid and reversible acid–base equilibrium with its conjugate base **69a** or **69b**. The equilibrium **69,H**$\rightleftharpoons$**69** was found to lie strongly on the side of **69**, in accordance with a subsequent flow NMR characterization of the intermediate **69a** (see Section 1.5)[10,189] Formation of **69a** and **69b** is not base catalyzed. The second stage is the transformation of these anionic species into the expected naphthylamines **70a** and **70b**, *which was found to be first order in butylammonium ion but independent of amine concentration.*[21] This observation is fully consistent with general acid catalysis nucleofuge expulsion as indicated in Scheme 1.3. Note that because **70a** and **70b**, which derive from primary amines [R_1 = H, R_2 = C_4H_9 or $(CH_3)_3C$], have a relatively acidic NH proton in DMSO, these compounds exist in solution largely in an anionic form.[21]

A similar overall SB-GA behavior in DMSO has been recently reported for the reactions of 2,4,6-trinitroanisole, 2,4,6-trinitrophenetole, and methyl 4-methoxy-3,5-dinitrobenzoate with *n*-butylamine, and for the reaction of this latter compound (eq. 1-26) and of the naphthyl ether **68** (Scheme 1.2) with piperidine and pyrrolidine.[11,132,134,191,192,215,216] Comparison of the substitution reactions involving the two secondary amines is of special interest. While the rate parameters (k_1) obtained for formation of the zwitterionic inter-



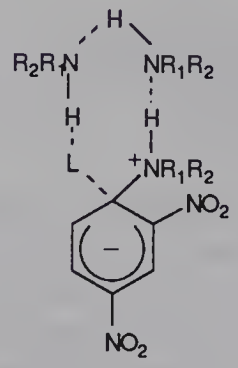
(a) NR_1R_2 = piperidino

(b) NR_1R_2 = pyrrolidino

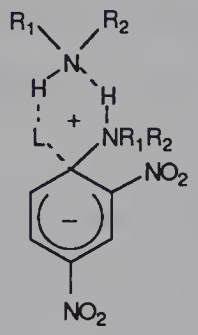
(1-26)

mediates **69c,H** and **69d,H** or **74a,H** and **74b,H** are consistent with the general trend observed in S_NAr reactions (pyrrolidine is more reactive than piperidine by a factor of about 2.5), the results obtained for the second stage of the reactions were rather unexpected.[132,134,191,192] The rate constant k_4 for decomposition of the pyrrolidine adduct **69d** is about 11,000 times greater than that for the piperidine analogue **69c**.[132,134] Similarly, the general acid catalyzed decomposition of the pyrrolidine intermediate **74b** is considerably faster than that of the piperidine analogue **74a**.[192] All the available information indicates that the most plausible interpretation of these huge differences between systems apparently so similar is in terms of stereoelectronic or conformational factors that result in destabilization of the transition states for general acid catalyzed expulsion of the leaving group in the piperidine systems relative to pyrrolidine.[132,134] Interestingly, the sensitivity of the efficiency of the acid catalysis of the leaving group departure to structural factors is in itself a criterion for the validity of the SB-GA mechanism.

Convincing evidence for the SB-GA mechanism has been obtained in other dipolar aprotic solvents like acetone or acetonitrile.[217,218] In the latter solvent, efficient base catalysis by Cl^- ion has been found in the substitution of 1-fluoro-2,4-dinitrobenzene with *N*-methylaniline.[219] In nonpolar aprotic solvents like benzene or toluene, different modifications of the Bunnett mechanism have been suggested to account for the inability of these solvents to stabilize ionic species.[161b,220–222] Most proposals assume that decomposition of the intermediate then proceeds via a cyclic transition state like **91**. Another possibility in these solvents is the so-called dimer mechanism, which involves initial attack of a dimer of the amine to give first the cyclic intermediate **92**.[161b,222] Mechanisms involving bifunctional catalysis have been suggested in specific instances.[7,8,223]

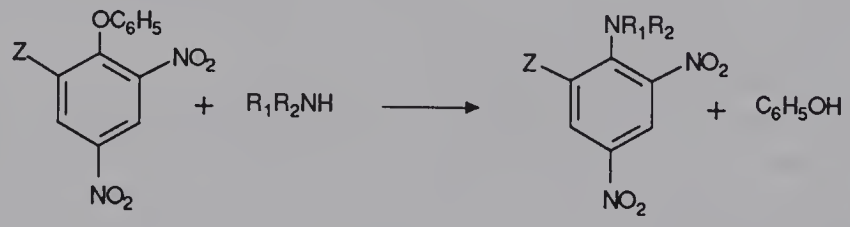


91



92

The occurrence of the SB-GA mechanism in protic solvents was questioned after the discovery that rate-limiting proton transfer may in fact be more favored in such media.[19,20] There is little doubt, however, that this mechanism operates in such systems. A recent study by Bunnett and Cartano of the reactions of 2,4-dinitrophenyl phenyl ether (**93a**) and 2,4-dinitro-6-methylphenyl phenyl ether (**93b**) with pyrrolidine and piperidine in 60% dioxane/40% water is relevant.[131] All four amino-dephenoxylation reactions shown in eq. 1-27 are catalyzed by NaOH, and the rate of base-catalyzed transformation of the intermediate σ-adducts to products is an order of magnitude faster for pyrrolidine than for piperidine systems. Although the reactivity difference between the two amines in these instances is smaller than in the naphthyl systems in DMSO (Scheme 1.2), the trend is in the same direction and calls for a similar explanation (i.e., destabilization of the transition state for general acid catalyzed expulsion of the OC_6H_5 group in the piperidine system), thus supporting the view of an SB-GA mechanism.[131]



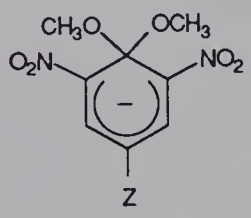
(1-27)

93 (a) Z=H ; (b) Z=CH_3

R_1R_2N = piperidino or pyrrolidino

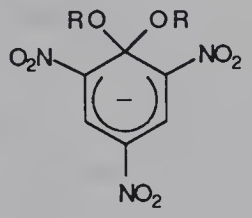
The SB-GA mechanism, as discussed above, would imply that leaving group departure from stable σ-complexes is also subject to general acid catalysis. A number of studies of this type have in fact been performed on the reversion to reactants of various 1,1-dialkoxy σ-adducts, **94** and **95**, and of spiro adducts, **96** and **97**, with interesting results.[224–228] Catalysis of the reactions by acids whose pK_a values are 6 or less was found in aqueous and/or

methanolic solution.[224–228] The slopes of the corresponding Brønsted plots ($\alpha \sim 0.5 \pm 0.1$) together with the magnitude of some observed isotope effects (e.g., $k^{D_3O^+}/k^{H_3O^+} = 1.5$ for the picryl adduct **96**) indicate that the decomposition occurs via a transition state like **98**.[224–228] This is consistent with the concerted mechanism suggested for acid catalysis of leaving group expulsion from the anionic intermediate in the SB-GA mechanism. However, a noteworthy feature is that the observed acid catalysis is relatively weak, suggesting that the influence of the acid present under typical reaction conditions of S_NAr substitutions by amines is too weak to be kinetically significant in most cases in protic solvents. Accordingly, the SB-GA mechanism would be the exception (e.g., eq. 1-27) rather than the rule in these solvents.[19,20]



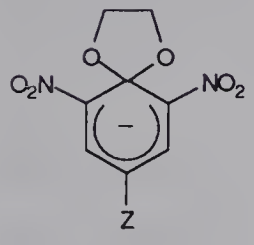
94

Z = SO_2CF_3, NO_2, CN, SO_2CH_3



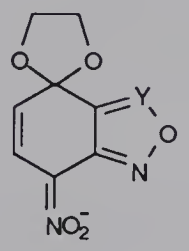
95

R = CH_3, C_2H_5, $CH_3OCH_2CH_2$, $ClCH_2CH_2$, $HC{\equiv}C{-}CH_2$



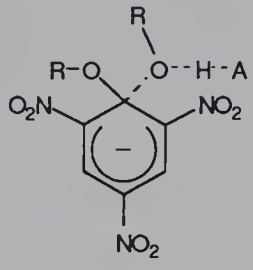
96

Z = SO_2CF_3, NO_2, CN, SO_2CH_3, Cl, H



97

Y = N, N→O



98

R as in **94** - **97**

1.6.2 The Rate-Limiting Proton Transfer Mechanism

In the RLPT mechanism, the initially formed zwitterion ZH (Scheme 1.3) undergoes rate-limiting, base-induced deprotonation followed by rapid uncatalyzed or acid-catalyzed leaving group departure from the anionic inter-

mediate Z^-.[19,20] For a better understanding of this situation, let us consider the reaction in protic solvents and express Scheme 1.3 as indicated in eq. 1-28.

$$\mathrm{ArL} + \mathrm{R_1R_2NH} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{ZH} \underset{k_{-3p}}{\overset{k_{3p}}{\rightleftharpoons}} \mathrm{Z^-} \xrightarrow{k_4} \mathrm{P} \qquad (1\text{-}28)$$

$$k_{3p} = \sum_i k_{3p}^{B_i}[Bi] + k_{3p}^{RO}[RO^-] \qquad (1\text{-}29)$$

$$k_{-3p} = \sum_i k_{-3p}^{BH_i}[BHi] + k_{-3p}^{ROH} \qquad (1\text{-}30)$$

$$k_4 = \sum_i k_4^{BH_i}[BHi] + k_4^{ROH} \qquad (1\text{-}31)$$

The rate constants k_{3p} and k_{-3p} are defined by eqs. 1-29 and 1-30, where $k_{3p}^{B_i}$ and k_{3p}^{RO} refer to deprotonation of ZH by general bases B_i (notably R_1R_2NH) and by the lyate ion (RO^-), respectively, while $k_{-3p}^{BH_i}$ and k_{-3p}^{ROH} refer to protonation of Z^- by general acids ($R_1R_2NH_2^+$) and by the solvent (ROH). Rate constant k_4 is defined by eq. 1-31, where $k_4^{BH_i}$refers to catalysis of leaving group departure by general acids ($R_1R_2NH_2^+$), while k_4^{ROH} refers to the unassisted or solvent-assisted leaving group departure.

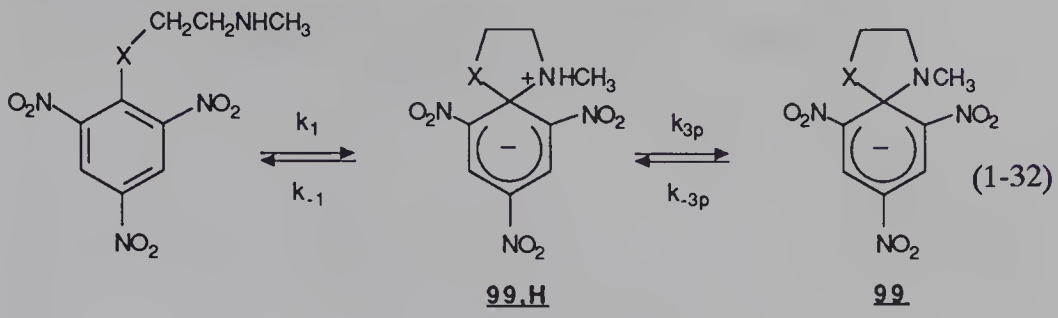
Typically, ZH and Z^- are steady-state intermediates. It follows from eq. 1-28 that for deprotonation of ZH to be the overall rate-limiting step and thus responsible for the observed base catalysis, the necessary conditions are:

$$k_4 >> k_{-3p} \quad \text{and} \quad k_{-1} > (>) k_{3p}$$

If the first but not the second condition were met, no catalysis would be observed.[8,19,20]

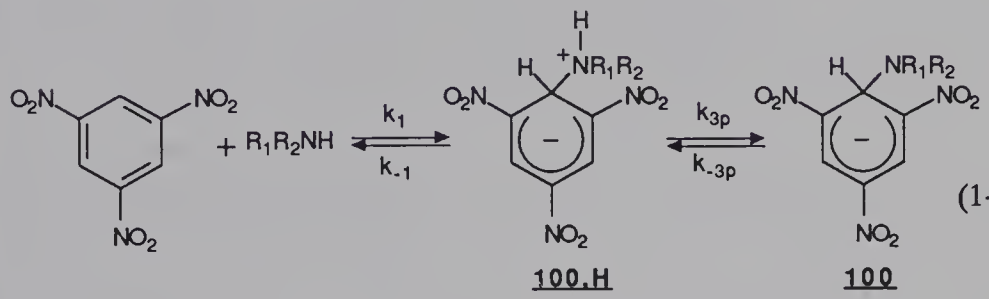
At present, the evidence that the RLPT mechanism can operate in S_NAr reactions has mainly come from studies of the formation and decomposition of stable σ-adducts, rather than from studies of actual displacements.[194,229–236] Various temperature-jump studies on model reactions such as shown in eq. 1-32 (X = N—CH_3, O) or eq. 1-33 have been decisive in this regard.[194,229–231,233] These reactions have revealed that amine departure from zwitterionic complexes like **99,H** or **100,H** is remarkably fast, for example:

$k_{-1} = 1.9 \times 10^5\ s^{-1}$ in aqueous solution when X=NCH_3 in **99,H** or
$k_{-1} = 1.5 \times 10^5\ s^{-1}$ in 10% dioxane/90% water when R = H, R′ = *n*-C_4H_9 in **100,H**.[229,231]



(1-32)

X = NCH_3 , O

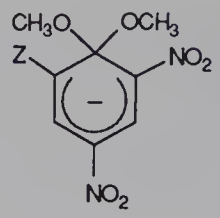


(1-33)

R_1R_2NH=n-$C_4H_9NH_2$, CH_3NH_2 , $C_6H_5CH_2NH_2$,$(CH_3)_2CHNH_2$, $CF_3CH_2NH_2$,
$C_6H_5NH_2$, $C_5H_{11}N$, C_4H_9N , $(CH_3)_2NH$, $(C_2H_5)_2NH$

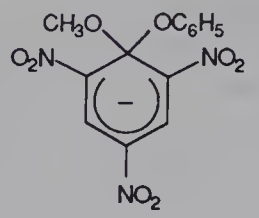
As a consequence, deprotonation of **99,H** or **100,H**, even though thermodynamically favored and thus essentially diffusion-controlled, becomes rate limiting ($k_{3p} << k_{-1}$) or partially so ($k_{3p} < k_{-1}$) at low pH and low buffer concentrations.[19,20] Extrapolation of these results to typical S_NAr substrates like the less activated 2,4-dinitrobenzene derivatives of Scheme 1.3 leads to estimated k_{-1} values of the order of 10^7 to 10^8 s^{-1}. Hence for these derivatives, and even more so for mononitro derivatives, the first relationship ($k_{3p} << k_{-1}$) required for the RLPT mechanism can be expected to hold even in the rather high base concentrations commonly used in studies of base catalysis of S_NAr reactions.[19,20]

Other results show that the second condition to be fulfilled, $k_4 >> k_{-3p}$, is most probably met in many cases. From studies of the rates of alkoxide and phenoxide ion departure from complexes like **101** and **102**, Bernasconi has safely extrapolated $k_4^{H_2O}$ values of 4–8 × 10^7 s^{-1} for the spontaneous or solvent-assisted departure of typical leaving groups in reactions (eq. 1-28 and Scheme 1.3) occurring in aqueous solution.[19] This means that k_4 must always be very high even though the contribution of the catalytic term $k_4^{BH_i}$ [BH_i] is low.[19] On the other hand, studies of reactions shown in eqs. 1-32 and 1-33 have indicated that the basicity of the amino moieties in anionic adducts like **99** and **100** is much less than the basicity of the parent amine ($\Delta pK \geq 2$).[229–231] As a consequence, the k_{-3p} step



101

Z = H , NO_2



102

refers to a thermodynamically unfavorable proton transfer under all typical conditions, with a corresponding low rate. This implies that the condition $k_4 >> k_{-3p}$ must hold for all reactions involving good leaving groups.[8,19,20]

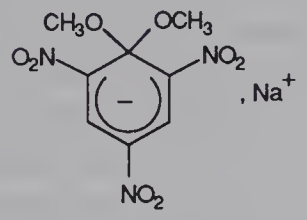
First proposed by Bunnett and Randall in 1958,[113] the RLPT mechanism was initially rejected when it became known that proton transfers between "normal" (O,N) acids and bases generally proceed at close to diffusion-controlled rates.[237] However, it is now established that diffusion-controlled proton transfer steps can be overall rate determining in multistep processes where the species undergoing deprotonation is present in a highly unfavorable equilibrium, or where reversion of this species is extremely rapid.[20] Clearly, the S_NAr reactions of nitro activated aromatics with amine nucleophiles represent a remarkable example of this situation.

1.7 Medium Effects

The solvent is an important parameter determining the energetics of S_NAr substitutions of nitroaromatics. Changes in reactivity due to transfer from protic to dipolar aprotic solvents have especially been studied.[8,60,61,67–69,76,238–243] Reactions with anionic nucleophiles in the presence of crown ethers or under conditions of phase transfer catalysis (PTC) are the subject of increasing investigation.[244–248] Much attention is also paid to the effect of micellar surfactants or oil–water microemulsions and related alcohol-modified micelles.[123,249–251] Effects of molten dodecyltributylphosphonium salts on nucleophilic aromatic substitutions by halide ions have been recently reported.[252]

1.7.1 S_NAr Reactions Involving Anionic Nucleophiles

The effect of dipolar aprotic solvents is to increase the energy of small anions with high charge density and to decrease that of large polarizable anions.[239,240] Since they have a negative charge that is largely dispersed through one or more NO_2 groups, nitrocyclohexadienyl anions belong to the latter category. This is evidenced by measurements of notably exothermic heats of transfer (ΔH_T,) for the sodium salts of the picryl σ-adducts **103** and **104** in CH_3OH/DMSO mixtures.[253,254] The ΔH_T, values are –28.3 and –41 kJ/mol for **103** and **104**, respectively, in 5–95 (v/v) CH_3OH/DMSO, as



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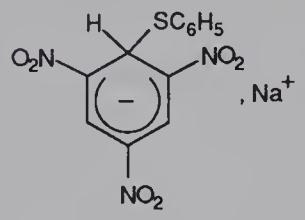


104

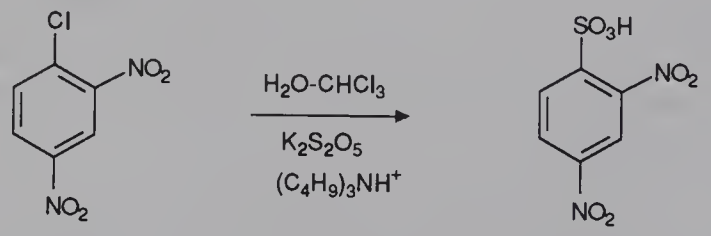
compared with a ΔH_T value of +44.5 kJ/mol for $NaOCH_3$ in the same solvent.[253,254] Hence, and even though the stabilization of mononitro- or dinitro-substituted cyclohexadienyl anions is less than that of trinitro analogues, the effect of a transfer from a protic to a dipolar aprotic solvent on reactions shown in eq. 1-3 [i.e., $(O_2N)_x$ Ar—L + Nu^- → $(O_2N)_x$ Ar—Nu + L^-], is commonly to raise or to leave unchanged the energy of the initial and final states and to decrease that of the intermediate and related transition states. In most cases, the net result of the solvent transfer is an increase in the rate of the overall substitutions. For similarly nitro-activated substrates, this increase is usually greater for small and strongly hydrogen-bonded anionic nucleophiles (e.g., F^-, OH^-, RO^-) than for more polarizable nucleophiles (e.g., ArO^-, ArS^-).

Of special interest is the behavior of F^-, which is a poor nucleophile in water or alcohols but becomes a relatively powerful nucleophile in solvents like DMSO or DMF. Even in heterogeneous reactions, fluoride–halogen exchanges can then be achieved in these solvents, providing a useful route to nitro activated aryl fluorides from the treatment of other aryl halides with alkali fluorides.[117,255,256] Displacement of an NO_2 group by F^- also occurs under such conditions.[257] Use of crown ethers may help in solubilizing alkali fluorides, the complexation of the metal ion being accompanied by generation

of a poorly solvated—"naked"—and very reactive fluoride anion.[245,255] Desolvation of a number of anionic reagents (e.g., OH^-, N_3^-, $HOCH_2CH_2S^-$, SO_3^{2-}) has been achieved in a protic solvent [75–25 (v/v) H_2O/CH_3OH) through inclusion into the molecular cavities of various macrocyclic quaternary ammonium salts. This causes a significant acceleration of the substitutions of halonitroarenes such as 1-chloro-2,4-dinitrobenzene, 1-fluoro-2,4-dinitrobenzene, and 4-chloro-3,5-dinitrobenzoate ion with these reagents.[248]

More generally, crown ethers have been used to promote S_NAr reactions in solvents of low ionizing character. They reduce the ion pairing and thereby increase the nucleophilicity of the anionic species.[245,258] A prototype example is the 2000-fold increase in reactivity of potassium *t*-butoxide with 1-fluoro-4-nitrobenzene to give 1-*t*-butoxy-4-nitrobenzene when 18-crown-6-ether is added to the *t*-butanol solution.[244]

Substitutions of nitroaromatic substrates under PTC conditions have recently been developed.[246,247,259–262] The almost complete desolvation of the anion increases the nucleophilicity to about the same extent as that induced by dipolar aprotic solvents. This technique is very powerful for synthetic purposes.[259–264] A reaction that is readily achieved under PTC conditions is the sulfodechlorination of 1-chloro-2,4-dinitrobenzene by sulfite anion to give 2,4-dinitrobenzenesulfonic acid (eq.1-34).[247,261] PTC conditions have also



(1-34)

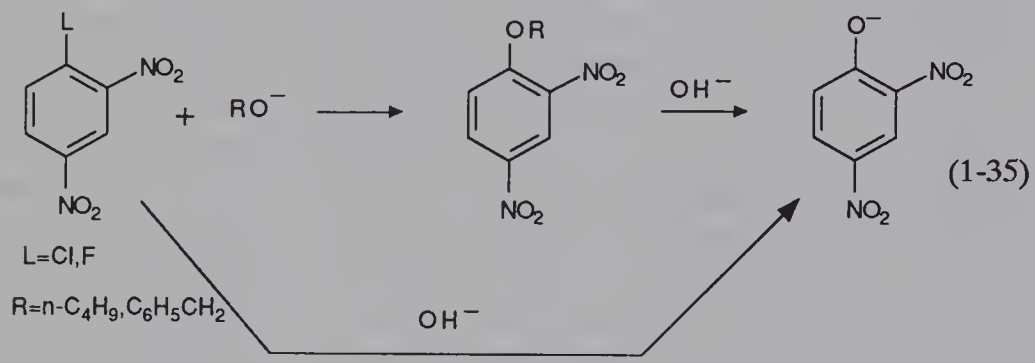
been successfully applied to promote S_NAr reactions of aryl halides not containing NO_2 groups.[265] Several kinetic studies have shown that the rate-determining step of the reactions is not necessarily affected by PTC conditions. For instance, rates of substitution of 1-halo-4-nitrobenzenes with hexadecyltributylphosphonium azide in a water–chlorobenzene two-phase system are linearly related to the concentration of N_3^- in the organic phase and decrease in the order F >> Cl ~ Br.[266] This indicates that addition of the nucleophile is rate limiting, as found under classical S_NAr conditions. In contrast, there is evidence that the rate-limiting step of analogous substitutions with 1-halo-2,4-dinitrobenzenes depends on the nature of the halogen. Whereas the reaction of the chloro derivative follows regular kinetics with rate-determining addition of the nucleophile, those of the fluoro and bromo

compounds are mainly or partly controlled by anion diffusion at the interface.[266]

In aqueous solution, cationic micelles like cetyltrimethylammonium bromide (CTABr) increase, while anionic micelles like sodium lauryl sulfate (NaLS) decrease the rates of substitution of 1-halo-2,4-dinitrobenzenes and related halonitro derivatives with OH^-.[249a,267,268] Kinetic investigations of the reactions have shown that rate enhancements by cationic micelles are typically the result of the concentration of both the nitroaromatic and the nucleophile in the small volume of the micellar pseudophase.[267b] Thus, the second-order rate constants reflecting the reactivity of the nucleophile in the micellar pseudophase (k_{Nu}^{m}) are often very similar to or smaller than those in water ($k_{Nu}^{H_2O}$).[267b,268] This situation is similar to that found in many other rate enhancements of bimolecular reactions by cationic micelles.[269] Interesting exceptions are the reactions with N_3^-, since the second-order rate constants for substitution of 1-chloro-2,4-dinitrobenzene and 1-chloro-2,4-dinitronaphthalene are much larger in the micellar pseudophase than in water: the ratios $k_{N_3}^{-m}/k_{N_3}^{-H_2O}$ are about 50 and 200, respectively.[270] As discussed in Section 1.3.2.2, N_3^- is unusually unreactive in S_NAr reactions, suggesting that unfavorable transition state interactions disappear in reactions carried out in cationic micelles as compared with those in water. Electrostatic interactions do not favor the incorporation of anionic nucleophiles into anionic micelles, accounting for the observed decrease in the rates of substitutions carried out in the presence of such surfactants.[249a,271a] Recently, it has been shown that the effects of zwitterionic surfactants are strongly dependent on the structure of the aromatic.[271b]

Several S_NAr reactions of 1-halo-2,4-dinitrobenzenes have been investigated in oil–water microemulsions and related alcohol-modified micelles.[249b,250] For reactions involving only OH^-, the rate effects are much smaller than those in aqueous micelles. For example, a cationic microemulsion modestly speeds up the substitution, while an anionic microemulsion slightly inhibits it.[250] This suggests that the concentration of OH^- in the cationic droplets is lower than in cationic micelles and that the anionic droplets are less effective at excluding OH^- than anionic micelles. Both these effects are due to the greater volume of droplets as compared with micelles and to the decreased charged density at the aggregate surface, due to the presence of the alcohol.[250] In microemulsions containing a primary alcohol as the cosurfactant (1-butanol, benzyl alcohol), reactions of 1-fluoro-2,4-dinitrobenzene and 1-chloro-2,4-dinitrobenzene with lyate RO^- ions occur at higher rates than those with OH^-, so that the overall substitutions with OH^- are the sum of two distinct S_NAr processes (eq. 1-35).[272,273] Attack by RO^- first gives an ether, which

subsequently reacts with OH^- to give 2,4-dinitrophenoxide ion. Competitive formation of the latter anion through direct attack by OH^- is not always negligible (e.g., in 1-butanol).[272b] A similar reactivity sequence was found in the presence of hydroxyethyl and related surfactants in aqueous micelles.[267a,273] Interestingly, the σ-adducts leading to the intermediate aryl micellar ethers could be detected in some instances—for example, with a surfactant like cetyl(2,3-dihydroxypropyl)dimethylammonium bromide.[273b] S_NAr reactions with N_3^- ion in microemulsions show the same exceptional acceleration as that found in cationic aqueous micelles.[249]



(1-35)

1.7.2 S_NAr Reactions Involving Neutral Nucleophiles

Several studies have recently pointed out that the nature of the solvent may be important in determining whether the formation or the decomposition of the zwitterionic intermediate will be the rate-limiting step of S_NAr substitutions involving amines as nucleophiles.[7,19,20,131,218,274] Reactions are known, however, that exhibit the same rate-limiting step in a variety of solvents, allowing us to assess how the rate of a given process may be affected by a solvent transfer.[243,275] A simple example is the reaction of 1-chloro-2,4-dinitrobenzene with piperidine, which does not exhibit base catalysis in any of the protic and aprotic solvents studied; that is, addition of piperidine is rate limiting in all cases.[275] For aprotic solvents, the rates increase with increasing solvent polarity (Table 1.11), as a result of increased stabilization of the transition state leading to the zwitterionic intermediate. The observation of a satisfactory correlation between reactivity and the Dimroth parameter E_T in hydrogen bond acceptor aprotic solvents suggests that strong intramolecular hydrogen bonding between the ammonio proton and the ortho-NO_2 group, as described in Section 1.4.1, is responsible for the stabilization of the zwitterionic intermediate and of the corresponding transition state in these solvents. In

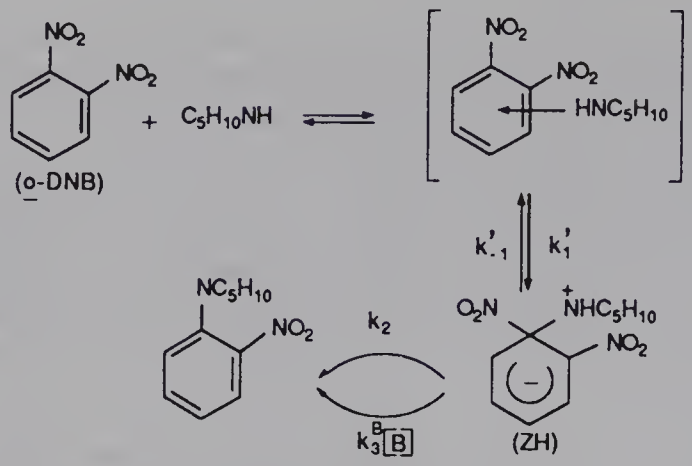
Table 1.11. Second-Order Rate Constants k_A for the Reactions of 1-Chloro-2,4-dinitrobenzene with Piperidine in Various Protic and Dipolar Aprotic Solvents at 25°C[a]

Protic solvents	$10^2 \times k_A$ ($l\ mol^{-1}\ s^{-1}$)	E_T (30)	Aprotic solvents	$10^2 \times k_A$ ($l\ mol^{-1}\ s^{-1}$)	E_T (30)
Methanol	1.41	55.5	Cyclohexane	3.84	31.2
Ethanol	1.80	51.9	Benzene	7.83	34.5
2-Methyl-1-propanol	1.90	49	Chloroform	8.65	39.1
1-Propanol	1.92	50.7	Dioxane	11	36
2-Propanol	2.51	48.6	1,1,1-Trichloroethane	18.9	36.2
2-Butanol	2.57	47.1	Chlorobenzene	20.2	37.5
Benzyl alcohol	1.02	50.8	Ethyl acetate	26.7	38.1
2-Phenoxyethanol	1.68	52	THF	29.5	37.4
2-Methoxyethanol	4.01	52.3	Acetone	49.1	42.2
Diethylene glycol	5.50	53.8	Nitromethane	79.1	46.3
			DMF	112	43.8
			DMSO	193	45

[a]Data reproduced with permission from Mancini, P. E. M.; Martinez, R. D.; Vottero, L. R.; Nudelman, N. S. *J. Chem. Soc., Perkin Trans. 2*, **1984**, 1133; Martinez, R. D.; Mancini, P. E. M.; Vottero, L. R.; Nudelman, N. S. *ibid.* **1986**, 1427.

hydroxylic solvents the reactivity is lower than in any of the aprotic solvents studied and no correlation exists with E_T values.[65] In this instance, the reactivity is inversely proportional to the hydrogen bond donating ability of the solvent, supporting the view that the relatively low rates of substitution are the result of a strong solvation of the amine molecules.[65]

Recent investigations have revealed that the reactions of *o*-dinitrobenzene (*o*-DNB) with piperidine in hexane and of 1-chloro- and 1-fluoro-2,4-dinitrobenzenes with various substituted anilines in benzene and THF involve the initial formation of molecular complexes that were formulated as charge–transfer complexes.[28,29,31] These complexes have been identified by UV–visible and NMR spectroscopy, and the equilibrium constants (K) for their formation were measured.[28,29,31] Interestingly, the corresponding substitution processes were all found to be subject to base catalysis by the various amines studied, but the observed catalysis could not be understood solely on the basis of the classical mechanisms depicted in eq. 1-21 or Scheme 1.3. In the case of

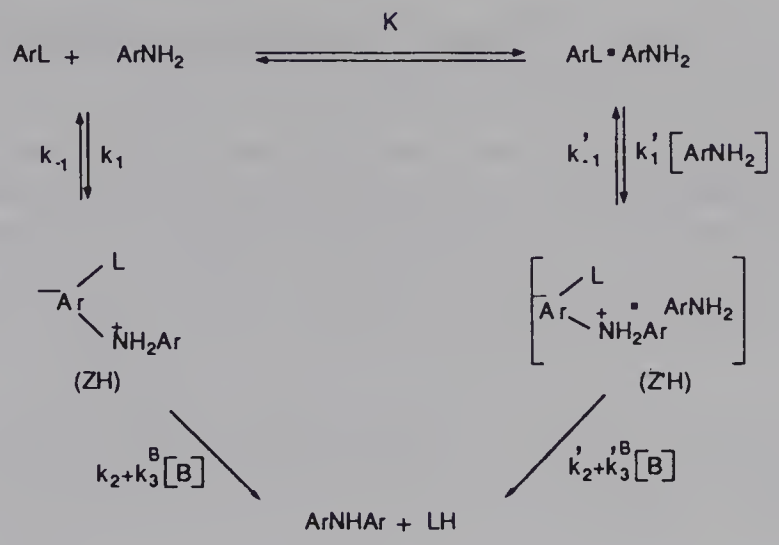


Scheme 1.4.

the *o*-DNB–piperidine system, the data were satisfactorily explained by Scheme 1.4, which assumes that the formation of the molecular complex precedes that of the σ-complex ZH during the overall substitution.[31] A similar mechanism was proposed to account for the base catalysis observed in the substitutions of picryl fluoride and 1,2,3,5-tetranitrobenzene with various aromatic amines in cyclohexane.[27] Contrasting with this view, Forlani and Tortelli have suggested that the molecular complexes formed in the reactions of 1-fluoro- and 1-chloro-2,4-dinitrobenzenes (ArL) with substituted anilines ($ArNH_2$) are not capable of further conversion to ZH.[28,29] Instead, they will suffer nucleophilic addition by a second molecule of aniline to give rise to a more reactive intermediate viewed as Z'H in Scheme 1.5. The substitutions would then proceed by the two competitive pathways, the latter contributing for the most part to the catalysis.[28,29]

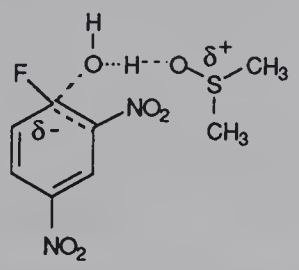
The idea that the reversible formation of a molecular complex of some stability can precede σ-complex formation in S_NAr substitutions, especially those conducted in nonpolar solvents of low dielectric constant, has long been advanced.[3,32] The foregoing studies give some experimental support to this hypothesis, but they do not definitely establish the exact role of the molecular complex in the reaction sequence. Further discussion of this important question, including the results of recent MNDO and AM1 calculations, is given in Chapter 7.

As in the case of amines, the nucleophilic reactivity of water and alcohols is strongly enhanced upon transfer from aqueous or alcoholic solutions to dipolar aprotic solvents. The first-order rate constant k^{H_2O} for solvolysis of 1-fluoro-2,4-dinitrobenzene changes from 2×10^{-7} s^{-1} in H_2O to about 10^{-5}



Scheme 1.5.

s^{-1} in 88.2% DMSO (by weight) at 40°C.[276] Considering the decrease in the water content of the solutions and assuming that only one water molecule participates in the reaction, this increase in k^{H_2O} reflects a 10^3-fold increase in the ability of a water molecule to act as a nucleophile. The reaction probably proceeds via a rate-determining transition state like **105**, where the DMSO molecule acts as a base catalyst.[277]

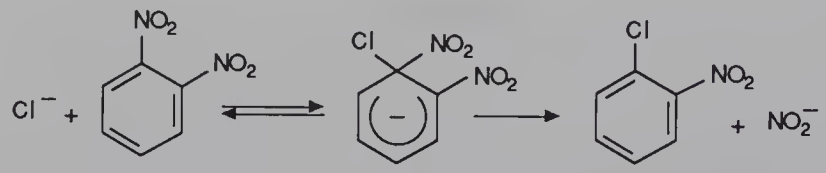


105

S_NAr substitutions of nitroaromatics like 1-chloro-2,4-dinitrobenzene and 2,4,6-trinitroanisole with amines are accelerated in aqueous micelles or microemulsions.[278,279] As with anionic nucleophiles, the rate enhancement is mainly the effect of a high local concentration of both the nitroaromatic and amine reagents in the micelles or in the microemulsion droplets.

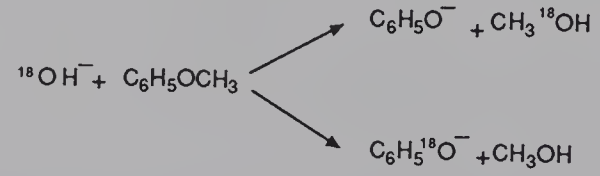
1.8 Gas Phase S_NAr Reactions

Gas phase nucleophilic substitutions in nitro-activated systems have so far received little consideration.[280] In 1977 Bowie and Stapleton reported a study of the reaction of chloride anion with *o*-dinitrobenzene (*o*-DNB) and observed an ion corresponding to a $[Cl,C_6H_4(NO_2)_2]^-$ species.[281] Although the exact structure of this ion could not be established, strong support for the S_NAr mechanism of eq. 1-36 was provided by the detection of the neutral chloronitrobenzene formed in the reaction. Small amounts of a chlorodinitrobenzene derivative were also detected, suggesting that competitive nucleophilic attack of chloride ion at an unsubstituted carbon of *o*-DNB occurred to a minor extent.



(1-36)

In fact, most reactions studied in the gas phase have involved nonactivated aromatic substrates.[280] Reaction of anisole with $^{18}OH^-$ was found to produce unlabeled phenoxide ion and ^{18}O/phenoxide ion in a 85:15 ratio.[282] On these grounds, it was suggested that the hydrolysis of anisole proceeds for 85% via an S_N2 pathway (eq. 1-37a) and for 15% via an S_NAr pathway (eq. 1-37b). The S_NAr mechanism would prevail in substitutions of pentafluoroanisole with various nucleophiles (OH^-, CH_3O^-, CH_3S^-, etc.).[283]

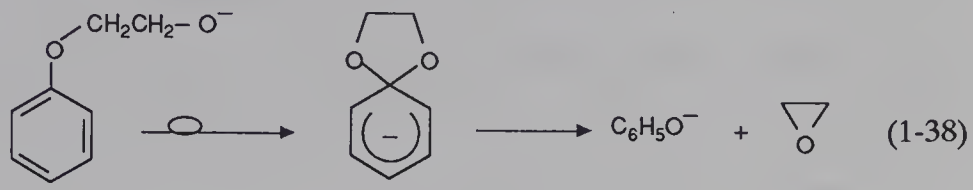


(1-37a)

(1-37b)

These results tend to indicate that gas phase S_NAr substitutions do not necessarily require activation of the aromatic system by electron-withdrawing substituents. Confirmation of this idea has recently come from a heavy atom (^{13}C, ^{18}O) labeling study of the formation of phenoxide ion from the decomposition of 2-phenoxy ethoxide ion **106** in the gas phase.[284] Thus, collisional activation mass spectra of $C_6H_5O(CH_2)_2{}^{18}O^-$ ion showed similar abundances of ^{16}O- and ^{18}O-phenoxide ions, suggesting that the decomposition of **106** proceeds via the symmetrical spiro complex **107**, as shown in eq. 1-38. That

nucleophilic attack of the alkoxide functionality occurs initially at the ring substituted carbon rather than at an unsubstituted ring carbon (e.g., the ortho carbon of **106**) was further demonstrated by the finding that the decomposition of a sample of **106** labeled with ^{13}C at position 1 of the benzene ring afforded phenoxide ion labeled exclusively with ^{13}C at position 1. The decomposition of 2-thiophenoxyethoxide ion to phenoxide and thiophenoxide ions was shown to proceed similarly via the intermediacy of an oxathiolane spiro adduct.[284]



(1-38)

106 **107**

To date, published data on nucleophilic aromatic substitutions in the gas phase do not provide comprehensive information concerning the role of electron-withdrawing substituents on the overall rates of these reactions.

References

1. Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273.
2. Bunnett, J. F. *Q. Rev. Chem. Soc.* **1958**, *12*, 1.
3. Miller, J. "*Aromatic Nucleophilic Substitution*", Elsevier: Amsterdam, 1968.
4. Ross, S. D. *Prog. Phys. Org. Chem.* **1963**, *1*, 31.
5. Buncel, E.: Norris, A. R.; Russell, K. F. *Q. Rev. Chem. Soc.* **1968**, *22*, 123.
6. Paradisi, C. In "*Comprehensive Organic Synthesis*", Vol. 4, Part 2, Trost, B. M., ed. Pergamon Press: Oxford, 1991.
7. Bernasconi, C. F. *MTP Int. Rev. Sci. Org. Chem. Ser. 1* **1973**, *3*, 33.
8. Buncel, E.; Crampton, M. R.; Strauss, M. J. Terrier, F. "*Electron-Deficient Aromatic– and Heteroaromatic–Base Interactions*". Elsevier: Amsterdam, 1984.
9. (a) Illuminati, G. *Adv. Heterocycl. Chem.* **1964**, *3*, 285; (b) Illuminati, G.; Stegel, F. *ibid.* **1983**, *34*, 305.

10. Fyfe, C. A.; Koll, A.; Damji, S. W. H.; Malkiewich, C. D.; Forte, P. A. *J. Chem. Soc., Chem. Commun.*, **1977**, 335.
11. Fyfe, C. A.; Damji, S. W. H.; Koll, A. *J. Am. Chem. Soc.* **1979**, *101*, 951.
12. Jackson, C. L.; Gazzolo, F. H. *J. Am. Chem. Soc.* **1900**, *23*, 376.
13. Meisenheimer, J. *Ann. Chem.* **1902**, *323*, 205.
14. Crampton, M. R. *Adv. Phys. Org. Chem.* **1969**, *7*, 211.
15. Strauss, M. J. *Chem. Rev.* **1970**, *70*, 667.
16. Segikuchi, S. *Yugi Grosei Kagaku Kyokaishi*, **1978**, *36*, 633.
17. Terrier, F. *Chem. Rev.* **1982**, *82*, 77.
18. Artamkina, G. A.; Egorov, M. P.; Beletskaya, I. P. *Chem. Rev.* **1982**, *82*, 427.
19. Bernasconi, C. F. *Acc. Chem. Res.* **1978**, *11*, 147.
20. Bernasconi, C. F. *Chimia* **1980**, *34*, 1.
21. Orvik, J. A.; Bunnett, J. F. *J. Am. Chem. Soc.* **1970**, *92*, 2417.
22. Birch, A. J.; Hinde, A. L.; Radom, L. *J. Am. Chem. Soc.* **1980**, *102*, 6430.
23. Olah, G. A.; Ascensio, G.; Mayr, H.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1978**, *100*, 4347.
24. Haddon, R. C. *J. Org. Chem.* **1979**, *44*, 3608.
25. Dotterer, S. K.; Harris, R. L. *J. Org. Chem.* **1988**, *53*, 777.
26. (a) Bacaloglu, R.; Bunton, C. A.; Ortega, F. (a) *J. Am. Chem. Soc.* **1989**, *111*, 1041; (b) *ibid.* **1988**, *110*, 3503.
27. Hayami, J. I.; Otani, S.; Yamaguchi, F.; Nishikawa, Y. *Chem. Lett.* **1987**, 739.
28. Forlani, L. *Gazz. Chim. Ital.* **1982**, *112*, 205.
29. Forlani, L.; Tortelli, V. *J. Chem. Res.(S)* **1982**, *62*, 258.
30. Forlani, L.; Sintoni, M.; Todesco, P. E. *J. Chem. Res.(S)* **1986**, *66*, 344.
31. Cattana, R. I.; Singh, J. O.; Anunziata, J. D.; Silber, J. J. *J. Chem. Soc., Perkin Trans. 2*, **1987**, 79.
32. Colter, A. K.; Hui, S. H. *J. Org. Chem.* **1968**, *33*, 1935.
33. Foster, R. In *"Organic Charge-Transfer Complexes"*, Blomquist, A. T., ed. Academic Press: London, 1969.
34. Ainscough, J. B.; Caldin, E. F. *J. Chem. Soc.* **1956**, 2528, 2540, 2546.
35. Politzer, P.; Abrahmsen, L.; Sjoberg, P. *J. Am. Chem. Soc.* **1984**, *106*, 855.
36. Politzer, P.; Laurence, P. R.; Abrahmsen, L.; Zilles, B. A.; Sjoberg, P. *Chem. Phys. Lett.* **1984**, *111*, 75.

37. Dewar, M. J. *"The Electronic Theory of Organic Chemistry"*. Oxford University Press: London, 1949, p. 77.
38. Burdon, J.; Parsons, I. W.; Avramides, E. J.; J. Chem. Soc., Perkin Trans. 2, **1979**, 1268.
39. Semmelhack, M. F.; Hall, H. T.; Farina, R.; Yoshifuji, M.; Clark, G.; Bargar, T.; Hirotsu, K.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 3535.
40. Abe, T. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 627; **1964**, *37*, 508.
41. Caveng, P.; Fischer, P. B.; Heilbronner, E.; Miller, A. L.; Zollinger, H. *Helv. Chim. Acta*, **1967**, *50*, 848.
42. Hosoya, H.; Hosoya, S.; Nagakura, S. *Theor. Chim. Acta*, **1968**, *12*, 117.
43. Wennerström, H.; Wennerström, O. *Acta Chem. Scand.* **1972**, *26*, 2883.
44. Grovenstein, E.; Akabori, S. *J. Am. Chem. Soc.* **1975**, *97*, 4620.
45. Grovenstein, E.; Lu, P. C. *J. Am. Chem. Soc.* **1982**, *104*, 6681.
46. Shein, S. M.; Ignatov, V. A.; Kozorez, L. A.; Chervatyuk, L. F. *Zh. Obshch. Khim.* **1967**, *37*, 114.
47. Terrier, F.; Millot, F.; Chatrousse, A. P.; Yagupolskii, L. M.; Boiko, V. N.; Shchupak, G. M.; Ignatev, N. V. *J. Chem. Res.* **1979** (S) 272.
48. Terrier, F.; Millot, F. *Nouv. J. Chim.* **1980**, *4*, 255.
49. Terrier, F.; Millot, F.; Morel, J. *J. Org. Chem.* **1976**, *41*, 3892.
50. Bevan, C. W. L.; Foley, A. J.; Hirst, J.; Uwamu, W. O. *J. Chem. Soc. B*, **1970**, 794.
51. Fendler, J. H.; Hinze, W. L.; Liu, L. J. *J. Chem. Soc., Perkin Trans. 2*, **1975**, 1768.
52. Fendler, J. H.; Fendler, E. J.; Byrne, W. E.; Griffin,C. E. *J. Org. Chem.* **1968**, *33*, 977.
53. Millot, F.; Terrier, F. *Bull. Soc. Chim. Fr.* **1971**, 3897.
54. Hinze, W. L.; Liu, L. J.; Fendler, J. H. *J. Chem. Soc., Perkin Trans. 2*, **1975**, 1751.
55. Fraenckel, G.; Cooper, J. C. *Tetrahedron Lett.* **1968**, 1825.
56. Foster, R.; Fyfe, C. A. *Tetrahedron* **1969**, *25*, 1489.
57. Giam, C. S.; Stout, J. L. *J. Chem. Soc., Chem. Commun.* **1969**, 142.
58. Bodor, N.; Pearlman, P. *J. Am. Chem. Soc.* **1978**, *100*, 4946.
59. Olah, G. A.; Hunadi, R. J. *J. Org. Chem.* **1981**, *46*, 715.
60. Murto, J.; Nummela, L.; Hyvönen, M. L.; Murto, M. L. *Acta Chem. Scand.* **1972**, *26*, 1351.
61. Bowden, K.; Nadvi, N. S. *J. Chem. Soc., Perkin Trans. 2*, **1987**, 189.
62. Chapman, N. B.; Rees, C. W. *J. Chem. Soc.* **1954**, 1190.

63. Brower, K. R.; Way, J. W.; Samuels, W. P.; Amstutz, E. D. *J. Org. Chem.* **1954**, *19*, 1830.

64. Capon, S.; Chapman, N. B. *J. Chem. Soc.* **1957**, 600.

65. Martinez, R. D.; Mancini, P. M. E.; Vottero, L. R.; Nudelman, N. S. *J. Chem. Soc., Perkin Trans. 2*, **1986**, 1427.

66. Dondoni, A. J.; Mangini, A.; Mossa, G. *J. Heterocycl. Chem.* **1969**, *6*, 143.

67. Murto, J.; Kääriäinen, L. *Suom. Kemistil.* **1966**, *39B*, 40.

68. Murto, J. *Acta Chem. Scand.* **1966**, *20*, 310.

69. Signor, A.; Sciffione, E.; Biondi, L.; Bezzi, S. *Gazz. Chim. Ital.* **1965**, *93*, 65.

70. Murto, J.; Nummela, L.; Hyvönen, M. L.; Wartiovaara, I. *Suom. Kemistil.* **1970**, *B43*, 517.

71. Terrier, F.; Chatrousse, A. P.; Schaal, R. *J. Org. Chem.* **1972**, *37*, 3010.

72. Bunting, J. W. *Adv. Heterocycl. Chem.* **1979**, *25*, 1.

73. Van der Plas, H. C. *Acc. Chem. Res.* **1978**, *11*, 462.

74. De Bie, D. A.; Geurtsen, B.; Berg, I. E.; Van der Plas, H. C. *J. Org. Chem.* **1986**, *51*, 3209.

75. Reinheimer, J. D.; Sourbatis, N.; Lavallée, R. L.; Goodwin, D.; Gould, G. L. *Can. J. Chem.* **1984**, *62*, 1120.

76. Bowden, K.; Prasannan, S.; Ranson, R. J. *J. Chem. Soc., Perkin Trans. 2*, **1987**, 181.

77. Terrier, F.; Chatrousse, A. P.; Paulmier, C.; Schaal, R. *J. Org. Chem.* **1975**, *40*, 2911.

78. Baldini, G.; Doddi, G.; Illuminati, G.; Stegel, F. *J. Org. Chem.* **1976**, *41*, 2153.

79. Attia, M.; Dave, D.; Gore, P. H.; Ikejiani, A. O. O.; Morris, D. F. C.; Short, E. L.; Consiglio, G.; Spinelli, D.; Frenna, V. *J. Chem. Soc. Perkin Trans. 2*, **1984**, 1637.

80. Doddi, G.; Illuminati, G.; Mencarelli, P.; Stegel, F. *J. Org. Chem.* **1976**, *41*, 2824.

81. Mencarelli, P.; Stegel, F. *J. Org. Chem.* **1977**, *42*, 3550.

82. Bazzani, F.; Mencarelli, P.; Stegel, F. *J. Org. Chem.* **1984**, *49*, 2375.

83. Annulli, A.; Mencarelli, P.; Stegel, F. *J. Org. Chem.* **1984**, *49*, 4065.

84. Dell'Erba, C.; Spinelli, D. *Tetrahedron*, **1965**, *21*, 1061.

85. Dell'Erba, C.; Guareschi, A.; Spinelli, D. *J. Heterocycl. Chem.* **1967**, *4*, 438.

86. Chierici, L.; Dell'Erba, C.; Guareschi, A.; Spinelli, D. *Ann. Chim. (Rome)* **1967**, *57*, 632.
87. Spinelli, D.; Dell'Erba, C.; Salvemoni, A. *Ann. Chim. (Rome)* **1962**, *52*, 1156.
88. Spinelli, D.; Consiglio, G.; Corrao, A. *J. Chem. Soc., Perkin Trans. 2*, **1972**, 1866.
89. Spinelli, D.; Consiglio, G.; Noto, R.; Corrao, A. *J. Chem. Soc. Perkin Trans. 2*, **1975**, 620.
90. Spinelli, D.; Consiglio, G. *J. Chem. Soc., Perkin Trans. 2*, **1975**, 989.
91. Spinelli, D.; Consiglio, G.; Noto, R. (a) *J. Chem. Soc., Perkin Trans. 2*, **1976**, 1495 ; (b) *J. Chem. Res.* **1978** (S), 242; (M) 2984.
92. Guanti, G.; Thea, S.; Dell'Erba, C.; Leandri, G. *J. Heterocycl. Chem.* **1975**, *12*, 945.
93. Sancassan, F.; Novi, M.; Guanti, G.; Dell'Erba, C. *J. Heterocycl. Chem.* **1975**, *12*, 1083.
94. De Santis, F.; Stegel, F. *Gazz. Chim. Ital.* **1973**, *103*, 649.
95. Guanti, G.; Dell'Erba, C.; Macera, P. *J. Heterocycl. Chem.* **1971**, *8*, 537.
96. Bosco, M.; Forlani, L.; Liturri, V.; Riccio, P.; Todesco, P. E. *J. Chem. Soc. B*, **1971**, 1373.
97. Forlani, L.; Todesco, P. E. *J. Chem. Soc., Perkin Trans. 2*, **1980**, 313.
98. Habraken, V. L.; Poels, E. K. *J. Org. Chem.* **1977**, *42*, 2893.
99. Goldman, P.; Wuest, J. W. *J. Am. Chem. Soc.* **1981**, *103*, 6224.
100. Gasco, A.; Boulton, A. J. *Adv. Heterocycl. Chem.* **1981**, *29*, 251.
101. Boulton, J. J. K.; Kirby, P. *J. Chem. Soc., Chem. Commun.* **1970**, 1618.
102. Dal Monte, D.; Sandri, E.; Di Nunno, L.; Florio, S.; Todesco, P. E. *J. Chem. Soc. B* **1971**, 2209.
103. Terrier, F.; Ah-Kow, G.; Chatrousse, A. P. *J. Org. Chem.* **1985**, *50*, 4583.
104. (a) Di Nunno, L.; Florio, S.; Todesco, P. E. *J. Chem. Soc., Perkin Trans. 2*, **1975**, 1469; (b) del Rosso, M. D.; Di Nunno, L.; Florio, S.; Amorese, A. *ibid.* **1980**, 239.
105. Terrier, F.; Chatrousse, A. P.; Soudais, P.; Hlaibi, M. *J. Org. Chem.* **1984**, *49*, 4176.
106. Terrier, F.; Hlaibi, M. Unpublished results.
107. Di Nunno, L.; Florio, S.;Todesco, P. E. (a) *Tetrahedron*, **1974**, *30*, 863; (b) *ibid.*, **1976**, *32*, 1037.
108. Sharnin, G. P.; Mukharlyamov, R. I.; Golovin, V. V. *Zh. Org. Khim.* **1983**, *19*, 2358.
109. Ghosh, P.; Ternai, B.; Whitehouse, M. W. *Med. Res. Rev.* **1981**, *1*, 159.

110. Read, R. W.; Norris, W. P. *Aust. J. Chem.* **1985**, *38*, 435.

111. Latham, D. W. S.; Meth-Cohn, O.; Suschitzky, H. *J. Chem. Soc., Perkin Trans. 1*, **1976**, 2216.

112. Dal Monte, D.; Sandri, E. *Ann. Chim. (Rome)* **1963**, *53*, 1697.

113. Bunnett, J. F.; Randall, J. J. *J. Am. Chem. Soc.* **1958**, *80*, 6020.

114. Bartoli, G.; Todesco, P. E. (a) *Acc. Chem. Res.* **1977**, *10*, 125; (b) *Tetrahedron*, **1968**, 4867.

115. Lam, K. B.; Miller, J.; Moran, P. J. S. *J. Chem. Soc., Perkin Trans. 2*, **1977**, 457.

116. Gore, P. H.; Hammond, S. D.; Morris, D. F. C. *J. Chem. Soc. Perkin Trans. 2*, **1973**, 1883.

117. Cacace, F.; Speranza, M.; Wolf, A. P.; Fowler, J. S. *J. Label Compd. Radiopharm.* **1981**, *18*, 1721.

118. Miller, J.; Parker, A. J. *J. Am. Chem. Soc.* **1961** , *83*, 117.

119. Terrier, F.; Ah-Kow, G.; Pouet, M. J.; Simonnin, M. P. *Tetrahedron Lett.* **1976**, 227.

120. Chisari, A.; Maccarone, E.; Parisi, G.; Perrini, G. *J. Chem. Soc., Perkin Trans. 2*, **1982**, 957.

121. Maurer, W.; Szele, I.; Zollinger, H. *Helv. Chim. Acta* **1979**, *62*, 1079.

122. Means, G. E.; Feeney, R. E. In *"Chemical Modifications of Proteins"*, Holden-Day: San Francisco, 1971, Chapter 6.

123. Bunton, C. A.; Ihara, Y.; Wright, J. L. *J. Org. Chem.* **1976**, *41*, 2520.

124. Peishoff, C. E.; Jorgensen, W. L. *J. Org. Chem.* **1985**, *50*, 1056.

125. Buncel, E.; Menon, B. C. *J. Am. Chem. Soc.* **1977**, *99*, 4457.

126. Terrier, F.; Millot, F.; Norris, W. P. *J. Am. Chem. Soc.* **1976**, *98*, 5883.

127. Brooke, D. N.; Crampton, M. R.; Corfield, G. C.; Golding, P.; Hayes, G. F. *J. Chem. Soc., Perkin Trans. 2*, **1981**, 526.

128. Buncel, E.; Menon, B. C. *J. Organomet. Chem.* **1977**, *141*, 1.

129. Sekiguchi, S.; Takei, T.; Matsui, K.; Tone, N.; Tomoto, N. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3009.

130. Takahashi, H.; Hiraide, T.; Hashida, Y.; Sekiguchi, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 185.

131. Bunnett, J. F.; Cartano, A. V. *J. Am. Chem. Soc.* **1981**, *103*, 4861.

132. Bunnett, J. F.; Sekiguchi, S.; Smith, L. A. *J. Am. Chem. Soc.* **1981**, *103*, 4865.

133. Sekiguchi, S.; Itagaki, T.; Hirose, T.; Matsui, K.; Sekine, K. *Tetrahedron*, **1973**, *29*, 3527.

134. Fujinuma, H.; Hosokawa, M.; Suzuki, T.; Sato, M.; Sekiguchi, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1969.

135. Dixon, J. E.; Bruice, T. C. *J. Am. Chem. Soc.* **1972**, *94*, 2052.

136. Leahy, G. D.; Liverio, M.; Miller, J.; Parker, A. J. *Aust. J. Chem.* **1956**, *9*, 382.

137. Ryan, J. J.; Humffray, A. A. *J. Chem. Soc. B*, **1967**, 1300.

138. Nadar, P. A.; Gnanasekaran, C. *J. Chem. Soc., Perkin Trans. 2,* **1978**, 671.

139. Crampton, M. R.; Willison, M. J. *J. Chem. Soc., Perkin Trans. 2*, **1974**, 238.

140. Bishop, R. R.; Cavell, E. A. S.; Chapman, N. B. *J. Chem. Soc.* **1952**, 437.

141. Chapman, N. B.; Chandhury, D. K.; Shorter, J. *J. Chem. Soc.* **1962**, 1975.

142. Spinelli, D.; Consiglio, G.; Noto, R.; Frenna, V. *J. Org. Chem.* **1976**, *41*, 968.

143. Consiglio, G.; Noto, R.; Spinelli, D.; Arnone, C. *J. Chem. Soc., Perkin Trans. 2*, **1979**, 219.

144. Bordwell, F. G.; Hughes, D. L. *J. Am. Chem. Soc.* **1986**, *108*, 5991.

145. (a) Bartoli, G.; Ciminale, F.; Todesco, P. E. *J. Org. Chem.* **1975**, *40*, 872. (b) Bartoli, G.; Di Nunno, L.; Forlani, L.; Todesco, P. E. *Int. J. Sulfur Chem., C*, **1971**, *6*, 77.

146. Hine, J.; Weimar, R. D., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 3387.

147. Ritchie, C. D. *Acc. Chem. Res.* **1972**, *5*, 348.

148. Ritchie, C. D.; Virtanen, P. O. I. *J. Am. Chem. Soc.* **1973**, *95*, 1882.

149. Ritchie, C. D.; Sawada, M. *J. Am. Chem. Soc.* **1977**, *99*, 3754.

150. Jencks, W. P. In *"Catalysis in Chemistry and Enzymology"*, McGraw-Hill: New York, 1969, p. 107.

151. Ritchie, C. D. *Pure Appl. Chem.* **1978**, *50*, 1281.

152. Jencks, W. P.; Brant, S. R.; Gandler, J. R.; Fendrich, C.; Nakamura, C. *J. Am. Chem. Soc.* **1982**, *104*, 7045.

153. Jencks, W. P.; Haber, M. T.; Herschlag, D.; Nazaretian, K. L. *J. Am. Chem. Soc.* **1986**, *108*, 479.

154. Terrier, F.; Degorre, F.; Kiffer, D.; Laloi, M. *Bull. Soc. Chim. Fr.* **1988**, 415.

155. Bernasconi, C. F.; Bunnell, R. D. *Isr. J. Chem.* **1985**, *26*, 420.

156. Bernasconi, C. F. *Tetrahedron*, **1985**, *41*, 3219.

157. de Rossi, R. H.; de Vargas, E. B. *J. Am. Chem. Soc.* **1981**, *103*, 1533.

158. Parker, R. E.; Read, T. O. *J. Chem. Soc.* **1962**, 3149.

159. (a) Greizerstein, W.; Brieux, J. A. *J. Am. Chem. Soc.* **1962**, *84*, 1032; (b) Porto, A. M.; Altieri, L.; Castro, A. J.; Brieux, J. A. *J. Chem. Soc. B*, **1966**, 963.

160. Bamkole, T. O.; Hirst, J.; Udoessien, E. J. *J. Chem. Soc., Perkin Trans. 2*, **1973**, 2114.

161. (a) Nudelman, N. S. *An. Asoc. Quim. Arg.* **1980**, *68*, 95; (b) Nudelman, N. S.; Palleros, D. *J. Org. Chem.* **1983**, *43*, 1607, 1613.

162. Bunnett, J. F.; Morath, R. J. *J. Am. Chem. Soc.* **1955**, *77*, 5051.

163. Bernasconi, C. F. *J. Phys. Chem.* **1971**, *75*, 3636.

164. Minetti, R.; Bruylants, A. *Bull. Acad. R. Belg.* **1970**, *56*, 1047.

165. Nudelman, N. S.; Mac Cormack, P. *Tetrahedron*, **1984**, *40*, 4227.

166. (a) Pietra, F.; Vitali, D.; Del Cima, F.; Cardinali, G. *J. Chem. Soc. B*, **1970**, 1659. (b) Pietra, F.; Del Cima, F. *J. Org. Chem.* **1968**, *33*, 1411.

167. Terrier, F. *Ann. Chim. (Paris)* **1969**, *4*, 153.

168. Crampton, M. R.; Gibson, B.; Gilmore, F. W. *J. Chem. Soc., Perkin Trans. 2*, **1979**, 91.

169. Buncel, E. ; Pregel, M. J. *J. Chem. Soc., Chem. Comm.* **1989**, 1566.

170. Terrier, F. *Compt. R. Acad. Sci. Paris*, **1965**, *261*, 1001.

171. Nudelman, N. S.; Cerdeira, S. *J. Chem. Soc., Perkin Trans. 2*, **1986**, 695.

172. Heaton, A.; Hunt, M. *J. Chem. Soc., Perkin Trans. 1*, **1978**, 1204.

173. Gibson, B.; Crampton, M. R. *J. Chem. Soc., Perkin Trans. 2*, **1979**, 648.

174. Gan, L. H.; Norris, A. R. *Can. J. Chem.* **1974**, *52*, 18.

175. Gan, L. H. *Aust. J. Chem.* **1975**, *28*, 2403.

176. (a) Kavalek, J.; Machacek, V.; Pastrnek, M.; Sterba, V. *Collect. Czech. Chem. Commun.* **1977**, *42*, 2928; (b) Kavalek, J.; Pastrnek, M.; Sterba, V. *ibid.* **1978**, *43*, 1401.

177. (a) Crampton, M. R.; Kee, T. P.; Wilcock, J. R. *Can. J. Chem.* **1986**, *64*, 1714. (b) Crampton, M. R.; Greenhalgh, C. *J. Chem. Soc., Perkin Trans. 2*, **1986**, 187.

178. Hasegawa, Y. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2186.

179. Bassani, A; Prats, M.; Rampazzo, P.; Quintily, U.; Scorrano, G. *J. Org. Chem.* **1980**, *45*, 2263.

180. Fyfe, C. A.; Malkiewich, C. D.; Damji, S. W. H.; Norris, A. R. *J. Am. Chem. Soc.* **1976**, *98*, 6983.

181. Bernasconi, C. F. *J. Org. Chem.* **1971**, *36*, 1671.

182. Benedetti, F.; Marshall, D. R.; Stirling, C. J. M.; Lang, J. L. *J. Chem. Soc., Chem. Commun.* **1982**, 918.

183. Buncel, E. In "*The Chemistry of Functional Groups*", Suppl. I, Patai, S., ed. Wiley: London, 1982, pp. 1225–1260.

184. Gaboriaud, R.; Schaal, R. *Bull. Soc. Chim. Fr.* **1969**, 2683.

185. Crampton, M. R.; El Ghariani, M. A.; Khan, H. A. *J. Chem. Soc. D*, **1971**, 834.

186. Crampton, M. R.; Davis, A. B.; Greenhalgh, C.; Stevens, J. A. *J. Chem. Soc., Perkin Trans. 2*, **1989**, 675.

187. Leffek, K. T.; Tremaine, P. H. *Can. J. Chem.* **1973**, *51* , 1659.

188. Chatrousse, A. P.; Terrier, F. *Bull. Soc. Chim. Fr.* **1972**, 4549.

189. Fyfe, C. A.; Koll, A.; Damji, S. W. H.; Malkiewich, C. D.; Forte, P. A. *Can. J. Chem.* **1977**, *55*, 1468.

190. Sekiguchi, S.; Fujisawa, S.; Ando, Y. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1451.

191. Hasegawa, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1314.

192. Hasegawa, Y. *J. Org. Chem.* **1985**, *50*, 649.

193. Knyazev, V. N.; Drozd, V. N. *Izv. Sib. Otd. Akad. Nauk. SSR, Ser. Khim. Nauk*, **1983**, *4*, 43.

194. Bernasconi, C. F.; Gehriger, C. L.; de Rossi, R. H. *J. Am. Chem. Soc.* **1976**, *98*, 8451.

195. Bernasconi, C. F.; de Rossi, R. H.; Gehriger, C. L. *J. Org. Chem.* **1973**, *38*, 2838.

196. Okada, K.; Matsui, K.; Sekiguchi, S. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2601.

197. Sekiguchi, S.; Hoshino, O.; Hirai, M.; Okada, K.; Tomoto, N. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2173.

198. Buncel, E.; Hamaguchi, M.; Norris, A. R. *J. Chem. Soc., Perkin Trans. 1*, **1980**, 2205.

199. Knyazev, V. N.; Drozd, V. N.; Minov, V. M.; Akimova, N. P. *Zh. Org. Khim.* **1977**, *13*, 1255.

200. Knyazev, V. N.; Drozd, V. N.; Mozhaeva, T. Ya. *Zh. Org. Khim.* **1979**, *15*, 2561.

201. Knyazev, V. N.; Klimov, A. A.; Yaryshev, N. G.; Drozd, V. N. *Zh. Org. Khim.* **1974**, *10*, 2587.

202. Crampton, M. R.; Willison, M. J. *J. Chem. Soc., Perkin Trans. 2*, **1976**, 901.

203. Knyazev, V. N.; Drozd, V. N.; Minov, V. M. *Zh. Org. Khim.* **1978**, *14*, 105.

204. Machacek, V.; Hassanien, M. M. M.; Sterba, V.; Lycka, A. *Collect. Czech. Chem. Commun.* **1986**, *51*, 1972.
205. Machacek, V.; Hassanien, M. M. M.; Sterba, V. *J. Chem. Soc., Perkin Trans. 2*, **1986**, 813.
206. Bunnett, J. F.; Bernasconi, C. F. *J. Am. Chem. Soc.* **1965**, *87*, 5209.
207. Bunnett, J. F.; Bernasconi, C. F. *J. Org. Chem.* **1970**, *35*, 70.
208. Pietra, F.; Vitali, D. *J. Chem. Soc. B*, **1968**, 1200.
209. Spinelli, D.; Consiglio, G.; Noto, R. *J. Org. Chem.* **1978**, *43*, 4038.
210. Consiglio, G.; Arnone, C.; Spinelli, D.; Noto, R. *J. Chem. Soc., Perkin Trans. 2*, **1981**, 642.
211. Consiglio, G.; Noto, R.; Spinelli, D. *J. Chem. Soc., Perkin Trans. 2*, **1979**, 222.
212. Spinelli, D.; Consiglio, G.; Noto, R. *J. Heterocycl. Chem.* **1977**, *14*, 1325.
213. Kirby, A. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1965**, *87*, 3217.
214. Bunnett, J. F.; Garst, R. H. *J. Am. Chem. Soc.* **1965**, *87*, 3879.
215. Hasegawa, Y. *J. Chem. Soc., Perkin Trans. 2*, **1984**, 547.
216. Crampton, M. R.; Routledge, P. J. *J. Chem. Soc., Perkin Trans. 2*, **1984**, 573.
217. de Rossi, R. H.; Rossi, R. A. *J. Org. Chem.* **1974**, *39*, 3486.
218. Bamkole, T. O.; Hirst, J.; Onyido, J. *J. Chem. Soc., Perkin Trans. 2*, **1982**, 889.
219. Bamkole, T. O.; Hirst, J.; Hussain, G. *J. Chem. Soc., Perkin Trans. 2*, **1984**, 681.
220. Hirst, J.; Onyido, J. *J. Chem. Soc., Perkin Trans. 2*, **1984**, 711.
221. Banjoko, O.; Otiono, P. *J. Chem. Soc., Perkin Trans. 2*, **1981**, 399.
222. (a) Palleros, D.; Nudelman, N. S. *J. Chem. Soc., Perkin Trans. 2*, **1985**, 479. (b) Nudelman, N. S. *J. Phys. Org. Chem.* **1989**, *2*, 1.
223. Guanti, G.; Petrillo, S.; Thea, S.; Pero, F. *J. Chem. Soc.* (S) **1982**, 282; (M) 2764.
224. Bernasconi, C. F.; Gandler, J. R. *J. Am. Chem. Soc.* **1978**, *100*, 8117.
225. Bernasconi, C. F.; Howard, K. A. *J. Am. Chem. Soc.* **1982**, *104*, 7248.
226. Crampton, M. R.; Willison, M. J. *J. Chem. Soc., Perkin Trans. 2*, **1974**, 1686.
227. Ah-Kow, G.; Terrier, F.; Lessard, F. *J. Org. Chem.* **1978**, *43*, 3578.
228. Terrier, F.; Ah-Kow, G.; Chatrousse, A. P. *J. Org. Chem.* **1985**, *50*, 4583.
229. Bernasconi, C. F.; Gehriger, C. L. *J. Am. Chem. Soc.* **1974**, *96*, 1092.
230. Bernasconi, C. F.; Terrier, F. *J. Am. Chem. Soc.* **1975**, *97*, 7458.

231. Bernasconi, C. F.; Muller, M. C.; Schmid, P. *J. Org. Chem.* **1979**, *44*, 3189.

232. Buncel, E.; Eggimann, W. *J. Am. Chem. Soc.* **1977**, *99*, 5958.

233. Crampton, M. R.; Gibson, B. *J. Chem. Soc., Perkin Trans. 2*, **1981**, 533.

234. Crampton, M. R.; Greenhalgh, C. *J. Chem. Soc., Perkin Trans. 2*, **1983**, 1175.

235. Bamkole, T. O.; Hirst, J.; Onyido, I. *J. Chem. Soc., Perkin Trans. 2*, **1981**, 1201.

236. Buncel, E.; Innis, C.; Onyido,I. *J. Org. Chem.* **1986**, *51*, 3680.

237. Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1.

238. de Vargas, E. R.; de Rossi, R. H. *J. Org. Chem.* **1984**, *49*, 3978.

239. Parker, A. J. *Chem. Rev.* **1969**, *69*, 1.

240. Buncel, E.; Wilson, H. *Adv. Phys. Org. Chem.* **1977**, *14*, 133.

241. Bowden, K.; Cook, R. S.; Price, M. J. *J. Chem. Soc. B*, **1971**, 1778.

242. Kavalek, J.; Machacek, V.; Lycka, A.; Sterba, V. *Collect. Czech. Chem. Commun.* **1976**, *51*, 590.

243. Zhong-Yuan, Z.; Cheng, E. S.; Te-Kang, H. *J. Chem. Soc., Perkin Trans. 2*, **1985**, 929.

244. Del Cima, F.; Biggi, G.; Pietra, F. *J. Chem. Soc., Perkin Trans. 2*, **1973**, 55.

245. Paradisi, C.; Scorrano, G. In "*Nucleophilicity*", Harris, J. M.; McManus, S. P. eds., ACS Advances in Chemistry Series, No. 215. American Chemical Society: Washington, DC, 1987, p. 339.

246. Makosza, M.; Jagusztyn-Grochowska, M.; Ludwikow, L. *Tetrahedron*, **1974**, *30*, 3723.

247. Gisler, M.; Zollinger, H. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 203.

248. Schmidtchen, F. P. *Chem. Ber.* **1984**, *117*, 725, 1287.

249. (a) Bunton, C. A.; Robinson, L. *J. Am. Chem. Soc.* **1968**, *90*, 5965. (b) Bunton, C. A.; Moffatt, J. R.; Spillane, J. *J. Chem. Soc., Perkin Trans. 2*, **1986**, 1799.

250. Athanassakis, V.; Bunton, C. A.; de Buzzaccarini, F. *J. Phys. Chem.* **1982**, *86*, 5002.

251. (a) Cipiciani, A.; Germani, R.; Savelli, G.; Bunton, C. A.; Mhala, M.; Moffatt, J. R. *J. Chem. Soc., Perkin Trans. 2*, **1987**, 541; (b) Cipiciani, A.; Fracassini, M. C.; Germani, R.; Savelli, G.; Bunton, C. A. *ibid.* **1987**, 547.

252. Fry, S. E.; Pienta, N. J. *J. Am. Chem. Soc.* **1985**, *107*, 6399.

253. Larsen, J. W.; Amin, K.; Fendler, J. H. *J. Am. Chem. Soc.* **1971**, *93*, 2910.

254. (a) Fendler, J. H.; Larsen, J. W. *J. Org. Chem.* **1972**, *37*, 2608. (b) Larsen, J. W.; Amin, K.; Ewing, S.; Magid, L. L. *J. Org. Chem.* **1972**, *37*, 3857.

255. Liotta, C. L.; Harris, H. P. *J. Am. Chem. Soc.* **1974**, *96*, 2250.

256. Clark, J. H.; Macquarrie, D. *J. Fluor. Chem.* **1987**, *35*, 591.

257. Attina, M.; Cacace, F.; Wolf, A. P. *J. Chem. Soc., Chem. Commun.* **1983**, 108.

258. Paradisi, C.; Quintily, U.; Scorrano, G. *J. Org. Chem.* **1983**, *48*, 3022.

259. Reeves, W. P.; Simmons, A.; Keller, K. *Synth. Commun.* **1980**, *10*, 633.

260. Imai Y.; Veda, M.; Li, M. *J. Polym. Sci., Polym. Lett. Ed.* **1979**, *17*, 85.

261. Bunnett, J. F.; Gisler, M.; Zollinger, H. *Helv. Chim. Acta*, **1982**, *65*, 63.

262. Alemagna, A.; del Buttero, P.; Gorini, C.; Landini, D.; Licandro, E.; Maiorana. S. *J. Org. Chem.* **1983**, *48*, 605.

263. Andrews, S. M.; Konstantinou, C.; Feld, W. A. *Synth. Commun.* **1987**, *17*, 1041.

264. Soula, G. *J. Org. Chem.* **1985**, *50*, 3717.

265. Landini, D.; Montanari, F.; Rolla, F. *J. Org. Chem.* **1983**, *48*, 604.

266. Landini, D.; Maia, A.; Montanari, F. *J. Chem. Soc., Perkin Trans. 2*, **1983**, 461.

267. (a) Bunton, C. A.; Diaz, S. *J. Am. Chem. Soc.* **1976**, *98*, 5663. (b) Bunton, C. A.; Cerichelli, G.; Ihara, Y.; Sepulveda, L. *J. Am. Chem. Soc.* **1979**, *101*, 2429.

268. Broxton, T. J.; Christie, J. R.; Chung, R. P. T. *J. Org. Chem.* **1988**, *53*, 3081.

269. Bunton, C. A. *Catal. Rev. Sci. Eng.* **1979**, *83*, 680. In "*Solution Chemistry of Surfactants*", Vol. 2, Mittal, K. L., ed., Plenum Press: New York, 1979, p. 519.

270. (a) Bunton, C. A.; Moffatt, J. R.; Rodenas, E. *J. Am. Chem. Soc.* **1982**, *104*, 2653. (b) Broxton, T. J.; Christie, J. R.; Chung, R. P. T. *Aust. J. Chem.* **1989**, *42*, 855.

271. (a) Bunton,C. A.; Robinson, L. *J. Org. Chem.* **1969**, *34*, 780. (b) Cipiciani, A.; Primieri, S. *J. Chem. Soc., Perkin Trans. 2*, **1990**, 1365.

272. (a) Bunton, C. A.; Savelli, G.; Sepulveda,L. *J. Org. Chem.* **1978**, *43*,1925; (b) Bunton, C. A.; de Buzzaccarini, F.; Hamed, F. H. *ibid.* **1983**, *48*, 2461.

273. (a) Broxton, T. J.; Christie, J. R.; Chung, R. P. T. *J. Phys. Org. Chem.* **1990**, *2*, 519; (b) Broxton, T. J.; Chung, R. P. T. *J. Org. Chem.* **1990**, *55*, 3886.

274. Ayediran, D.; Bamkole, T. O.; Hirst, J.; Onyido, I. *J. Chem. Soc., Perkin Trans. 2*, **1977**, 597; 1580.

275. Mancini, P. E. M.; Martinez, R. D.; Vottero, L. R.; Nudelman, N. S. *J. Chem. Soc., Perkin Trans. 2*, **1984**, 1133.

276. Murto, J.; Hiiro, A. M. *Suom. Kemistil.* **1964**, *37B*, 177.

277. Terrier, F.; Millot, F.; Hallé, J. C.; Schaal, R. *Can. J. Chem.* **1980**, *58*, 1155.

278. Lelièvre, J.; Haddad-Fahed, O.; Gaboriaud, R. *J. Phys. Chem.* **1987**, *84*, 449.

279. Lelièvre, J.; Haddad-Fahed, O.; Gaboriaud, R. *J. Chem. Soc., Faraday Trans. 1*, **1986**, *82*, 2301.

280. (a) Riveros, J. M.; Jose, S. M.; Takashima, K. *Adv. Phys. Org. Chem.* **1985**, *21*, 234. (b) Bowie, J. H. *Acc. Chem. Res.* **1980**, *13*, 76.

281. Bowie, J. H.; Stapleton, B. J. *Aust. J. Chem.* **1977**, *30*, 795.

282. Kleingeld, J. C.; Nibbering, N. M. M. *Tetrahedron Lett.* **1980**, *21*, 1687.

283. Ingemann, S.; Nibbering, N. M. M.; Sullivan, S. A.; De Puy, C. H. *J. Am. Chem. Soc.* **1982**, *104*, 6520.

284. Eichinger, P. C. H.; Bowie, J. H.; Hayes, R. N. *J. Am. Chem. Soc.* **1989**, *111*, 4224.

CHAPTER 2.
Structure and Reactivity of Anionic σ-Complexes

2.1 Introduction

A number of situations in which covalent addition of a nucleophile to an aromatic substrate activated by electron-withdrawing groups (EWG) can result in a σ-complex of some stability, according to eq. 2-1, were pointed out in Chapter 1. The relationship between the formation of such adducts and that of the metastable cyclohexadienyl intermediates postulated in S_NAr reactions has been qualitatively emphasized. In fact, considerable attention has been devoted over the past two decades to the chemistry of σ-complexes, commonly referred to as Jackson–Meisenheimer or Meisenheimer complexes.[1] The detailed structures of these adducts are now well known, and their reactions, the kinetics and thermodynamics of their formation and decomposition, as well as their spectral properties, have been investigated in detail.[1–10]

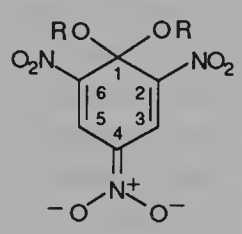
(2-1)

This chapter surveys the main features of σ-complex formation. As will be seen, many of the results we present give a clear picture of why the NO_2 group plays a major role in determining the course of S_NAr and other nucleophilic aromatic processes.

2.2 Structural Features of σ-Complexes

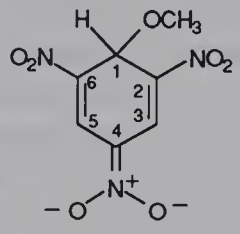
2.2.1 X-Ray Crystallography

Crystal structure determinations of four σ-complexes, namely the picryl dimethoxy and diethoxy adducts **1a** and **1b** and the methoxide adducts **2** and **3** of 1,3,5-trinitrobenzene (TNB) and 7-methoxy-4,6-dinitrobenzofurazan have been made.[11–14] For the most part, these studies give support to the quinoid structures proposed by early workers in the field, in which the carbon para to the tetrahedral ring carbon, C-4, bears a formal nitronate function (i.e. $C{=}NO_2^-$)[15,16] The finding in **1a**, **1b**, **2**, and **3** of a significant shortening of the bond between C-4 and NO_2 relative to the bonds between C-6 and/or C-2 and NO_2 is particularly revealing in this regard. Illustrative diagrams for **1a** and **3** are given in Figs. 2.1 and 2.2.



1

(a) R = CH_3 ; (b) R = C_2H_5



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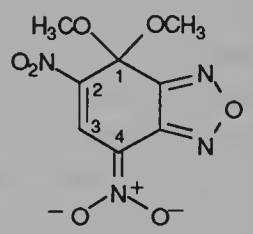


3

For the dialkoxy adducts **1a** and **1b**, the ring was found to be essentially planar, with the two alkoxy oxygens being contained in a perpendicular plane, in accord with sp^3 hybridization at C-1.[11,12] The two NO_2 groups ortho to C-1 are nearly coplanar with the ring, in marked contrast to the situation in the parent ethers. Dihedral angles up to 62° have been observed between the ring and NO_2 groups ortho to the OC_2H_5 group in 2,4,6-trinitrophenetole, apparently owing to steric compression between these functions.[17]

The benzofurazan adduct **3** has also a planar though somewhat distorted cyclohexadienylide ring.[14] In contrast, the anionic ring of the methoxide adduct of TNB, **2**, is not planar, and adopts a boatlike conformation.[13] This structure would reflect steric repulsion of the methoxyl at C-1 and the two NO_2

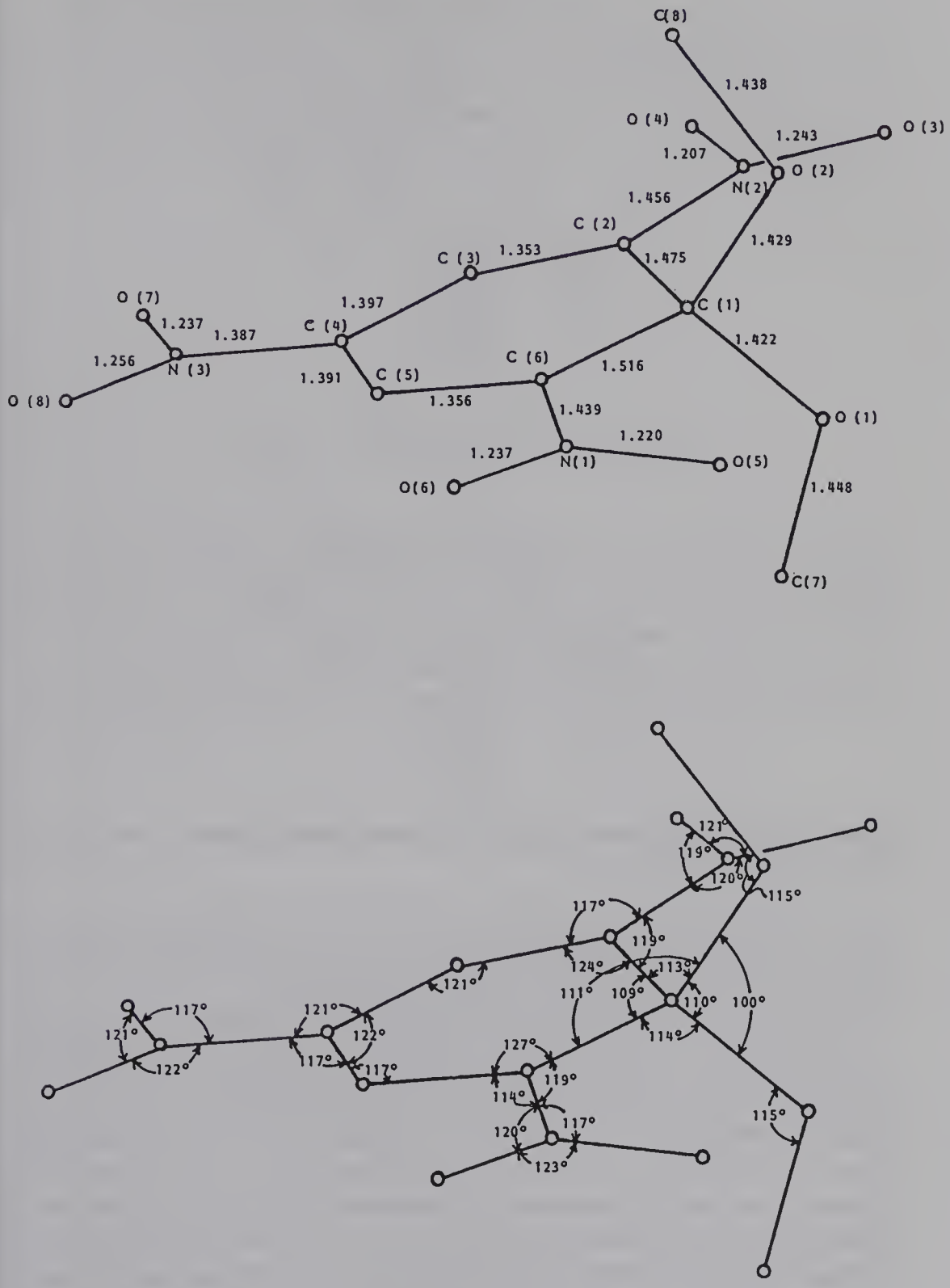


Figure 2.1. Bond lengths and bond angles in the *gem*-dimethoxy complex **1a** (Reproduced with permission from ref. 12.)

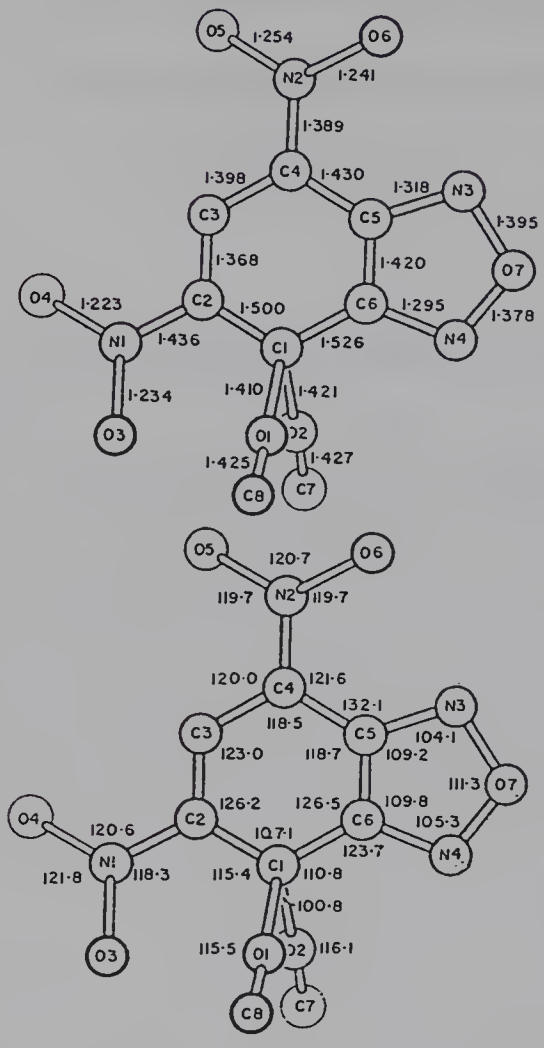
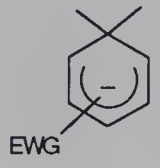


Figure 2.2. Bond lengths and bond angles in the *gem*-dimethoxy complex **3**. (Reproduced with permission from ref. 14.)

groups at C-2 and C-6. Similar repulsion in the analogous geminal dimethoxy complex **1a** will tend to balance on each side of the ring.

Although conformations and bond lengths may be significantly affected upon transfer from a crystal lattice to solution, the results above provide a definitive picture of σ-adducts. They point out in particular the ability of an NO_2 group para to the sp^3 carbon of a σ-complex to carry a large portion of the charge originally associated with the attacking nucleophile, thus confirming a major conclusion of theoretical calculations.[18–24] They also reveal that release of steric compression at the position of nucleophilic addition may be very significant in the formation of σ-adducts like **1a** and **1b**. As will be seen, such steric relief is of prime importance in determining rate and equilibrium parameters for formation of such complexes.

Theoretical calculations show that localized canonical structures of type **1**–**3** are no longer especially favored for adducts lacking a NO_2 group para to the sp^3 carbon. Hence, visualization of the σ-complexes by structures of type **4** in which the negative charge is shown to be delocalized through the ring and any electron-withdrawing substituent becomes more appropriate for a general discussion.



4

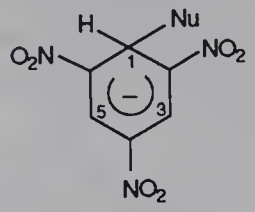
2.2.2 NMR Spectroscopy

It is NMR spectroscopy that contributed most to the structural characterization of σ-adducts.[1] Because of the change from sp^2 to sp^3 hybridization that occurs at the aromatic or heteroaromatic carbon atom undergoing nucleophilic addition, there is normally a pronounced shift to high field of the resonance due to the atom (e.g., H) or group (e.g., OCH_3) at that carbon atom. Hence NMR spectroscopy allows the position(s) of nucleophilic attack to be readily defined.

2.2.2.1 Complexation at Unsubstituted Carbons

Data pertaining to ^1H NMR characterization of a number of adducts **5** of TNB in DMSO are illustrative of the spectral changes occurring upon σ-complexation at an unsubstituted carbon (Table 2.1). In all instances, the formation of **5** is characterized by the disappearance of the singlet from TNB (δ = 9.20 ppm) and the concomitant appearance of an AX_2 system at higher field. In accord with the change in hybridization from sp^2 to sp^3, the ring proton at C-1 exhibits a high field resonance but, importantly, this resonance is sensitive to the nature of the atom or group bonded to that carbon. For simple substituents (Nu = OR, NR_2, SR, CR_3), the shielding of H_1 tends to increase with decreasing electronegativity of the attached atom (i.e., according to the sequence O < N ~ S < C).[1,8] Loss of aromaticity and increased negative charge in the ring cause the C-3,5 protons also to be shifted upfield on formation of **5**, but to a much lesser extent than the C-1 proton.[1] Table 2.1 shows that these protons absorb in a narrow range (δ = 8.2–8.6 ppm), but again the exact shift depends to some

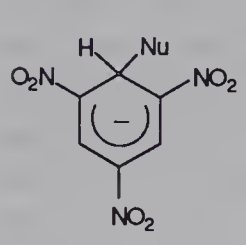
Table 2.1. ^{1}H NMR Data for Various σ-Complexes 5 of 1,3,5 Trinitrobenzene in DMSO[a]



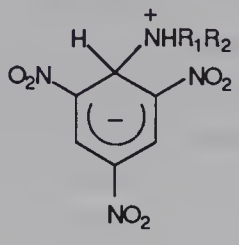
Nucleophile	δ (ppm) H-1	δ (ppm) H-3, H-5	δ (ppm) Nu	$J_{H1-3,5}$ (Hz)
OH	6.1	8.2	4.5	
OCH_3[b]	6.1	8.4	3.1	1.0
OC_6H_5	6.2	8.4	6.5–7.4	2
$OC_6H_2(CH_3)_3$[c]	6.2	8.35	6.67 2.10, 2.06	
SC_2H_5	5.75	8.30		
NH_2	5.5	8.3		
$NHCH_2C_6H_5$	5.7	8.4	3.5 (CH_2) 7.2 (C_6H_5)	
NHOH	5.7	8.4		0.6
NHC_6H_5	6.2	8.4	5.8 (NH)	0.6
3-Methylindole[d]	7.2	8.6		0.6
$+P(OCH_3)_3$	5.4	8.5	3.9 (CH_3)	2.5
H	3.9	8.3		0.5
CH_3	4.6	8.2	1.1	0.75
CCl_3	6.4	8.6		1.5
CH_2COCH_3	5.1	8.4	2.7 (CH_2)	1
Cyclopentanone	5	8.28, 8.38		0.7
$CH(CH_3)NO_2$	5.7	8.5		0.5
C_6H_4OH	5.6	8.4	6.9 (C_6H_5)	
$Sn(CH_3)_3$	6.2	8.3	0.3	
$Ge(C_2H_5)_3$	6.2	8.4		
$Si(CH_3)_3$	6.1	8.3	0	

[a] Data from ref. 1, p. 23.
[b] Complex **2**.
[c] O-adduct of 2,4,6-trimethylphenoxide ion.
[d] *N*-adduct of 3-methylindole.

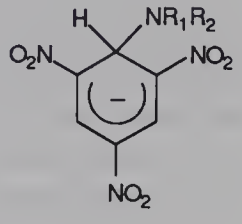
degree on the electronegativity of the atom or group at C-1. Also, $^4J_{1\text{-}3,5}$ coupling constants are characteristic of the nature of **5**, having values of 1.2–1.5 Hz for O-bonded adducts, 0.4–0.8 Hz for N-bonded adducts, and < 0.5 Hz for C-bonded adducts.[8,25]



5



6,H

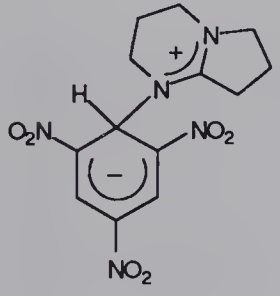


6

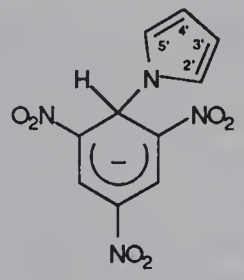
R_1 = H, alkyl or aryl

R_2 = H or alkyl

As discussed in Chapter 1, covalent addition of primary and secondary amines to an aromatic ring carbon normally results in initial formation of a zwitterionic σ-adduct (i.e., **6,H**). However, **6,H** is expected to undergo subsequent thermodynamically favored deprotonation of the ammonio moiety, to give its anionic counterpart **6**.[1,7] Indeed, all TNB adducts of primary and secondary amines that have been characterized in DMSO are of anionic type **6** (R_1 = alkyl or aryl, R_2 = H or alkyl).[1] A similar situation prevails in liquid ammonia, where the adduct **6** ($R_1 = R_2$ = H) has been identified by ^{1}H and ^{13}C NMR spectroscopy.[26] So far, even the characterization of stable zwitterionic adducts resulting from attack of tertiary amines has proved to be very difficult.[1] In this context, recent evidence that the adduct **7** is formed when TNB is treated with diazabicyclononene in DMF or DMSO is an important finding.[27] In **7**, the positive charge is not localized on the nitrogen atom adjacent to the ring, and this may contribute to its stability.



7



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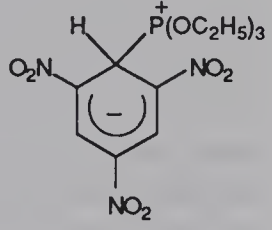
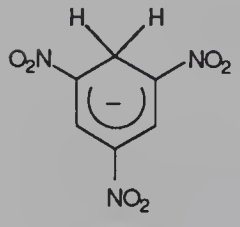


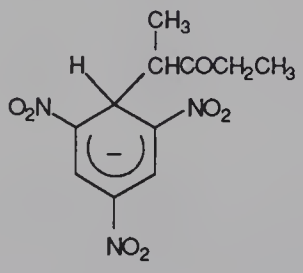
9

In many instances, particular structural features in the nucleophilic moiety

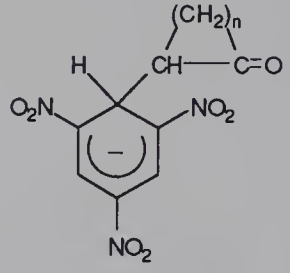
lead to NMR characteristics that provide additional support for structures **5**. A typical example is the N-adduct **8** in which the symmetrical structure of the pyrrole moiety is evidenced by the presence of an AA′BB′ system in the ^1H spectrum.[28] Also revealing in this case is the presence of only two signals ascribable to the pyrrole ring in the ^{13}C spectrum: $\delta C_{2',5'}$ = 120.2 ppm and $\delta C_{3',4'}$ = 107.6 ppm in DMSO (internal reference, TMS).[28] Another interesting example is the phosphorus adduct **9** whose ^1H spectrum shows a typical coupling constant J_{P-H_1} of 21 Hz.[29] As to the hydride adduct **10**, which may be considered to be the prototype of the TNB series of σ-complexes, the methylene protons at C-1 give rise to a characteristic triplet at δ = 3.88 ppm ($J_{H1-3,5}$ = 0.5 Hz) in DMSO.[30]



10

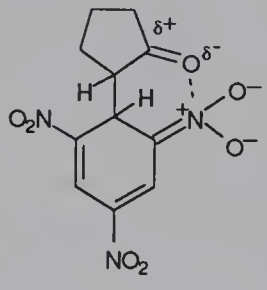


11

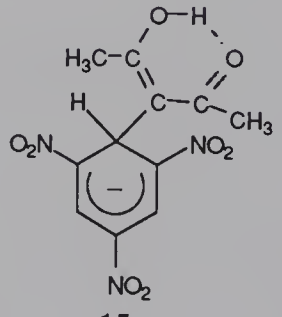


12 n = 3

13 n = 4



14



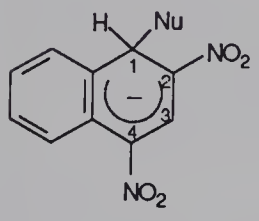
15

On the other hand, the presence of an asymmetric carbon α to C-1, as in the diethylketone, cyclopentanone, and cyclohexanone adducts **11**, **12**, and **13**, causes nonequivalence of the H-3 and H-5 ring protons as well as of the C-2 and C-6, and C-3 and C-5 carbons or the N-2 and N-6 nitrogens.[8,31–33] The nonequivalence appears to be especially important in the cyclopentanone adduct **12**, and this feature, together with an unusually low field position of the carbonyl carbon in **12**, has been taken as evidence for the conformation **14** in which the carbonyl function is highly polarized.[31,33]

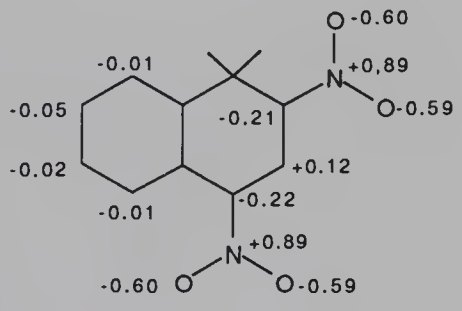
While most TNB-ketone and -ester complexes are present in the keto form,

those derived from very acidic and therefore very enolizable carbonyl compounds may exist largely in the enol form. A typical example is the 2,4-pentanedione-TNB adduct **15**, which shows in particular a C_α resonance at 112.67 ppm, as compared with δC_α in the 50–60 ppm range for adducts **11**–**13** in DMSO.[32]

Structures of 1,3-dinitronaphthalene adducts **16**, [e.g., **16a** (Nu = OCH_3)] have been readily elucidated.[1,34] As expected, the ring hydrogen at C-1 suffers an upfield shift that is large but dependent on the –I effect of the bonded nucleophilic moiety on formation of **16**. However, the interesting feature lies in a concomitant, though slight, downfield shift of H-3 from the position in the parent molecule.[1,34] In this regard, recent SCF-MO-Cl calculations by Sekiguchi have revealed the π-charge distribution shown in **17**.[35] This suggests that the low field position of H-3 in **16** may derive in part from the electron deficiency at C-3 and in part from the proximity of positive charge on the nitrogen atoms of the NO_2 groups. The result of the calculations, that about 60% of the negative charge of 1,1-disubstituted 2,4-dinitronaphthalene adducts is localized on the two NO_2 groups, demonstrates the exceptional ability of NO_2 to attract electrons.[35]



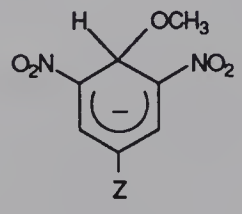
16 (a) Nu = OCH_3

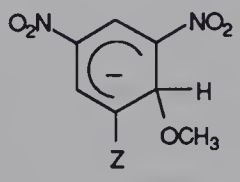


17

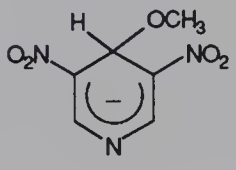
NMR studies have confirmed the original kinetic finding that isomeric addition can occur at structurally different unsubstituted positions of a nitroaromatic.[36–40] Prototype systems are the reactions of CH_3O^- ion with 1-Z-3,5-dinitrobenzenes in which the Z group is less electron withdrawing than the NO_2 group. In some cases, as with 1-cyano- and 1-methoxycarbonyl-3,5-dinitrobenzenes, the ^1H spectra, recorded at equilibrium in DMSO, show the presence of AX_2 and AMX systems, consistent with formation of both isomeric adducts **18** and **19**.[36,39] However, many of the adducts of type **18** [Z = H, CF_3, SO_2CH_3, $CON(C_2H_5)_2$], which lack an NO_2 group in the position para to the sp^3 carbon, have much lower thermodynamic stabilities than their isomers **19**,

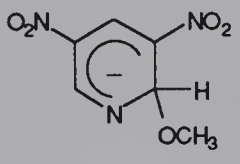
and they can be seen only as transient species.[39] Use of high resolution NMR in flowing systems has helped in the characterization of **18** in these instances.[40]



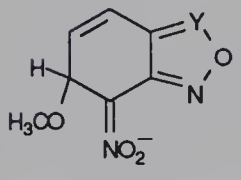


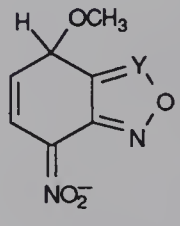
18 Z = H, CN , CF_3 , SO_2CH_3 , $CON(C_2H_5)_2$ **19**





20 **21**

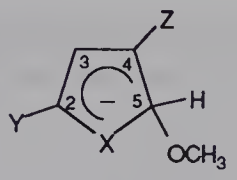




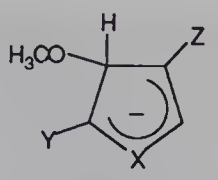
22 (a) Y = N ; (b) Y = N→O **23**

Concurrent addition at unsubstituted positions has been similarly detected by NMR spectroscopy in heterocyclic systems. The isomeric methoxide adducts **20** and **21** of 3,5-dinitropyridine, and **22** and **23** of 4-nitrobenzofurazan and -benzofuroxan (Y = N, N→ O) are representative examples.[41–44]

Nucleophilic addition at activated 2,4-Y,Z-disubstituted furans, pyrroles, thiophenes, and selenophenes occurs exclusively at the α-position to the heteroatom.[45–49] Measurements with selenophenes have provided an elegant demonstration of the formation of **X-24** rather than **X-25**, since the NMR spectra show strong coupling of the high-field C-5 proton to ^{77}Se: $J_{H5—Se^{77}} \sim$ 30 Hz.[46]

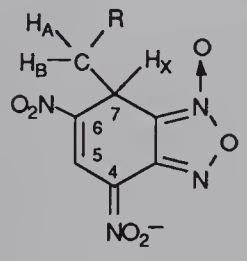


X = O , S , Se , N-R

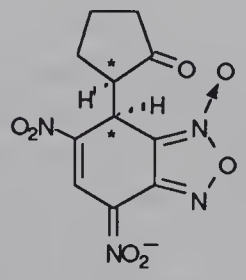


24 (a) Y = Z = NO_2 ; (b) Y = NO_2 , Z = CN ; (c) Y = CN , Z = NO_2 **25**

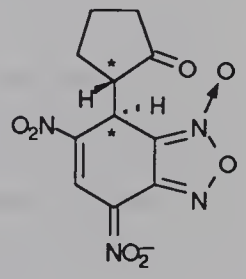
Owing to chirality of the tetrahedral ring carbon C-7, interesting stereoisomerism was found in σ-adducts of 4,6-dinitrobenzofuroxan (DNBF).[50] Thus, the geminal protons of the acetone and nitromethane complexes **26a** and **26b** are diastereotopic and appear as the AB part of an ABX system that is particularly well resolved for **26a** ($J_{AX} = J_{BX} = 4.15$ Hz; $J_{AB} = -17.7$ Hz).[50a] Introduction of a second chiral center α to C-7 results in the possible formation of two diastereoisomeric complexes.[50a] Such adducts have been clearly identified in the case of the cyclopentanone- and nitroethane-DNBF systems (e.g., **27a** and **27b**).[50] Diastereoisomeric complexes are also formed on addition of L-cysteine to DNBF.[51] Because the asymmetric center in L-cysteine is relatively far from the nucleophilic sulfur, both diastereoisomers **28a** and **28b** are formed in essentially equal amounts.



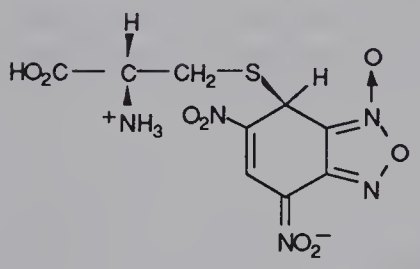
26a R = $COCH_3$
26b R = NO_2



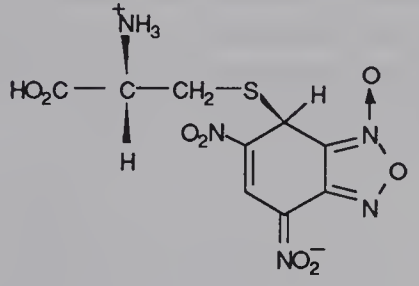
27a



27b

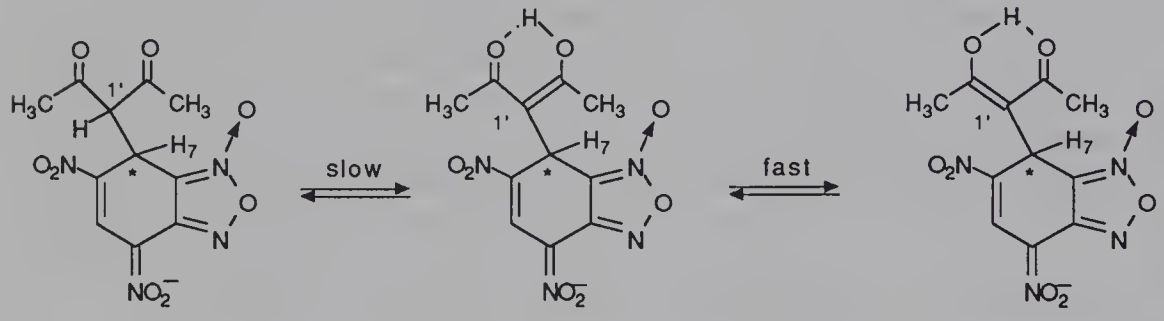


28a



28b

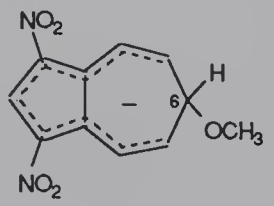
Addition of 2,4-pentanedione to DNBF resulted in an interesting sequence of reactions in DMSO.[50a] The ketonic σ-complex **29** with two nonequivalent methyl groups was initially observed by NMR but it underwent a slow and only partial conversion into the enolic form **30**. While H_7 gave a doublet in **29** ($^3J_{1',7}$ = 2.6 Hz), it became a singlet in **30**. After complete equilibration of the reaction at 32°C, **29** and **30** were present in a ratio of 30:70, essentially identical with the ratio of keto and enol forms of 2,4-pentanedione itself in DMSO at the same temperature.[50a] The observation of two broad singlets for the methyl resonances of **30** provided evidence of a fast equilibrium between the two tautomers **30a** and **30b**.



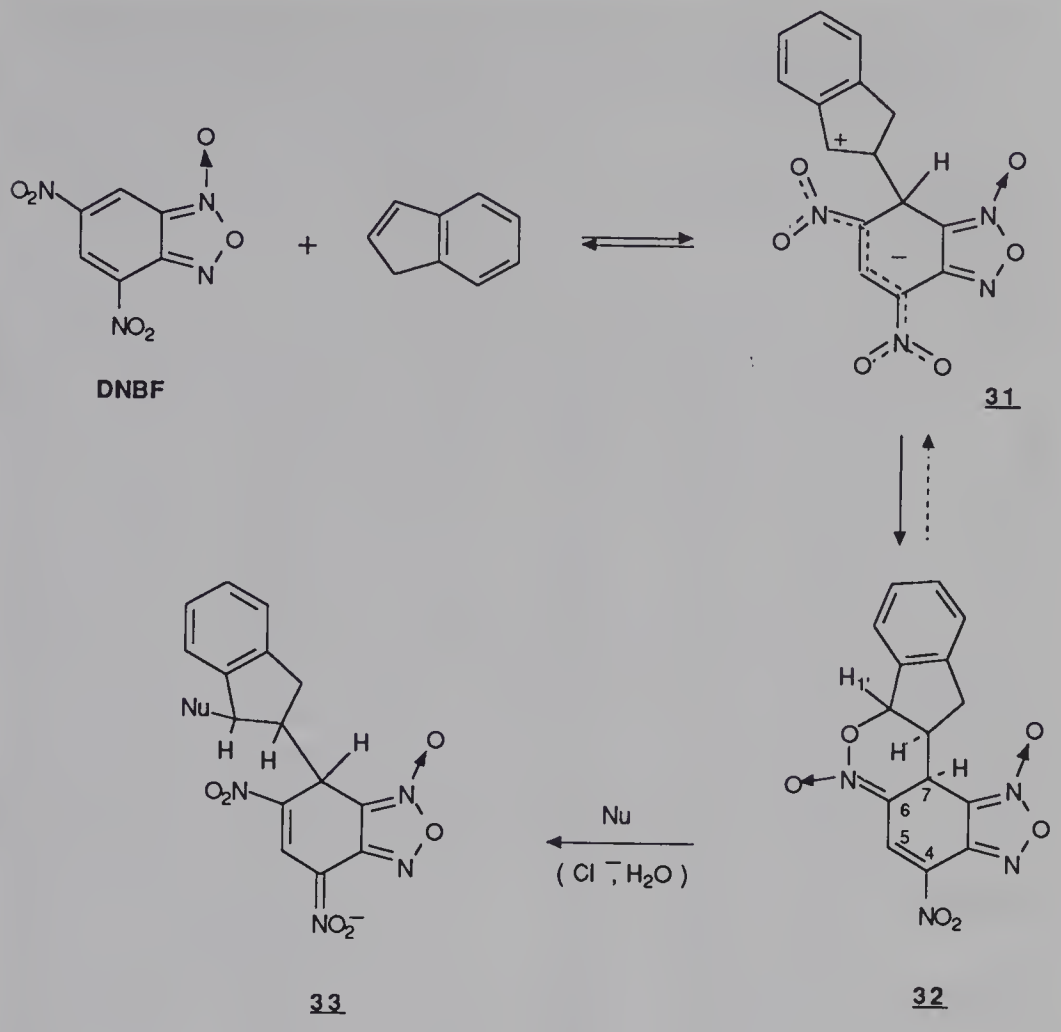
29 **30a** **30b**

Combination of ^1H, ^{13}C, and ^{15}N NMR spectroscopy has allowed unambiguous characterization of the reaction sequence shown in Scheme 2.1.[52] The dihydrooxazine *N*-oxide **32** is a very unusual structure in σ-complex chemistry, and it results presumably from intramolecular nucleophilic attack of an oxygen atom of the ortho-like 6-NO_2 group of the DNBF moiety of the initially formed zwitterionic adduct **31** at the partially positively charged carbon center in the indene ring. Besides exhibiting C-4 and C-5 chemical shifts and $J^{15}_{N—H_5}$ and $J^{15}_{N—H_7}$ coupling constants closely resembling those for neutral DNBF rather than those for DNBF σ-adducts, including **33**, structure **32** was strongly supported by the observation of a large $^3J^{15}_{N—H_1}$ coupling constant (7.1 Hz).[52]

σ-Adduct formation at an unsubstituted ring position of nitro-activated nonbenzenoid aromatics is exemplified by the 1,3-dinitroazulene–methoxide complex **34**. The ring hydrogen at C-6 suffers a very large upfield shift (Δδ = 4.81 ppm) upon formation of **34**.[53]



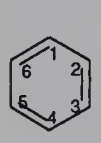
34



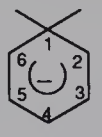
Scheme 2.1.

Olah and Mayr have assumed that changes in carbon chemical shift upon adduct formation will largely reflect changes in charge densities at the ring positions.[54] On this basis, they have compared the shifts of cyclohexadienyl and trinitrocyclohexadienyl anions with their precursors. As shown in Table 2.2, formation of the unsubstituted anion **36** from benzene **35** is accompanied by an overall shielding of the sp^2 ring carbons of about 150 ppm, which is close to that predicted for the shielding of aromatic carbons by one electron.[55] In contrast, the formation of adducts **2** or **5** from TNB results in a much weaker shielding of about 57 ppm, indicating that the electron density of the sp^2 carbons is increased by about 0.4 e^- while 0.6 e^- is absorbed by the NO_2 groups.[32,54,56] Although changes other than simple charge effects may determine ^{13}C shifts on adduct formation,[57] this conclusion is interesting because

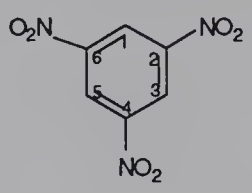
Table 2.2. Changes in ^{13}C NMR Chemical Shifts of the sp^2 Ring Carbons upon Formation of σ-Complexes in Benzene Series[a]



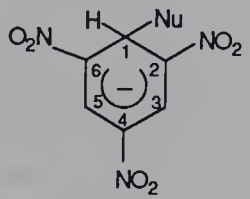
35



36

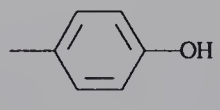


TNB



2 or 5[b]

	C-2	C-3	C-4	C-5	C-6	ΣΔδ	Ref.
35	128.7	128.7	128.7	128.7	128.7		54
36	75.8	131.8	78	131.8	75.8		54
Δδ(36-35)	–52.9	3.1	–50.7	3.1	–52.9	–150.3	
TNB	149.5	125.2	149.5	125.2	149.5		54
2	132.6	127	122.2	127	132.6		54
	131.9	125.9	121.3	125.9	131.9		56
Δδ(2-TNB)	–16.9	1.8	–27.3	1.8	–16.9	–57.5	
5a	132.9	127.3	121.2	127.3	132.9		33
	133.5	127.7	121.0	127.7	133.5		32
	136.3	125.5	120.2	125.5	136.3		56
Δδ(5a-TNB)	–16.6	2.1	–28.3	2.1	–16.6	–57.3	
5b	135.2	125.0	121.0	125.0	135.2		32
Δδ(5b-TNB)	–14.3	–0.2	–28.5	–0.2	–14.3	–57.5	
5c	136.3	125.8	120.3	125.8	136.3		32
Δδ(5c-TNB)	–13.2	0.6	–29.2	0.6	–13.2	–54.4	

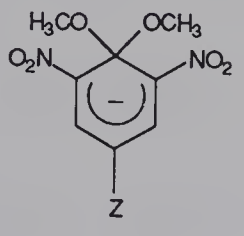
[a] All data in DMSO; δ in ppm.
[b] 2, Nu = OCH_3; 5a, Nu = CH_2COCH_3; 5b, Nu = OC_6H_5; 5c, Nu = 

it agrees with conclusions reached from SCF-MO calculations.[1,18] It is nicely illustrative of the capability of the NO_2 groups to absorb the negative charge of σ-adducts.

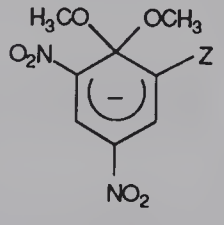
2.2.2.2 Complexation at Substituted Carbons

In part because it is generally associated with release of steric compression, complexation at a substituted carbon often results in the formation of stable

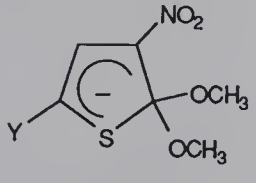
1,1-disubstituted adducts that have been readily identified by ^{1}H and ^{13}C NMR spectroscopy.[1,8,54,58] Some pertinent ^{13}C NMR data obtained in DMSO for 1,1-adducts derived from nitro-activated ethers are given in Table 2.3. In the 1,1-dimethoxy complexes **37-Me** and **38-Me** of the various 4-Z-2,6- and 2-Z-4,6-dinitroanisoles studied, the C-1 carbon and the methoxy carbon are strongly shifted upfield ($\Delta\delta C_1 \sim 50$ ppm; $\Delta\delta_{OCH_3} \sim 12$ ppm) from the position in the parent compounds, consistent with the change in hybridization.[54,58] In agreement with SCF-MO theory, which predicts an increase in negative charge at the 2,4- and 6-positions and a decrease at the 3- and 5-ring positions,[18,19] the resonances of C-2,6 and C-4 move markedly to high field and those of C-3,5 slightly to low field. In keeping with Olah and Mayr's idea mentioned above that the sum $\Sigma\Delta\delta$ of the changes in ^{13}C shifts of the sp^2 carbons gives a semiquantitative measure of the increase in electron density on the ring following adduct formation, it is interesting to note in Table 2.3 that all the $\Sigma\Delta\delta$ values are in the range between –65 and –44 ppm; that is, they are much lower than the value of –150 ppm corresponding to the shielding of aromatic carbons by one electron.[55] However, there is not a good correlation between the $\Sigma\Delta\delta$ values and the thermodynamic stability of the adducts, suggesting that this approach is rather qualitative. Based on similar findings for the *gem*-dimethoxythiophene adducts **S-39** and **S-40**, it has been recently proposed that



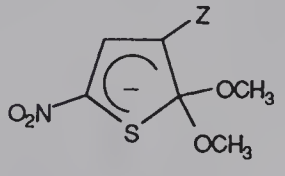
37-Me



38-Me



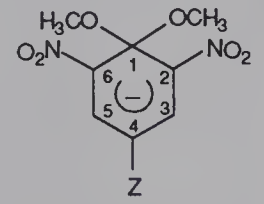
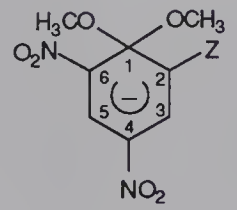
S-39



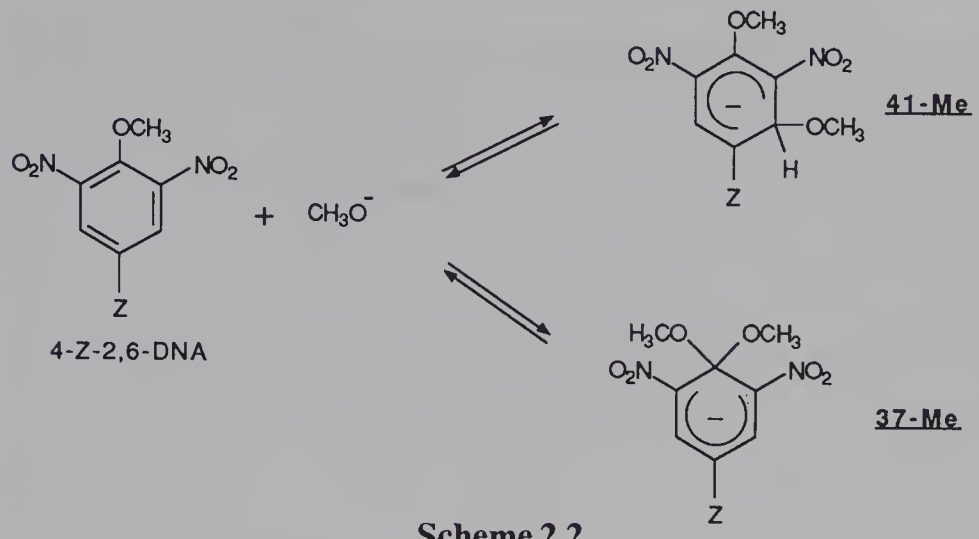
S-40

Y or Z : (a) NO_2 ; (b) SO_2CF_3 ; (c) CN ; (d) SO_2CH_3 ; (e) CHO ; (f) CO_2CH_3 ; (g) $COCH_3$; (h) $CONH_2$; (i) CF_3 ; (j) Cl ; (k) F ; (l) H

Table 2.3. ^{13}C NMR Shifts (ppm) of the 1,1-Dimethoxy Adducts 37,Me and 38,Me of 4-Z-2,6-Dinitroanisoles and 2-Z-4,6-Dinitroanisoles in DMSO: Comparison with Thermodynamic Stability[a]

Complex	Z	C-1	C-2	C-3	C-4	C-5	C-6	OCH_3	$\Sigma\Delta\delta$[b]	K_1 (l/mol)[c]
	SO_2CF_3	102.1	128.9	133.0	87.8	133.0	128.9	52.2	–65.3	1.2×10^6
	NO_2	102	128.6	128.9	117.4	128.9	128.6	52.1	–45.9	19,500
	CN	102.7	127.9	136.4	73.7	136.4	127.9	51.9	–60.9	168
	SO_2CH_3	103.0	126.8	132.7	103.8	132.7	126.8	51.9	–58.5	101
	COC_6H_5	102.6	128.4	135.7	104.2	135.7	128.4	51.9	–48.2	45
37-Me	CF_3	104.5	126.3	131.7	94.4	131.7	126.3	51.95	–57.6	5
	NO_2	104.3	129.2	131.2	119.3	131.2	129.2	53.2	–44.2	19,500
	CF_3	104.8	111.3	129.7	119.8	131.8	123.5	52.6	–50.6	29
	Cl	104.9	120.7	126.0	120.6	130.5	121.2	52.5	–52.9	3
	F	103.7	148.3	107.8	118.4	128.8	121.2	52.8	–52.5	0.3
	H	104.1	118.5	125.4	121.7	131.1	122.9	52	–29.9	6.7×10^{-5}
38-Me	CH_3	106	125.4	123.9	122.6	130.9	120.7	52	–51.4	

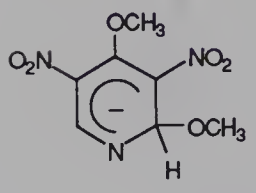
[a] Data reproduced with permission from ref. 58 for adducts 37,Me and ref. 54 for adducts 38,Me.
[b] $\Sigma\Delta\delta$ represents the sum of the differences between the ^{13}C NMR shifts of the sp^2 ring carbons of the adducts and those of the parent anisoles.
[c] K_1 is the equilibrium constant for the formation of 37,Me and 38,Me in methanol; values at 20°C from ref. 2.



Scheme 2.2.

the lack of regular trends in $\Sigma\Delta\delta$ may reflect the fact that the main effect of most substituents (e.g., CN, $CONH_2$, CO_2CH_3), would be not so much to accept part of the negative charge of the adducts but rather to stabilize a larger charge density at the carbon atom to which they are bonded, probably by a charge–dipole interaction.[59,60]

NMR spectroscopy was the tool that first revealed that many nitroaromatics undergo nucleophilic addition at an unsubstituted activated ring position prior to addition at a substituted one.[1] Again this behavior is best exemplified by the reaction of 4-Z-2,6- and 2-Z-4,6-dinitrophenyl ethers with RO^- ions.[61–65] Thus, addition of CH_3O^- to 4-Z-2,6-DNA in DMSO yields initially the 1,3-dimethoxy complexes **41-Me** whose ^1H spectra show an AX system consisting of two spin-coupled bands in the ranges 7.13–8.42 and 5.45–6.11 ppm ($J_{H3,5} \approx 1.3$–1.95 Hz) and two singlets at $\delta \sim 3.8$ and 3.1 ppm due to the methoxy protons at C-1 and C-3, respectively.[61,62] With time, complete or partial isomerization of **41-Me** to the 1,1-dimethoxy complexes **37-Me** occurs, depending on whether the Z group is (Z = NO_2, SO_2CF_3, CN, SO_2CH_3) or is not (Z = CF_3, Cl, F) very electron withdrawing (Scheme 2.2). Interestingly, 4-methoxy-2,6-dinitropyridine behaves as a 4-aza-2,6-dinitroanisole, yielding first the 1,3-complex **42**, which undergoes complete conversion into **43**.[66,67] With 2-Z-4,6-dinitroanisoles (Z = CN, CF_3, Cl), which have two nonequivalent unsubstituted positions, both the 1,5- and 1,3-dimethoxy adducts **44-Me** and **45-Me** were found to form as short-lived species prior to the thermodynamically more stable 1,1-isomers **38-Me**.[63,68] The competitive formation of **44-Me** and **45-Me** prior to **38-Me** is reminiscent of that of the 4- and 2-complexes **18** and **19** of 1-Z-3,5-dinitrobenzenes (see Section 2.2.2.1). The complexes **44-Me**, which lack an NO_2 group in the



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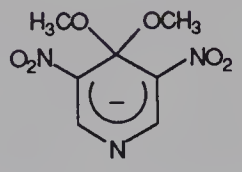

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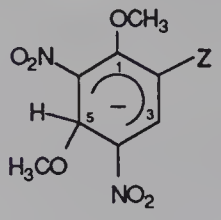
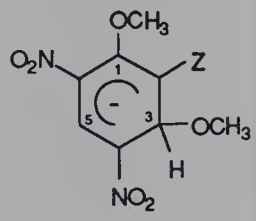
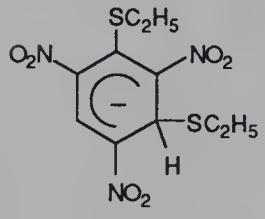


44-Me



45-Me



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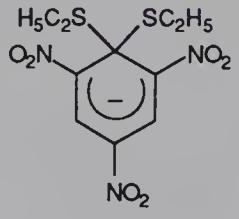

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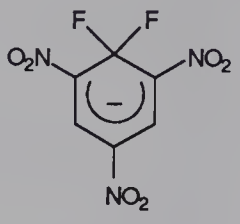

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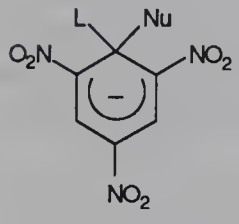

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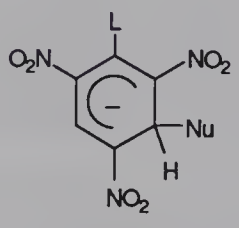

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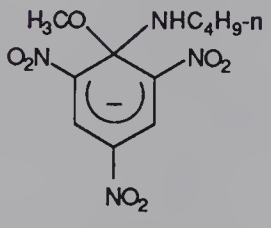
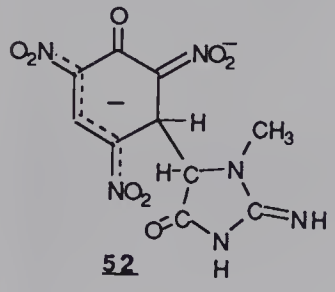


51

position para to the sp^3 carbon, form faster but have lower thermodynamic stabilities than their isomers **45-Me**.

A number of other systems have been found to obey the foregoing relationship which is, however, markedly dependent on the nature of the substituent at C-1 and on the nucleophile. Thus, the reaction of ethylthiopicrate with $C_2H_5S^-$ in DMSO results in a mixture of **46** and **47**, while the reaction of picryl fluoride with "naked" fluoride ion yields only the *gem*-difluoro complex **48** in acetonitrile.[69,70] Unambiguous identification of **48** has come from the observation that the ring protons give a triplet due to H—F coupling ($J_{F—H}$ ~ 3.9 Hz). When L is a displaceable group (Cl, Br, I, NO_2, SO_3^-), adducts of type **49** are intrinsically unstable and only the adducts **50** may be observed as transient species prior to the formation of substitution products (Nu = OH, OR, NH_2, SR, CR_3).[1,71,72] However, the unsymmetrical 1,1-adduct **51**, which is the actual intermediate in the S_NAr displacement of 2,4,6-trinitroanisole (TNA) with butylamine, has been successfully characterized using a flow NMR system.[73] Stable unsymmetrical 1,1-adducts have also been identified when L has a poor departing ability; for example, the reactions of methyl 2,4,6-trinitrobenzoate or *N-tert*-butyl-2,4,6-trinitrobenzamide with OH^- or CH_3O^-

give **49** (L = CO_2CH_3 or $CONHC(CH_3)_3$; Nu = OH, OCH_3).[1,74,75] Change of the nucleophile to sulfite or acetonate ions favors the 1,3-adduct **50** (L = CO_2CH_3, Nu = SO_3^-, CH_2COCH_3).[1] Because of steric hindrance between the creatinine residue and nitro groups, the 1,3-adduct **52**, which forms from the addition of creatinine to picric acid in alkaline solution (Jaffé reaction), exists as a mixture of diastereoisomers and shows separate resonances due to ring protons at δ = 5.38 and 8.85 ppm and 5.28 and 8.76 ppm.[76,77] This reaction as well as the analogous reaction of picrate anion with cardenolides, the Baljet reaction, have useful applications in clinical chemistry.[78]



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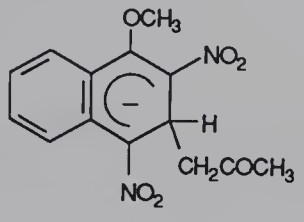
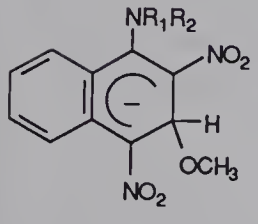
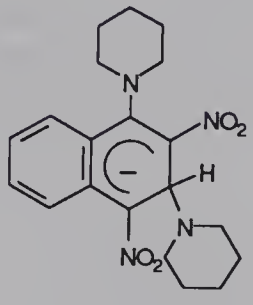


53



54



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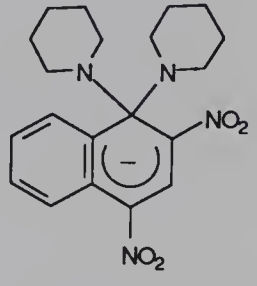
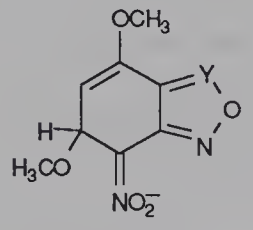


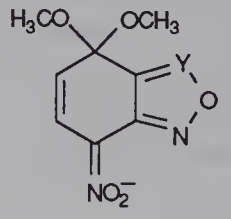
56

The unsubstituted 3-position of 1-substituted-2,4-dinitronaphthalenes lacks the activation by a para-NO_2 group. Therefore, complexation at this position is thermodynamically very unfavorable and there are only a few NMR identifications of the corresponding adducts.[79] Reaction of acetonate ion with 1-methoxy-2,4-dinitronaphthalene gives **53** whose ^1H spectrum shows a high field H-3 resonance at δ = 5.34 ppm and a methoxy singlet at δ = 3.81 ppm in DMSO.[80] Similarly, reactions of RO^- ions with 1-(*N*,*N*-dialkylamino)-2,4-dinitronaphthalenes result initially in the formation of 1,3-complexes **54**, which have been characterized by ^1H NMR techniques.[81,82] Interestingly, due to strong steric constraint, the 1,3-dipiperidino complex **55** is relatively stable and undergoes a very slow and partial conversion into the 1,1-dipiperidino isomer **56**.[82] 1-Piperidino-2,4-dinitrophenanthrene affords a relatively long-lived 1,3-complex, reminiscent of **54**, upon reaction with methoxide ion in 90% DMSO/10% CH_3OH.[83]

NMR work has also confirmed the occurrence of competitive nucleophilic attacks at unsubstituted and substituted positions of 4-nitrobenzofurazans and 4-nitrobenzofuroxans. The adducts **57a** and **57b** both have been characterized prior to their conversion to the *gem*-dimethoxy isomers **58a** and **58b**.[43,44]

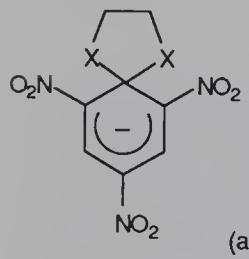


57 (a) Y = N ; (b) Y = N→O



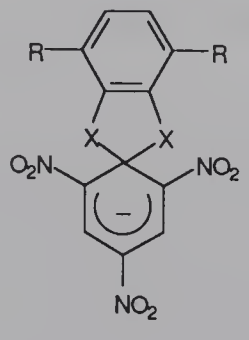
58

Intramolecular nucleophilic attack at a substituted carbon results in formation of spiro adducts, which often have a high thermodynamic stability. Firmly characterized complexes are the symmetrical adducts **59** and **60** of the glycol and catechol picryl ethers and thioethers (X = O, S), and the zwitterionic adduct **61**.[84–90] While the H-3,5 resonance of the dioxolane adducts (X = O) compare well with those of 1,1-dialkoxy analogues, it is noteworthy that the protons in the dioxolane ring absorb at much lower field than the OCH_2 protons in **62**. It has been shown that this difference derives from the conformational differen-

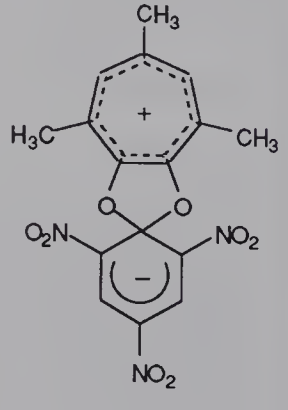


59

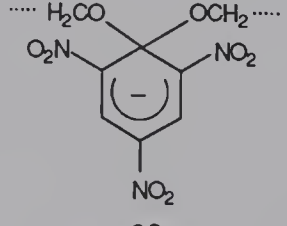
(a) X = O , R = H
(b) X = O , R = CH_3
(c) X = O , R = $C(CH_3)_3$
(d) X = S , R = H



60

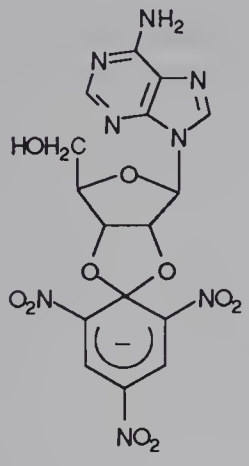


61

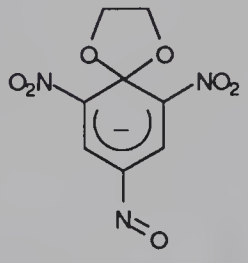


62

ces between the 1,1-dialkoxy (**62**) and spiro (**59**; X = O) adducts—a fact of overwhelming importance to the understanding of the differences in the rates of spontaneous and H^+-catalyzed decompositions of **59** and **62** (see Section 2.3.4).[91] ^1H and ^{13}C data have been reported for the spiro complex of adenosine **63** in DMSO.[92] In accord with the unsymmetrical substitution of the dioxolane ring, the two sides of the cyclohexadienylide ring of **63** are found to be nonequivalent. However, the magnitude of the anisochrony observed here suggests that the dissymmetry is enhanced by the twisting of an NO_2 group. A noteworthy result is that stereoselective opening of the dioxolane ring of **63** occurs in acid solution.[92] The nonequivalence of the ring protons of the nitroso adduct **64** derives from restricted rotation around the C—NO bond.[93] Dioxolane and/or dithiolane adducts have also been identified from nitronaphthalenes, thiophenes, benzofurazans, and benzofuroxans as well as from nonbenzenoid nitroaromatics like nitrotropones.[94–97] The adduct **65** is a rare example of σ-complexation at the β-position of a five-membered ring.[95]



63



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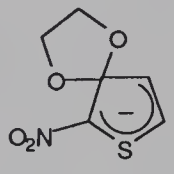
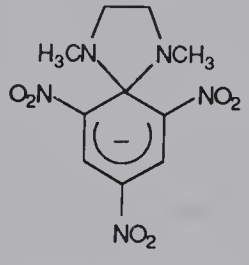
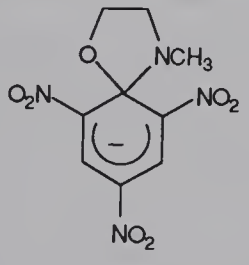


65

A number of symmetrical (e.g., **66**) as well as unsymmetrical (e.g., **67**) spiro adducts formed by intramolecular cyclization of picramide and related derivatives have been characterized as stable or transient species.[1,98–101] However, many of these systems were discussed in Chapter 1. Interactions that



66

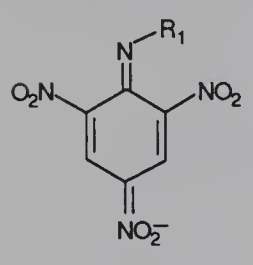


67

involve spiro complex formation and concurrent intramolecular displacement of an NO_2 group are considered in Chapter 4.

2.2.2.3 Complexation Versus Proton Abstraction

Proton transfer to give **68** competes with the formation of the 3-complex **69** upon reaction of picramide and *N*-substituted derivatives with oxygen bases (Nu = RO^-), with the fraction of the parent compound reacting by proton loss increasing upon transfer from a protic to a dipolar aprotic solvent.[1,102] The fraction of proton loss also increases with the steric bulk of the nucleophile, being greater for $(CH_3)_2CHO^-$ than for CH_3O^- or OH^- ions.[102] In contrast with oxygen bases, sulfur, nitrogen, or carbon bases give essentially **69**. A feature of interest is the presence of two NH signals in the ^1H spectrum of the thioethoxide adduct of picramide; this is consistent with hydrogen bonding involving the ortho-NO_2 groups, as shown in **70**.[103] Positive identification of 1,1-adducts **71**, even from 1-(*N*,*N*-dialkyl)picramides remains very questionable.[104–106]



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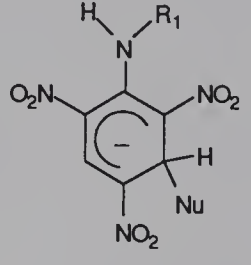

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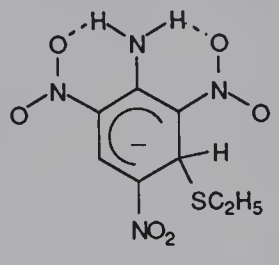
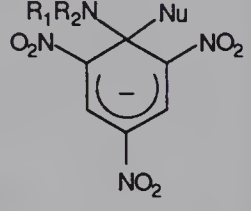
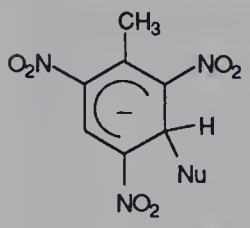


70

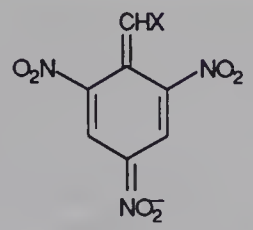


71

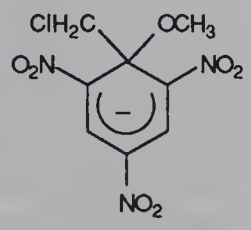
Strong oxygen bases (OH^-, RO^-) react with 2,4,6 trinitrotoluene (TNT) in aqueous or alcoholic DMSO mixtures to give first the 3-complex **72**, which undergoes rapid and quantitative conversion to the more stable trinitrobenzyl anion **73a**.[1] Successful identification of **72** (Nu = OCH_3) by flow NMR spectroscopy has been made.[107] Similarly, **72** (Nu = NH-alkyl) forms prior to **73a** upon treatment of TNT with aliphatic amines in DMSO.[108] In contrast, in liquid ammonia, only the 3-complex **72** (Nu = NH_2) is formed.[26b] Use of nucleophiles such as CN^-, SO_3^{2-} or H^- leads exclusively to **72**.[1] Substitution of a methyl hydrogen of TNT for chlorine allows the formation of the 1,1-adduct **74**, which is observed together with that of the carbanion **73b**.[109] Similarly, alkoxide attack on 2,2′,4,4′,6,6′-hexanitrobibenzyl yields the adduct **75** as a thermodynamically stable species.[109b]



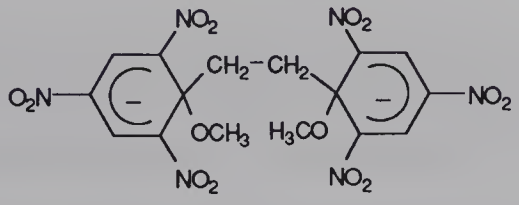
72



73 (a) X = H
(b) X = Cl

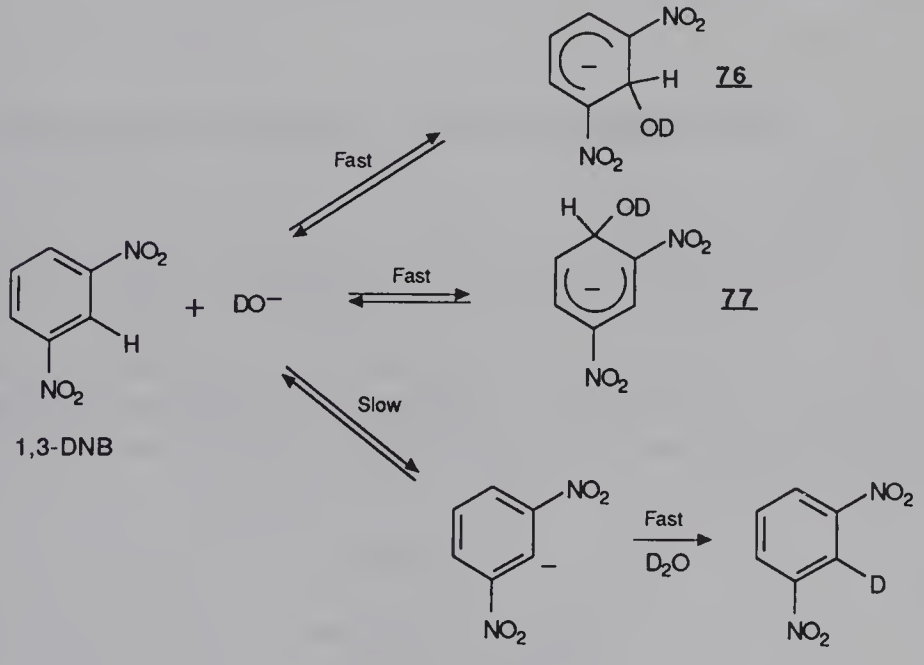


74



75

The observation of isotopic exchange on compounds like TNB or 1,3-DNB in basic media shows that ionization of an aryl hydrogen in polynitroarenes can occur.[4] The process competes with σ-complex formation, as illustrated in Scheme 2.3, which refers to a recent study of 1,3-DNB in the NaOD-D_2O-DMF system.[110] As can be seen, the σ-adducts 76 and 77 are both involved in



Scheme 2.3.

rapidly established side equilibria as unreactive species. Accordingly, the exchange rates are decreased in media of high DMF content where there is immediate and complete conversion of 1,3-DNB to 76 and/or 77, compared with relatively aqueous media, where there is only partial formation of 76 and/or 77.[110] Note that the exchange from the 2-position occurs 2000 times more rapidly than from the 4(6) positions, as shown by a kinetic study performed with tritiated DNB.[111]

2.3 Thermodynamics and Kinetics of σ-Complex Formation

Predominant factors determining the stability and ease of formation of σ-complexes are the nature of the aromatic or heteroaromatic residue itself and the number, kind, and position(s) of the electron-withdrawing substituents ensuring the activation of the ring(s).[1,2] Also of importance are the substituted or unsubstituted character of the site of nucleophilic attack and the steric effects adjacent to this position. The reactivity of σ-adducts depends equally on the intermolecular or intramolecular character of the nucleophilic addition.[1,2] These factors are considered in the ensuing discussion.

2.3.1 The Nature of the Aromatic System

Table 2.4 summarizes rate and equilibrium constants (k_1, k_{-1}, K_1) for formation and decomposition of methoxy σ-complexes (C) that result from the addition of methoxide ion to an unsubstituted ring position of various nitroaromatic compounds (S) in methanol. Since steric effects are of minor importance in these interactions, the data can be used to assess the influence of the aromatic system on σ-complex formation.[1] The k_1, k_{-1} and K_1 constants are defined by eq. 2-2.

$$S + CH_3O^- \underset{k_{-1}}{\overset{(K_1)\ k_1}{\rightleftharpoons}} C \qquad (2\text{-}2)$$

Table 2.4. Rate and Equilibrium Constants for Formation and Decomposition of Methoxy Complexes of Nitroaromatic and Nitroheteroaromatic Derivatives in Methanol at 25°C

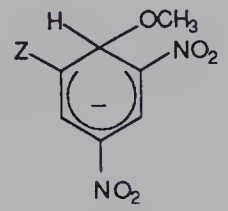
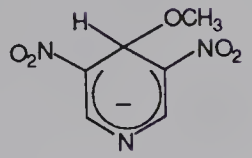
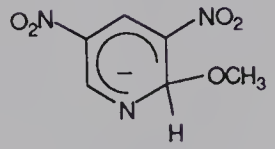
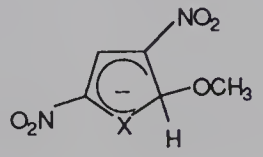
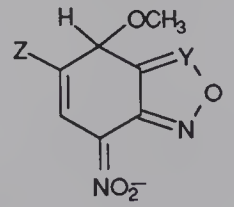
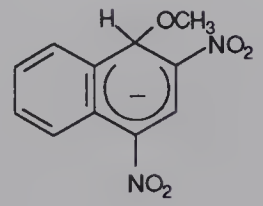
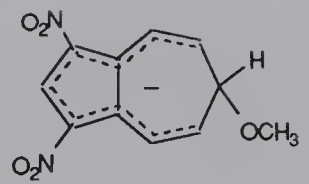
	Complex	X or Z	Y	k_1 ($l\ mol^{-1}\ s^{-1}$)	k_{-1} (s^{-1})	K_1 ($l\ mol^{-1}$)	Ref.
	2	NO_2		7050	305	23.1	112
	78	H				$\sim 10^{-6}$	113
	20			6150[a]	2660[a]	2.3[a]	37
	21			2460	35.5	69.5	37
	O-24a	O		4500	$\leq 9 \times 10^{-3}$	$\geq 5 \times 10^{5}$	45
	Se-24a	Se		27.7	4.8×10^{-4}	5.78×10^{4}	114
	S-24a	S		14.9	1.75×10^{-2}	850	114
	NCH_3-24a	NCH_3		([b])	([b])	([b])	115

Table 2.4. *(Continued)*

	Complex	X or Z	Y	k_1 ($l\ mol^{-1}\ s^{-1}$)	k_{-1} (s^{-1})	K_1 ($l\ mol^{-1}$)	Ref.
	23a	H	N	6	2.04×10^{-3}	2940	116
	23b		N → O	28.5	3.35×10^{-3}	8500	116
	79a	NO_2[c]	N	9.3×10^{5}	2×10^{-5}	4.65×10^{10}	117
	79b		N → O	1.87×10^{6}	8.9×10^{-5}	2.1×10^{10}	117
	16a			11.2	124	0.09	118
	34					~1000[d]	53

[a] Values estimated from a combination of data in ref. 37 for OH^- and CH_3O^- attacks on 3,5-dinitropyridine in water or methanol.
[b] Undetected due to a very low stability.
[c] $t = 20°C$.
[d] Value estimated from data in ref. 53.

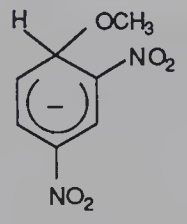
Table 2.4 shows that the trinitrobenzene complex **2** has a thermodynamic stability that is of the same order of magnitude as that of the isomeric dinitropyridine complexes **20** and **21**. In contrast, **2** is much less stable than three of the four dinitro-activated five-membered ring adducts **X-24a** (X = O, S, Se), as well as the two mononitro benzofurazan and benzofuroxan complexes **23a** and **23b**.

Because there is no major change in geometry upon going from benzene to pyridine, differences in the ease of complex formation in the two series reflect the lower aromaticity of the pyridine ring and the intrinsic activation of this ring by the electronegative nitrogen atom.[119] The results point to the remarkable effect on complex stability of an ortho-aza functionality relative to an ortho-NO_2 group, since the adduct **21** is three times more stable than **2** in methanol.[37] In contrast, aza activation is less effective than nitro activation in the position para to the sp^3 carbon; the adduct **20** is 10 times less stable than **2**. The three complexes **2**, **20**, and **21** behave analogously in that they all have high rates of formation and decomposition in methanol.[37]

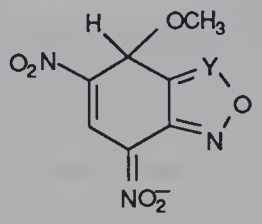
Although the pyrrole, thiophene, selenophene, and furan rings have a π-excessive character, comparable to that of benzene, at least three factors make the heterocyclic derivatives intrinsically more reactive: (1) a lower aromaticity, (2) the known ability of heteroatoms such as O, S, and Se to accommodate a negative charge, and (3) a more favorable geometry.[119] The latter influence relates to the finding that the $X–C_5–C_4$ angle at the reactive carbon center in the parent heterocycles has a value close to that for tetrahedral carbon (i.e., ≈ 110°), while the analogous angle in the benzene series is about 120°.[1,119] This implies much more bond strain upon forming a σ-complex in the six- than in the five-membered ring series. Finally, activation by a similar number of NO_2 groups is much more effective in promoting σ-complex formation in a five-membered ring, with the exception of the pyrrole ring.[115,119] While the equilibrium constants K_1 for formation of the furan, selenophene, and thiophene adducts **O-24a**, **Se-24a**, and **S-24a** are 5×10^5, 5.78×10^4, and 850 l/mol, that for the dinitrobenzene complex **78** is only about 10^{-6} l/mol in methanol (t = 25°C).[39,45,113–115] Even activation by a third NO_2 group is not sufficient to yield a benzene adduct with a stability comparable to that of the thiophene analogue. As can be seen in Table 2.4, **2** forms 470 times more rapidly than **S-24a**, but it decomposes so much faster ($k_{-1}^{\mathbf{2}}/k_{-1}^{\mathbf{S-24a}} = 1.75 \times 10^5$) that it is 40 times less stable than **S-24a**.

The heterocycles benzofurazan and benzofuroxan combine low aromaticity and high electron deficiency, as a result of the powerful electron-withdrawing effect exerted by the annelated furazan and furoxan rings.[1,119] It follows that mononitro activation is sufficient to ensure high complex

stability.[116] It is also noteworthy that the dinitro activated adducts **79a** and **79b** are the most stable methoxide σ-complexes ever characterized in methanol.[117] The K_1 values for formation of **79a** and **79b** are so high that these adducts form in the absence of any added methoxide ion in methanol.[117]



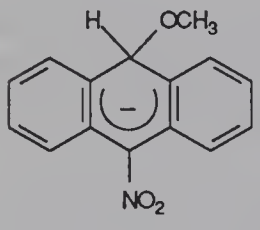
78



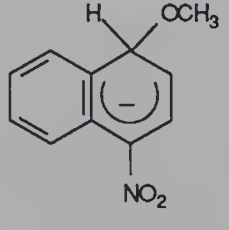
79a Y = N

79b Y = N→O

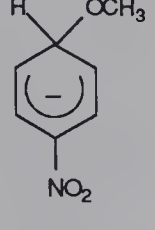
The dinitronaphthalene complex **16a** is 100 times less stable than **2** but 10,000 times more stable than the dinitrobenzene analogue **78**.[39,113,118] This corresponds to an estimated standard free energy contribution of an added fused aromatic ring to the stabilization of benzene complexes through increased delocalization of the negative charge of approximately –30 kJ/mol.[2,118] For comparison, the contribution of the third NO_2 group upon going from **78** to **2** is –42 kJ/mol.[2] Further extension of the aromatic system to anthracene has allowed the characterization of the mononitro adduct **80** in DMSO.[34] Despite the large contribution of this solvent to the stabilization of σ-adducts (see Section 2.3.6), no evidence for formation of the mononitro analogues **81** and **82** in appreciable contribution could be found under similar experimental conditions. The notable stability of the dinitroazulene complex **34** in methanol ($K_1 \sim 1000$ l/mol) is another example that emphasizes the effect of an extensive delocalization of the negative charge on the ease of complexation.[2,53]



80



81



82

2.3.2 The Effect of Ring Substituents

The influence of NO_2 relative to other substituents is born out by the data listed in Table 2.5, which refer to homogeneous series of structurally similar *gem*-dimethoxy adducts. Again, the rate and equilibrium constants k_1, k_{-1}, and K_1 are defined by eq. 2-2.

In the benzene series, replacement of one or several NO_2 groups in the trinitroanisole complex **37a-Me** (= **1a**) by less electron-withdrawing groups has the expected effect of decreasing complex stability. Table 2.5 reveals the following reactivity order for monosubstitution, both in the para and ortho positions to the sp^3 carbon of the adducts **37-Me** and **38-Me**[1,2]:

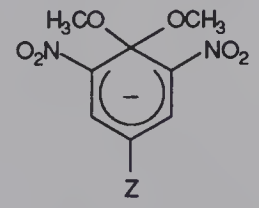
$$NO_2 > CN > CHO, SO_2CH_3 > CF_3 > CO_2CH_3 > Cl > F > H$$

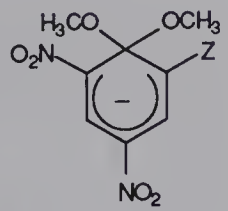
Rather similar trends are obtained in comparing data for the naphthalene complexes **83** (see structures in Table 2.5) as well as for the five-membered ring complexes **S-39** and **S-40**.[59,60] In most cases, the decrease in the equilibrium constant K_1, brought about by the substitution, arises from a decrease in the rate constant for formation (k_1) and a concomitant increase in the rate constant for decomposition (k_{-1}).[2] Similar conclusions have been drawn in comparing data for hydroxy and other alkoxy analogues of the various methoxy complexes.[2,126]

The most significant feature to emerge from Table 2.5 is that substitution at the 4-position para to the sp^3 carbon in **37a-Me** causes a much larger decrease in stability than a similar substitution at the ortho 2-position. Thus, changing NO_2 for CN or Cl at C-2 in **37a-Me** results in 6.5- and 2180-fold decreases in K_1, as compared with 60- and 7.8×10^6-fold decreases in K_1 for a similar change at C-4. The only exception is seen when an NO_2 group is replaced by H in **37a-Me**; in this instance, the resulting 2,4-dinitro complex **38l-Me** is less stable than its 2,6-dinitro isomer **37l-Me** because its formation does not involve as much steric relief as that of **37l-Me** and the other *gem*-dimethoxy complexes **37-Me** and **38-Me** (see below).[1,2] In a similar manner, substituting the para-like NO_2 group of the 2,4-dinitrothiophene adduct **S-39a** for a less electron-withdrawing substituent has more effect on K_1 than a similar variation in the ortho-like position.[59,60]

The results above express quantitatively the conclusions drawn from MO calculations[1,18–21] and are reflected in X-ray crystal determinations[11–14]: namely, a para-NO_2 group has a much stronger capability than an ortho-NO_2 group to withdraw electrons by resonance and to stabilize σ-complexes. This capability is further illustrated by the finding in benzene series that changes in stability due to para substitution are linearly correlated with substituent con-

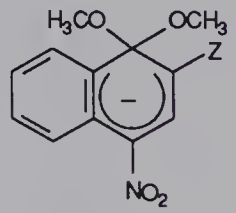
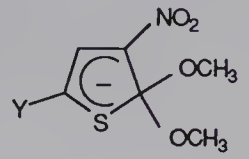
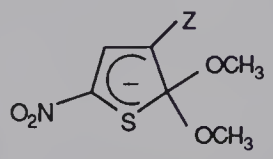
Table 2.5. Effect of Ring Substituents on the Rate and Equilibrium Constants for Formation and Decomposition of Various *gem*-Dimethoxy Complexes in Methanol



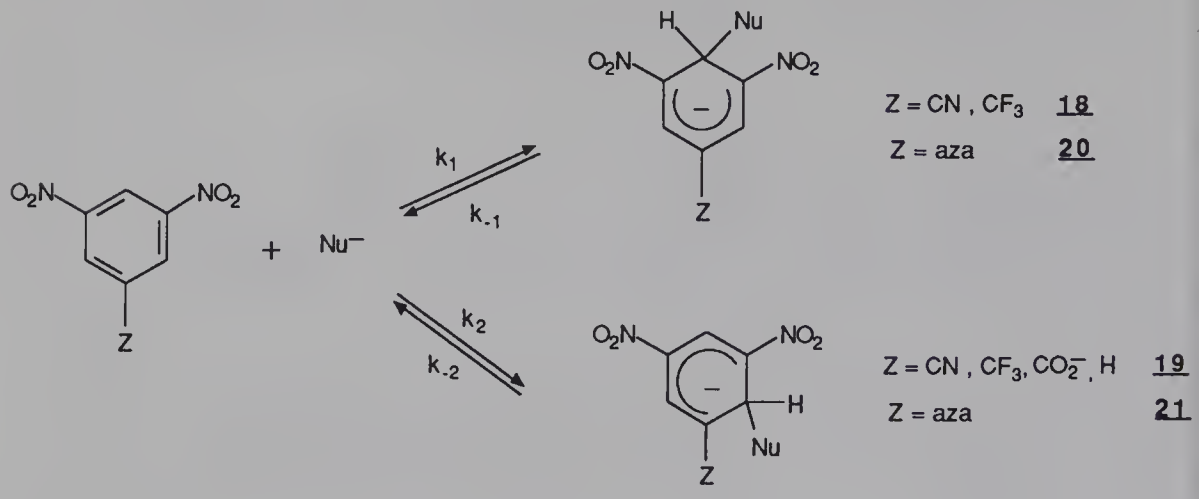


Complex	Z (Y)	t (°C)	k_1 ($l\ mol^{-1}s^{-1}$)	k_{-1} (s^{-1})	K_1 ($l\ mol^{-1}$)	Ref.
37a-Me	NO_2	20	11.7	6×10^{-4}	19,500	112
		25	17.3	1.04×10^{-3}	17,000	112
37b-Me	SO_2CF_3	20	141	1.17×10^{-4}	1.2×10^{6}	123
37c-Me	CN	25	6.1	0.022	280	120
37d-Me	SO_2CH_3	20	1.75	0.017	101	123
37e-Me	CHO	25			210	124
37f-Me	CO_2CH_3	25	0.36	0.06	6	121
37i-Me	CF_3	20			5	123
37j-Me	Cl	20	0.012	5	2.5×10^{-3}	123
37k-Me	F	20	2.5×10^{-3}	30	8.5×10^{-5}	123
37l-Me	H	20	1.5×10^{-3}	20	7.5×10^{-5}	123
38b-Me	SO_2CF_3	20	17.5	1.32×10^{-4}	1.32×10^{-5}	2
38c-Me	CN	25	18.8	7.20×10^{-3}	2600	120
38f-Me	CO_2CH_3	25	0.22	0.022	10	121
38i-Me	CF_3	20	0.35	0.012	29	2
38j-Me	Cl	20	0.28	0.036	7.8	2
38k-Me	F	20	0.10	0.4	0.245	2
38l-Me	H	25	2.12×10^{-3}	42	5.05×10^{-5}	122

Table 2.5. *(Continued)*

	Complex	Z (Y)	*t* (°C)	k_1 ($l\ mol^{-1}s^{-1}$)	k_{-1} (s^{-1})	K_1 ($l\ mol^{-1}$)	Ref.
	83a	NO_2	25	0.95	3.95×10^{-3}	240	125
	83b	CN	25			3.3	23a
	83c	CN[a]	25			14.4	23a
	S-39a	NO_2	20	27.2	7.80×10^{-5}	3.5×10^5	114
	S-39c	CN	20	1.30	1.70×10^{-4}	7650	60
	S-39d	SO_2CH_3	20	0.769	2.46×10^{-4}	3130	60
	S-39f	CO_2CH_3	20	0.115	1.06×10^{-3}	109	60
	S-39g	$COCH_3$	20	0.301	1.96×10^{-3}	152	60
	S-39h	$CONH_2$	20	0.0278	8.13×10^{-4}	34.2	60
	S-40c	CN	20	2.80	3.99×10^{-5}	7.27×10^4	114
	S-40d	SO_2CH_3	20	0.573	3.32×10^{-5}	1.73×10^4	59a
	S-40f	CO_2CH_3	20	0.209	8.10×10^{-5}	2580	59a
	S-40g	$COCH_3$	20	0.489	1.48×10^{-4}	3300	59a
	S-40h	$CONH_2$	20	0.257	1.03×10^{-4}	2500	59a

[a] CN and NO_2 at the 4- and 2- positions, respectively.

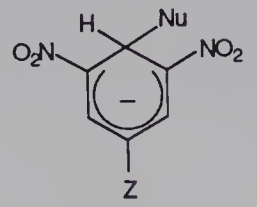


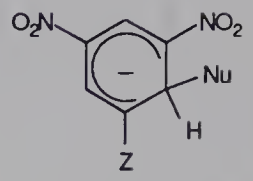
Scheme 2.4.

stants, provided the σ_p– and not σ_p is used for NO_2.[59] Comparison of equilibrium constants for appropriate sets of σ-adducts makes it possible to quantify the situation in terms of free energy values.[2,8,118,127] It thus appears that the free energy contribution of a para-NO_2 group ($\delta\Delta G$ = –48 kJ/mol) is greater than that of an ortho-NO_2 group ($\delta\Delta G$ = –42 kJ/mol) by about 6 kJ/mol. Considering the effect on the equilibrium constant, this means that a *p*-NO_2 group is about 12 times as effective as an *o*-NO_2 group in stabilizing a benzene-type σ-complex.[2] However, this quantitative estimation is not valid for the thiophene series, where there is evidence that the stabilizing influence of an *o*-NO_2 group increases with decreasing influence of the group attached to the para position.[59,60,126] This behavior, known as the hyper–ortho relationship, is responsible for the observation of a curvilinear Hammett correlation on plotting log *K* versus σ_p (or σ_p^-) for the *gem*-dimethoxy adducts **S-39**.[59]

The overwhelming importance of the presence of an NO_2 group para to the site of addition in determining complex stability largely accounts for the observation of isomeric addition of nucleophiles to 1-Z-3,5-dinitrobenzenes and 3,5-dinitropyridine (Scheme 2.4).[36–42] As can be seen in Table 2.6, OH^-, CH_3O^-, or CN^- ions add 2–5 times more rapidly at the 4-position para to the Z or aza group, to give **18** or **20**, than at the 2-position to give **19** or **21**.[37,38] Accordingly, it is because they benefit from the stabilizing influence of a para-NO_2 group that the 2-complexes **19** and **21** decompose more slowly and are thermodynamically more stable than their 4-isomers **18** and **20**[37,38] A similar situation is encountered in comparing data for the 1,5- and 1,3-dimethoxy complexes **44-Me** and **45-Me**, whose formation precedes that of

Table 2.6. Rate and Equilibrium Constants for Isomeric Addition of Hydroxide or Methoxide Ions to the Unsubstituted Carbon Centers of 1-Z-3,5-Dinitrobenzenes and 3,5-Dinitropyridine[a]



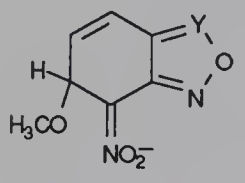


				Adducts 18 or 20			Adducts 19 or 21			
Z	Nu	Solvent	*t* (°C)	k_1 ($l\ mol^{-1}\ s^{-1}$)	k_{-1} (s^{-1})	K_1 ($l\ mol^{-1}$)	k_2 ($l\ mol^{-1}\ s^{-1}$)	k_{-2} (s^{-1})	K_2 ($l\ mol^{-1}$)[b]	Ref.
Aza	OH	H_2O/DMSO, 60:40	20	345	9	38.4	138	0.12	1,150	37
CN	OH	H_2O/DMSO, 50:50	25	325	9.25	35	134	0.372	360	38
	OCH_3	CH_3OH/DMSO, 50:50	20	40,000	118	340	19,300	4.5	4,300	38
	CN	CH_3OH/DMSO, 28:72	25	721	4.28×10^{-3}	1.68×10^5	259	5.4×10^{-4}	4.8×10^5	128
CF_3	OH	H_2O/DMSO, 30:70	25	750	6	94	126	0.086	1,460	38
	OCH_3	CH_3OH/DMSO, 30:70	20	36,000	150	240	10,000	4.6	2,180	38
COO^-	OH	H_2O/DMSO, 5:95	25	240	2.4	100	60	0.07	860	130
H	OH	H_2O/DMSO, 5:95	25	700	3.5	200	800	0.07	11,400	130

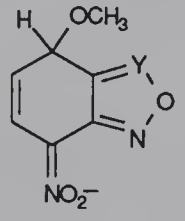
[a] Rate and equilibrium constants as defined in Scheme 2.4.
[b] Statistically uncorrected.

the thermodynamically more stable 1,1-complexes **38-Me** in the reactions of CH_3O^- ions with 2-Z-4,6-dinitroanisoles (see above).[38,63,68]

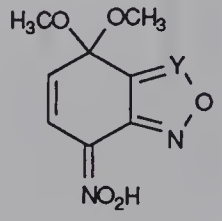
In view of the high intrinsic activation provided by the annelated furazan and furoxan moieties, it is also a significant behavior that isomeric addition of CH_3O^- to 4-nitrobenzofurazan and 4-nitrobenzofuroxan results in **22** (k_1, k_{-1}, K_1) as the product of kinetic control and **23** (k_2, k_{-2}, K_2) as the product of thermodynamic control: the ratios k_2/k_1 and K_2/K_1 are approximately 10^{-2} and 20, respectively, for CH_3O^- addition in methanol.[116] This suggests that the negative charge remains essentially delocalized through the para-like NO_2 group of **23**. Support for this proposal derives from the recent identification of the nitronic acids **84** in methanolic solution.[129] Comparison of the reactions leading to the naphthalene complexes **85** and **86** (see structures in Table 2.7) is equally instructive concerning the role of the NO_2 group.[118] In the first series,



22



23



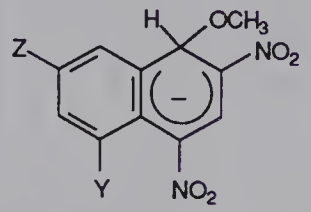
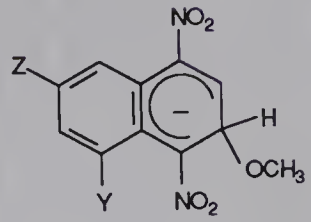
84

(a) Y = N (b) = N → O

the incoming lyate ion adds to a position both ortho and para with respect to the two NO_2 groups in the ring undergoing substitution. In the second series, addition takes place at a position ortho and/or meta with respect to the NO_2 groups in the ring undergoing substitution. Table 2.7 clearly shows that, for the same number and type of NO_2 groups in the second aromatic ring, complexes **86** are of much lower stability that those of type **85**. Table 2.7 also shows that the additional stabilization by the NO_2 group(s) at the 5- and 7-positions of the second aromatic ring is of the order of 10^2–10^3, corresponding to free energy values of about 15 kJ/mol.[2] This is considerably less than those found for ortho- and para-NO_2 groups directly bonded to the ring undergoing the complexation.

Only substitution of an NO_2 group for an SO_2CF_3 group enhances the stability of σ-complexes in the benzene series. Comparison of the data for the adducts **37a-Me**, **37b-Me**, and **38b-Me** in Table 2.5 shows that the effect is greater for a para than for an ortho substitution.[123] The behavior of SO_2CF_3 is essentially the same as that observed for NO_2, and suggests a higher capacity of resonance stabilization by a para than by an ortho SO_2CF_3 group. This agrees

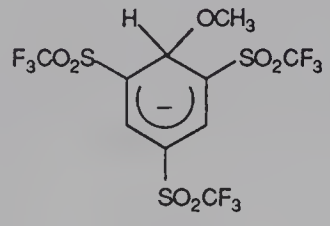
Table 2.7. Rate and Equilibrium Constants for the Methoxynaphthalene Complexes 85 and 86 in Methanol at $t = 25°C$[a,b]

	Complex	Y	Z	k_1 ($l\ mol^{-1}\ s^{-1}$)	k_{-1} (s^{-1})	K_1 ($l\ mol^{-1}$)
	85a	H	H	11.2	124	0.09
	85b	NO_2	H	304.6	22	13.8
	85c	NO_2	NO_2	2.32×10^4	<3	>7700
	86a	NO_2	H			1.5
	86b	NO_2	NO_2	7900	18	438

[a]Rate and equilibrium constants as defined in eq. 2-2.

[b]Data from Fendler, J. H.; Hinze, W. L.; Liu, L. J. *J. Chem. Soc., Perkin Trans. 2*, **1975**, 1751, 1768.

with earlier conclusions that the SO_2CF_3 group exerts a large conjugative effect, presumably involving the *d* orbitals of the sulfur atoms, in addition to an expected large inductive effect.[131–133] Substituting the three NO_2 groups of the TNB-methoxide adduct **2** for three SO_2CF_3 groups gives the adduct **87**, which is 10^6-fold more stable than **2**.[134] Very unexpectedly, the SO_2CF_3 group is less effective than a NO_2 group in stabilizing the five-membered ring adducts **S-39** and **S-40**. So far, this situation is not very well understood.[115] The SO_2CF_3 group is normally more effective than a NO_2 group in promoting the formation of benzofuroxan adducts.[135]



87

2.3.3 Nucleophilic Reactivity at Substituted Versus Unsubstituted Carbons: Steric Effects

2.3.3.1 Relative Reactivities and Stabilities of 1-Substituted and 1,1-Disubstituted Complexes

Let us compare the reactions of alkoxide anions with TNB to give the adducts **88-R** (eq. 2-3; **88-Me** = **2**) and with picryl ethers **89a-R** to give the adducts **37a-R** (eq. 2-4) as a prototype illustration of the role of steric factors on the course of complexation. Table 2.8 shows that the 1-alkoxy adducts **88-R** have high rates of formation and decomposition but a low to moderate thermodynamic stability.[2] On the other hand, the corresponding 1,1-dialkoxy adducts **37a-R** form slowly but have such a low tendency to spontaneous decomposition (k_{-1}) that they exhibit a very high thermodynamic stability.[2] This contrasting behavior is readily understood in terms of steric effects.[2,65,136] As mentioned in Section 2.2.1, crystallographic measurements have revealed that the NO_2 groups at the 2- and 6-positions are strongly twisted from the plane of the ring in the picryl ethers **89a-R** but not in the adducts [e.g., **37a-Me** (= **1a**) or **37a-Et** (= **1b**).[11,12] Upon formation of **37a-R** from **89a-R**, the acquisition of the tetrahedral geometry at C-1 is therefore accompanied by a

Table 2.8. Relative Reactivities and Stabilities of 1-Alkoxy and 1,1-Dialkoxy Complexes[a]

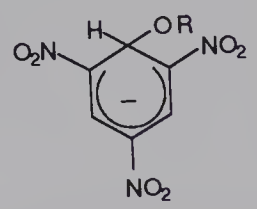
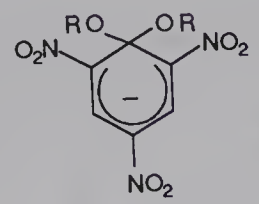
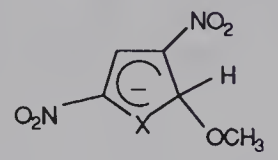
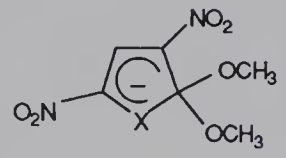
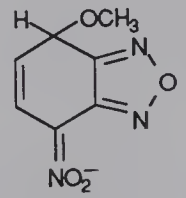
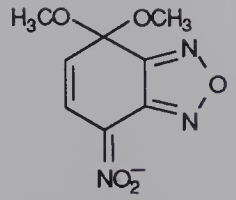
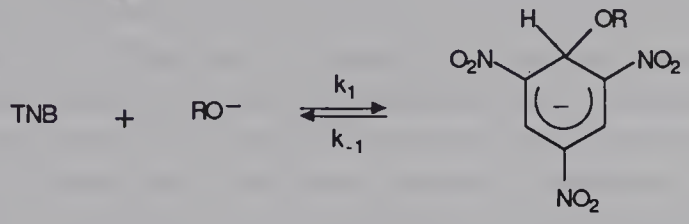
	Complex	R or X	Solvent	t (°C)	k_1 ($l\ mol^{-1}\ s^{-1}$)	k_{-1} (s^{-1})	K_1 ($l\ mol^{-1}$)	Ref.
	88-Me	CH_3	CH_3OH	25	7,050	305	23.1	112
	88-Et	C_2H_5	C_2H_5OH	25	33,400	27.5	1,210	112
	88-nPr	C_3H_7	n-C_3H_7OH	25	92,600	11.9	7,800	138
	88-iPr	*i*-C_3H_7	$(CH_3)_2CHOH$	25	96,700	1.7	2.04×10^5	138
	37a-Me	CH_3	CH_3OH	25	17.3	1.04×10^{-3}	17,000	136
	37a-Et	C_2H_5	C_2H_5OH	25	17	6×10^{-5}	3×10^5	65
	37a-nPr	C_3H_7	*n*-C_3H_7OH	25	28		$>2 \times 10^5$	65
	37a-iPr	*i*-C_3H_7	$(CH_3)_2CHOH$	25	≥50			65
	S-24a	S	CH_3OH	20	10.3	1.25×10^{-2}	825	114
	Se-24a	Se	CH_3OH	20	18.2	2.85×10^{-4}	6.40×10^4	114
	S-39a	S	CH_3OH	20	28.2	7.8×10^{-5}	3.6×10^5	139
	Se-39a	Se	CH_3OH	20	69	1.04×10^{-5}	6.8×10^6	139

Table 2.8. *(Continued)*

	Complex	R or X	Solvent	t (°C)	k_1 ($l\ mol^{-1}\ s^{-1}$)	k_{-1} (s^{-1})	K_1 ($l\ mol^{-1}$)	Ref.
	23a		CH_3OH	25	6	2.04×10^{-3}	2,940	116
	58a		CH_3OH	25	14.5	7.1×10^{-3}	2,050	140

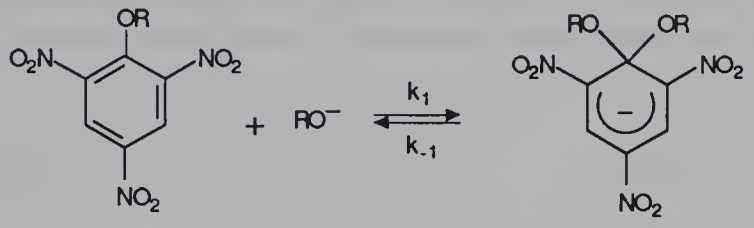
[a]Rate and equilibrium constants as defined by eq. 2-2.

considerable release of steric strain, and there is no doubt that this relief is largely responsible for the finding of much greater K_1 values for the formation of the adducts **37a-R** than for the formation of the adducts **88-R**. The greater stabilizing influence of a double alkoxy substitution relative to monoalkoxy at the sp^3 carbon of a σ-complex is an additional factor enhancing the stability of **37a-R** relative to **88-R**.[2,136]



(2-3)

88-R



(2-4)

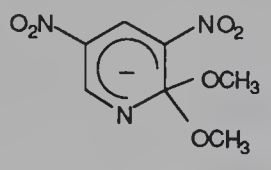
89a-R **37a-R**

On the other hand, the much slower attack of RO^- ions at the alkoxy-bearing carbon of each of the ethers **89a-R** than at the unsubstituted carbon of TNB has been attributed to steric hindrance of approach of the nucleophile to the substituted carbons (F-strain), and to ground-state resonance stabilization involving the alkoxy group in the ethers **89a-R**, as shown in **89a′** and **89a″**.[2,38,136]

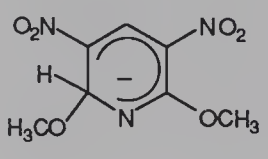
89a' **89a''**

The conclusions above are confirmed by many observations in benzene and heterocyclic series. Substitution of NO_2 for H in TNA (**89a-Me**) must

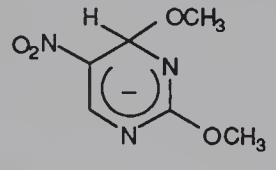
result in loss of steric compression at C-1; consistent with this expectation, the *gem*-dimethoxy adduct **38l-Me** of 2,4-DNA is found to be only one order of magnitude more stable than the adduct **78** of 1,3-DNB.[113,122] Also illustrative is the different behavior of 4-methoxy- and 2-methoxy-3,5-dinitropyridines.[67] In accordance with a similar crowding around the OCH_3 group, the former behaves like TNA, giving the 1,1-adduct **43**, which is much more stable than the analogue **20** of 3,5-dinitropyridine.[37,67] In contrast, steric strain at a methoxy-bearing carbon ortho to an aza functionality is minimized.[137] As a result, formation of the 1,1-complex **90** of 2-methoxy-3,5-dinitropyridine does not occur to a measurable extent, despite the favorable effect of *gem*-dimethoxy substitution and the greater stabilizing effect of an ortho-aza functionality compared to an ortho-NO_2 group (see above).[37] In this instance, it is the formation of **91** that is thermodynamically favored. A similar situation holds in the pyrimidine series, in which the reactions of 2-methoxy- and 4-methoxy-5-nitropyrimidines with methoxide ion afford the adducts **92** and **94** as the stable products rather than the *gem*-dimethoxy isomers **93** and **95**.[2]



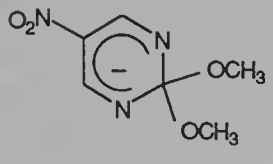
90



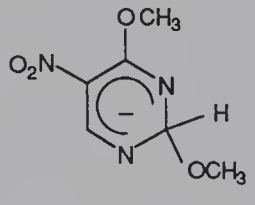
91



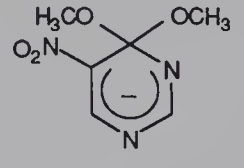
92



93



94



95

Reduced steric release at the site of addition in the methoxy parent compounds also accounts for the observation that the dinitrothiophene and dinitroselenophene methoxy and *gem*-dimethoxy complexes **X-24a** and **X-39a** (X = S, Se) as well as the benzofurazan complexes **23a** and **58a** have comparable stabilities.[1,2] Table 2.8 shows that the rates of formation of adducts of both types are relatively similar in these instances, indicating that the loss of steric compression is also accompanied by a decrease in the role of F-strain on 1,1-complex formation.[1,2]

Although relatively few quantitative data allow comparison of the reactivity of other nucleophiles such as sulfur, nitrogen, and carbon nucleophiles, at substituted and unsubstituted carbons of nitroaromatics, some results point

to situations reminiscent of the contrasting behavior between alkoxy and *gem*-dialkoxy complexes. Comparison in Table 2.9 of the rate and equilibrium parameters for the reactions shown in eqs. 2-5 and 2-6 is of particular significance. As can be seen, addition of primary amines like methylamine and *n*-butylamine, or secondary amines like piperidine and pyrrolidine, at an unsubstituted carbon of TNB, to give the zwitterionic σ-complexes **96,H**, occurs at very high rates in aqueous or DMSO solutions.[141,142] Concomitantly, the k_{-1} values measuring the susceptibility of **96,H** to spontaneous decomposition are also very high, so that the corresponding equilibrium constants K_1 for complex formation are relatively low. In contrast, the naphthalene complexes **98,H**, which result from amine addition at an amino-substituted carbon, form at very low rates compared to the TNB analogues in DMSO.[143] The changes in k_1 upon going from eq. 2-5 to eq. 2-6 are so high that they cannot be accounted for merely on the basis of a lower activation for the 2,4-dinitronaphthyl than for the picryl system (e.g., the formation of the methoxy adducts **2** and **16a** in Table 2.4). In addition, the low k_1 values for formation of **98,H** are coupled with low k_{-1} values. Clearly, the differences between the reactions shown in eqs. 2-5 and 2-6 must be understood in the same terms as those between the reactions shown in eqs. 2-3 and 2-4. Ground-state stabilization through resonance interaction involving the amino group in the parent naphthalenes **97**, as well as steric hindrance to the approach of the amine reagent to the substituted amino carbon, and relief of steric strain on complex formation, must be the major effects determining the rate and equilibrium parameters in eq. 2-6. An additional effect shown to be of stereoelectronic origin explains the especially low reactivity of piperidine compared to pyrrolidine in eq.

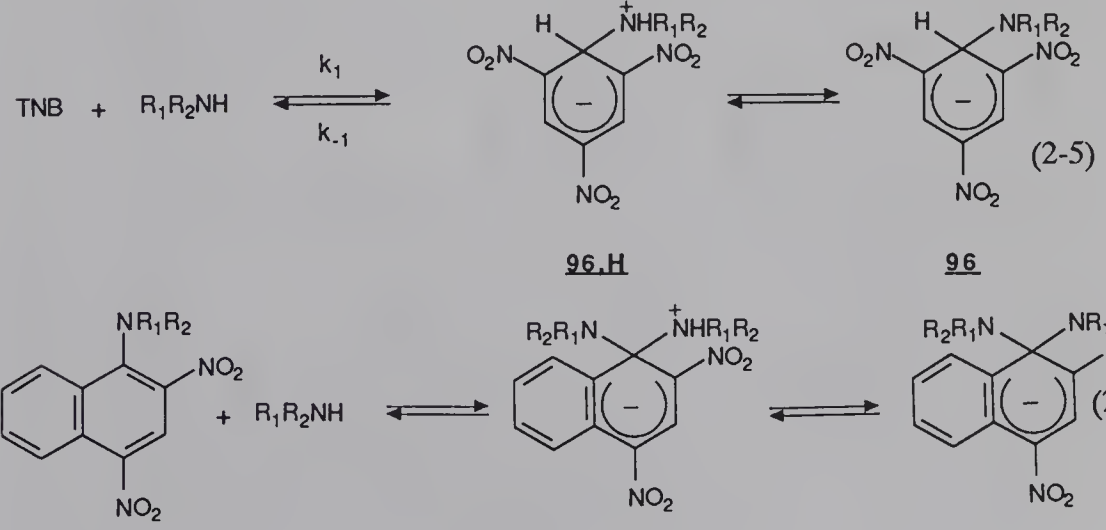
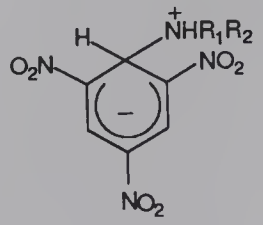
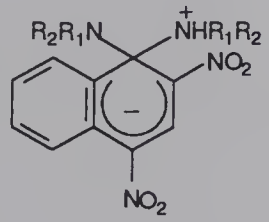
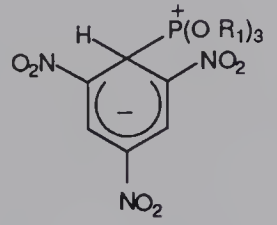


Table 2.9. Relative Reactivities and Stabilities of 1-Amino and 1,1-Diamino Complexes at $t = 25°C$[a]

	R_1	R_2	Solvent	k_1 ($l\ mol^{-1}\ s^{-1}$)	k_{-1} (s^{-1})	K_1 ($l\ mol^{-1}$)
	CH_3	H	10% Dioxane	160	1.5×10^5	1.07×10^{-3}
	n-C_4H_9	H	10% Dioxane	123	1.5×10^5	8.2×10^{-4}
			DMSO	4.5×10^4	2×10^4	2
	Pyrrolidine		10% Dioxane	8.1×10^3	1.5×10^6	5.80×10^{-3}
	Piperidine		10% Dioxane	3×10^3	2.1×10^6	1.43×10^{-3}
			DMSO	$>6 \times 10^4$	$>7 \times 10^3$	9
	n-C_4H_9	CH_3	DMSO	3.1×10^{-4}	0.095	3.26×10^{-3}
	Pyrrolidine		DMSO	2.1×10^{-3}	0.38	5.52×10^{-3}
	Piperidine		DMSO	Very low		
	CH_3		DMSO	1.19×10^{-3}	1.2×10^{-5}	101
	C_2H_5		DMSO	1.81×10^{-3}	2.6×10^{-5}	71
	n-C_3H_7		DMSO			230

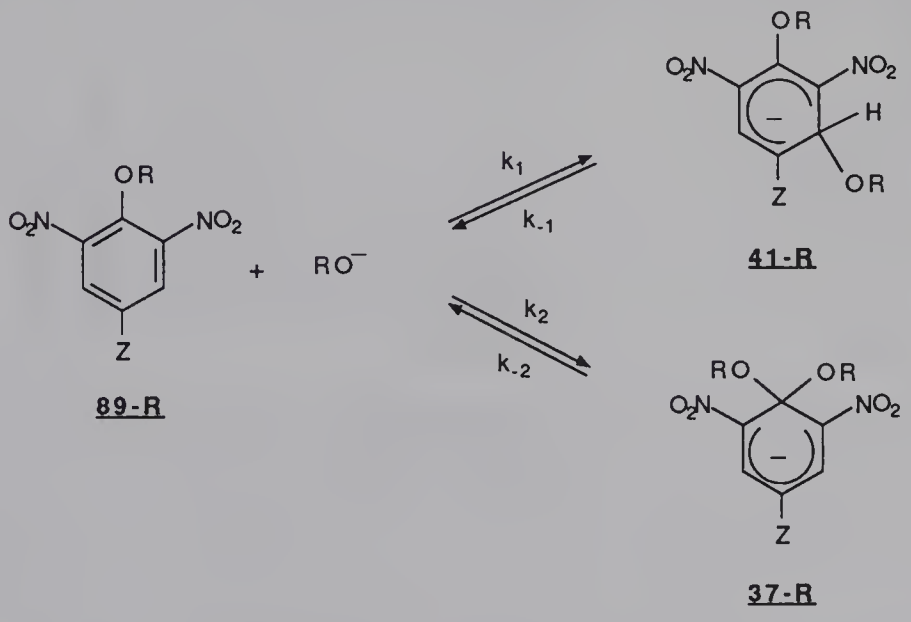
[a]Data at 25°C from refs. 141, 142, 143, and 170.

2-6.[143] This effect is not operating in eq. 2-5, where the two amines exhibit very similar rates of nucleophilic attack, as expected.

It will be seen in Section 2.3.5 that the differences in the k_{-1} values for reactions 2-5 and 2-6 are of major importance in governing the rate-limiting step of the overall reactions leading to the anionic complexes **96** and **98**, which are the thermodynamically stable products of the addition reactions.

2.3.3.2 Isomeric Addition at Substituted and Unsubstituted Carbons of Nitro-aromatics: Relevance to Nucleophilic Aromatic Substitution Processes

Perhaps the most spectacular manifestation of the differences in nucleophilic reactivity and tendency to complexation at substituted and unsubstituted carbons is the ability of a number of nitroaromatics to behave as ambident electrophiles, reacting with nucleophiles to yield competitively 1-substituted and 1,1-disubstituted complexes. The behavior of picryl ethers **89a-R** according to Scheme 2.5 (Z = NO_2) is illustrative. Table 2.10 shows that the 1,3-complexes **41a-R** have in all cases high rates of formation and

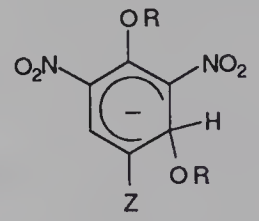


(a) Z = NO_2 ; (b) Z = SO_2CF_3 ; (c) Z = CN ;

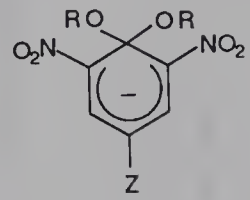
(d) Z = SO_2CH_3 ; (i) Z = CF_3 ; (j) Z = Cl ; (k) Z = F

Scheme 2.5.

Table 2.10. Rate and Equilibrium Constants for Isomeric Addition of Alkoxide Anions to 4-Z-2,6-Dinitrophenyl Ethers[a]



41-R



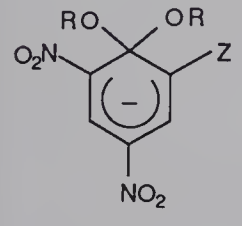
37-R

Z	RO^-	Solvent	t (°C)	k_1 ($l\ mol^{-1}\ s^{-1}$)	k_{-1} (s^{-1})	K_1 ($l\ mol^{-1}$)	k_2 ($l\ mol^{-1}\ s^{-1}$)	k_{-2} (s^{-1})	K_2 ($l\ mol^{-1}$)	Ref.
NO_2	CH_3O^-	CH_3OH	25	950	350	2.71	17.3	1.04×10^{-3}	17,000	136
	$C_2H_5O^-$	C_2H_5OH	25	2100	30	70	17	6×10^{-5}	3×10^5	65
	n-$C_3H_7O^-$	n-C_3H_7OH	25	4500	16	280	28	—	$>2 \times 10^5$	65
SO_2CF_3	CH_3O^-	CH_3OH	20	750	25	30	141	1.17×10^{-4}	1.2×10^6	123
CN		CH_3OH/DMSO, 50:50	20	2460	11	224	60	8.5×10^{-4}	70,500	2
SO_2CH_3		CH_3OH/DMSO, 60:40	20	362	30	12	17	1.36×10^{-3}	12,500	123
CF_3		CH_3OH/DMSO, 20:80	20	5500	2.75	2000	152	0.013	11,700	144
Cl		CH_3OH/DMSO, 20:80	20	1260	2.80	440	10	6.85×10^{-3}	1,460	144
F		CH_3OH/DMSO, 15:85	20	1260	4.67	270	3.47	0.021	165	144

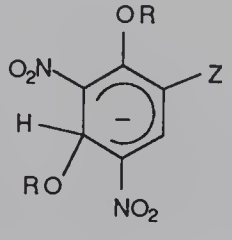
[a] Rate and equilibrium constants as defined by Scheme 2.5.

decomposition but a relatively low thermodynamic stability, comparable to that of the corresponding alkoxy σ-complexes **88-R** of TNB (see Table 2.8). Accordingly, subsequent rearrangement of **41a-R** occurs to give the 1,1-dialkoxy complexes **37a-R**, which are the thermodynamically more stable products.[1,2] For example, the ratio K_2/K_1 of the equilibrium constants for formation of **37a-R** and **41a-R** is 6250 and 4300 in methanol (R = CH_3) and ethanol (R = C_2H_5), respectively.[65,136]

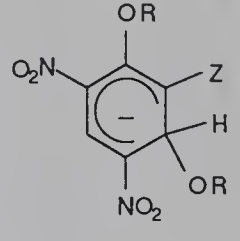
Table 2.10 also shows that other 4-Z-2,6-dinitrophenyl ethers behave similarly. However, the nature of the Z substituent is a factor of importance governing the relative stabilities of the 1,3- and 1,1-adducts.[123] Decreasing the electron-withdrawing character of Z decreases the stability difference between **37-R** and **41-R** in the anisole series (R = CH_3): the ratio K_2/K_1 changes from 6.25×10^3 for Z = NO_2 to 3.3 and 0.63 for Z = Cl and F, respectively.[123,144] The greater stability of the fluoro-1,3-dimethoxy complex **41k-Me** relative to the 1,1-isomer **37k-Me** emphasizes the importance of this structural change and further confirms the conclusion alluded to in Section 2.3.2, that complex stability is more sensitive to changes in the substituent para to the site of nucleophilic attack than ortho to it. On this basis, it can be readily anticipated that the effect of changing the nature of Z is much less important in the 2-Z-4,6-dinitrophenyl ether systems. Indeed, all 1,1-complexes **38-R** arising from rearrangement of the initially formed 1,5- and 1,3-isomers **44-R** and **45-R** are thermodynamically very much favored.[1,2,68]



38-R



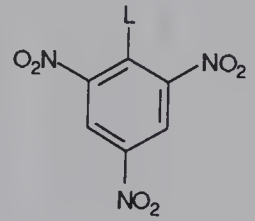
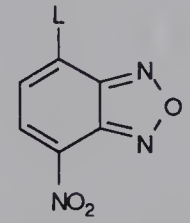
44-R



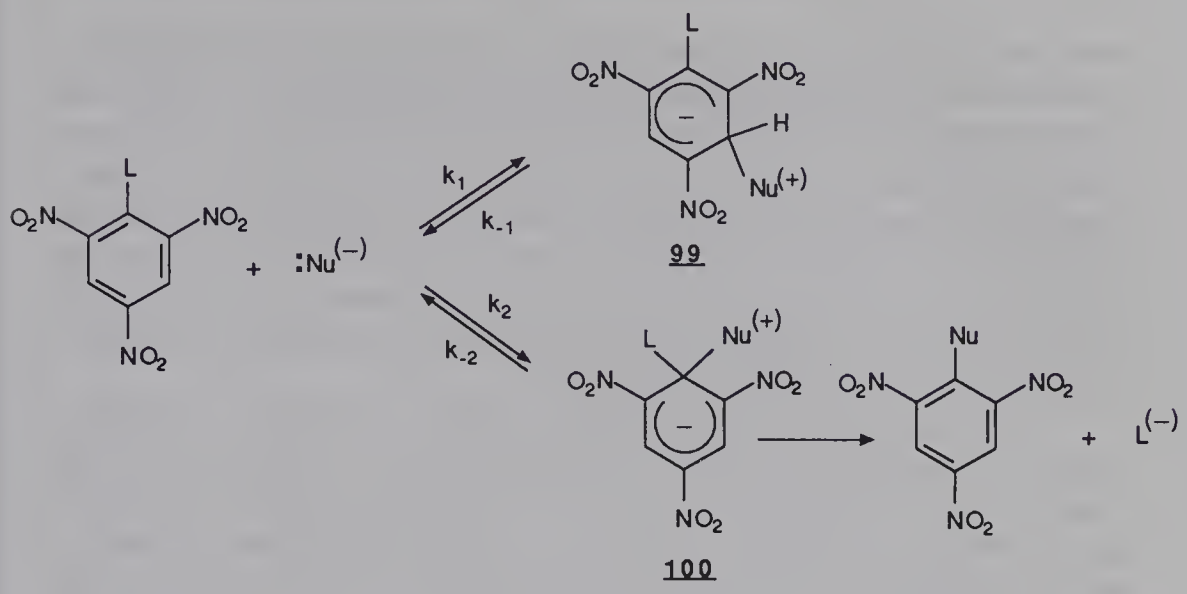
45-R

The greater susceptibility of an unsubstituted over a substituted ring carbon to undergo nucleophilic addition is of considerable relevance to the mechanisms of nucleophilic aromatic substitution reactions. As pointed out in Chapter 1, the occurrence of an S_NAr process is frequently preceded by the formation of "unreactive" σ-complexes in side-equilibrium reactions. The situation is expressed quantitatively in Table 2.11, which summarizes kinetic and thermodynamic data for many S_NAr substitutions of picryl halides and TNA with various nucleophiles (OH^-, CH_3O^-, butylamine, carbon bases), proceeding according to Scheme 2.6.[71,72 145–151] Data for substitutions of 7-halo-4-nitrobenzofurazans according to Scheme 2.7 are also given as an

Table 2.11. Rate and Equilibrium Constants for Reactions of Various Nucleophiles with Picryl Halides, 2,4,6-Trinitroanisole, and 7-Halo-4-Nitrobenzofurazans[a,b]

Parent nitroaromatic	L	Nu	Solvent	k_1 ($l\ mol^{-1}\ s^{-1}$)	k_{-1} (s^{-1})	K_1 ($l\ mol^{-1}$)	k_2 ($l\ mol^{-1}\ s^{-1}$)	Ref.
	F	OH^-	H_2O	100	2.2	46	750	71b
	Cl			12	14	0.85	0.4	145
	Br			6.2	14	0.44	0.24	71b
	I			2.5	15	0.166	0.07	71b
	Cl	CH_3O^-	CH_3OH	912	303	2.58	19.8	72a, 146
		$C_2H_5O^-$	C_2H_5OH	5,770	19.7	293		146b
		$CH(CN)_2^-$	CH_3OH	30,000	4400	7	1750	71a
		$CH(CO_2CH_3)_2^-$	CH_3OH	30,000	8.6	3500	82	72b
		$CH(CN)(CO_2CH_3)^-$	CH_3OH	5,200	37	140	141	146a
	OCH_3	OH^-	H_2O	12	8.4	1.4	1.4	145
		$C_2H_5O^-$	C_2H_5OH	2,500	24	104	58	148
		n-$C_4H_9NH_2$	DMSO	3,900			310	149
		$CH(CO_2CH_3)_2^-$	CH_3OH	29,500	14.2	2090	~66	150
		$CH(CN)(CO_2CH_3)_2^-$	CH_3OH	7,600	72	106	8	72a
		SO_3^{2-}	H_2O	4,800	35	140		151
	F	CH_3O^-	CH_3OH	5,800	2.5	2300	3500	140
	Cl			5,100	1.8	2800	7.7	140
	Br			5,200	3.8	1300	2	140

[a] Rate and equilibrium constants as defined by Schemes 2.6 and 2.7
[b] $t = 25°C$.

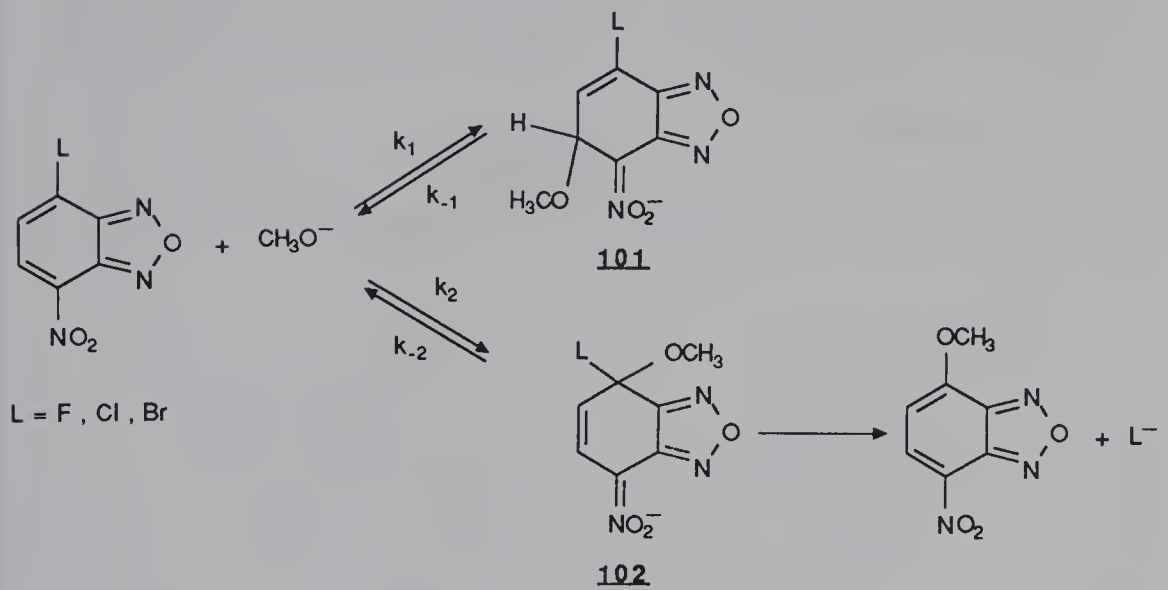


L = Cl , OCH_3

$Nu^{(-)}$ = OH^-, CH_3O^-, $C_2H_5O^-$, $SO_3^=$, $CH(CN)_2^-$,

$CH(CO_2CH_3)_2^-$, $CH(CN)(CO_2CH_3)^-$, n-$C_4H_9NH_2$

Scheme 2.6.



L = F , Cl , Br

Scheme 2.7.

example of heterocyclic substrates.[140] Except for the interactions involving the fluoro derivatives, initial formation of the monosubstituted adducts **99** or **101** is kinetically very much favored compared to that of the 1,1-substituted isomers **100** or **102**, which are the actual intermediates for the S_NAr processes. Here, it is perhaps worthwhile to recall that because the conversion of these intermediates to substituted products is generally very fast, they cannot accumulate, hence remain commonly undetected. However, the *n*-butylamine adduct **100** (= **51**, L = OCH_3, Nu = NHC_4H_9) of TNA is an exception: it has been detected by flow NMR spectroscopy.[73]

The finding that nucleophilic additions proceed in general at much faster rates at an unsubstituted than at a substituted carbon is also the key for the understanding of why certain anomalous nucleophilic aromatic substitutions like the vicarious substitutions (VS_NAr^H) and the ANRORC substitutions can develop at the expense of the expected S_NAr processes. The reader is referred to Chapters 5 and 8 for a detailed consideration of these reactions.

2.3.4 Intramolecular Additions: Spiro Complexes

Intramolecular nucleophilic additions lead to spiro complexes, the formation of which is both thermodynamically and kinetically very much favored compared to that of analogous σ-complexes arising from intermolecular processes.[1,2] Thus, it is apparent from Table 2.12 that the rate constants (k_2)

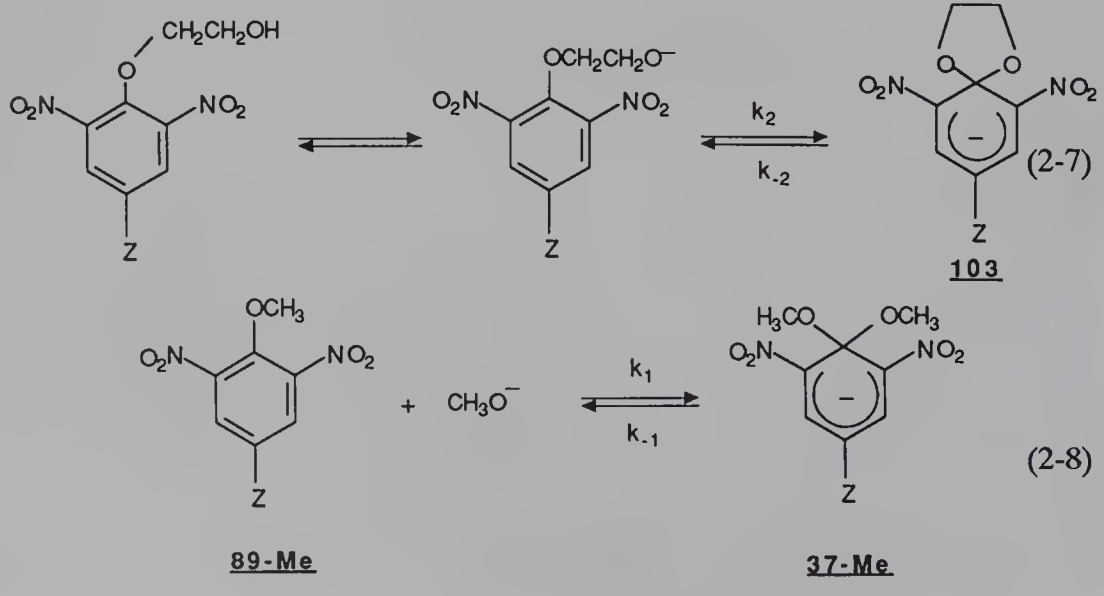


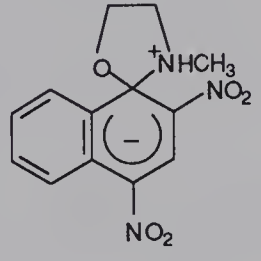
Table 2.12. Comparison of Rate and Equilibrium Constants for Reactions Shown in Equations 2-7 and 2-8

	Z				
Reaction	SO_2CF_3	NO_2	CF_3	Cl	H
Eq. 2-8[a]					
k_1, l mol^{-1}s^{-1}	132	17.5	0.52	5.71×10^{-3}	7.26×10^{-4}
k_{-1}, s^{-1}	2.56×10^{-4}	4.96×10^{-4}	0.134	57.5	575
K_1 l mol^{-1}	5.16×10^{5}	3.53×10^{4}	3.89	10^{-4}	1.26×10^{-6}
Eq. 2-7[b]					
k_2, s^{-1}	3.64×10^{7}	5.69×10^{6}	1.40×10^{5}	3250	582
k_{-2}, s^{-1}	0.089	0.10	4.30	50.5	137
K_2, l mol^{-1}	4.09×10^{8}	5.69×10^{7}	3.25×10^{4}	64.4	4.25
EM_k	4.37×10^{5}	5.15×10^{5}	5×10^{5}	8.96×10^{5}	1.27×10^{6}
EM_{eq}	7.93×10^{3}	1.61×10^{4}	8.35×10^{4}	6.44×10^{6}	3.37×10^{7}

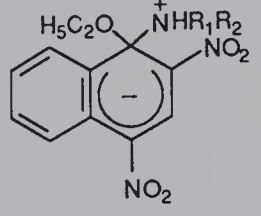
[a] Data at t = 25°C in 5% CH_3OH/95% water; reproduced with permission from ref.91.

[b] At t = 25°C in H_2O; the EM_k and EM_{eq} values calculated from the k_2/k_1 and K_2/K_1 ratios after correction of the experimental k_2 and K_2 values for the lower basicity of the glycoxide ion compared to methoxide ion: ref. 91.

for formation of the dioxolane complexes **103**, as described in eq. 2-7 are several orders of magnitude greater than those for the similarly activated 1,1-dimethoxy complexes **37-Me** (eq. 2-8) in aqueous or 5% CH_3OH/95% water solutions. Despite rates of ring opening (k_{-2}) much higher than the rates of methoxide expulsion (k_{-1}) from **37-Me**, the spiro adducts also exhibit much higher stabilities (K_2).[91,152] Similar observations have been made in comparing the formation of the zwitterionic amino adducts **104,H** and **105,H**.[153]



104,H

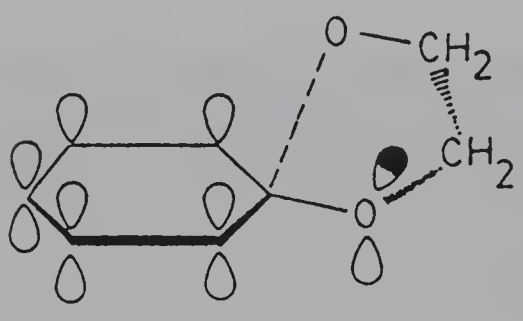


105,H

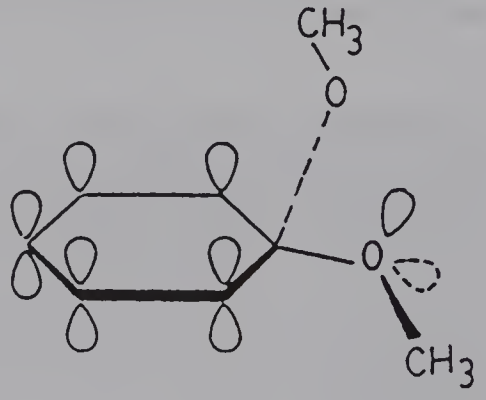
For a better assessment of the effect of intramolecularity, kinetic and equilibrium effective molarities (EM_k, EM_{eq}) have been calculated in compar-

ing the formation and decomposition of the oxygen adducts **103** and **37-Me**.[91] Table 2.12 includes the EM_k and EM_{eq} values as determined from the k_2/k_1 and K_2/K_1 ratios after correction for the approximately 10-fold lower basicity of the glycoxide oxyanion GO^- compared to the CH_3O^- ion.[91] As can be seen, the values of EM_{eq} are much lower than those for EM_k. Such a result is unexpected[154] and provides evidence that another factor besides intramolecularity contributes to making spiro complex formation intrinsically faster than dimethoxy complex formation. Other evidence is the finding of k_{-2}/k_{-1} ratios larger than unity.[91] The reason for these anomalies has been shown to be enhanced stabilization of the transition state for the spiro complex reactions due to p-π overlap of one of the lone pairs of the nonreacting oxygen with the aromatic π-system, as shown in **106**. Such overlap is not possible in the transition state **107** for the dimethoxy reactions.[91] In a similar way, both stereoelectronic effects and intramolecularity contribute to enhancing the rates of formation and decomposition of the spiro catechol complex **60a** (k_2 = 1.2 × 10^9 s^{-1}, k_{-2} = 10^4 s^{-1}) compared to the 1-methoxy-1-phenoxy complex **108** (k_1 = 425 l mol^{-1} s^{-1}, k_{-1} = 850 s^{-1}) in 50% H_2O/50% DMSO (t = 25°C).[155]

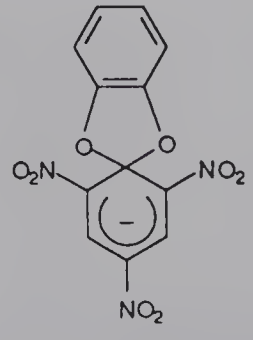
Notwithstanding the interest of the role played by stereoelectronic effects in some reactions, the important fact remains that intramolecularity is in itself a



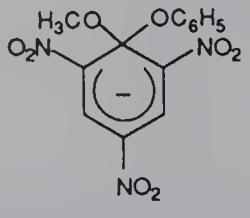
106



107

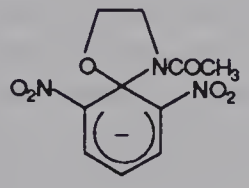


60a

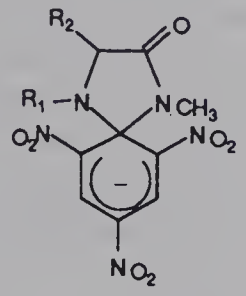


108

driving force for spiro complex formation.[1,2,84,91,156] This explains why cyclohexadienyl intermediates have been more readily identified in intramolecular than in intermolecular S_NAr reactions. Well-known examples are the adducts **104**, the conjugate base of **104,H**, **109**, or **110** (see also Chapter 1)[106,153,157,158]



109



110

(a) $R_1 = CH_3$, $R_2 = H$

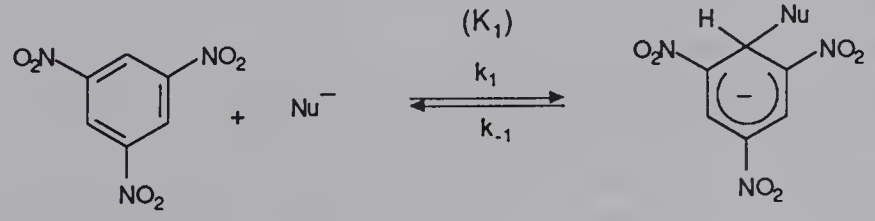
(b) $R_1 = H$, $R_2 = CH_3$

Increasing the size of the spiro moiety from five to six to seven members decreases the stability of spiro complexes by several orders of magnitude. Steric effects provide the primary factor responsible for this behavior.[94,152]

2.3.5 The Effect of the Nucleophile

The effect of the nature of the nucleophile on the stability and ease of formation of a σ-complex is best appreciated with respect to the reactions of TNB (eq. 2-9). Values of the equilibrium constant K_1 give a measure of the thermodynamic affinity of the nucleophile for the electrophilic carbon center, a quantity commonly known as the carbon basicity of the nucleophile.[159] On the other hand, the values of the rate constant k_1 measure the nucleophilicity of the incoming nucleophile, while those of k_{-1} measure its leaving group ability (nucleofugality).

Representative data for the reactions of anionic nucleophiles with TNB in aqueous and methanolic solutions are given in Table 2.13. As can be seen, the k_1



TNB **5** (2-9)

values for the reactions of the three most common oxygen bases, OH^-, CH_3O^-, and $C_2H_5O^-$, are in the order $k_1^{OH} << k_1^{CH_3O} < k_1^{C_2H_5O}$, showing no correlation of the nucleophilicities with the relative Brønsted basicities, which are in the ratio 1:0.62:1.80 in water.[112,160] However, this result is in agreement with reactivity patterns found in other nucleophilic reactions, including S_NAr processes, and is attributed to the greater solvation of OH^- compared to CH_3O^- and $C_2H_5O^-$.[166,167] The carbon basicity of the three bases follows the same sequence as k_1.

In a more general way, comparison of the k_1 and K_1 values in Table 2.13 reveals that carbon and sulfur bases have nucleophilicities and carbon basicities that are enhanced relative to those for oxygen bases. Thus, and despite the much lower pK_a values, thiolate and sulfite anions add to TNB much faster than do OH^- or CH_3O^- ions: the ratios $k_1^{SO_3^{2-}}/k_1^{OH^-}$ and $k_1^{GlS^-}/k_1^{OH^-}$ (GlS^- is the anion of glutathione) are of the order of 10^3 and 5×10^4, respectively.[161,162] Concomitantly, the stability of the corresponding sulfur adducts is greater by factors of 100 and 5, respectively, than that of the TNB-hydroxide adduct. Considering the carbon bases, they are very reactive, but no regular trend in reactivity appears within this class of nucleophiles. Malonitrile, methyl acetoacetate, and nitroethane anions have similar pK_a values in methanol but exhibit quite different nucleophilicities toward TNB: $CH(CN)_2^-$ ($k_1 = 3 \times 10^5$ l/mol^{-1} s^{-1}) > $CH_3COCH(CO_2CH_3)^-$ ($k_1 = 5500$ l mol^{-1} s^{-1}) > $CH_3CHNO_2^-$ ($k_1 = 34$ l mol^{-1} s^{-1}).[164,165] On the other hand, $CH_3CHNO_2^-$ has such a low leaving group ability that the nitroethane adduct is more stable than the malonitrile and methyl acetoacetate adducts by factors of 10 and 30, respectively. It seems that this behavior must be understood in terms of intrinsic barriers rather than steric effects.[164] Reactions involving delocalized cyano-substituted carbanions are known to have lower intrinsic barriers than reactions involving carbanions from ketoesters, β-diketones, or nitroalkanes.[168]

Table 2.9 summarized data for the reactions of TNB with various aliphatic and alicyclic amines. As can be seen, the rate constants k_1 for nucleophilic attack of these amines follow the familiar pattern found for S_NAr reactions, with the more basic secondary amines being more reactive than primary amines in aqueous solvents as well as in dipolar aprotic solvents like DMSO.[141,142] The most important result, however, consists of the high values of the rate constants k_{-1} for amine expulsion ($k_{-1} \sim 10^5$ s^{-1} in 10% dioxane/90% H_2O).[141] In some cases, these make the observed rate of formation of the zwitterionic adducts, ($k_{obs} = k_{-1} + k_1$ [amine] $\sim k_{-1}$ under most experimental conditions employed), much higher than the rate of the proton transfer step ($k_p = k_p^{OH}[OH^-] + k_p^{amine}$[amine]).[7,141] This occurs even though this latter step is thermodynamically favored by about 2 pK units, and the rate constants k_p^{OH} and k_p^{amine} are close to the diffusion-controlled limit ($k_p^{OH} \sim 5 \times 10^9$ l mol^{-1} s^{-1}) or ≥ 10^7 l mol^{-1} s^{-1} (k_p^{amine}). Recent studies

Table 2.13. Rate and Equilibrium Constants for Formation and Decomposition of TNB Adducts 5 with Various Anionic Nucleophiles in Water and Methanol

Nucleophile	$(pK_aNu)^b$	Solvent	k_1 ($l\ mol^{-1}s^{-1}$)	k_{-1} (s^{-1})	K_1 ($l\ mol^{-1}$)	Ref.
OH^-	15.74	H_2O	37.5	9.8	3.73	112
CH_3O^-	18.22	CH_3OH	7050	305	23.1	112
	15.50[c]	H_2O/CH_3OH, 77.5:22.5	2460	134	18.3	160
$C_2H_5O^-$	15.90[c]	H_2O/C_2H_5OH, 81:19	7700	32	241	160
SO_3^{2-}	6.9	H_2O	3.54×10^4	125	286	161
GIS^-	8.7	H_2O/dioxane, 90:10	1.8×10^6	1.2×10^5	15	162
$C_2H_5S^-$	10.60	H_2O			170	163
	15	CH_3OH			3500	71
$C_6H_5S^-$	10.90	CH_3OH			1.95	71
$(CH_3)_2CNO_2^-$	13.50	CH_3OH	0.36	0.09	4	165
$CH(CN)_2^-$	14.14	CH_3OH	3×10^5	6500	40	165
$CH_3CHNO_2^-$	14.20	CH_3OH	34	0.09	380	165
$CH_3COCHCO_2CH_3^-$	14.29	CH_3OH	5500	470	11.7	164
$CNCHCO_2CH_3^-$	15.18	CH_3OH	1.3×10^5	62	1660	164
$CH_2NO_2^-$	15.60	CH_3OH	800	0.011	7×10^4	165
$C_2H_5C(CN)_2^-$	15.60	CH_3OH			33	71a
$CH(CO_2CH_3)_2^-$	17.22	CH_3OH	2.5×10^5	20.5	1.22×10^4	164
CN^-	13.3	H_2O/CH_3OH, 20:80	16	0.08	200	71 a

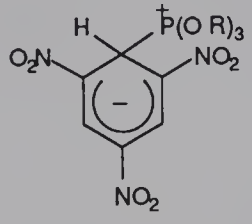
[a] $t = 25°C$.

[b] Refers to the conjugate acid of the nucleophile.

[c] pK_a in water from Ballinger,P.; Long F.A. *J. Am. Chem. Soc.* **1960**, *82*, 795.

have shown that the proton transfer step may also be rate limiting in the formation of amine σ-adducts in DMSO.[142,169] In some systems, however, (e.g., the naphthalene reactions of eq. 2-6), the k_{-1} values are too low to fulfill the condition $k_{-1} >> k_p$ required for the observation of a kinetically significant proton transfer step.[2,143] The relevance of these results to the mechanisms of S_NAr reactions was discussed in Chapter 1.

Table 2.9 includes some data on formation of the phosphorus adducts **111**. Compared with the zwitterionic amino analogues **96,H**, these complexes form more slowly, but they exhibit higher thermodynamic stabilities in DMSO.[170]



111

R = CH_3, C_2H_5, n-C_3H_7

2.3.6 The Effect of the Solvent

The strong capability of dipolar aprotic solvents like DMSO or DMF to enhance the stability of 1:1 σ-adducts is the major feature to be considered in this section, since it has greatly facilitated structural characterizations of these species. Quantitatively, this effect is reflected in an increase of several orders of magnitude in the equilibrium constant K_1 for complex formation on transfer from a protic to a dipolar aprotic solvent.[2] For example, K_1 for the TNB-methoxide complex **2** is estimated to be 10^8 times greater in DMSO than in methanol.[103] However, the increase in K_1 is strongly dependent on the nucleophile, as evidenced by Fig. 2.3, which shows that plots of log K_1 versus the mole fraction of DMSO are all linear for a variety of reactions but that the slopes can differ widely.[2] In fact, much higher slopes are observed with hydroxide, methoxide, or sulfite complexes (>10) than with phenoxide or thiophenoxide complexes (4.6). In contrast, there are no major differences in the slopes when complexes formed from the reactions of differently activated aromatics with a given nucleophile are compared.[2]

Calorimetric studies of the reactions of TNA (= **89a-Me**) with sodium methoxide to give **37a-Me** and of TNB with sodium thiophenoxide to give **112** (eqs. 2-10 and 2-11) over the complete range of methanol-DMSO mixtures

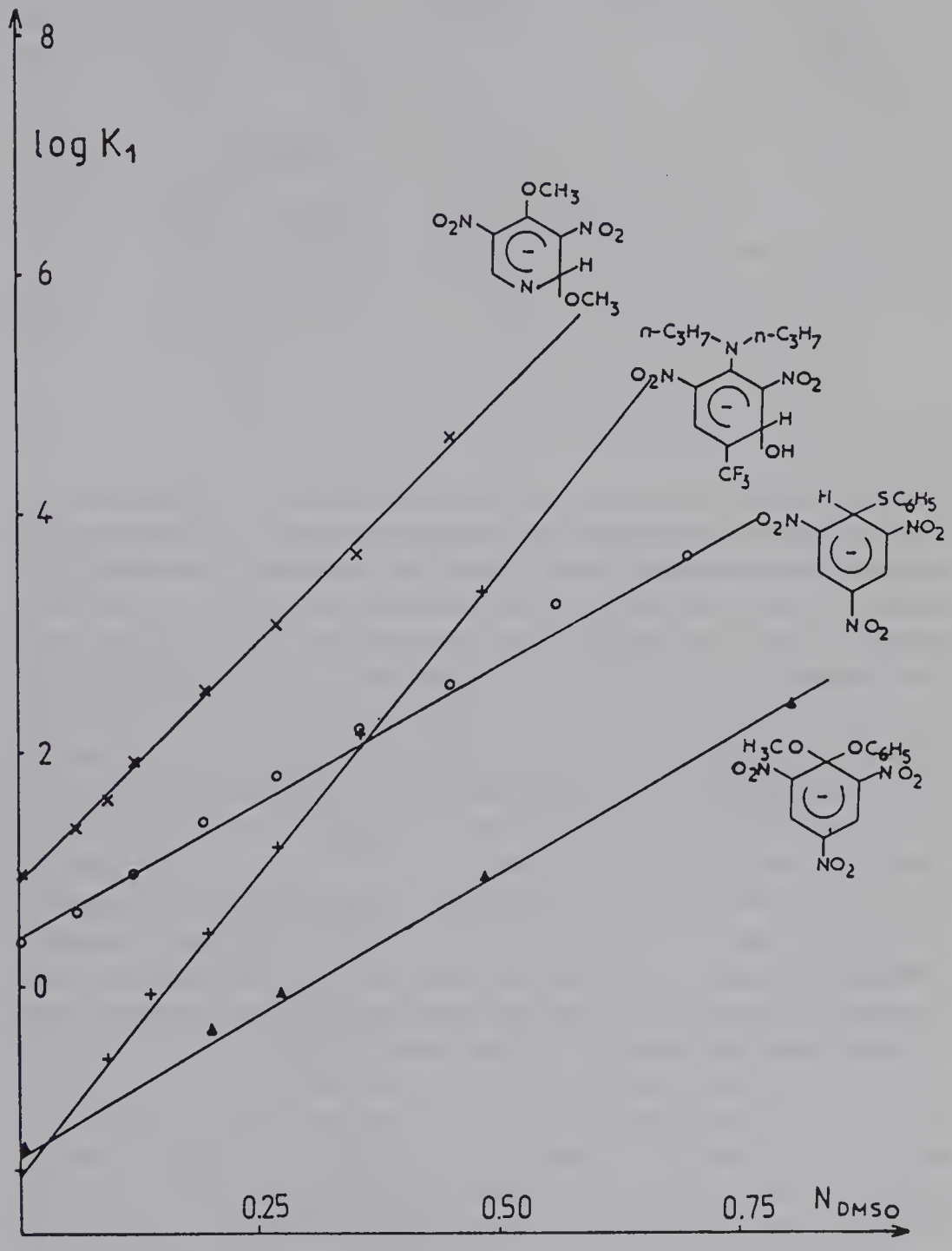
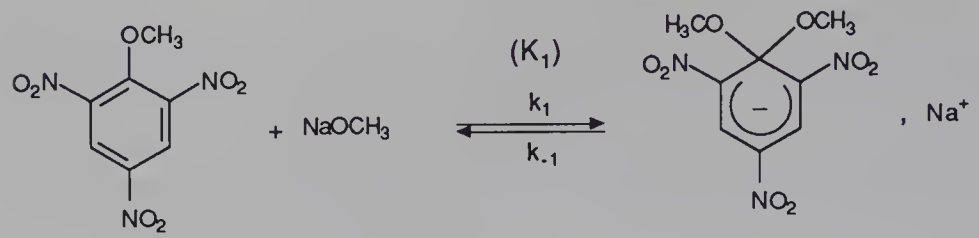
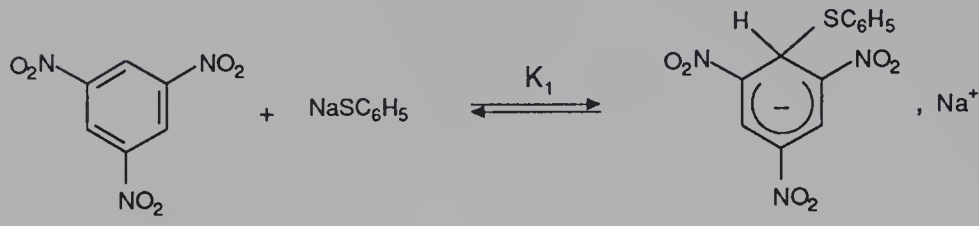


Figure 2.3. Dependence of the equilibrium constant K_1 for formation of various 1:1 complexes on the mole fraction of DMSO in aqueous or methanolic solutions.



(2-10)

TNA **37a-Me**



(2-11)

TNB **112**

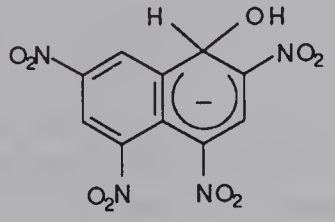
have provided a clear explanation of this solvent effect.[171–173] In accordance with the observed increase in the K_1 values for formation of **37a-Me** and **112**, there is an increase in the exothermicity of both reactions, as measured by the enthalpies of reaction ΔH_R, but this increase is much higher for the TNA-methoxide than for the TNB-thiophenoxide reaction ($\Delta\Delta H_R$ values for transfer from methanol to 95% DMSO/5% methanol are –65.4 and –26.1 kJ/mol for eqs. 2-10 and 2-11, respectively). Interestingly, the enthalpies of transfer (ΔH_T) for the sodium salts of the two complexes as well as those for the two parent substrates are quite similar, so that the differences in the heats of reaction (ΔH_R) derive essentially from the differences in the ΔH_T values for $NaOCH_3$ and $NaSC_6H_5$: $\Delta H_T^{NaOCH_3}$ = 44.5 kJ/mol; $\Delta H_T^{NaSC_6H_5}$ = –13.6 kJ/mol in 95% DMSO. Thus, the formation of **112** is easier in DMSO than in methanol only because the increase in stabilization of this complex is greater than that of sodium thiophenoxide.[173] In contrast, the formation of **37a-Me** is favored to an enormous extent because there is concomitantly an increase in stabilization of this complex and a decrease in stabilization of $NaOCH_3$.[172]

The results above reflect the well-known differences in hydrogen bonding ability of protic and dipolar aprotic solvents and the tendency of the latter to stabilize large polarizable anions ($C_6H_5O^-$, $C_6H_5S^-$, cyclohexadienyl anions) and to destabilize small or doubly charged ions (OH^-, RO^-, SO_3^{2-}).[174] In this regard, comparison of the ΔH_T values for $NaOCH_3$, $NaSC_6H_5$, and the adducts salts **37a-Me,Na** and **112,Na** is revealing. Since in all cases the cation is Na^+, the observed differences in the ΔH_T values are due to the anions. For the complexes **37a-Me** and **112**, which both have a highly delocalized negative

charge, ΔH_T is markedly negative ($\Delta H_T^{37a\text{-}Me,Na} = -28.3$; $\Delta H_T^{112,Na} = -41$ kJ/mol in 95% DMSO), consistent with effective stabilization upon transfer from methanol to DMSO.[172,173] For the less polarizable, less delocalized thiophenoxide ion, ΔH_T is still negative but much less than for **37a-Me** and **112**: $\Delta H_T^{NaSC_6H_5} = -13.6$ kJ/mol in 95% DMSO.[173] In contrast, for the small CH_3O^- ion, which has a highly localized negative charge and is a strong hydrogen bond acceptor, ΔH_T is strongly positive (~ 45 kJ/mol in 95% DMSO), reflecting the considerable decrease in solvation of this ion upon going from methanol to DMSO.[172] In fact, the destabilization of such anions as CH_3O^- or OH^- is so important that this is the main factor determining the heats of formation (ΔH_R) of most methoxide or hydroxide adducts, accounting for the observation that the effect of DMSO on the stability of such σ-complexes depends very little on the activation of the parent aromatics.[2]

In all systems studied, the effect of DMSO on the stability of the complexes is the result of an increase in the rate constant of formation (k_1) and a decrease in the rate constant of decomposition (k_{-1}).[2,123,155b,175] The relative contributions of the changes in k_1 and k_{-1} to changes in K_1 are governed by relative differences in stabilization of the reactants, complexes, and transition states upon going from aqueous or alcoholic solvents to DMSO. Some quantitative information is available only for the reaction (eq. 2-10) in methanol-DMSO mixtures.[172] In this case, it is found that the free energy of the transition state leading to **37a-Me** is essentially unaffected by the solvent transfer ($\Delta G_T \sim 0$), so that the changes in k_1 and k_{-1} parallel, respectively, the destabilization of the reactants (in fact CH_3O^-) and the increased stabilization of the complex **37a-Me**. Just as for log K_1, the dependence of log k_1 on the mole fraction of DMSO is generally linear, with the slopes of the linear plots being primarily dependent on the nucleophile.[2] This observation has proved to be very useful in estimating rate parameters not directly accessible in water or alcohols.[2]

The effect of micellar surfactants on complex formation has been studied. Cationic micelles like hexadecyltrimethylammonium bromide (CTABr) increase, while anionic micelles like sodium dodecyl sulfate (NaLS) decrease the stability of hydroxide complexes like **113**.[176] These effects arise primarily



113

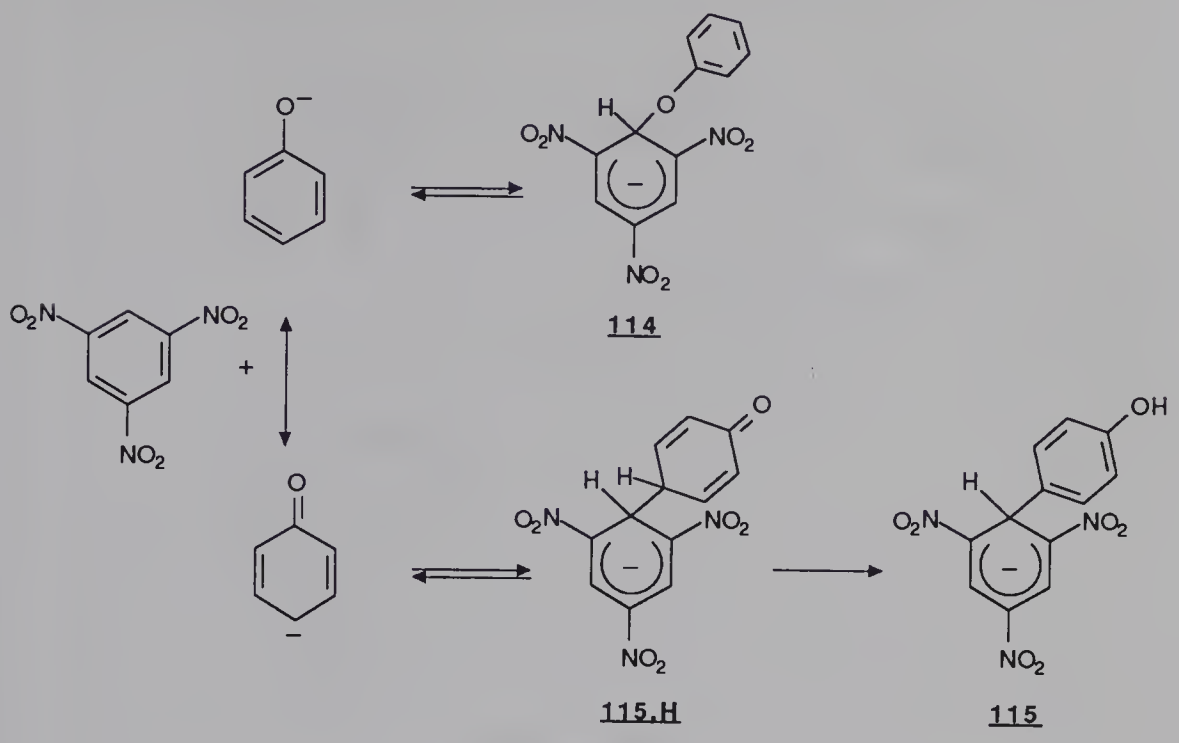
from those on the rate constant k_1. The results resemble those observed in S_NAr reactions of 2,4-dinitrohalobenzenes, where the rate-determining step is the addition of the nucleophile; they are explicable in the same terms of simple electrostatic interactions (see Chapter 1).

2.4 Some Remarkable Structure–Reactivity Relationships

2.4.1 Reactions of Nitroaromatics with Ambident Nucleophiles

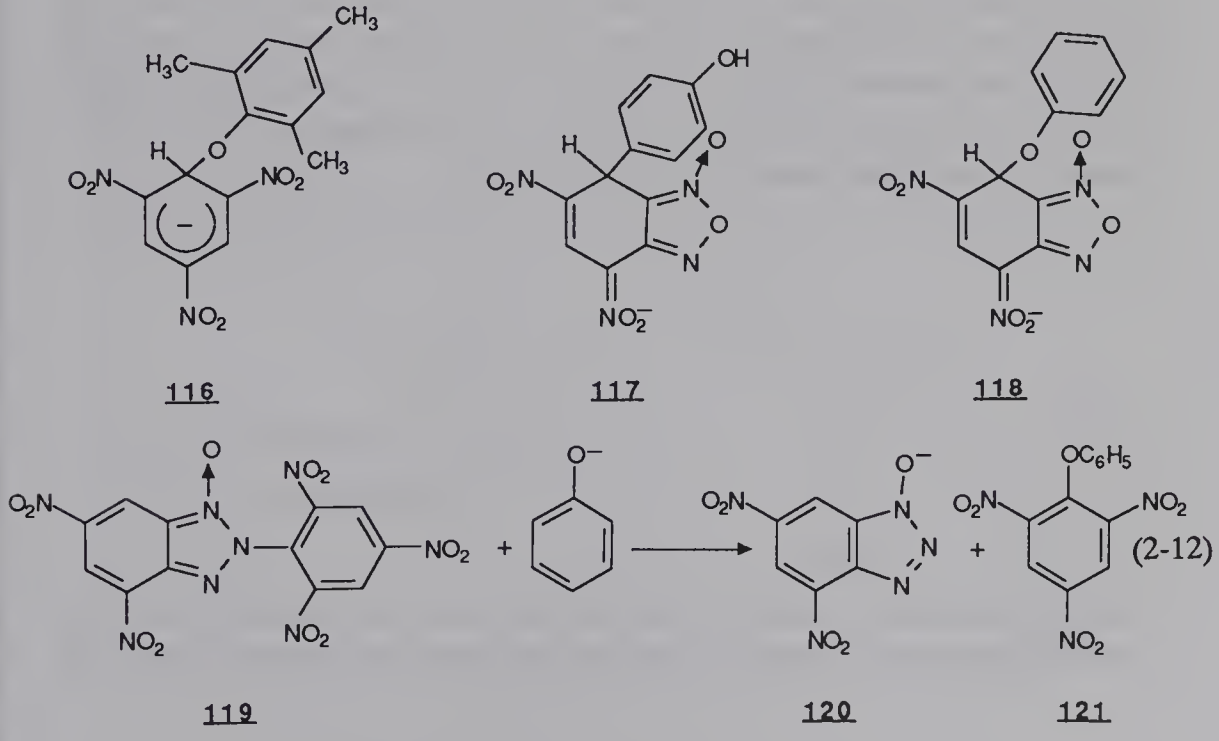
1,3,5-Trinitrobenzene (TNB) and more recently the highly electrophilic 4,6-dinitrobenzofuroxan (DNBF) and 4,6-dinitrobenzofurazan (DNBZ) have proved to be very suitable substrates for studying the behavior of potentially ambident bases and assessing the reactivity of some very weak nucleophiles.[1,2] Carbon versus oxygen base additions have received considerable attention. Addition of phenoxide ion to TNB results in the formation of the C-adduct **115** as the thermodynamically stable species, but the initial and reversible formation of the O-adduct **114** under kinetic control has been observed under some experimental conditions.[177–180] Scheme 2.8 depicts the interaction in which the carbon attack followed by proton loss from **115,H** gives rise to the rearomatized product **115** in an effectively irreversible process. For para-substituted phenoxide anions, C-addition occurs at the ortho position.[180] Buncel *et al.* have succeeded in characterizing the O-adduct **116** as an observable species in the reaction of TNB with 2,4,6-trimethylphenoxide ion, though the final product in the reaction is 2,4,6-trimethyl-3′,5′-dinitrodiphenyl ether, formed by S_NAr nucleophilic displacement of NO_2.[181]

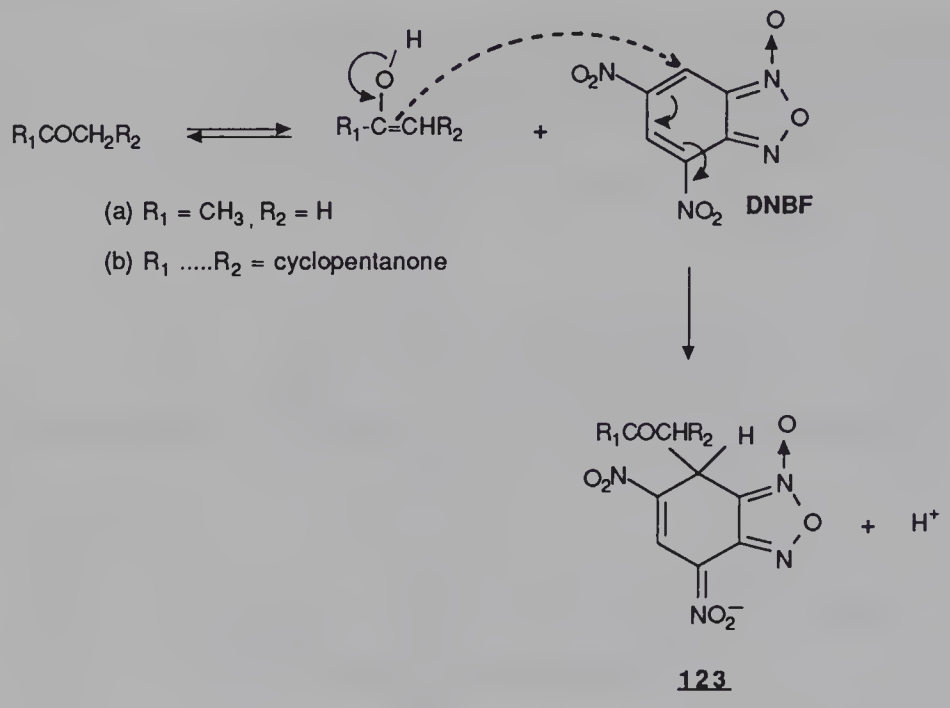
Despite its much stronger electrophilicity, DNBF affords exclusively C-adducts (e.g., **117**) upon reaction with aryloxide anions.[182] The failure to observe O-adducts (e.g., **118**) suggests that the anticipated added stability of **118**, relative to that of the O-bonded TNB complex **114**, is compensated by the decreased barriers to carbon attack and the lesser stability of DNBF relative to TNB.[183] Interestingly, the reaction of 4,6-dinitro-2-(2,4,6-trinitrophenyl)benzotriazole 1-oxide (**119**) with phenoxide ions is found to be



Scheme 2.8.

exclusively the S_NAr displacement of the picryl moiety via ArO^- acting as an oxygen base, to afford 1-hydroxybenzotriazole anion **120** and picrylphenyl ether (**121**) (eq. 2-11).[182]

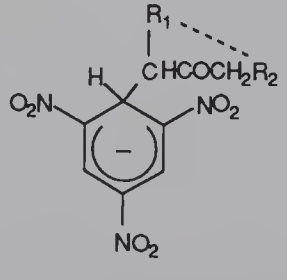




123

Scheme 2.9.

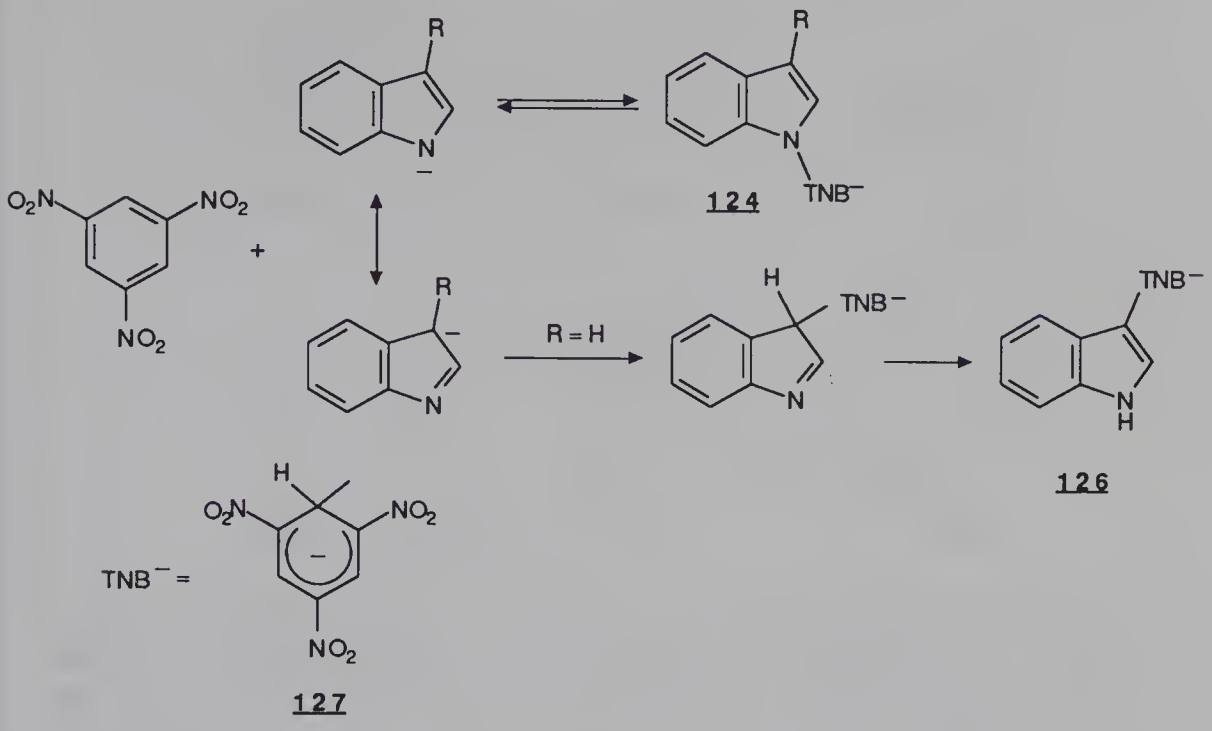
Thermodynamic preference for C-adduct formation compared to O-adduct formation is also the rule in the reactions of TNB with enolate anions of carbonyl compounds such as ketones, esters, or keto esters.[1,2] Although these anions are potentially susceptible to reacting via their oxygen or carbon atom centers, the only adducts so far characterized are the C-adducts **122**. Even the use of DNBF has not allowed the detection of oxygen attack. An interesting feature in the DNBF systems is that the addition of the carbonyl compounds occurs in the absence of any added base in DMSO.[50a] The formation of **123** undoubtedly results from attack of equilibrium concentrations of the weakly basic enols on DNBF, as shown in Scheme 2.9.[50a]



(a) $R_1 = R_2 = H$
(b) $R_1 = H$; $R_2 = CH_3$
(c) $R_1 = R_2 = CH_3$
(d) R_1.....R_2 = cyclopentanone
(e) R_1.....R_2 = cyclohexanone

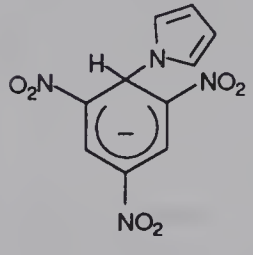
122

Various interesting carbon versus nitrogen base interactions have been reported. In general, pyrrolide, indolide, and imidazolide anions react with



Scheme 2.10.

TNB to give initially an N-adduct (e.g., **8**, **124a**, and **125**), which subsequently rearranges to a much more stable C-adduct.[28,183,184] Scheme 2.10 illustrates the interaction for the indole systems, which leads exclusively to the C-3 adducts **126** in accordance with the greater susceptibility of the β-position of the indole ring to electrophilic additions.[183] However, 3-substituted indoles give rise to stable N-adducts **124**; for simplicity, the symbol TNB^- is used to denote the negatively charged trinitrocyclohexadienyl moiety (structure **127**) of the adducts. With pyrroles, TNB addition occurs normally at C-2—for example, to give **128**; but 2,5-disubstituted pyrroles undergo TNB attack at the β-position.[28] Steric factors preclude initial formation of an N-adduct in these instances. In the case of imidazoles, C-adduct formation occurs preferentially at C-4 or C-5, but substitution at C-2 has been observed in 4,5-disubstituted



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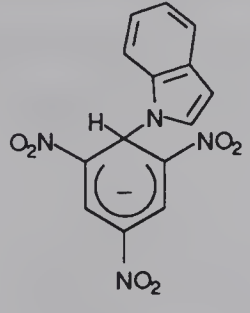
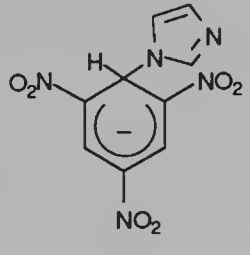


124a



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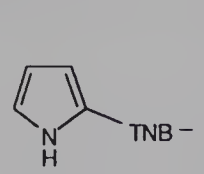

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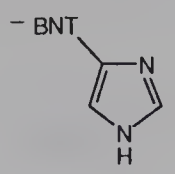
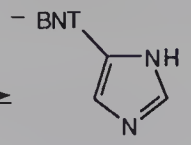
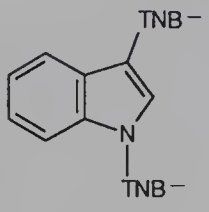


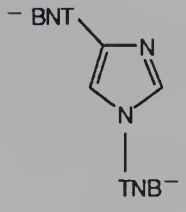
129a



129b



130



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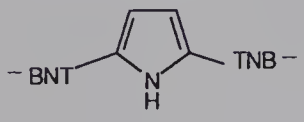
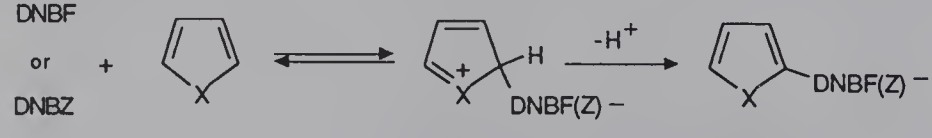


132

imidazoles.[184] Tautomeric exchanges of the type **129a** ⇔ **129b** have been observed in the C-adducts of imidazole and 2-methylimidazole. A further remarkable illustration of the ambident reactivity of indolide and imidazolide anions in σ-complex formation is the characterization of N,C-diadducts such as **130** and **131**.[184,185] The formation of C,C-diadducts such as **132** has been reported.[28]

While TNB does not react with neutral pyrroles, indoles, or imidazoles, DNBF and DNBZ add readily either to a carbon center, giving rise to pyrrole and indole C-adducts such as **133** (X = NH, eq. 2-13) or **134**, respectively, or as a nitrogen center, giving rise to the zwitterionic N-adduct **135**.[185] Other five-membered ring heterocycles like furans and thiophenes behave similarly as carbon nucleophiles, affording the C-adducts **133** according to eq. 2-13 (X = O, S).[185] Not unexpectedly, 2,5-dimethylpyrrole and 2,5-dimethylthiophene undergo DNBF or DNBZ additions at C-3 to give **136** (X = NH, S). 2,5-Dimethylfuran exhibits an original unexpected behavior, affording the adduct **137**, which results from a formal electrophilic substitution on one of the methyl groups. The mechanism for this substitution has been elucidated.[185] The significance of the $DNBF^-$ and $DNBZ^-$ moieties of the various adducts is given in structure **138**.

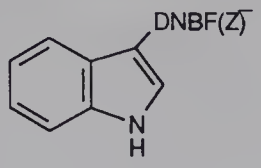
Examples of nitrogen versus carbon ambident behavior are provided by the reactions of DNBF with aromatic amines.[186–188] While TNB reacts with these nucleophiles only in the presence of an external base (triethylamine,



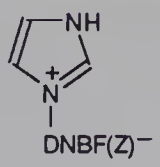
(2-13)

X = NH, O, S

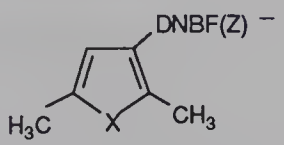
133



134

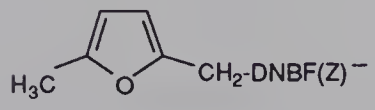


135

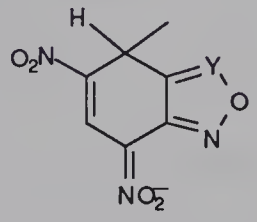


136

X = NH , S



137



138

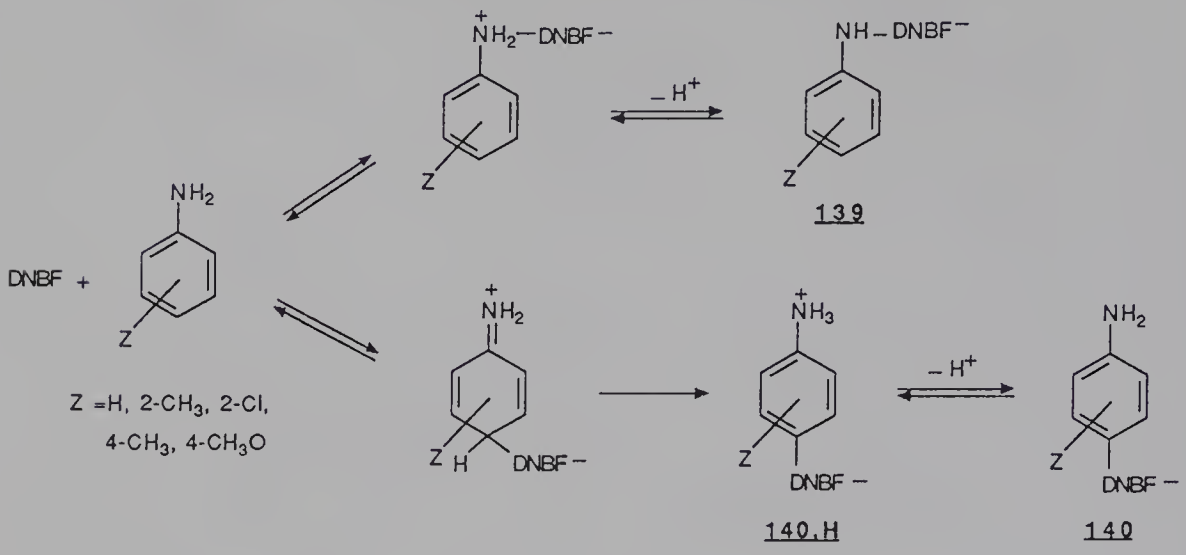
Y = N→O DNBF⁻

Y = N DNBZ⁻

DABCO, CH_3O^-) as catalyst, yielding solely N-bonded adducts in DMSO, DNBF undergoes addition to aniline without a catalyst, with rapid formation of the zwitterionic C-bonded adduct **140,H**. When the reaction is carried out with excess aniline or in the presence of triethylamine as catalyst, the formation of the nitrogen-bonded adduct **139** is seen to precede that of **140**, which is the thermodynamically stable product.[188] Scheme 2.11 describes the various steps of the interaction. Note the exclusive formation of the N-adduct **139** when the nucleophilic carbon sites of the aniline are blocked, as in 2,4,6-trimethylaniline.[186–188] However, when the reactivity of the anilines is lessened by ortho or *N*-methyl substitution, C-adduct formation is favored.

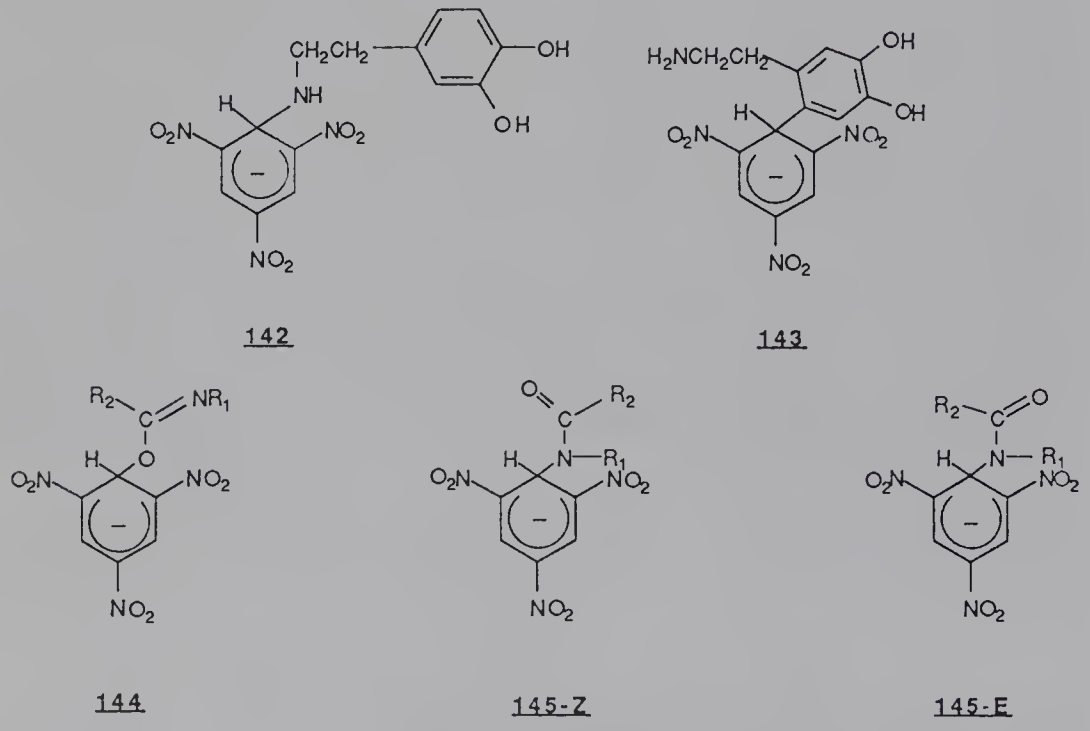
Although there is little possibility of bringing even one of the dimethylamino groups into the plane of the ring, resulting in a very low resonance interaction between the nitrogen lone pairs and the aromatic system, 1,8-bis(dimethylamino)naphthalene acts as a carbon nucleophile toward DNBF and DNBZ.[189] The reactions afford the C-adducts **141,H**.

141,H



Scheme 2.11.

As a structural analogue of phenoxide, the reaction of dopamine, (a physiologically important catecholamine) with TNB has been studied.[190] However, no initial formation of an oxygen-bonded adduct was observed in

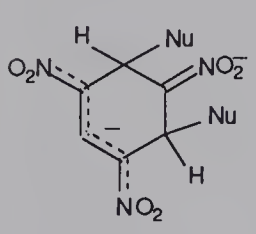


this instance. Instead, the formation of the N-adduct **142** was found to precede that of the thermodynamically stable C-adduct **143**.[190]

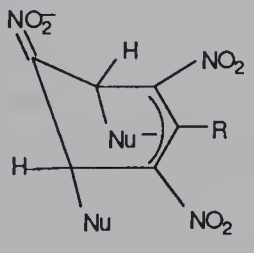
Nitrogen versus oxygen base additions have been considered in investigating interactions of TNB with structurally different amide anions.[25] However, no formation of the O-adducts **144** could be detected. Among the various N-adducts studied, those of formamide, *N*-methylformamide, and *N*-methylacetamide (**145a**, **145b**, and **145c**) were found to exist as a mixture of the Z and E isomers. In these instances, the E configuration, in which the bulky TNB-substituent is trans to the carbonyl oxygen, is largely preferred.[25]

2.4.2 Diadduct Formation: meta Bridging

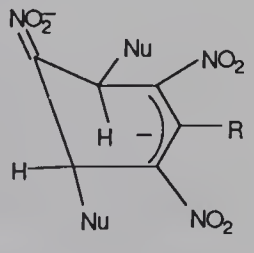
As a remarkable illustration of the strong delocalization of negative charge, especially through NO_2 groups, it is found that the cyclohexadienylide rings of many σ-complexes are susceptible to further nucleophilic addition with formation of 1:2 diadducts.[1,2] For example, many adducts of structure **146** have been obtained from the reactions of a number of oxygen (OH^-, RO^-), sulfur (SO_3^{2-},RS^-), nitrogen (NH_2^-, $NHOH^-$), and carbon ($C_6H_5COCH_2^-$) nucleophiles with TNB.[1] Evidence for the possibility of cis–trans isomerism in these species has been found in the case of the sulfite diadduct **147a** in aqueous solution.[2,160] A pair of similar geometrical isomers has also been identified from the reaction of picramide with liquid ammonia, affording **147b**.[26] Diadduct formation can arise from nucleophilic additions at both substituted and unsubstituted ring positions—for example, the 1:2 methoxide adduct **148a** of TNA and the 1:2 amino adduct of TNT **148b**.[1,26] The latter shows geometrical isomerism.[26] In contrast to the situation of monoadducts, diadducts of type **146** or **148**, which bear at least two relatively localized negative charges, are more stabilized in protic than in dipolar aprotic solvents.[2]



146



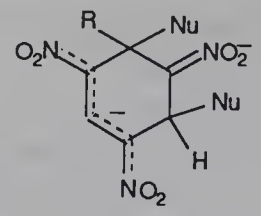
147-cis



147-trans

(a) R = H , Nu = SO_3^-

(b) R = NH_2 , Nu = NH_2

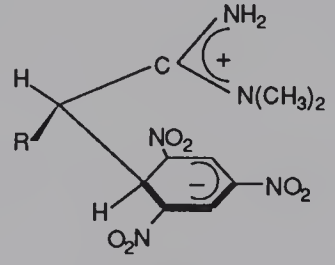


(a) R = OCH_3, Nu = OCH_3

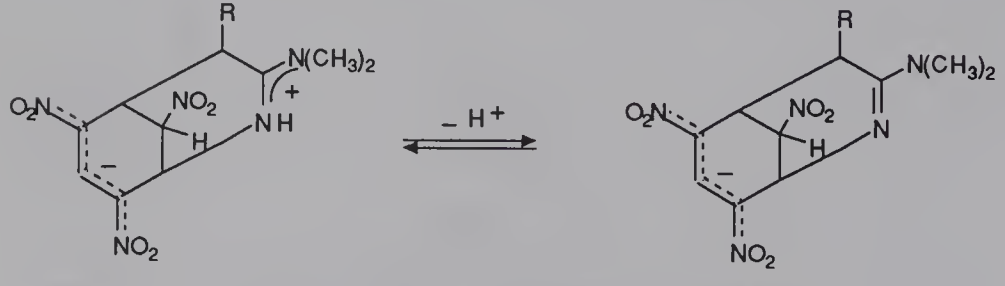
(b) R = CH_3, Nu = NH_2

148

A related process that also exemplifies the susceptibility of negatively charged nitrocyclohexadienylide rings to further nucleophilic attack is meta bridging.[191] The reactions of TNB with certain amidines like *N,N*-dimethylacetamidine or *N,N*-dimethylpropionamidine are illustrative.[192] In these instances, the zwitterionic C-adducts **149a** and **149b** form initially as very stable species, because of a favorable stabilizing interaction between the positively charged amidinium moiety and the negatively charged cyclohexadienylide ring. However, addition of a strong base (RO^-) to **149** results in deprotonation of the amidinium functionality and intramolecular nucleophilic attack of the resulting imino group, to give bicyclic adducts that have been characterized both as the zwitterions **150,H** and the anions **150**.[192] Clearly, these bridged adducts are structurally comparable to the 1:2 complexes **146**, while providing the demonstration of the ambident character of amidines.

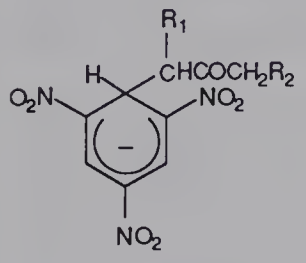


149 (a) R = H (b) R = CH_3

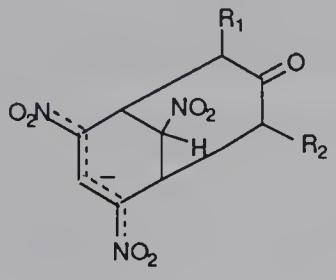


150,H **150**

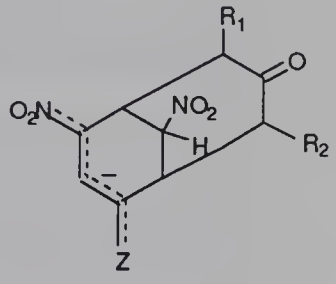
TNB monoadducts **122** of ketones or keto esters that have an ionizable CH group γ to the sp^3 carbon may also undergo further intramolecular reaction to yield the meta-bridged C,C-adducts **151**.[1,191,193–195] Ketone adducts of 1-Z-3,5-dinitrobenzenes undergo similar behavior, with the resulting bridged adducts having the structure **152** (Z = CN, CO_2CH_3), in which the Z group is part of the delocalized anionic function.[196] In other words, bridging occurs ortho–para and not ortho–ortho to Z. This behavior is also found in multiple addition.[197]



122



151



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References

1. Buncel, E.; Crampton, M. R.; Strauss, M. J.; Terrier, F. In "*Electron-Deficient Aromatic– and Heteroaromatic–Base Interactions*". Elsevier: Amsterdam, 1984.
2. Terrier, F. *Chem. Rev.* **1982**, *82*, 77.
3. Artamkina, G. A.; Egorov, M. P.; Beletskaya, I. P. *Chem. Rev.* **1982**, *82*, 427.
4. Buncel, E. In "*The Chemistry of Amino, Nitro and Nitroso Compounds*", Supplement F, Patai, S., ed. Wiley: London, 1982, p. 1225.
5. Sekiguchi, S. *Yugi Grosei Kagaku Kyokaishi*, **1978**, *36*, 633.
6. Gitis, S. S.; Kaminskii, A. Ya. *Usp. Khim.* **1978**, *47*, 1970.
7. Bernasconi, C. F. *Acc. Chem. Res.* **1978**, *11*, 147.
8. Strauss, M. J. *Chem. Rev.* **1970**, *70*, 667.
9. Crampton, M. R. *Adv. Phys. Org. Chem.* **1969**, *7*, 211.
10. Foster, R.; Fyfe, C. A. *Rev. Pure Appl. Chem.* **1966**, *16*, 61.
11. Destro, R.; Grammacioli, C.; Simonetta, M. *Acta Crystallogr.* **1968**, *B24*, 1369.
12. Ueda, H.; Sakabe, N.; Tanaka, J.; Furusaki, A. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2866.

13. Destro, R.; Pilati, T.; Simonetta, M. *Acta Crystallogr.* **1979**, *B35*, 733.
14. Messmer, G.; Palenik, G. J. *Acta Crystallogr.* **1971**, *B27*, 316.
15. Jackson, C. J.; Gazzolo, F. H. *Am. Chem. J.* **1900**, *23*, 376.
16. Meisenheimer, J. *Justus Liebigs Ann. Chem.* **1902**, *323*, 205.
17. Grammacioli, C.; Destro, R.; Simonetta, M. *J. Chem. Soc., Chem. Commun.* **1967**, 331.
18. Wennerström, H.; Wennerström, O. *Acta Chem. Scand.* **1972**, *26*, 2883.
19. Hosoya, H.; Hosoya, S.; Nakagura, S. *Theor. Chim. Acta*, **1968**, *12*, 117.
20. Birch, A. J.; Hinde, A. L.; Radom, L. *J. Am. Chem. Soc.* **1980**, *102*, 6430.
21. Nudelman, N. S.; McCormack, P. *J. Chem. Soc., Perkin Trans. 2*, **1987**, 227.
22. Strauss, M. J.; Fleischmann, S.; Buncel, E. *J. Mol. Struct.* **1985**, *121*, 37.
23. (a) Sekiguchi, S.; Hirose, T.; Tsutsumi, K.; Aizawa, T.; Shizuka, H. *J. Org. Chem.* **1979**, *44*, 3921; (b) Sekiguchi, S.; Hirai, M.; Ota, E.; Hiratsuka, H.; Mori, Y.; Tanaka, S. *ibid.* **1985**, *50*, 5105.
24. Attia, M.; Dave, D.; Gore, P. H.; Ikejiani, A. O. O.; Morris, D. F. C.; Short, E. L.; Consiglio, G.; Spinelli, D.; Frenna, V. *J. Chem. Soc., Perkin, Trans. 2*, **1984**, 1637.
25. Halle, J. C.; Zah-letho, J.; Simonnin, M. P.; Terrier, F. *J. Chem. Soc., Perkin Trans. 2*, **1987**, 805.
26. (a) Chudek, J. A.; Foster, R. *J. Chem. Soc., Perkin Trans. 2*, **1979**, 628; (b) Chudek, J. A.; Ellingham, R. A.; Foster, R. *ibid.* **1985**, 1477.
27. Forlani, L.; Sintoni, M.; Todesco, P. E. *J. Chem. Res.* **1986**, (S) 344.
28. Hallé, J. C.; Pouet, M. J.; Simonnin, M. P.; Debleds, F.; Terrier, F. *Can. J. Chem.* **1982**, *60*, 1988.
29. (a) Gololobov, Yu. G.; Onys'ko, P. P.; Fadeev, V. N.; Gusar, N. I. *J. Gen. Chem. USSR*, **1975**, *45*, 1361; (b) Onys'ko, P. P.; Gololobov, Yu. G. *ibid.* **1977**, *47*, 2267.
30. Taylor, R. P. *J. Chem. Soc., Chem. Commun.* **1970**, 1463.
31. Foreman, M. I.; Foster, R.; Strauss, M. J. *J. Chem. Soc. B*, **1970**, 147.
32. Machacek, V.; Sterba, V.; Lycka, A.; Snobl, D. *J. Chem. Soc., Perkin Trans. 2*, **1982**, 355.
33. Renfrow, R. A.; Strauss, M. J.; Terrier, F. *J. Org. Chem.* **1980**, *45*, 471.
34. Foster, R.; Fyfe, C. A.; Emslie, P. H.; Foreman, M. I. *Tetrahedron*, **1967**, *23*, 227.
35. Sekiguchi, S.; Tsutsumi, K.; Shizuka, H.; Matsui, K.; Itagaki, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1521.
36. Terrier, F.; Millot, F.; Simonnin, M. P. *Tetrahedron Lett.* **1971**, 2933.

37. Terrier, F.; Chatrousse, A. P. *Bull. Soc. Chim. Fr.* **1972**, 4549.
38. Millot, F.; Terrier, F. *Bull. Soc. Chim. Fr.* **1974**, 1823.
39. Crampton, M. R.; Khan, H. A. *J. Chem. Soc., Perkin Trans. 2*, **1973**, 710.
40. Fyfe, C. A.; Cocivera, M.; Damji, S. W. H. *J. Am. Chem. Soc.* **1975**, *97*, 5707.
41 . Schaal, R.; Terrier, F.; Hallé, J. C.; Chatrousse, A. P. *Tetrahedron Lett.* **1970**, 1393.
42. Biffin, M. E. C.; Miller, J.; Moritz, A. G.; Paul, D. B. *Aust. J. Chem.* **1970**, *23*, 963.
43. Terrier, F.; Millot, F.; Chatrousse, A. P.; Pouet, M. J.; Simonnin, M. P. *Org. Magn. Resonance,* **1976**, *8*, 56.
44. Buncel, E.; Chuaqui-Offermanns, N.; Hunter, B. K.; Norris, A. R. *Can. J. Chem.* **1977**, *55*, 2852.
45. Doddi, G.; Stegel, F.; Tanasi, M. T. *J. Org. Chem.* **1978**, *43*, 4303.
46. Paulmier, C.; Simonnin, M. P.; Chatrousse, A. P.; Terrier, F. *Tetrahedron Lett.* **1973**, 1123.
47. (a) De Santis, F.; Stegel, F. *Tetrahedron Lett.* **1974**, 1079; (b) Baldini, G.; Doddi, G.; Illuminati, G.; Stegel, F. *J. Org. Chem.* **1976**, *41*, 2153.
48. Sancassan, F.; Dell'Erba, C. *Chem. Scr.* **1988**, *28*, 349.
49. (a) Newcombe, P. J.; Norris, R. K. *Aust. J. Chem.* **1978**, *31*, 2463; (b) *ibid.* **1979**, *32*, 1709.
50. (a) Terrier, F.; Simonnin, M. P.; Pouet, M. J.; Strauss, M. J. *J. Org. Chem.* **1981**, *46*, 3537. (b) Terrier, F.; Chatrousse, A. P.; Boubaker, T. unpublished results.
51. Strauss, M. J. ; De Fusco, A.; Terrier, F. *Tetrahedron Lett.* **1981**, *22*, 1945.
52. Terrier, F.; McCormack, P.; Hallé, J. C.; Pouet, M. J. *J. Org. Chem.* **1988**, *53*, 4407.
53. Lok, C. M.; Den Boer, M. E.; Cornelisse, J. *Recl. Trav. Chim. Pays-Bas*, **1973**, *92*, 340.
54. Olah, G.; Mayr, H. *J. Org. Chem.* **1976**, *41*, 3448.
55. Farnum, O. G. *Adv. Phys. Org. Chem.* **1975**, *11*, 123.
56. Chudek. J. A.; Foster, R.; Marr, A. W. *J. Chem. Soc., Perkin Trans.*, **1987**, 1341.
57. Van der Stoel, R. E.; Van der Plas, H. C. *Recl. Trav. Chim. Pays-Bas*, **1978**, *97*, 116.
58. Simonnin, M. P.; Pouet, M. J.; Terrier, F. *J. Org. Chem.* **1978**, *43*, 855.
59. (a) Consiglio, G.; Spinelli, D.; Arnone, C.; Sancassan, F.; Dell'Erba, C.;

Noto, R.; Terrier, F. *J. Chem. Soc., Perkin Trans. 2,* **1984**, 317; (b) Dell'Erba, C.; Sancassan, F., Novi, M.; Spinelli, D.; Consiglio, G.; Arnone, C.; Ferroni, F. *ibid.* **1989**, 1779.

60. Consiglio, G.; Arnone, C.; Spinelli, D.; Sancassan, F.; Dell'erba, C.; Leandri, G.; Terrier, F. *Gazz. Chim. Ital.* **1987**, *117*, 267.
61. Servis, K. L. *J. Am. Chem. Soc.* **1965**, *87*, 5495.
62. Simonnin, M. P.; Lecourt, M. J.; Terrier, F.; Dearing, C. A. *Can. J. Chem.* **1972**, *50*, 3558.
63. Terrier, F.; Hallé, J. C.; Simonnin, M. P. *Org. Magn. Resonance* **1971**, *3*, 361.
64. Crampton, M. R. *J. Chem. Soc., Perkin Trans. 2,* **1977**, 1442.
65. Al Alaluri, A. D. A.; Crampton, M. R. *J. Chem. Res.* **1980** (S) 140; (M) 2157.
66. Biffin, M. E. C.; Miller, J. ; Moritz, A. G.; Paul, D. B. *Aust. J. Chem.* **1970**, *23*, 957.
67. Terrier, F.; Chatrousse, A. P.; Schaal, R. *J. Org. Chem.* **1972**, *37*, 3010.
68. Terrier, F.; Millot, F.; Schaal, R. *J. Chem. Soc., Perkin Trans. 2*, **1972**, 1192.
69. Biggi, G.; Pietra, F. *J. Chem. Soc., Perkin Trans. 1*, **1973**, 1980.
70. Terrier, F.; Ah-Kow, G.; Pouet, M. J.; Simonnin, M. P. *Tetrahedron Lett.* **1976**, 227.
71. (a) Crampton, M. R.; Kee, T. P.; Wilcock, J. R. *Can. J. Chem.* **1986**, *64*, 1714; (b) Crampton, M. R.; Davis, A. B.; Greenhalgh, C.; Stevens, J. A. *J. Chem. Soc., Perkin Trans. 2*, **1989**, 675.
72. (a) Kavalek, J.; Ashfaq, A.; Sterba, V. *Collect. Czech. Chem. Commun.* **1979**, *44*, 1453; (b) Kavalek, J.; Pastrnek, M.; Sterba, V. *ibid.* **1978**, *43*, 1401.
73. Fyfe, C. A.; Damji, S. W. H.; Koll, A. *J. Am. Chem. Soc.* **1979**, *101*, 951.
74. Kaminskaya, E. G.; Gitis, S. S.; Kaminski, A. Ya.; Grudtsyn, Yu. D. *J. Org. Chem. USSR*, **1976**, *12*, 917.
75. Fendler, E. J.; Camaioni, D. M.; Fendler, J. H. *J. Org. Chem.* **1971**, *36*, 1544.
76. Kohashi, K.; Tsuruta, T.; Yamaguchi, M.; Ohkura, Y. *Chem. Pharm. Bull.* **1979**, *27*, 2122.
77. Ellinger, A.; Seidel, R.; Kovar, K. A. *Arch. Pharm.* **1976**, *309*, 603.
78. Butler, A. R. *Clin. Chim. Acta*, **1975**, *59*, 227.
79. Millot, F.; Terrier, F. *Bull. Soc. Chim. Fr.* **1972**, 3897.
80. Kaminskaya, E. G. *J. Org. Chem., USSR*, **1978**, *14*, 2371.

81. Sekiguchi, S.; Fujisawa, S.; Ando, Y. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1451.
82. Sekiguchi, S.; Hikage, R.; Obana, K.; Matsui, K.; Ando, Y.; Tomoto, N. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2921.
83. Takahashi, H.; Hiraide, T.; Hashida, Y.; Sekiguchi, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 185.
84. Bernasconi, C. F.; Fairchild, D. E. *J. Am. Chem. Soc.* **1988**, *110*, 5498.
85. Crampton, M. R.; Willison, M. J. *J. Chem. Soc., Perkin Trans. 2*, **1974**, 1681.
86. Foster, R.; Fyfe, C. A., Morris, J. W. *Recl. Trav. Chim. Pays-Bas*, **1965**, *84*, 516.
87. Drozd, V. N.; Knyazev, V. N.; Klimov, A. A. *J. Org. Chem., USSR*, **1974**, *10*, 828.
88. Morozova, T. I.; Gitis, S. S.; Kaminskii, A. Ya.; Glaz, A. I.; Mel'nikov, A. I.; Grudtsyn, Yu. D. *J. Org. Chem. USSR*, **1977**, *13*, 1778.
89. Minkin, V. J.; Olekhnovich, L. P.; Zhdanov, Yu. A.; Budarina, Z. N.; Metlushenko, V. P.; Orenshtein, I. B. *J. Org. Chem. USSR*, **1977**, *13*, 707.
90. Knyazev, V. N.; Lipovtsev, V. N.; Belostskaya, I. S.; Vol'eva, V. B.; Drozd, V. N.; Ershov, V. V. *J. Org. Chem. USSR*, **1986**, *22*, 1753.
91. Bernasconi, C. F.; Howard, K. *J. Am. Chem. Soc.* **1982**, *104*, 7248.
92. Ah-Kow, G.; Terrier, F.; Pouet, M. J.; Simonnin, M. P. *J. Org. Chem.* **1980**, *45*, 4399.
93. Drozd, V. N.; Grandberg, N. V. *J. Org. Chem. USSR*, **1979**, *15*, 659.
94. Crampton, M. R.; Willison, M. J. *J. Chem. Soc., Perkin Trans. 2*, **1976**, 155.
95. Sancassan, F.; Novi, M.; Guanti, G.; Dell'Erba, C. *J. Heterocyclic Chem.* **1975**, *12*, 1083.
96. Ah-kow, G.; Terrier, F.; Lessard, F. *J. Org. Chem.* **1978**, *43*, 3578.
97. Cavazza, M.; Veracini, C. A.; Morganti, G.; Pietra, F. *J. Chem. Soc., Chem. Commun.* **1978**, 167.
98. Sekiguchi, S.; Shiojima, T. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 693.
99. Knyazev, V. N.; Klimov, A. A.; Minov, V. M.; Drozd, V. N. *J. Org. Chem., USSR*, **1975**, *11*, 1782.
100. Bernasconi, C. F.; Gehriger, C. H. *J. Am. Chem. Soc.* **1974**, *96*, 1092.
101. Machacek, V.; Hassanien, M. M. M.; Sterba, V. *Collect. Czech. Chem. Commun.* **1987**, *52*, 2225.

102. Crampton, M. R.; Gibson, B.; Matthews, R. S. *Org. Magn. Resonance* **1980**, *13*, 455.

103. Crampton, M. R. *J. Chem. Soc. B*, **1968**, 1208.

104. Boulton, J. J. K.; McFarlane, N. R. *J. Chem. Soc. B,* **1971**, 925.

105. Grudtsyn, Yu. D.; Gitis, S. S. *J. Org. Chem. USSR*, **1975**, *11*, 2616.

106. Machacek, V.; Hassanien, M. M. M.; Sterba, V.; Lycka, A. *Collect. Czech. Chem. Commun.* **1986**, *51*, 1972.

107. Fyfe, C. A.; Malkiewich, C. D.; Damji, S. W. H.; Norris, A. R. *J. Am. Chem. Soc.* **1976**, *98*, 6983.

108. Brooke, D. N.; Crampton, M. R. *J. Chem. Soc., Perkin Trans. 2*, **1982**, 231.

109. (a) Brooke, D. N.; Crampton, M. R.; Corfield, G. C.; Golding, P.; Hayes, G. F. *J. Chem. Soc., Perkin Trans. 2,* **1981**, 526; (b) Crampton, M. R.; Routledge, P. J.; Corfield, G. C.; King, R. M.; Golding, P. *ibid.* **1982**, 31.

110. Buncel, E.; Zabel, A. W. *Can. J. Chem.* **1981**, *59*, 3168, 3177.

111. Buncel, E.; Elvidge, J. A.; Jones, J. R.; Walkin, K. T. *J. Chem. Res.* **1980**, (S) 326.

112. Bernasconi, C. F. *J. Am. Chem. Soc.* **1970**, *92*, 4682.

113. Crampton, M. R.; Khan, H. A. *J. Chem. Soc., Perkin Trans. 2,* **1972**, 733.

114. Terrier, F.; Chatrousse, A. P.; Paulmier, C. *J. Org. Chem.* **1979**, *44*, 1634.

115. Hurtel, P.; Decroix, B.; Morel, J.; Terrier, F. *J. Chem. Res.* **1983**, (S) 58.

116. Terrier, F.; Chatrousse, A. P.; Millot, F. *J. Org. Chem.* **1980**, *45*, 2666.

117. Terrier, F.; Chatrousse, A. P.; Soudais, Y.; Hlaibi, M. *J. Org. Chem.* **1984**, *49*, 4176.

118. Fendler, J. H.; Hinze, W. L.; Liu, L. J. *J. Chem. Soc., Perkin Trans. 2,* **1975**, 1751, 1768.

119. Illuminati, G.; Stegel, F. *Adv. Heterocycl. Chem.* **1983**, *34*, 306.

120. Fendler, J. H.; Fendler, E. J.; Griffin, C. E. *J. Org. Chem.* **1969**, *34*, 689.

121. Crampton, M. R.; Khan, H. A. *J. Chem. Soc., Perkin Trans. 2,* **1972**, 1173.

122. Bernasconi, C. F. *J. Am. Chem. Soc.* **1968**, *90*, 4982.

123. Terrier, F.; Millot, F.; Morel, J. *J. Org. Chem.* **1976**, *41*, 3892.

124. Crampton, M. R.; El Ghariani, M. A.;. Willison, M. J. *J. Chem. Soc., Perkin Trans. 2*, **1974**, 441.

125. Fendler, J. H.; Fendler, E. J.; Byrne, W. E.; Griffin, C. E. *J. Org. Chem.* **1968**, *33*, 977.

126. Arnone, C.; Consiglio, G.; Spinelli, D.; Dell'Erba, C.; Sancassan, F.; Terrier, F. *J. Chem. Soc., Perkin Trans. 2,* **1989**, 1609.

127. Murphy, R. M.; Wulff, C. A.; Strauss, M. J. *J. Am. Chem. Soc.* **1974**, *96*, 2678.

128. Kavalek, J.; Kolb, I.; Machacek, V.; Sterba, V. *Collect. Czech. Chem. Commun.* **1975**, *40*, 3879.

129. Terrier, F.; Ah-Kow, G.; Chatrousse, A. P. *J. Org. Chem.* **1985**, *50*, 4583.

130. Crampton, M. R.; Greenhalgh, C. *J. Chem. Soc., Perkin Trans. 2*, **1986**, 187.

131. Sheppard, W. A. *J. Am. Chem. Soc.* **1963**, *85*, 1314.

132. Bordwell, F. G.; Vanier, N. R.; Matthews, W. S.; Hendrickson, J. B.; Skipper, P. L. *J. Am. Chem. Soc.* **1975**, *97*, 7160.

133. Terrier, F.; Chatrousse, A. P.; Kizilian, E.; Ignatev, N. V.; Yagupolskii, L. M. *Bull. Soc. Chim. Fr.* **1989**, 627.

134. Terrier, F.; Millot, F.; Chatrousse, A. P.; Yagupolskii, L. M.; Boiko, V. N.; Shchupak, G. M.; Ignatev, N. V. *J. Chem. Res. (S)* **1979**, 272.

135. Yagupolskii, L. M.; Gogoman, I. V.; Shchupak, G. M.; Boiko, V. N. *J. Org. Chem. USSR*, **1986**, *22*, 664.

136. Bernasconi, C. F. *J. Am. Chem. Soc.* **1971**, *93*, 6975.

137. Chatrousse, A. P.; Terrier, F.; Schaal, R. *J. Chem. Res.* **1977**, (S) 228, (M) 2413.

138. Norris, A. R.; Gan, L. H. *Can. J. Chem.* **1971**, *49*, 2490.

139. Terrier, F.; Chatrousse, A. P.; Paulmier, C.; Schaal, R. *J. Org. Chem.* **1975**, *40*, 2911.

140. Di Nunno, L.; Florio, S.; Todesco, P. E. *J. Chem. Soc., Perkin Trans. 2,* **1975**, 1469.

141. Bernasconi, C. F.; Muller, M. C.; Schmid, P. *J. Org. Chem.* **1979**, *44*, 3189.

142. Crampton, M. R.; Gibson, B. *J. Chem. Soc., Perkin Trans. 2,* **1981**, 533.

143. Sekiguchi, S.; Bunnett, J. F. *J. Am. Chem. Soc.* **1981**, *103*, 4871.

144. Terrier, F.; Millot, F. *Bull. Soc. Chim. Fr.* **1970**, 1743.

145. Gibson, B.; Crampton, M. R. *J. Chem. Soc., Perkin Trans. 2,* **1979**, 648.

146. (a) Gan, L. H.; Norris, A. R. *Can. J. Chem.* **1974**, *52*, 18. (b) Gan, L. H. *Aust. J. Chem.* **1975**, *28*, 2403.

147. Crampton, M. R.; *J. Chem. Soc., Perkin Trans. 2,* **1978**, 343.

148. Croney, A.; Crampton, M. R. *J. Chem. Soc., Perkin Trans. 2,* **1984**, 1793.

149. Hasegawa, Y. *J. Chem. Soc., Perkin Trans. 2,* **1985**, 87.

150. Kavalek, J.; Machacek, V.; Pastrnek, M.; Sterba, V. *Collect. Czech. Chem. Commun.* **1977**, *42*, 2928.

151. Crampton, M. R.; Willison, M. J. *J. Chem. Soc., Perkin Trans. 2*, **1976**, 160.

152. Bernasconi, C. F.; Gandler, J. R. *J. Org. Chem.* **1977**, *42*, 3387.

153. Bernasconi, C. F.; Gehriger, C. L.; De Rossi, R. H. *J. Am. Chem. Soc.* **1976**, *98*, 8451.

154. Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.

155. (a) Bernasconi, C. F.; Wang, H. C. *J. Am. Chem. Soc.* **1976**, *98*, 6265; (b) Bernasconi, C. F.; Muller, M. C. *ibid.* **1978**, *100*, 5530.

156. Knyazev, V. N.; Drozd, V. N.; Lipotsev, V. N.; Kurapov, P. B. *J. Org. Chem., USSR*, **1987**, *23*, 1161.

157. Sekiguchi, S.; Hoshino, O.; Hirai, M.; Okada, K.; Tomoto, N. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2173.

158. Machacek, V.; Hassanien, M. M. M.; Sterba, V. *J. Chem. Soc., Perkin Trans. 2*, **1986**, 813.

159. Hine, J.; Weimar, R. D. *J. Am. Chem. Soc.* **1965**, *87*, 3387.

160. Bernasconi, C. F.; Bergstrom, R. G. *J. Org. Chem.* **1971**, *36*, 1325.

161. Bernasconi, C. F.; Bergstrom, R. G. *J. Am. Chem. Soc.* **1973**, *95*, 3603.

162. Crampton, M. R.; Stevens, J. A. *J. Chem. Soc., Perkin Trans. 2*, **1989**, 925.

163. Crampton, M. R.; El Ghariani, M. A. *J. Chem. Soc. B*, **1971**, 1043.

164. Kolb, I.; Machacek, V.; Sterba, V. *Collect. Czech. Chem. Commun.* **1976**, *41*, 1914.

165. Cox, J. P. L.; Crampton, M. R.; Wight, P. *J. Chem. Soc., Perkin Trans. 2*, **1988**, 25.

166. Miller, J. "*Aromatic Nucleophilic Substitution*". Elsevier: Amsterdam, 1968.

167. Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1962**, *84*, 2910.

168. Bernasconi, C. F. *Tetrahedron*, **1985**, *41*, 3219.

169. (a) Buncel, E.; Eggimann, W. *J. Am. Chem. Soc.* **1977**, *99*, 5958; (b) Buncel, E.; Innis, C.; Onyido, J. *J. Org. Chem.* **1986**, *51*, 3680.

170. Onysko, P. P.; Kashukhin, F.; Gololobov, Yu. G. *Zh. Obshch. Khim.* **1978**, *48*, 342.

171. Larsen, J. W.; Amin, K.; Fendler, J. H. *J. Am. Chem. Soc.* **1971**, *93*, 2910.

172. Fendler, J. H.; Larsen, J. W. *J. Org. Chem.* **1972**, *37*, 2608.

173. Larsen, J. W.; Amin, K.; Ewing, S.; Magid, L. L. *J. Org. Chem.* **1972**, *37*, 3857.

174. Buncel, E.; Wilson, H. *Adv. Phys. Org. Chem.* **1977**, *14*, 133.

175. Brooke, D. N.; Crampton, M. R. *J. Chem. Soc., Perkin Trans. 2*, **1980**, 1850.

176. Casilio, L. M.; Fendler, E. J.; Fendler, J. H. *J. Chem. Soc., Perkin Trans. 2*, **1971**, 1377.

177. Shein, S. M.; Byval'kevich, O. G.; Khmelinskaya, A. D. *Zh. Org. Khim.* **1976**, *12*, 134.

178. Shein, S. M.; Byval'kevich, O. G. *Zh. Org. Khim.* **1972**, *8*, 328.

179. Buncel, E.; Webb, J. G. K. *J. Am. Chem. Soc.* **1973**, *95*, 8470.

180. Buncel, E.; Jonczyk, A.; Webb, J. G. K. *Can. J. Chem.* **1975**, *53*, 3761.

181. Buncel, E.; Moir, R. Y.; Norris, A. R.; Chatrousse, A. P. *Can. J. Chem.* **1981**, *59*, 2470.

182. (a) Buncel, E.; Renfrow, R. A.; Strauss, M. J. *J. Org. Chem.* **1987**, *52*, 488; (b) Buncel, E.; Dust, J. M. *Can. J. Chem.* **1988**, *66*, 1712.

183. Hallé, J. C.; Terrier, F.; Pouet, M. J.; Simonnin, M. P. *J. Chem. Res.* **1980** (S) 360.

184. Simonnin, M. P.; Hallé, J. C.; Terrier, F.; Pouet, M. J. *Can. J. Chem.* **1985**, *63*, 866.

185. Terrier, F.; Hallé, J. C.; Simonnin, M. P.; Pouet, M. J. *J. Org. Chem.* **1984**, *49*, 4363.

186. Spear, R. J.; Norris, W. P.; Read, R. W. *TetrahedronLett.* **1983**, *24*, 1555.

187. Read, W. R.; Spear, R. J.; Norris, W. P. *Aust. J. Chem.* **1984**, *37*, 985.

188. Strauss, M. J.; Renfrow, R. A.; Buncel, E. *J. Am. Chem. Soc.* **1983**, *105*, 2473.

189. Terrier, F.; Hallé, J. C.; Pouet, M. J.; Simonnin, M. P. *J. Org. Chem.* **1986**, *51*, 409.

190. Buncel, E.; Dust, J. M.; Manderville, R. A.; Pask, K. T.; Onyido, *J. Bull. Soc. Chim. Fr.* **1988**, 371.

191. Strauss, M. J. *Acc. Chem. Res.* **1974**, *7*, 181.

192. Bard, R. R.; Strauss, M. J. *J. Am. Chem. Soc.* **1975**, *97*, 3789.

193. Strauss, M. J.; Schran, H. R.; Bard, R. R. *J. Org. Chem.* **1973**, *38*, 3394.

194. Machacek, V.; Lycka, A. *Collect. Czech. Chem. Commun.* **1984**, *49*, 244.

195. Gnanadoss, L. M.; Kalaivani, D. *J. Org. Chem.* **1985**, *50*, 1174.

196. Strauss, M. J.; Jensen, T. C.; Schran, H. F.; O'Conner, K. *J. Org. Chem.* **1970**, *35*, 383.

197. Chudek, J. A.; Foster, R. *J. Chem. Soc., Perkin Trans. 2,* **1982**, 511.

CHAPTER 3.
Synthetic Aspects of Intermolecular S_NAr Reactions

3.1 Introduction

In protic or nonpolar solvents, where studies were confined for many years, most moderately activated aromatic substrates do not undergo facile S_NAr substitutions unless drastic experimental conditions are used.[1,2] This limitation precluded an extensive use of these processes for synthetic purposes until the discovery that many of these displacements can be performed under mild conditions and with excellent yields in dipolar aprotic solvents[2–6]; HMPA, DMSO, DMF, and acetonitrile are solvents that have been commonly used. In recent years, the development of the use of phase transfer catalysis (PTC) has also contributed to enhancing the synthetic potential of S_NAr reactions.[7–13]

As emphasized in Chapter 1, the NO_2 functionality contributes to the ease of S_NAr displacements in two different ways. Because of its strong electron-withdrawing character, in many cases, an NO_2 group supplies the activation required to displace a variety of appropriately located leaving groups (F, Cl, Br, I, OR, OAr, SO_3^-, etc.) from an aromatic or heteroaromatic ring. On the other hand, an NO_2 group has a high nucleofugality, and its departure from an aromatic or heteroaromatic system frequently occurs if there is appropriate activation by other electron-withdrawing groups.

It turns out that most of the intermolecular S_NAr substitutions of synthetic utility reported in recent years comprise nucleophilic displacement of an NO_2 group. On this ground, our discussion in this chapter focuses mainly on this class of reactions. Only the most notable syntheses involving displacement of other leaving groups, especially halo and alkoxy groups, are described. A

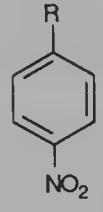
discussion of the synthetic aspects of S_NAr reactions of the nitro group appeared in 1978.[14]

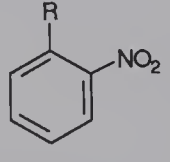
3.2 Intermolecular Displacements of a Nitro Group

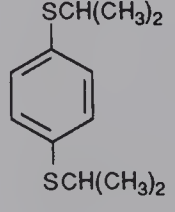
3.2.1 para-, ortho- and meta-Dinitrobenzenes: Related Substrates

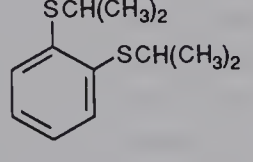
Early prototype examples of S_NAr displacements of a nitro group from moderately activated substrates included the reactions of *o*- and *p*-dinitrobenzenes with a variety of relatively strong and common nucleophiles, especially hydroxide and alkoxide ions and primary or secondary amines, in aqueous, alcoholic, or nonpolar (benzene) solvents. Use of dipolar aprotic or PTC conditions has allowed the achievement of a number of novel substitutions (Table 3.1).

Kornblum *et al.* reported that treatment of *p*- and *o*-DNB with either sodium thiophenoxide or sodium benzenesulfinate in HMPA or DMSO at room temperature afforded almost quantitative yields of the corresponding nitrophenyl phenyl sulfides **1a** or **2a** and phenylsulfones **1b** or **2b** (see entry pairs 1,8 and 2,9 in Table 3.1).[6] In a similar fashion, Tiecco *et al.* observed that the reaction of *p*-DNB and *o*-DNB with the sodium salt of 2-propanethiol gives the *p*- and *o*-nitrophenyl 2-propyl sulfides **1c** and **2c**.[15] Interestingly, these compounds exhibit a high tendency to react further with an excess of base to give the *p*- and *o*-bis(2-propylthio)benzenes **3** and **4**. In view of other









1a R = SC_6H_5 **2a**
1b R = $SO_2C_6H_5$ **2b**
1c R = $SCH(CH_3)_2$ **2c**

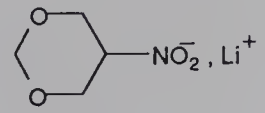
3

4

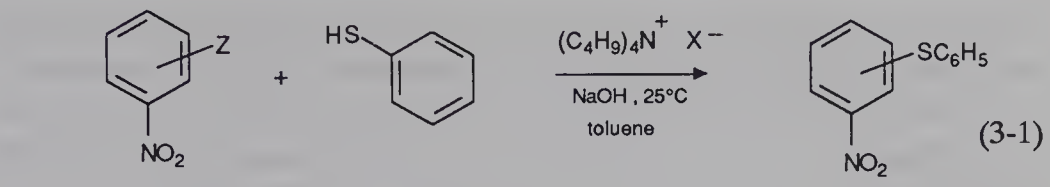
Table 3.1 S_NAr Displacement of the Nitro Group of Various Monosubstituted Nitrobenzenes

Entry	Z	Nucleophile	Solvent	t (°C)	Product yield (%)	Reaction time	Ref.
1	4-NO_2	$C_6H_5S^-Na^+$	HMPA	25	96	24 h[a]	6
2		$C_6H_5SO_2^-Na^+$	DMSO	25	84	50 h	6
3		$(CH_3)_2CNO_2^-Li^+$	DMSO	25	75	3h	6
4			DMSO	20	89	35 min	19
5		$CH_3COCH_2^-K^+$	NH_3	–70	59	1.5 h	22
6		$C_2H_5COCH(CH_3)^-K^+$	NH_3	–70	97	1 h	22
7		$[^{18}F^-]Rb^+$	DMSO	110	87	20 min	33a
8	2-NO_2	$C_6H_5S^-Na^+$	HMPA	25	80	18 h[a]	6
9		$C_6H_5SO_2^-Na^+$	HMPA	25	85	1.5 h	6
10		$F^-NBu_4^+$	THF	25	100	1.5 h	34
11	3-NO_2	$C_6H_5S^-Na^+$	HMPA	25	88	24 h	6
12		$CF_3CH_20^-Na^+$	HMPA	25	93	18–20 h	50
13	4-$CO_2C_2H_5$	$C_2H_5O^-Na^+$	HMPA	25	81	30 min	6
14		$C_6H_5CH_2S^-Na^+$	HMPA	25	88	30 min	6
15	4-CO_2CH_3	$CH_3O^-Na^+$	DMF	131	81	1.5 h	43

Table 3.1 (*Continued*)

Entry	Z	Nucleophile	Solvent	t (°C)	Product yield (%)	Reaction time	Ref.
16		$CF_3CH_2O^-Na^+$	HMPA	25	73	18–20 h	50
17	4-COC_6H_5	$CF_3CH_2O^-Na^+$	HMPA	25	70	18–20 h	50
18		$C_6H_5O^-Na^+$	HMPA	25	83	24 h	6
19		$(CH_3)_2CNO_2^-Li^+$	HMPA	25	78	24 h	6
20	4-CN	$CF_3CH_2O^-Na^+$	HMPA	25	95	18–20 h	50
21		$CF_3CH(CH_3)O^-Na^+$	HMPA	90	78	18–20 h	50
22		$C_6H_5SO_2^-Na^+$	HMPA	80	67	48 h	6
23		$(CH_3)_2CNO_2^-Li^+$	HMPA	25	82	12 h	6
24		$(CH_3)_2CNO_2^-NBu_4^+$	DMSO	20	62	3 h	19
25			HMPA	20	78	24 h	74
26	2-CN	$[^{18}F^-]\ Rb^+$	DMSO	150	85	20 min	33a
27	3-CN	$CF_3CH_2O^-Na^+$	HMPA	50	84	18–20 h	50
28	2-CF_3	$CF_3CH_2O^-Na^+$	HMPA	25	68	18–20 h	50
29	4-$SO_2C_6H_5$	$CH_3S^-Na^+$	HMPA	25	61	15 min	6
30		$(CH_3)_2CNO_2^-Li^+$	HMPA	25	76	12 h	6
31	4-$SO_2N(C_2H_5)_2$	$CF_3CH_2O^-Na^+$	HMPA	25	79	18–20h	50

[a]Reaction might possibly be complete in much shorter time.

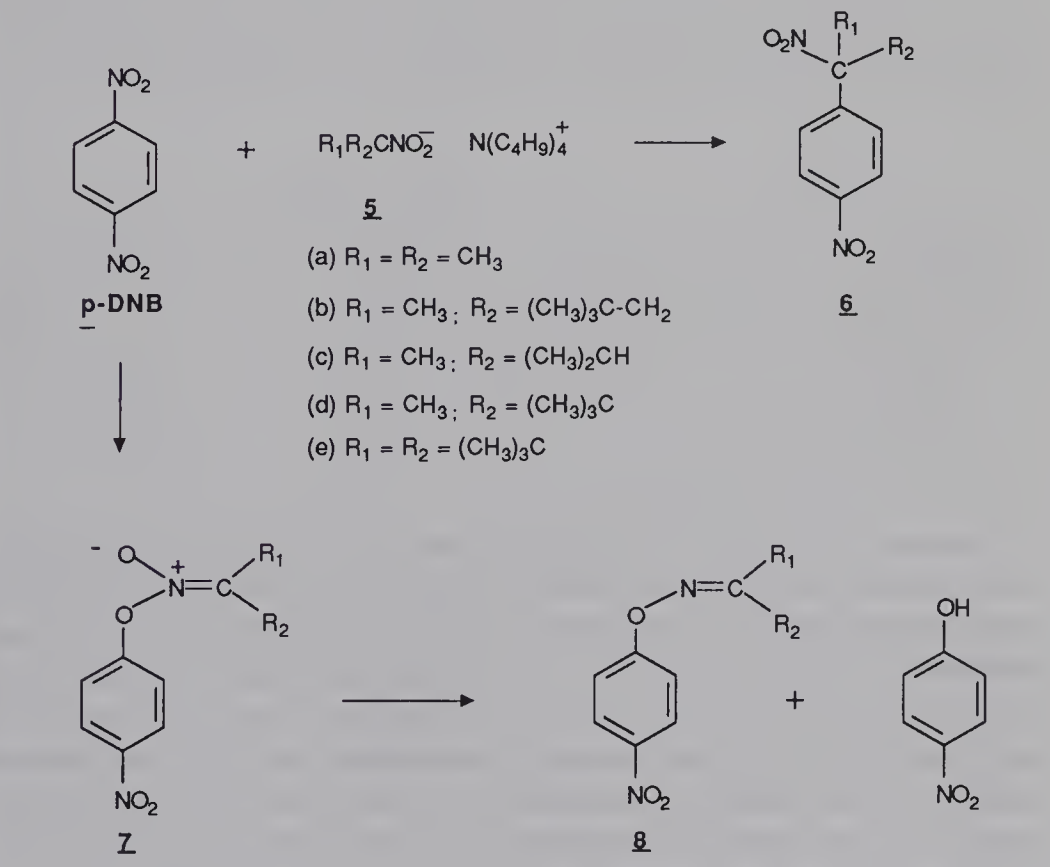


(3-1)

Z = 2-F , 2-Cl , 2-Br , 2-I,
4-F , 4-Cl , 4-Br , 4-I

findings of this sort involving thiomethoxide ion (see below),[16] this behavior suggested that an ortho or para thioether function provides enough activation to promote the displacement of a second nitro group. This result has made a number of poly(alkylthio) benzenes readily available. The diarylsulfides **1a** and **2a** have also been obtained in good yields from the reactions of *p*- and *o*-halonitrobenzenes with thiophenoxide ion under PTC conditions.[17,18] Equation 3-1 is representative of these reactions.

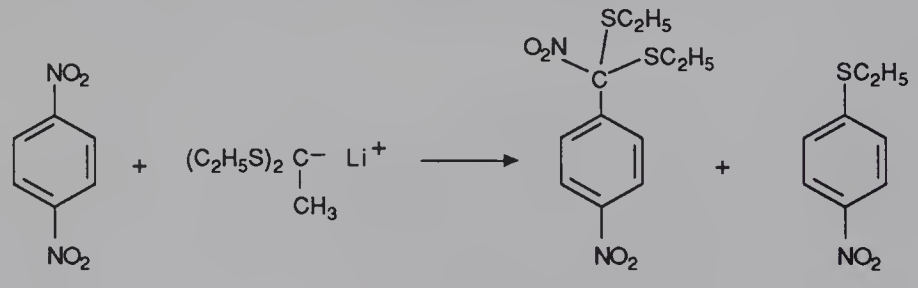
Reactions of *p*-DNB with many carbanions proceed very efficiently in dipolar aprotic solvents or in solvents like ammonia (entries 3–6 in Table



Scheme 3.1.

3.1).[6,19] For example, the reactions with the tetrabutylammonium salts of 2-nitropropane (**5a**) and 2-nitro-4,4-dimethylpentane (**5b**) are complete in a few minutes at 20°C in DMSO or acetone and give good yields of the expected C-substituted products: for example, *p*-(1-methyl-1-nitroethyl)-nitrobenzene (**6a**, in 73–89% yields) and *p*-(1,3,3-trimethyl-1-nitrobutyl)nitrobenzene (**6b**, in 70% yield) (Scheme 3.1).[19] Under comparable experimental conditions, the reactions of the lithium salts of **5a** and **5b** take more time but similar yields of **6a** and **6b** are obtained.[19] Interestingly, the salts **5c**, **5d**, and **5e** of the sterically hindered 3-methyl-2-nitrobutane, 3,3-dimethyl-2-nitrobutane, and 2,4-dimethyl-3-nitropentane, respectively, give low or negligible yields of the corresponding *C*-arylates **6c**, **6d**, and **6e**. In these instances, **5c**, **5d**, and **5e** attack *p*-DNB via an oxygen atom of the NO_2 group to give the *aci*-nitronate esters **7**, which undergo decomposition into the oxime ethers **8** and *p*-nitrophenol. The average yields of **8c**, **8d**, and **8e** which form as Z and E isomers, are about 40%.[19,20]

The reaction of the 1,1-bis(ethylthio)ethyl lithium salt **9** with *p*-DNB at –15°C in DMF gives 1,1-bis(ethylthio)-1-(*p*-nitrophenyl)ethane **10** in 56% yield.[21] Under the experimental conditions used, partial cleavage of the basic reagent to ethanethiolate occurs, with the result that an appreciable formation of the *p*-nitrophenyl ethyl sulfide **11** (28%) is also observed (eq. 3-2).

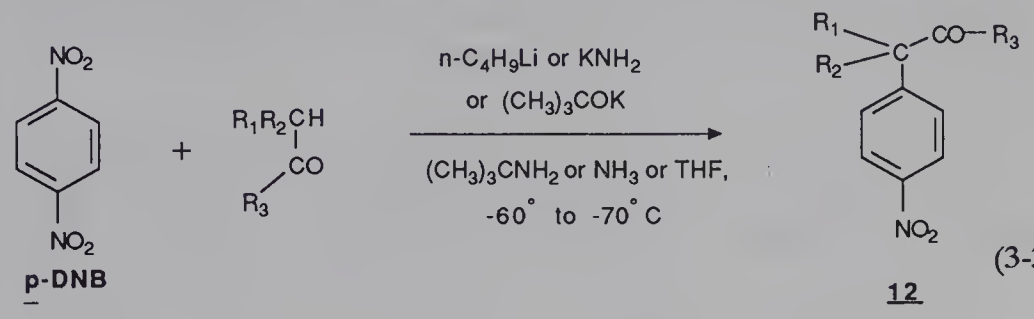


(3-2)

p-DNB **9** **10** **11**

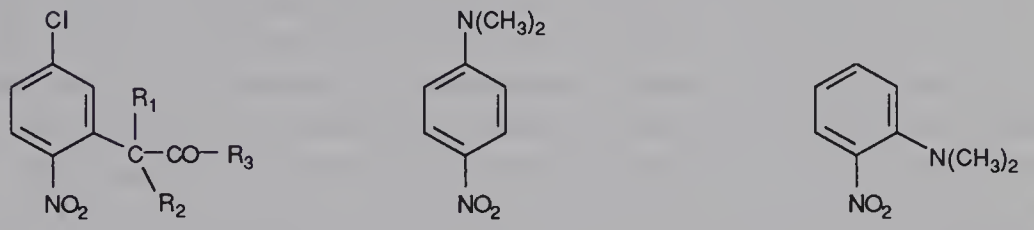
Iwasaki *et al.* described the displacement of an NO_2 group of *p*-DNB with carbanions derived from a large number of ketones, esters, and nitriles. The reactions occurred at low temperatures (~ –70°C) in either *t*-butylamine, liquid ammonia, or THF in the presence of a strong base (e.g., *t*-BuOK, *n*-butyl-lithium, or KNH_2).[22] Good to excellent yields of the C-substituted products **12** were obtained for reaction times of 90 minutes or less. In some instances, addition of small amounts of HMPA or N,N,N′,N′-tetramethylethylenediamine was helpful to achieve substitutions carried out in THF. Some of the carbon acids used in the reactions are indicated in eq. 3-3. A significant result is the failure to obtain similar substitution products by

reaction of the carbanions with *p*-chloronitrobenzene under similar experimental conditions.[23,24] In these instances, the C-substitutions occur at the hydrogen-bearing carbon ortho to the NO_2 group to give the 2-substituted 4-chloronitrobenzenes **13**.



(3-3)

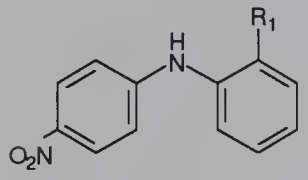
$R_1R_2CHCOR_3$ = acetone , 3-pentanone , 3-methyl-2-butanone cyclopentanone , cyclohexanone , ethyl acetate t-butyl acetate



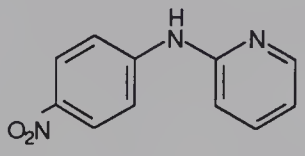
The use of HMPA to effect *N,N*-dimethylation of an aromatic substrate via an S_NAr pathway has received much attention in synthesis.[25–27] Upon heating HMPA solutions of *p*-DNB or *o*-DNB at temperatures in the range of 150–230°C, the corresponding *N,N*-dimethyl para- and ortho-nitroanilines **14** and **15** are formed in high yields.[26,27] Good conversion of *p*- and *o*-fluoro- or chloronitrobenzenes was also achieved.[26,27] It is believed that HMPA may have some ionic character at elevated temperatures, thereby being in equilibrium with *N,N*-dimethylamino anions.[27] These would be the active nucleophilic species in the S_NAr substitutions.

Substitutions of NO_2 in *p*-DNB by aniline and 2-aminopyridine to give **16a** and **17** were successfully achieved under conditions similar to those used for carbon acids shown in eq. 3-3.[22] Another convenient synthesis of diarylamines was recently reported.[28a] Gorvin found that a number of anilines whose N-acidity is enhanced by ortho or para electron-withdrawing groups (e.g., NO_2, CN, C_6H_5CO) in dipolar aprotic solvents (DMSO or DMF) undergo sufficient activation by potassium carbonate. Apparently, appreciable development of negative charge on the nitrogen atom occurs, to effect selectively the S_NAr departure of an NO_2 group of *o*-DNB and *p*-DNB. For example,

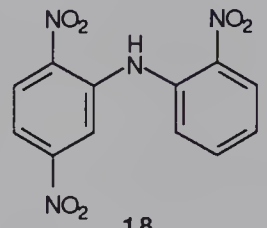
2,4′-dinitrodiphenylamine **16b** was obtained in 65–70% yield upon treatment of *p*-DNB with *o*-nitroaniline.[28] No formation of products (e.g., **18**) arising from nucleophilic displacements of hydrogen was observed, in contrast to previous observations in experiments involving *t*-BuOK in HMPA.[29] Similar syntheses have been successfully achieved through displacement of the fluorine atom of *o*- and *p*-nitrofluorobenzenes.[28b]



16a $R_1 = H$
16b $R_1 = NO_2$

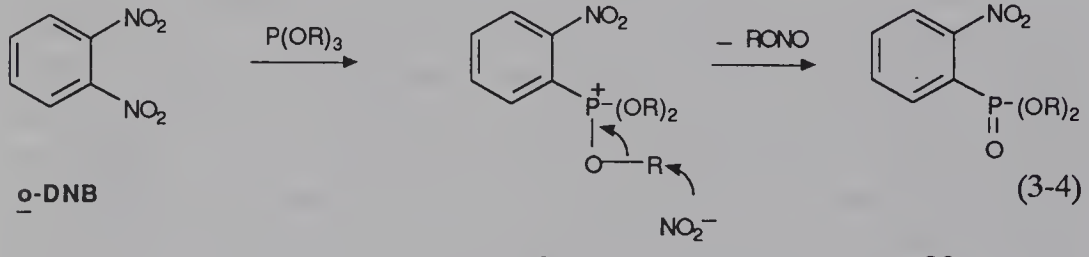


17



18

Reactions of *o*-DNB and *p*-DNB with tervalent phosphorus nucleophiles have been investigated.[30] Treatment of *o*-DNB with trimethyl, triethyl, and triisopropyl phosphites in boiling acetonitrile afford the dialkyl *o*-nitrophenylphosphonates **20** in high yields. As shown in eq. 3-4, the reactions proceed via initial S_NAr substitution of NO_2 to give the phosphonium salts **19**, which then undergo dealkylation to the phosphonate esters **20**.[30] Similar syntheses involving reaction of *o*-DNB with diethyl methylphosphonite and ethyl diphenylphosphonite were also successful.[30] Surprisingly, *p*-DNB did not react to an appreciable extent under comparable conditions.[30]



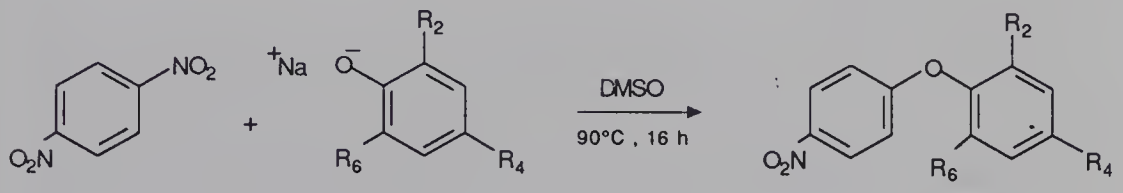
o-DNB (3-4)

19 **20**

(a) $R = CH_3$; (b) $R = C_2H_5$; (c) $R = (CH_3)_2CH$

In DMSO, *p*-DNB undergoes facile substitutions with a number of phenoxide ions, including several hindered and therefore weakly nucleophilic 2,6-disubstituted phenoxides, to give the hindered diphenyl ethers **21**.[31] The most favorable experimental conditions, and the yields obtained in the various reactions studied, are described in eq. 3-5. It may be, however, that some of these reactions proceed in part via a radical mechanism.[31] The reaction of *p*-cyanophenol with potassium fluoride results in the formation of a remarkably stable strongly hydrogen-bonded complex in which the negative charge

appears to be essentially localized on the oxygen atom.[32] This complex has proved to be an efficient nucleophile for an S_NAr synthesis of some 4-cyanodiphenyl ethers. For example 4-cyano-2′-nitrodiphenyl ether was obtained in 95% yield upon treatment of *o*-DNB with the preformed complex at 110°C in DMSO.[32]



p-DNB

	% yield
(a) $R_2 = R_6 = Br$, $R_4 = CH_3$	65
(b) $R_2 = R_6 = F$, $R_4 = H$	54
(c) $R_2 = R_6 = Cl$, $R_4 = H$	71
(d) $R_2 = R_6 = CH_3$, $R_4 = H$	38
(e) $R_2 = R_6 = i\text{-}C_3H_7$, $R_4 = H$	76
(f) $R_2 = R_6 = OCH_3$, $R_4 = H$	90
(g) $R_2 = CH_3$, $R_6 = CH_2\text{-}CH{=}CH_2$, $R_4 = H$	54

21 (3-5)

Use of dipolar aprotic conditions makes it feasible to carry out S_NAr substitutions of *o*- and *p*-DNB with fluoride ion.[33,34] Treatment of these compounds with rubidium ^{18}F-fluoride for 20 minutes at temperatures of 110–150°C in DMSO, or more simply with "anhydrous" tetrabutylammonium fluoride at room temperature in THF,* affords [4-^{18}F]- and [2-^{18}F]fluoronitrobenzenes in high yield (eq. 3-6 and entries 7 and 10 in Table 3.1).[33a,34] These fluorodenitration reactions constitute a more efficient labeling procedure than the S_NAr exchange reactions of *p*- and *o*-fluoronitrobenzenes with rubidium fluoride [^{18}F],[35] and the method has been extended to the preparation of various ^{18}F-labeled radiopharmaceuticals. A typical example is the synthesis of [^{18}F] spiroperidol from its inactive nitro analogue.[36] Recently, other convenient syntheses of [4-^{18}F]- and [2-^{18}F]fluoronitrobenzenes were reported which involved displacement of the activated trimethylammonium and dimethylsulfonium groups of 4- and/or 2-nitrophenyltrimethylammonium or dimethylsulfonium salts with cesium fluoride [^{18}F] in DMSO.[33c,d]

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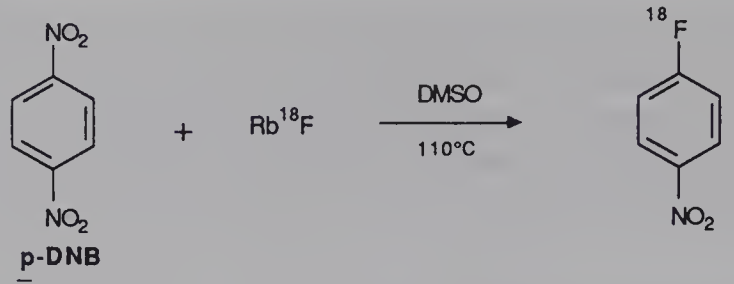
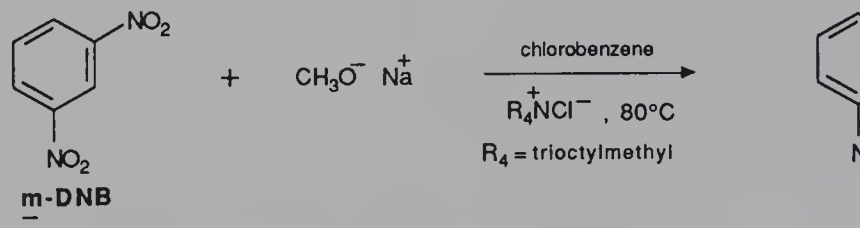
* A discussion of the structure of "anhydrous" quaternary ammonium fluorides has recently been published.[33e]



(3-6)

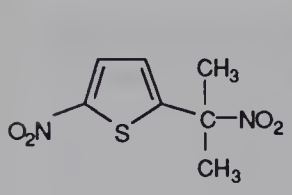
Although a meta-NO_2 group is poorly activating as compared with an ortho- or a para-NO_2 group, a few synthetically useful S_NAr displacements involving *m*-DNB have been reported. Kornblum *et al.* have obtained an essentially complete conversion of *m*-DNB to 3-nitroanisole and 1-nitro-3-(phenylthio)benzene by treatment with CH_3ONa or sodium thiophenoxide (entry 11 in Table 3.1) in HMPA at room temperature.[6] An efficient conversion to *m*-nitroanisole also occurred at 80°C under the PTC conditions described in eq. 3-7.[37] The reaction of potassium fluoride with *m*-DNB in HMPA at 180°C for 48 hours gave 1-fluoro-3-nitrobenzene in 45% yield.[38]



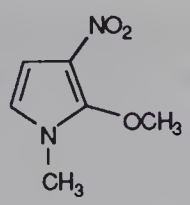
(3-7)

In general, nucleophilic substitutions of 2,5-dinitrofuran proceed similarly to those of *p*-DNB; that is, they occur with clean S_NAr displacement of a nitro group.[39a] This comparison also holds for reactions involving 2,5-dinitrothiophene and 2,5-dinitro-1-alkylpyrroles.[40,41] The S_NAr behavior of 2,5-dinitrothiophene is exemplified by the facile synthesis of 2-(1-methyl-1-nitroethyl)-5-nitrothiophene (**22**) from the reaction with the lithium or tetrabutylammonium salts of 2-nitropropane in DMSO or benzene.[41]

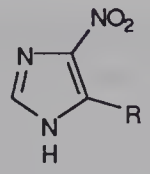
Stegel *et al.* reported that the reaction of 1-methyl-2,3-dinitropyrrole with methoxide ion occurs regiospecifically at the 2-position to produce 2-methoxy-1-methyl-3-nitropyrrole (**23**) in 93% yield.[39b] Exclusive nitro S_NAr displacement of the 5-nitro group occurs in the reactions of 4,5-dinitroimidazole **24a** with sodium sulfide, sodium sulfite, methylamine, dimethylamine, and aniline, which afford the 4(5)-nitroimidazole derivatives **24b**–**24f**.[42] The 4(5)-methoxy and ethoxy compounds **24g** and **24h** have also been obtained from the reactions of **24a** with methoxide and ethoxide ion. However, the latter reactions also produce a small amount of 4(5)-nitroimidazole (**24i**), suggesting that a radical process is involved in these systems.[42]



2.2



2.3



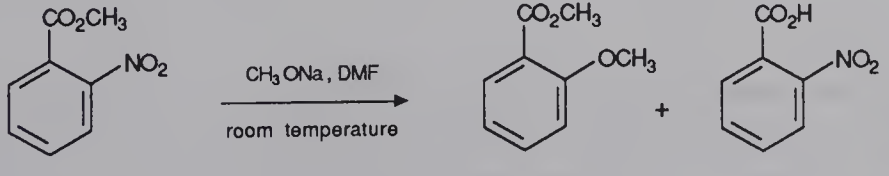
2.4

(a) R = NO_2 ; (b) R = SH ; (c) R = SO_3Na
(d) R = $NHCH_3$ (e) R = $N(CH_3)_2$; (f) R = NHC_6H_5
(g) R = OCH_3 ; (h) R = OC_2H_5 ; (i) R = H

3.2.2 Mononitro-substituted Benzenes and Heteroarenes

S_NAr displacements of an NO_2 group activated by a single ortho or para functionality other than nitro have received particular attention in synthesis. A variety of carbonyl groups (CO_2CH_3, $CO_2C_2H_5$, $COCH_3$, COC_6H_5, CHO, etc.), as well as the cyano group and different sulfonyl functionalities (e.g., SO_2R, SO_2Ar) have proved to be particularly effective in promoting such substitutions. This is shown in Table 3.1, in which several representative examples are summarized.

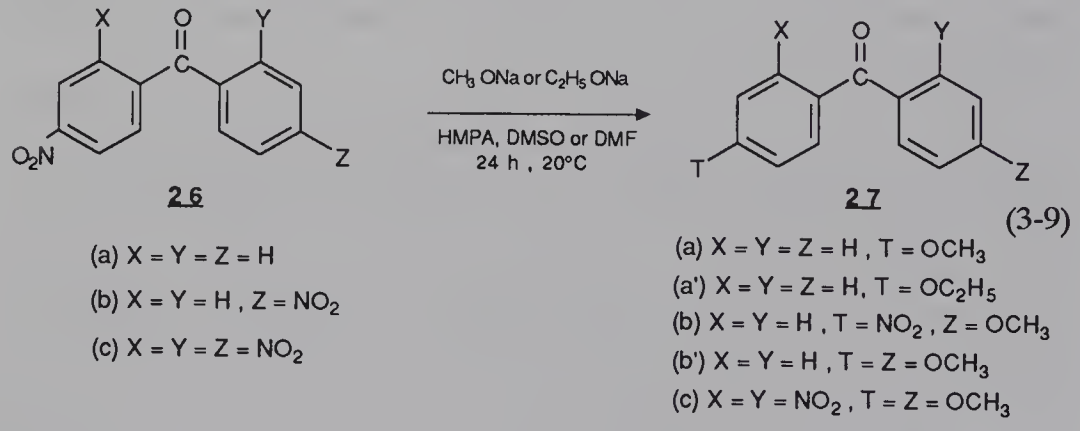
Substitutions involving strong to weak oxygen nucleophiles have been extensively studied. Kornblum reported that treatment of ethyl 4-nitrobenzoate with sodium ethoxide in HMPA at 25°C afforded almost quantitatively ethyl *p*-ethoxybenzoate (entry 13 in Table 3.1).[6] Similarly, methyl and isobutyl 4-nitrobenzoates underwent predominantly S_NAr displacement of their nitro group with methoxide and isobutoxide, respectively, in DMF.[43] In contrast, an attempted reaction of methyl *o*-nitrobenzoate with CH_3O^- yielded a mixture of the expected ester **2.5** and of *o*-nitrobenzoic acid (eq. 3-8). The latter arises from a competing S_N2 displacement on the ester group.[43] It may be recalled that the synthesis of ortho- and para- methoxybenzonitriles could be readily achieved from the reactions of sodium methoxide with ortho- and para-nitrobenzonitriles, respectively, in methanol.[44]



(3-8)

2.5

Gorvin found that reactions of 4-nitrobenzophenone (**26a**) with methoxide or ethoxide produced almost quantitative yields of the corresponding 4-alkoxybenzophenones **27a** and **27a'** when conducted at 20°C for 24 hours in HMPA, DMSO, or DMF (eq. 3-9).[45] Similarly, treatment of 4,4'-dinitrobenzophenone (**26b**) with a stoichiometric amount of $NaOCH_3$ yields the monomethoxy derivative **27b**. Further reaction of **27b** with a second equivalent of $NaOCH_3$ affords the 4,4'-dimethoxybenzophenone (**27b'**).[46] Under similar reaction conditions, 2-nitrobenzophenone did not react, while 2,2'-dinitrobenzophenone suffered replacement of only one nitro group to produce 2-methoxy-2'-nitrobenzophenone in a 93% yield. The reluctance of the ortho nitro group to depart in these systems was also observed with the more activated 2,2',4,4'-tetranitrobenzophenone (**26c**) whose para nitro groups could be preferentially displaced to obtain 4,4'-dimethoxy-2,2'-dinitrobenzophenone (**27c**) in excellent yield.[46] Related reactions are the facile substitutions by methoxide ion of the nitro group of 1-nitro- and 3-nitroxanthones in dipolar aprotic solvents.[45] The reaction of the more activated thioxanthone **28a** with methoxide ion to give **29a** is quantitative in refluxing methanol (eq. 3-10).[47]



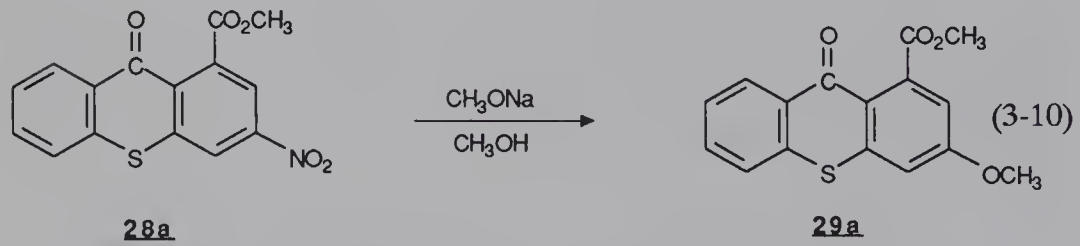
26

(a) X = Y = Z = H
(b) X = Y = H , Z = NO_2
(c) X = Y = Z = NO_2

27

(a) X = Y = Z = H , T = OCH_3
(a') X = Y = Z = H, T = OC_2H_5
(b) X = Y = H , T = NO_2 , Z = OCH_3
(b') X = Y = H , T = Z = OCH_3
(c) X = Y = NO_2 , T = Z = OCH_3

(3-9)

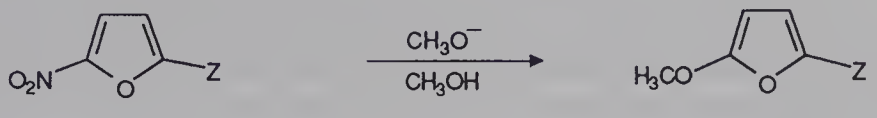


28a **29a**

(3-10)

In heteroaromatic series, the S_NAr substitution of the nitro group of 5-nitro-2-furancarboxaldehyde (**30a**) and methyl 5-nitro-2-furancarboxylate (**30b**) by methoxide ion occurred in methanol, affording the 5-methoxy derivatives **31a** (isolated as the oxime) and **31b**. (eq. 3-11).[48,49] Substitution of the

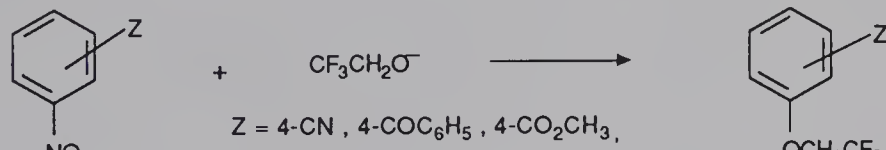
nitrile analogue **30c** did not proceed satisfactorily because of a preferred reaction at the cyano group.[49]



(3-11)

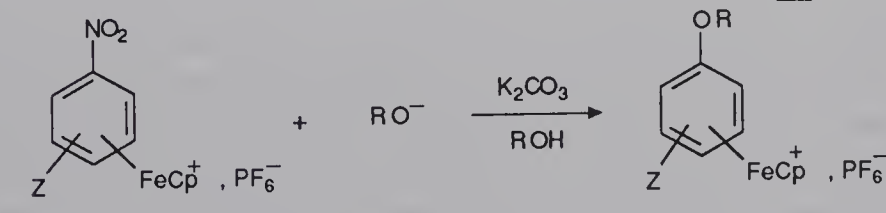
30 (a) Z = CHO ; (b) Z = CO_2CH_3 ; (c) Z = CN **31**

As indicated in eq. 3-12, a wide range of monosubstituted nitrobenzenes undergo facile S_NAr displacement of their nitro group upon treatment with the weakly basic 2,2,2-trifluoroethoxide ion at or near room temperature in HMPA.[50] Especially good yields (65–80%) of the fluoroalkoxylated products **32** have been obtained by supplying the activation by para and/or ortho cyano, trifluoromethyl, phenylsulfonyl, and phenylcarbonyl groups (entries 17, 20, 28, and 31 in Table 3.1). Even poorly activating functionalities like meta nitro and meta cyano groups were sufficiently effective in providing synthetically useful processes at 25°C (entries 12 and 27 in Table 3.1).[50] Similar reactions involving a fluoro instead of a nitro leaving group proceeded equally well, while those involving chloro leaving group substrates required high temperatures (150°C) to occur satisfactorily.[51,52] The reactivity of other fluoroalkoxide ions (e.g., 2,2,3,3,3-pentafluoropropoxide and α,α,α-trifluoroisopropoxide) was also investigated, emphasizing the importance of these S_NAr processes as a synthetic entry to fluoroalkoxy aromatics.[50] Trifluoroethoxylation of a benzene or toluene ring via S_NAr displacement of a nitro group activated by complexation to the cyclopentadienyliron moiety has been successfully carried out in the presence of potassium carbonate in trifluoroethanol (eq. 3-13).[53a] The strong electron-withdrawing character of the $FeCp^+$ moiety allowed the



(3-12)

32



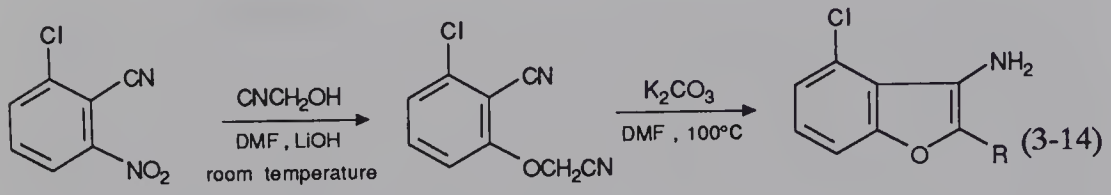
(3-13)

Z = H , o-CH_3 , m-CH_3 , p-CH_3

R = CH_3 , C_2H_5 , CF_3CH_2

achievement of similar reactions with most common alkoxide ions (e.g., CH_3O^- and $C_2H_5O^-$).[53b]

The cyanomethyl ether **33** was obtained by the S_NAr reaction of 2-chloro-6-nitrobenzonitrile with glycolonitrile anion in aqueous DMF.[54] Cyclization of **33** with potassium carbonate afforded the 3-amino-4-chloro-2-cyanobenzofuran (**34**) whereas treatment with alcoholic potassium hydroxide gave the carboxamide **35** (eq. 3-14).[54]

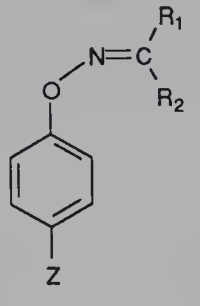


(3-14)

33

34 R = CN
35 R = $CONH_2$

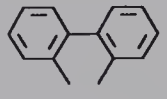
The nitro group of various *o*- and *p*-nitro-substituted benzenes is displaced in S_NAr reactions involving various aldoxime and ketoxime anions.[5,55,56] In contrast to the *O*-arylketoximes **36**, which were isolated,[56] the resulting *O*-arylaldoximes **37** were not stable, since they were rapidly cleaved by attack of a second oximate anion, yielding the phenols **38** related to the starting nitroaromatics and the nitriles related to the oxime anions (eq. 3-15).[5] Conversions of *p*-nitrobenzonitrile and ethyl *p*-nitrobenzoate into *p*-cyanophenol and ethyl *p*-hydroxybenzoate thus occurred in high yields.[5]



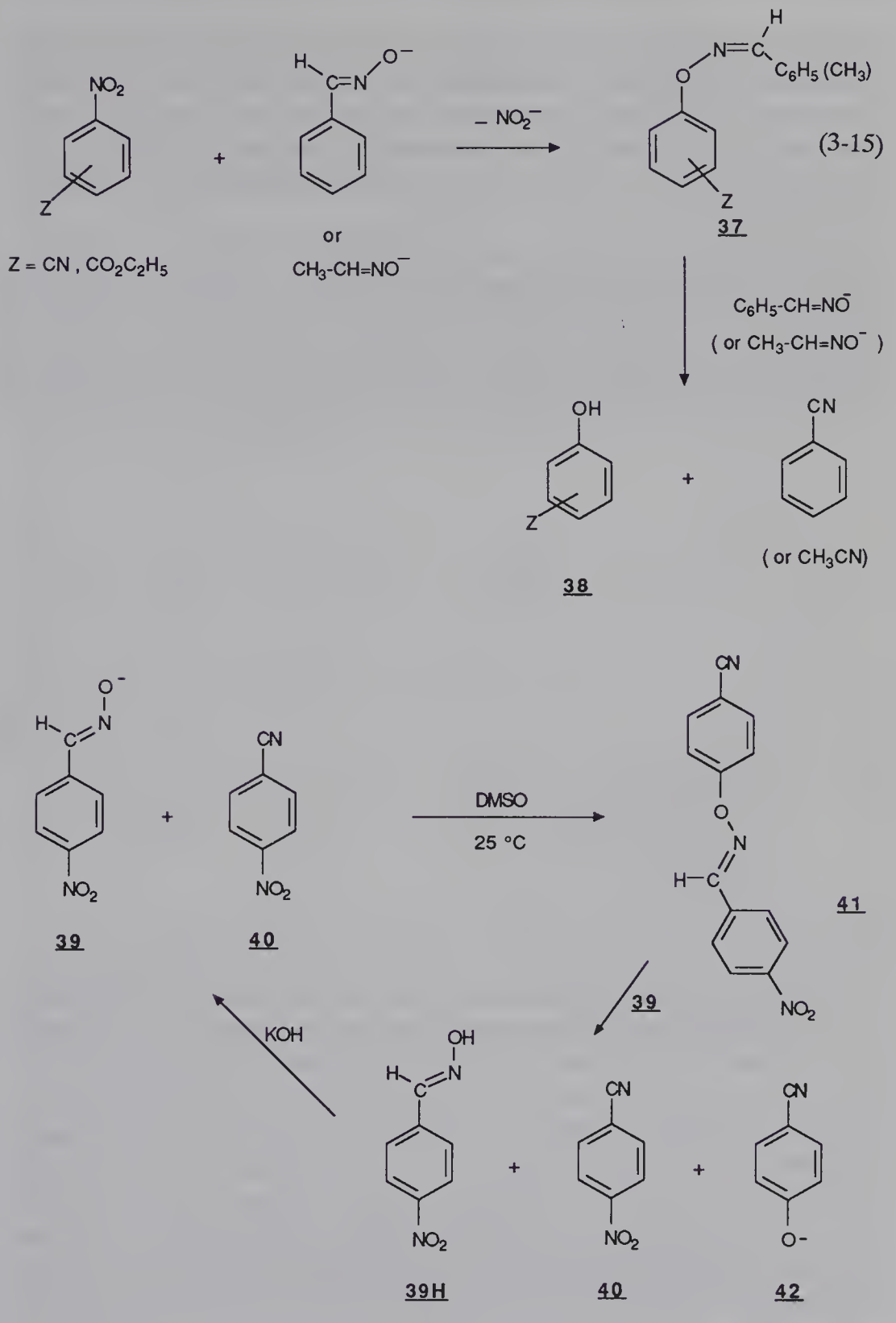
36

Z = CN , CO_2CH_3 , COC_6H_5 , CHO

$R_1 = R_2 = CH_3$, C_6H_5 , $-(CH_2)_5-$,



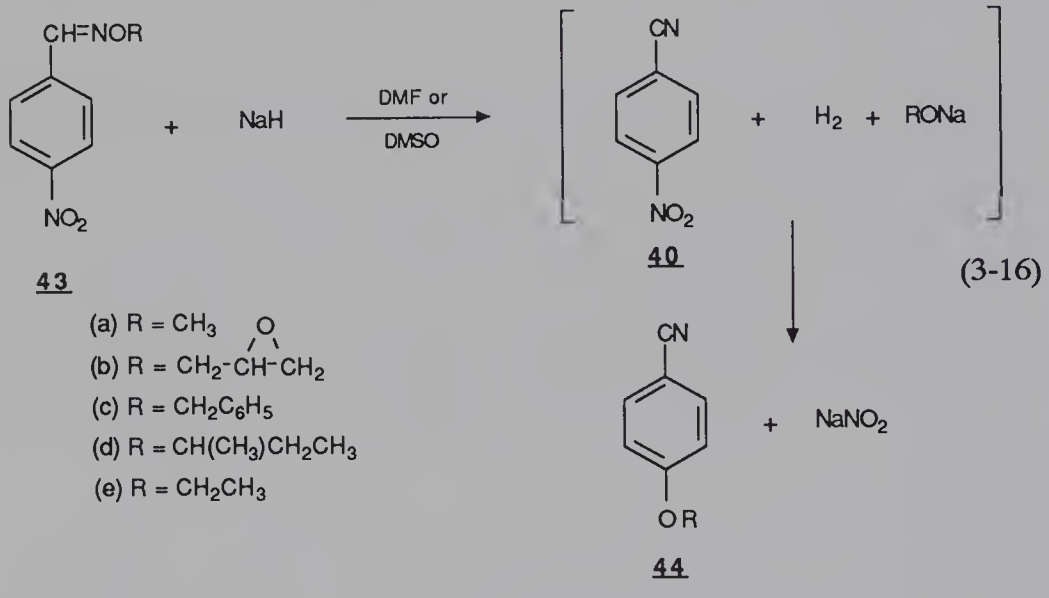
A modification of the process shown in eq. 3-15 has provided an even more facile preparation of *p*-cyanophenol.[55] A DMSO solution consisting of equimolar amounts of the sodium salt of (*E*)-4-nitrobenzaldoxime (**39**) and of potassium hydroxide and of a small amount of *p*-nitrobenzonitrile (**40**) was prepared. Reaction of **39** with **40** yielded *O*-(4-cyanophenyl)-4-nitrobenzaldoxime (**41**), which underwent cleavage as a result of attack by a second


NO2
Z
Z = CN , CO2C2H5
+
H
C=N
O−
or
CH3-CH=NO−
− NO2−
H
N=C
C6H5 (CH3)
O
Z
37
(3-15)
C6H5-CH=NO−
(or CH3-CH=NO−)
OH
Z
38
+
CN
(or CH3CN)
O-
H
C=N
NO2
39
+
CN
NO2
40
DMSO
25 °C
CN
O
N
H
C
NO2
41
39
KOH
OH
H
C=N
NO2
39H
+
CN
NO2
40
+
CN
O-
42

Scheme 3.2.

oximate ion (Scheme 3.2). The cleavage produced 4-cyanophenoxide anion (**42**), regenerating the nitronitrile **40**, which, reentering the cycle, acted as a chain carrier for the process, and also produced the free oxime **39,H**, which was reconverted to the reactive oximate ion **39** by reaction with KOH. A similar cycle involving (*E*)-2-nitrobenzaldoxime and *o*-nitrobenzonitrile afforded *o*-cyanophenol.[55]

A study concerned with 4-nitrobenzaldoxime ethers **43** is relevant.[57] Mauleon *et al.* have shown that treatment of various *O*-alkyl ethers of **39** with bases in DMF or DMSO afforded the corresponding 4-alkoxybenzonitriles **44** in good yields (eq. 3-16). In this case, initial elimination of the alkoxide moiety from the oxime ethers **43** precedes the S_NAr displacement of the nitro group of the resulting *p*-nitrobenzonitrile **40** by the alkoxide ions.[57]



43

(a) R = CH_3
(b) R = CH_2-CH-CH_2 (O)
(c) R = $CH_2C_6H_5$
(d) R = $CH(CH_3)CH_2CH_3$
(e) R = CH_2CH_3

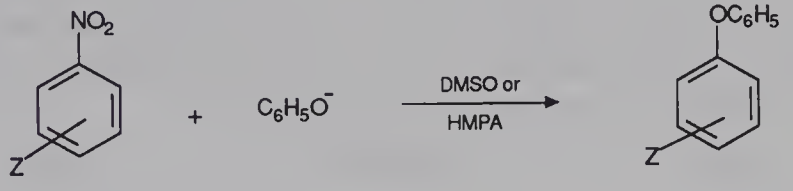
40

44

(3-16)

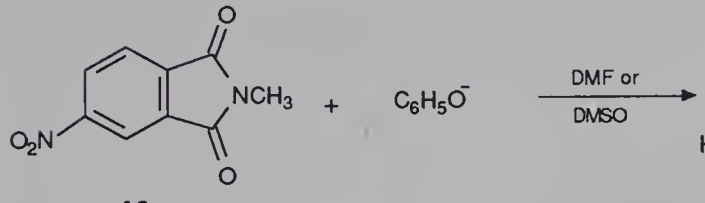
Several nitro S_NAr displacements by phenoxide ions have been carried out with excellent yields in dipolar aprotic media. Equation 3-17 describes the facile formation of the phenoxy derivatives **45** from ethyl *p*-nitrobenzoate, *o*- and *p*-benzonitriles, phenyl *o*-nitrobenzoate, or 4-nitrobenzophenone (26a)[6,31,32,58–62] The mobility of the nitro group in various nitrophthalic systems has received much attention.[59–63] Thus, treatment of 3- and 4-nitro N-substituted phthalimides (e.g., **46**) with phenoxide salts in DMF or DMSO gave high yields of the corresponding phenoxyphthalimides e.g. **47** (eq. 3-18).[59] Caswell and Kao have similarly obtained N-substituted 3-methoxy-phthalimides by the reaction of methoxide ion with the corresponding 3-nitrophthalimides.[63] In general, nitrophthalic esters (e.g., diethyl 4-nitrophthalate or 2-nitroisophthalate) undergo facile displacements of their

nitro group,[58,60] but side reactions involving nucleophilic attack on the ester group are sometimes important, especially for 3-nitrophthalate esters.[60] Electron transfer processes may also lower the yields of the displacement reactions.[61] Attempted reactions of 3- and 4-nitrophthalic anhydrides with sodium phenoxide in DMF at room temperature led to anhydride ring opening with no detectable nitro displacement.[60] In these instances, the desired phenoxy-substituted phthalic anhydrides were more appropriately prepared from S_NAr reactions involving 3- and 4-fluorophthalic anhydrides.[5] Useful polymers were obtained by polycondensation of bis(nitrophthalimides) and bisphenols in DMSO.[58b,64] Treatment of 4,4′-dinitrobenzophenone (**26b**) with alkali bis(phenoxides) has also afforded a number of interesting high molecular weight polyether ketones.[65]



(3-17)

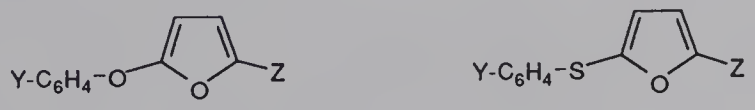
Z = 4-$CO_2C_2H_5$,2-$CO_2C_6H_5$, 4-CN ,2-CN , 4-COC_6H_5 **45**



(3-18)

46 **47**

S_NAr substitution of the nitrofurans **30a–c** (see eq. 3-11) with various phenoxide ions in DMSO gave a series of phenoxy compounds **48** in good yields.[49,66] Similar displacements with various thiophenoxide ions in DMF or acetonitrile to yield **49** were also successful with **30b** and **30c**.[49,66]

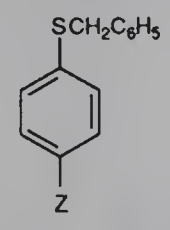


48 Z = CHO , CO_2CH_3 , CN **49**

Y = H ,4-NO_2 , 4-CO_2CH_3 ,4-Cl ,4-OCH_3 ,4-CH_3 ,3-NO_2 ,3-Cl , 3-OCH_3 ,3-CH_3 ,2-NO_2 ,2-CO_2CH_3 ,2-Cl ,2-OCH_3 ,2-CH_3

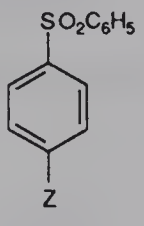
Many S_NAr displacements of the NO_2 group of substituted mononitrobenzenes by sulfur nucleophiles proved to be synthetically useful. For

example, the benzyl thioethers **50a–c** were readily obtained from the reaction of benzylthiol anion with 4-nitrobenzophenone (**26a**) and methyl and ethyl *p*-nitrobenzoates, respectively, in HMPA or DMF.[6,67] The reactions of *p*-nitrobenzonitrile with sodium benzenesulfinate to give 4-cyanophenyl phenyl sulfone (**51a**), and of 4-nitrophenyl phenyl sulfone with thiomethoxide ion to give 4-thiomethoxyphenyl phenyl sulfone (**51b**), proceeded very nicely in HMPA.[6] Another interesting reaction carried out in this solvent was the displacement of the meta-activated nitro group of 3,5-bis(trifluoromethyl)nitrobenzene by thiophenoxide ion which gave the diaryl sulfide **52** in 92% yield.[6] Reactions involving dodecylthiolate anion and a number of 2-Z- and 4-Z-substituted nitrobenzenes were attempted, but the expected alkylaryl sulfides were obtained only in low to moderate yields.[67] Recently, Fischer and Kvita have reported that the 3-nitro group of the thioxanthones **28** is readily substituted by *p*-chlorothiophenoxide or heptadecafluorodecylthiolate anions, as well as methanesulfinate and benzenesulfinate anions in DMF, to give the expected S_NAr products **29** (eq. 3-19).[47]



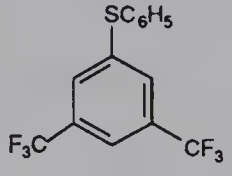
50

(a) Z = COC_6H_5
(b) Z = CO_2CH_3
(c) Z = $CO_2C_2H_5$

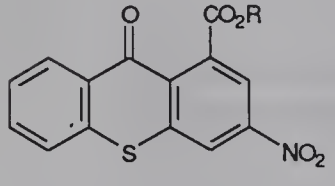


51

(a) Z = CN
(b) Z = SCH_3

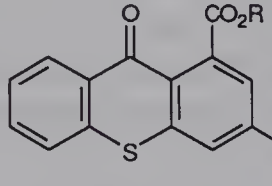


52



28

Nu^- / DMF

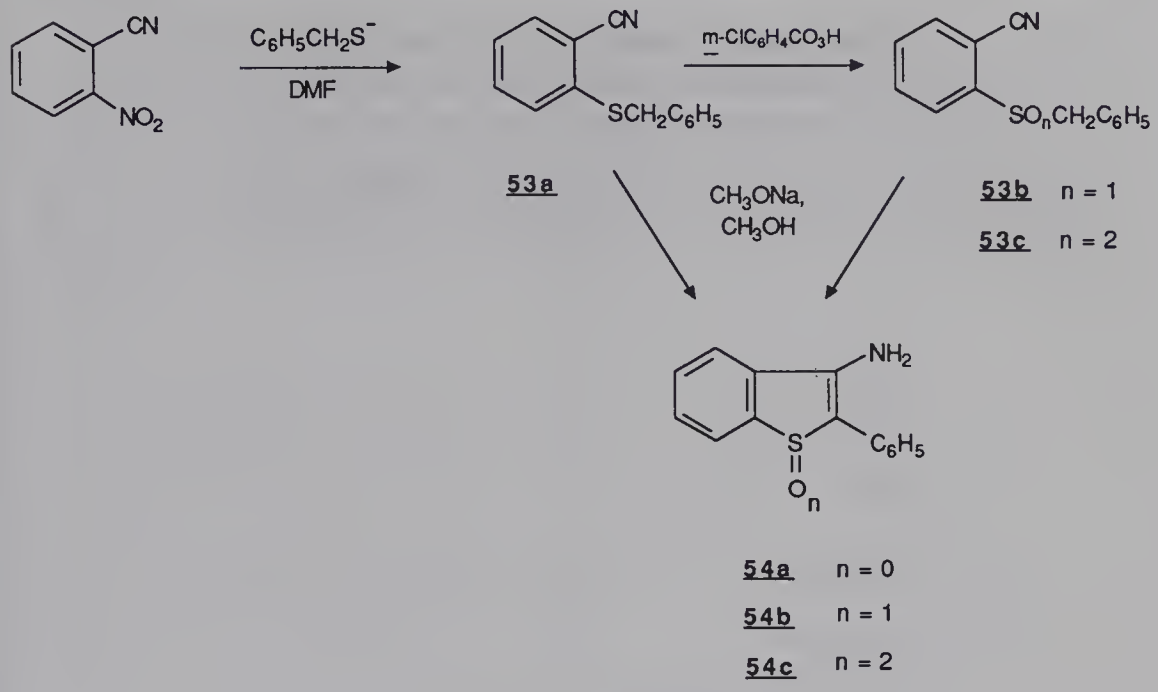


29

(3-19)

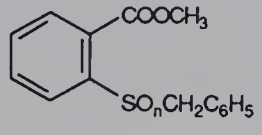
R = CH_3 , Nu^- = 4-Cl-$C_6H_4S^-$
R = C_2H_5 , Nu^- = n-$C_8F_{17}CH_2CH_2S^-$, $CH_3SO_2^-$, $C_6H_5SO_2^-$

The S_NAr substitution of *o*-nitrobenzonitrile with benzylthiol anion in DMF proceeded very well to give the thioether **53a**.[68] Subsequent oxidation of **53a** with *m*-chloroperoxybenzoic acid afforded the sulfoxide **53b** and the sulfone **53c**. All three compounds cyclized in basic media to yield the benzothiophene **54a**, the *S*-oxide and *S,S*-dioxide derivatives **54b** and **54c** (Scheme

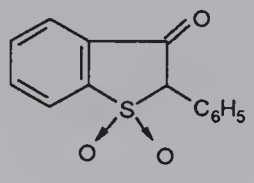


Scheme 3.3.

3.3).[68] The reaction of benzylthiol anion with methyl *o*-nitrobenzoate gave similarly the thioether **55a**, which was oxidized to **55c**. Cyclization of **55c** afforded the *S,S*-dioxide derivative **56**.[68]



55a n = 0
55 n = 2



56

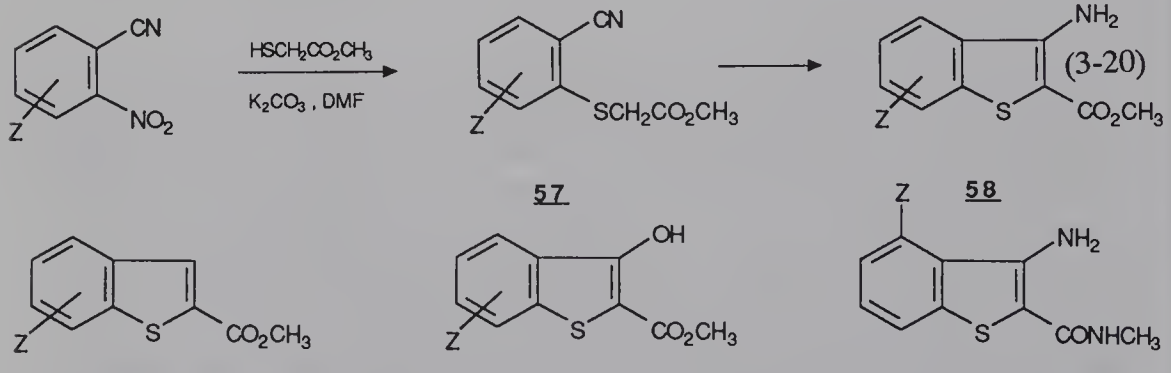
Beck reported that *o*-nitrobenzonitriles undergo facile substitution of their nitro group by methyl thioglycolate, as described in eq. 3-20.[3a] The resulting products **57** were not stable, however, since they rapidly underwent a base-catalyzed cyclization to afford the methyl 3-aminobenzo[*b*]thiophene-2-carboxylates **58** in excellent yields.[3a] The methyl benzo[*b*]thiophene-2 carboxylates **59** and the methyl 3-hydroxybenzo[b]thiophene-2-carboxylates **60** were similarly obtained upon treatment of *o*-nitrobenzaldehydes and methyl *o*-nitrobenzoates, respectively, with the same nucleophile.[3b] An interesting point is that these reactions were remarkably insensitive to the presence of other potential leaving group functionalities such as Cl or a second NO_2 group in the precursor electrophiles. For example, methyl 3-amino-4-nitroben-

Table 3.2. Synthesis of Various Methyl 3-Aminobenzo[*b*]thiophene-2-carboxylates 58 According to Equation 3-20[a]

Z	Yield (%)	Reaction time (h)
H	72	0.5
4-Cl	84	1
6-Cl	72	1
4-OCH_3	35	0.5
4-NO_2	67	0.5
6-NO_2	47	0.5
6-CF_3	69	0.5
4-NO_2-6-CF_3	80	0.12
4-NO_2-6-CH_3	55	0.5

[a]Data reproduced with permission from ref. 3a.

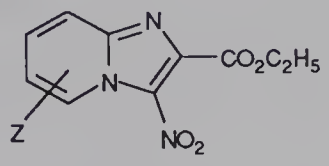
zothiophene-2-carboxylate (**58**; Z = 4-NO_2) and 3-hydroxy-4-nitrobenzothiophene-2-carboxylate (**60**; Z = 4-NO_2) were obtained from 2,6-dinitrobenzonitrile and methyl 2,6-dinitrobenzoate in 67 and 85% yields, respectively.[3] Table 3.2 illustrates the efficiency of the reactions leading to **58**.[3a] In a related process, the amides **61a** and **61b** were prepared from the reaction of mercapto-*N*-methylacetamide with 2-nitrobenzonitrile and 2-chloro-6-nitrobenzonitrile.



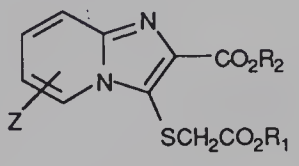
59 **60** **61a** Z = H **61b** Z = Cl

Z = H , 4-NO_2 , 6-NO_2 , 7-NO_2 , 4-Cl , 5-Cl , 6-Cl , 7-Cl , 4-OCH_3 , 7-OCH_3 , 6-CF_3 , 5,6-di(OCH_3) , 4-NO_2-6-CF_3 , 4-NO_2-6-CH_3

Teulade *et al.* described the displacement of the nitro group of some 3-nitroimidazo [1,2-*a*] pyridines **62** with ethyl thioglycolate in the presence of excess lithium hydroxide in DMF.[69] Subsequent hydrolysis of the two ester functions of the resulting thioacetates **63** occurred readily, however, allowing the investigators to obtain the thioacetic acids **64** in good yields. In some instances, the dicarboxylic acids **65** could be also obtained in satisfactory yields.[69]

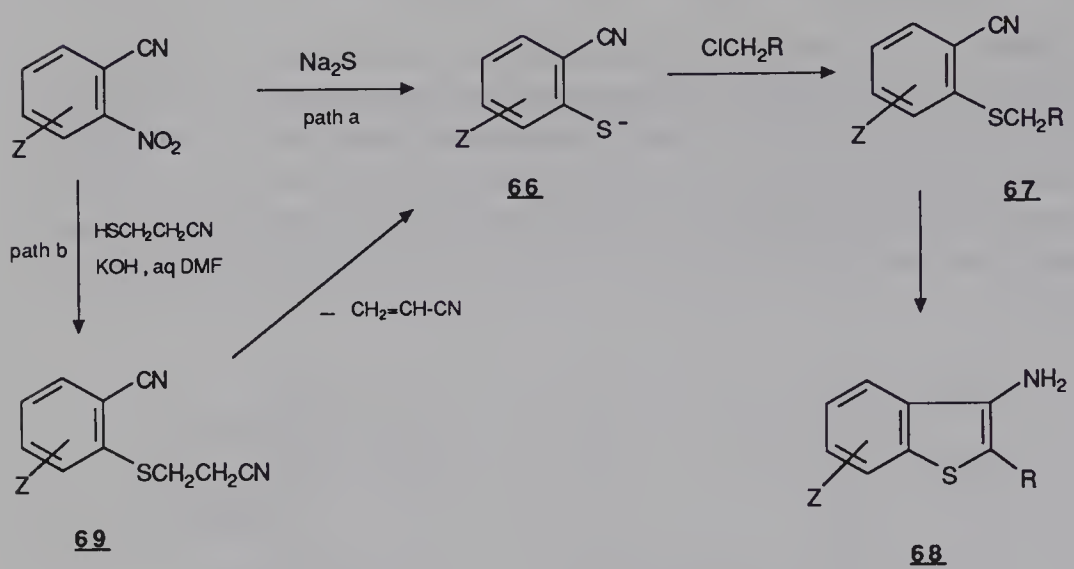


62 Z = H , 5-CH_3 , 6-CH_3 , 6-Cl
6-Br , 7-CH_3 , 8-CH_3



63 $R_1 = R_2 = C_2H_5$
64 $R_1 = H$, $R_2 = C_2H_5$
65 $R_1 = R_2 = H$

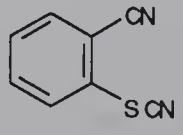
A general and rapid synthesis of a number of 3-aminobenzothiophenes **68**, substituted at the 2-position with a variety of electron-withdrawing functionalities, was reported by Beck. He used 3-mercaptopropionitrile or sodium sulfide as the nucleophilic reagents and various readily available *o*-nitrobenzonitriles as the electrophilic precursors.[4] With sodium sulfide (see path a in Scheme 3.4), initial displacement of the nitro group afforded directly the benzenethiolate anions **66**, which were alkylated *in situ* by the appropriate reagent to yield the thioethers **67**. Subsequent ring closure, catalyzed by excess sodium sulfide present, led to **68**. With 3-mercaptopropionitrile, (see path b in Scheme 3.4), S_NAr displacement of the nitro group of the nitrobenzonitrile precursors gave first the thioethers **69**, which rapidly underwent β-elimination in the basic medium. This resulted in loss of acrylonitrile and formation of the same benzenethiolate anions **66**, formed in path a, which were then allowed to react with the alkylating agents. Path b was used to obtain **68a** and **68b** from *o*-nitrobenzonitrile, since path a worked well only in the presence of a second electron-withdrawing group in the benzene ring. Thus, the 4-chloro derivatives **68c**–**68f** and the 4-nitro derivatives **68g**–**68j** were obtained from 2-chloro-6-nitrobenzonitrile and 2,6-dinitrobenzonitrile, respectively, in yields of 60–84%. Also synthesized by the procedure of path b were the 5-nitro derivatives **68k** and **68l** from 2-chloro-5-nitrobenzonitrile, by a similar process involving activated chlorine displacement.[4] Note the successful identification of the intermediate thioether **69** (Z = 3-Cl) in the 2-chloro-6-nitrobenzonitrile system.[4] The benzenethiolate anion **66** (Z = H), as generated from *o*-nitroben-



Z = H (a) R = CN ; (b) R = $COCH_3$
Z = 4-Cl (c) R = CN ; (d) R = $COCH_3$
(e) R = COC_6H_5 ; (f) R = $CONH_2$
Z = 4-NO_2 (g) R = CN ; (h) R = $COCH_3$
(i) R = COC_6H_5 ; (j) R = $CONH_2$
Z = 5-NO_2 (k) R = CN ; (l) R = COC_6H_5

Scheme 3.4.

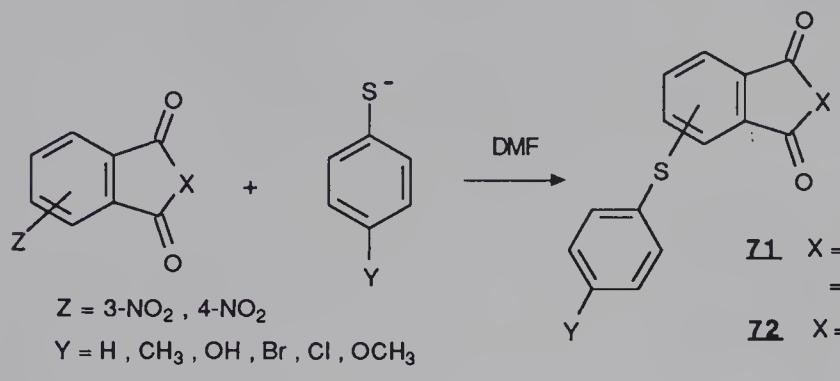
zonitrile in path b, was also allowed to react with excess cyanogen chloride, leading to the isolation of 70 in 72% yield. The procedure was applied to the synthesis of a number of thiocyanic, 2-cyanophenyl esters.[70]



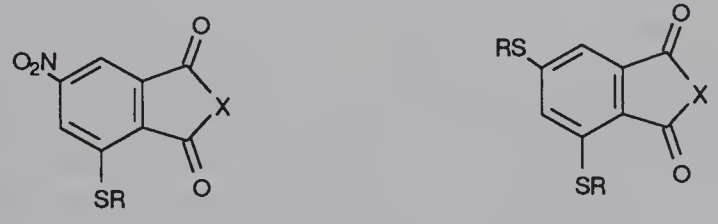
70

The S_NAr reactions of several thiophenoxide anions with 3- and 4-nitro N-substituted phthalimides occurred at room temperature in DMF, yielding the various thiophenoxyphthalimides 71 (eq. 3-21).[71a] Contrasting with the situation for phenoxide nucleophiles, 3- and 4-nitrophthalic anhydrides also undergo S_NAr substitution with ArS^- ions, giving the 3- and 4-thiophenoxyphthalic anhydrides 72.[71b] Because of such competing side processes as attack of the leaving nitrite ion on the anhydride function,[71b,72] however, better yields of 72 were obtained from similar substitutions involving 3- and 4-fluoro- or

3- and 4-chlorophthalic anhydrides.[71,72] The reactions above were extended to more activated 3,5-dinitrophthalimides and 3,5-dinitrophthalic anhydrides with the finding that the 3-substituted products **73** can be isolated before the 3,5-disubstituted products **74**.[73] This regioselectivity parallels the observed higher reactivity of 3-nitro versus 4-nitrophthalic acid derivatives in eq. 3-21.[71]

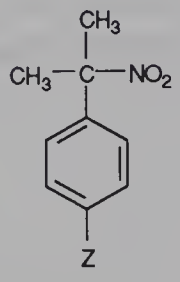


(3-21)

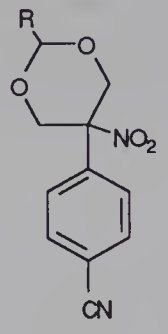


Kornblum *et al.* reported that 4-nitrobenzophenone (**26a**), methyl *p*-nitrobenzoate, *p*-nitrobenzonitrile, and 4-nitrophenyl phenyl sulfone suffer facile displacement of their nitro group by the carbanion of 2-nitropropane in HMPA (entries 19, 23, 24, and 30 in Table 3.1).[6] The substituted derivatives **75a-d** were obtained at room temperature in 78, 60, 82, and 76% yield, respectively. DMSO instead of HMPA was also used to prepare **75c**.[19] Recently, Kirillov *et al.* have described the formation of the various 5-nitro-5-(*p*-cyanophenyl)-1,3-dioxanes **76** from the reaction of *p*-nitrobenzonitrile with the lithium salts of the appropriate 5-nitro-1,3-dioxane precursors in HMPA.[74] Compounds **76** form in high yields as a single stereoisomer in which the nitro group and the *p*-cyanophenyl group at the 5-position are in the axial and equatorial positions, respectively. On the other hand, Makosza *et al.* have reported the displacement of the nitro group of various substituted 4-nitrobenzophenones by carbanions of α-substituted benzyl cyanides (eq. 3-22).[75] In this instance, a two-phase system was used consisting of 5% sodium hydroxide solution and the reactants (with or without added organic solvents) in the

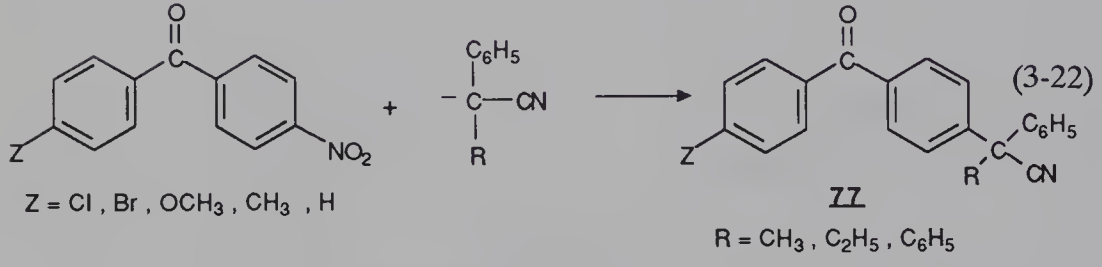
presence of a catalytic amount of benzyltrimethylammonium chloride. The yields of 77 were in the range of 65–90%.[75]



75 (a) Z = COC_6H_5
(b) Z = CO_2CH_3
(c) Z = CN
(d) Z = $SO_2C_6H_5$



76 R = H , CH_3 , C_6H_5



Z = Cl , Br , OCH_3 , CH_3 , H

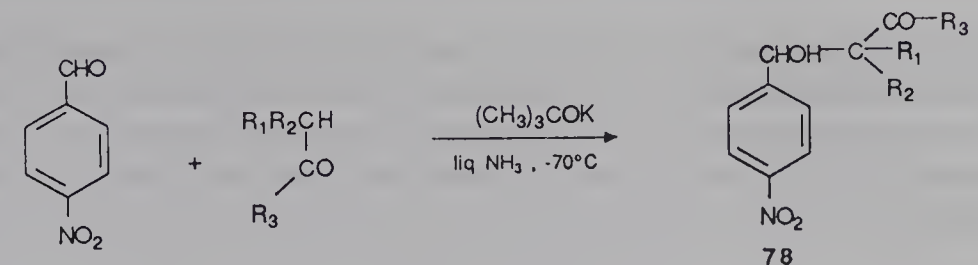
77
R = CH_3 , C_2H_5 , C_6H_5

(3-22)

While 4-nitrobenzaldehyde reacts with oxygen and sulfur nucleophiles to give the products of S_NAr displacement of the nitro group, it undergoes a *formal* S_NAr displacement of the formyl group on treatment with various carbanions, as described in eq. 3-23.[76] A detailed examination of these useful reactions has shown that there is initial formation of the aldol adducts 78 and subsequent S_NAr displacement of the carbinol moieties of these species by excess carbanion to give the *p*-nitro-substituted products 79.[76]

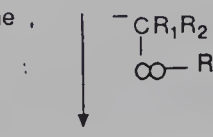
Useful S_NAr substitutions leading to direct formation of C—C bonds are those of the nitro group of the η^6-nitrobenzene-η^5-cyclopentadienyliron cations 80 by enolate-type carbanions.[53a] When 80a was allowed to react with acetylacetone, diethyl malonate, or ethyl acetoacetate in the presence of potassium carbonate in DMF at room temperature, the substitution products 81a$_1$–81a$_3$ were obtained in roughly 70% yield. Pyrolytic sublimation of these products gave the free substituted benzenes 3-phenyl-2,4-pentanedione (82a$_1$), diethyl phenylmalonate (82a$_2$), and ethyl α-phenylacetoacetate (82a$_3$), respectively, in yields greater than 80% (Scheme 3.5).[53a] Similar syntheses have been effected using chloroarene–cyclopentadienyliron complexes.[77,78]

Activation by the $FeCp^+$ group was also used to effect substitutions by amine reagents.[53a] The reactions of 80a and of its ortho-, meta-, and para-

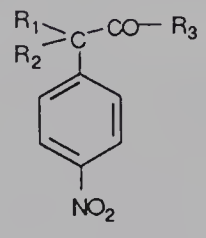


78

$R_1R_2CHCOR_3$ = 2-pentanone , 3-methyl-2-butanone , pinacolone , phenylacetone , cyclopentanone , cyclohexanone , ethyl acetate

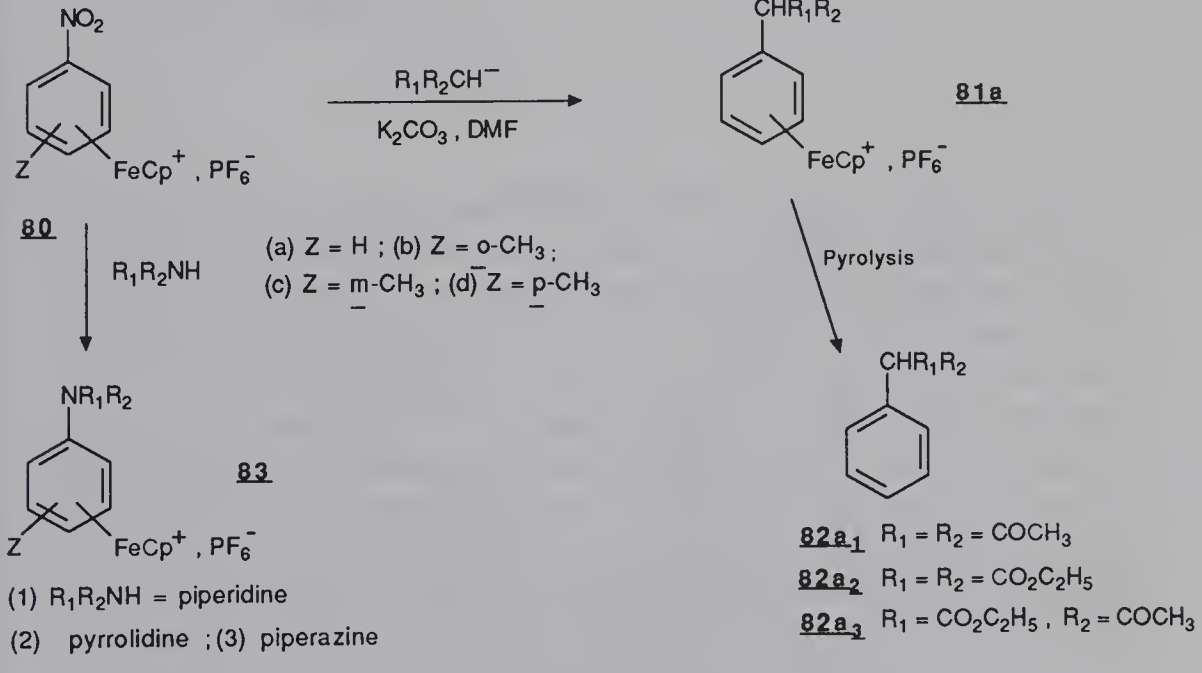


(3-23)



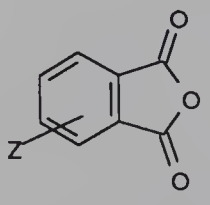
79

nitrotoluene analogues **80b–d** with pyrrolidine and piperidine in methylene chloride afforded the *N*-pyrrolidinyl and *N*-piperidinyl arene complexes **83a–d_1** and **83a–d_2**, respectively. With **80a** and piperazine, only a 1:1 N-substituted product **83a$_3$** was obtained. Subsequent elimination of the $FeCp^+$ moiety offers an easy access to the corresponding tertiary anilines.[53a]

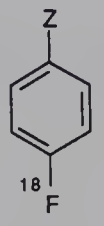


Scheme 3.5.

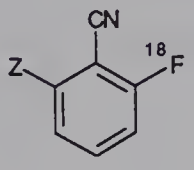
Ishikawa *et al.* have described the synthesis of the 3- and 4-fluorophthalic anhydrides **84a** and **84b** by treatment of the respective nitrophthalic anhydrides with potassium fluoride with or without a dipolar aprotic solvent.[79] A similar reaction with *N*-methyl-4-nitrophthalimide gave only poor yields of the 4-fluoro derivative.[72a]



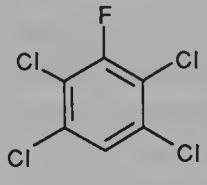
84a Z = 3-F
84b Z = 4-F



85a Z = CO_2CH_3
85b Z = CN



86a Z = H
86b Z = Cl
86c Z = NO_2
86d Z = F



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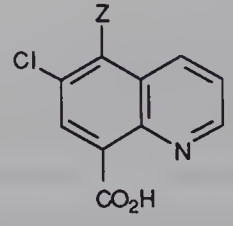


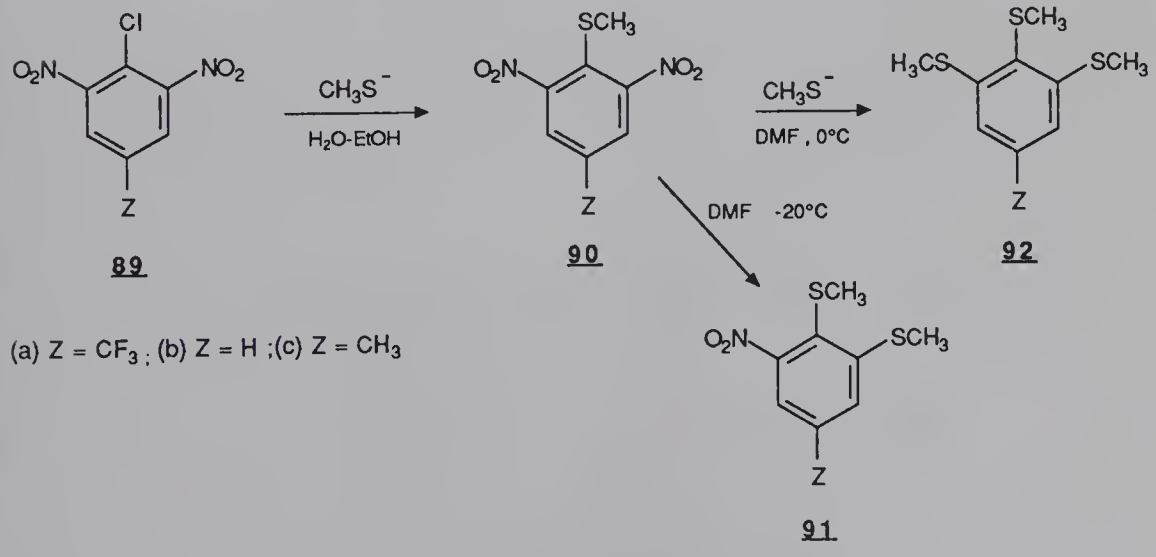
88a Z = NO_2
88b Z = Cl
88c Z = Br

The labeled methyl [4-^{18}F]fluorobenzoate **85a** and [2-^{18}F]fluorobenzonitriles **86a** and **86b** were obtained in satisfactory yields from reactions of the corresponding nitro precursors with rubidium fluoride [^{18}F] at 150°C in DMSO (entry 26 in Table 3.1).[33a] In the case of 2-chloro-6-nitrobenzonitrile, some exchange of the chlorine atom also occurs, giving [2-^{18}F]fluoro-6-nitrobenzonitrile (**86c**) as a minor product.[33a] Treatment of the same chloronitro precursor with "anhydrous" tetrabutylammonium fluoride, in the absence of solvent or in THF at room temperature, affords the unlabeled fluoro derivative **86b** in 70% yield, together with 25% of 2,6-difluorobenzonitrile (**86d**), which arises from subsequent chlorine exchange of **86b**.[34] With 2,3,5,6-tetrachloronitrobenzene, the nitro group is selectively replaced, yielding **87** in 70% yield.[34] Displacement of the nitro group of the chloronitroquinoline carboxylic acid **88a** by chloride and bromide ion in DMF is another noteworthy

substitution, which affords the dihalo derivatives **88b** and **88c**.[80] Recently, it has been reported that the application of microwave heating technology enhances the rates of nucleophilic aromatic substitutions involving halide ions such as F^- and I^- as it does in other organic syntheses.[81a] [4-^{18}F] Fluorobenzonitrile (**85b**) was also prepared, from the reaction of *p*-nitrobenzonitrile with no carrier added (nca) [^{18}F] fluoride in DMSO.[81b]

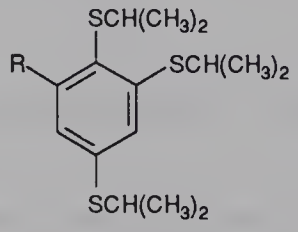
3.2.3 Dinitro and Trinitrosubstituted Benzenes

Most of the synthetically important displacements of a nitro group from dinitro- or trinitro-substituted benzenes have involved sulfur nucleophiles. Upon treatment of 4-chloro-α,α,α-trifluoro-3,5-dinitrotoluene (**89a**) with thiomethoxide ion in aqueous alcoholic solution, Beck and Yahner obtained the thioether **90a**, as expected from the substitution of the strongly activated chlorine atom.[16] However, when **90a** was allowed to react further with excess thiomethoxide ion at 0°C in DMF, α,α,α-trifluoro-3,4,5-tris(methylthio) toluene (**92a**) was obtained in 95% yield.[16] A similar workup of **89a** yielded **92a** directly, but the bis(thioether) **91a** could also be obtained from **89a** by lowering the reaction temperature to –20°C in DMF (Scheme 3.6).[16] Similar reactions with 1-chloro-2,6-dinitrobenzene (**89b**) and 4-chloro-3,5-dinitrotoluene (**89c**) afforded the bis(thioethers) **91b** and **91c** or the



Scheme 3.6.

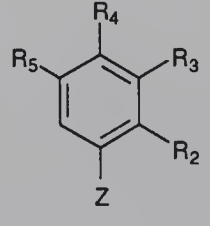
tris(thioethers) **92b** and **92c**, depending on the temperature and reaction time employed.[16] Tiecco et al. reported that the reactions of 1-chloro-2,4-dinitrobenzene and picryl chloride with an excess of the sodium salt of 2-propanethiol in HMPA afforded the products of S_NAr displacement of all chloro and nitro groups present in the substrates.[15] Compounds **93a** and **93b** were obtained in 50 and 69% yields, respectively.



93a R = H

93b R = $SCH(CH_3)_2$

All the syntheses above have added to the evidence (see Section 3.2.1) that an ortho- or para-alkylthioether function is capable of activating displacement of a nitro group, and this feature has been used for the synthesis of many poly(alkylthio)benzenes.[15,82] The reactions of thiomethoxide ion with a series of benzoic acid derivatives was investigated under *various* experimental conditions that afforded a number of bis- and tris(methylthio) derivatives.[82] Representative examples are the benzoic acids **94a–c**, the benzamide **95**, and the *S*-methyl thioesters **96a–b**. Also prepared were the 3,4,5-tris(methylthio)benzenesulfonamide **97** and 3,4,5-tris(methylthio)phenylacetamide (**98**).



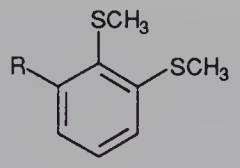
94 Z = CO_2H ; (a) $R_2 = H$, $R_3 = R_4 = SCH_3$, $R_5 = NO_2$
(b) $R_2 = H$, $R_3 = R_4 = R_5 = SCH_3$
(c) $R_2 = R_3 = R_5 = SCH_3$, $R_4 = H$

95 Z = $CONH_2$; (a) $R_2 = H$, $R_3 = R_4 = R_5 = SCH_3$

96 Z = $COSCH_3$; (a) $R_2 = H$, $R_3 = R_4 = R_5 = SCH_3$
(b) $R_4 = H$, $R_2 = R_3 = R_5 = SCH_3$

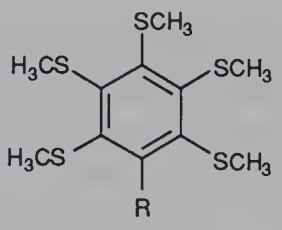
97 Z = SO_2NH_2 ; (a) $R_2 = H$, $R_3 = R_4 = R_5 = SCH_3$

98 Z = CH_2CONH_2 ; (a) $R_2 = H$, $R_3 = R_4 = R_5 = SCH_3$



99a R = Cl

99b R = OCH_3

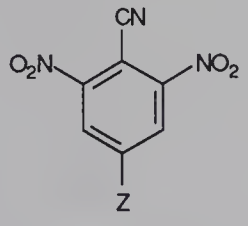


100a R = H

100b R = SCH_3

Other interesting compounds that were obtained are the bis(thioethers) **99a** and **99b** from 2,3-dichloro-1-nitrobenzene and 2-chloro-3-nitroanisole, respectively, and the pentakis- and hexakis(methylthio)benzenes **100a** and **100b** from 1,3,5-trichloro-2,4-dinitrobenzene and 1,3,4,5-tetrachloro-2,6-dinitrobenzene, respectively.[16] Several of the thioethers obtained were oxidized to the corresponding sulfones.[16,82]

An investigation of the substitution reactions of 2,6-dinitrobenzonitriles **101a** and **101b** by thiolate ions is worth mentioning.[83] Treatment of **101a,b** with thiomethoxide ion at 0°C for 5 minutes in aqueous DMF gave the 2,6-bis(methylthio) benzonitriles **102a** and **102b** in high yields. Exclusive displacement of the nitro groups occurs in these instances. Interestingly, the nitro groups of **101a** and **101b** could be *sequentially* displaced by a variety of other nucleophiles (methoxide, azide, and chloride ions; methylamine and



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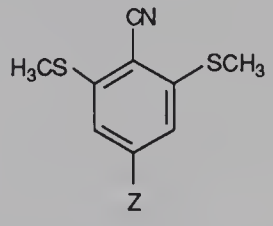

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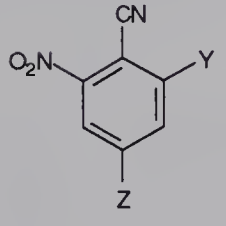
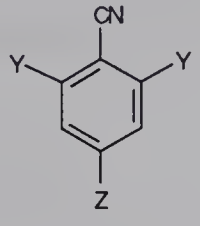
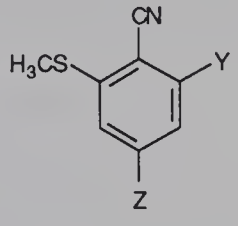


103



104



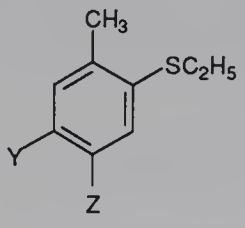
105

(a) Z = H ; (b) Z = CF_3

Y = OCH_3 , N_3 , $NHCH_3$, $N(CH_3)_2$, Cl

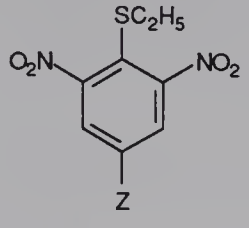
dimethylamine), giving first the monosubstituted compounds **103a** and **103b**, and finally the disubstituted compounds **104a** and **104b**. The isolation of **103a,b** also allowed the synthesizing of mixed derivatives like the thioethers **105a** and **105b**, which would be difficult to prepare by other routes.[78]

A remarkable regioselectivity of the displacement of nitro groups by thiolate ions has been observed in some instances. Stirling and coworkers studied the behavior of a number of polynitroaromatics and found that nitro groups adjacent to an alkyl group are preferentially displaced.[84] For example, reactions of 2,4-dinitrotoluene and 2,5-dinitrotoluene with ethanethiolate ion at 20°C in HMPA yielded quantitatively the ethyl thioethers **106a** and **106b**. The fact that a nitro group adjacent to a methyl group is out of the plane by about 35° is considered to be responsible for this regioselectivity, which disappears when either the thiolate ion or the alkyl group, or both, are bulky.[84] It is for the same reason that displacement of the 3-nitro group rather than of the 5-nitro group is preferred in 3,5-dinitrophthalic anhydride and 3,5-dinitrophthalimides (see above).[73] In contrast, a specific substitution of the para nitro group was observed on treatment of 1-ethylthio-2,4,6-trinitrobenzene (**107a**) by sodium ethanethiolate in DMSO, giving **107b** in 90% yield.[85]



106a Z = NO_2, Y = H

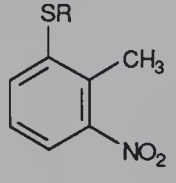
106b Z = H, Y = NO_2



107a Z = NO_2

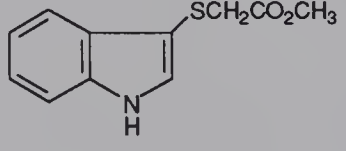
107b Z = SC_2H_5

Treatment of 2,6-dinitrotoluene with ethanethiolate or methyl thioglycolate in HMPA yielded the monosubstituted thioethers **108a** and **108b**.[84,86] The latter is a precursor of the indole **109**, which is a primary intermediate in the synthesis of the indole alkaloid chuangxinmycin.[86]



108a R = C_2H_5

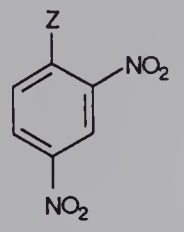
108b R = $CH_2CO_2CH_3$



109

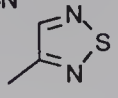
Some selective displacements of an ortho or a para nitro group by oxygen or nitrogen nucleophiles are noteworthy for synthetic purposes. Treatment of **110a** with methoxide ion in methanol and with phenoxide ion or dimethylamine in DMF resulted in the exclusive replacement of the nitro group para to the perfluoroisopropyl function to give **111a–c**.[87] A similar selectivity was observed in the reaction of 2,4-dinitrobenzonitrile (**110b**), whose reaction with piperidine yielded solely **112**.[88] In contrast, the reaction of **110c** with methoxide and ethoxide ions resulted in substitution of the *o*-nitro group to give **113a** and **113b**, respectively.[89]

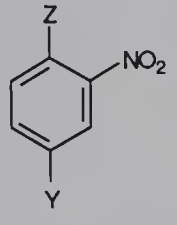
2,4-Dinitrobenzonitrile and 2,6-dinitrobenzonitrile readily undergo nitro displacement reactions of both nitro groups with phenoxide salts. High molecular weight aromatic polyethers containing pendant cyano groups (e.g., **114**) were thus prepared using bisphenoxide ions as nucleophiles in DMSO.[58b] These polymers exhibit relatively high glass transition temperatures and excellent thermal stabilities.



110a Z = $OCF(CF_3)_2$

110b Z = CN

110c Z = 

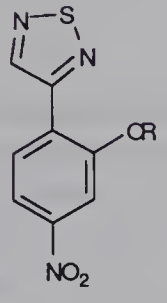


111a Z = $OCF(CF_3)_2$, Y = OCH_3

111b Y = OC_6H_5

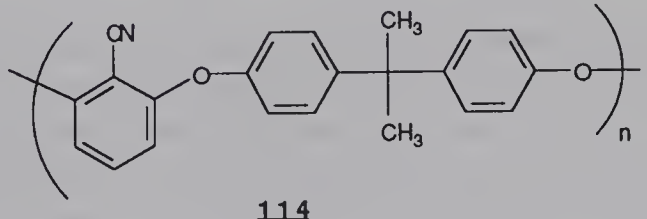
111c Y = $N(CH_3)_2$

112 Z = CN, Y = piperidino



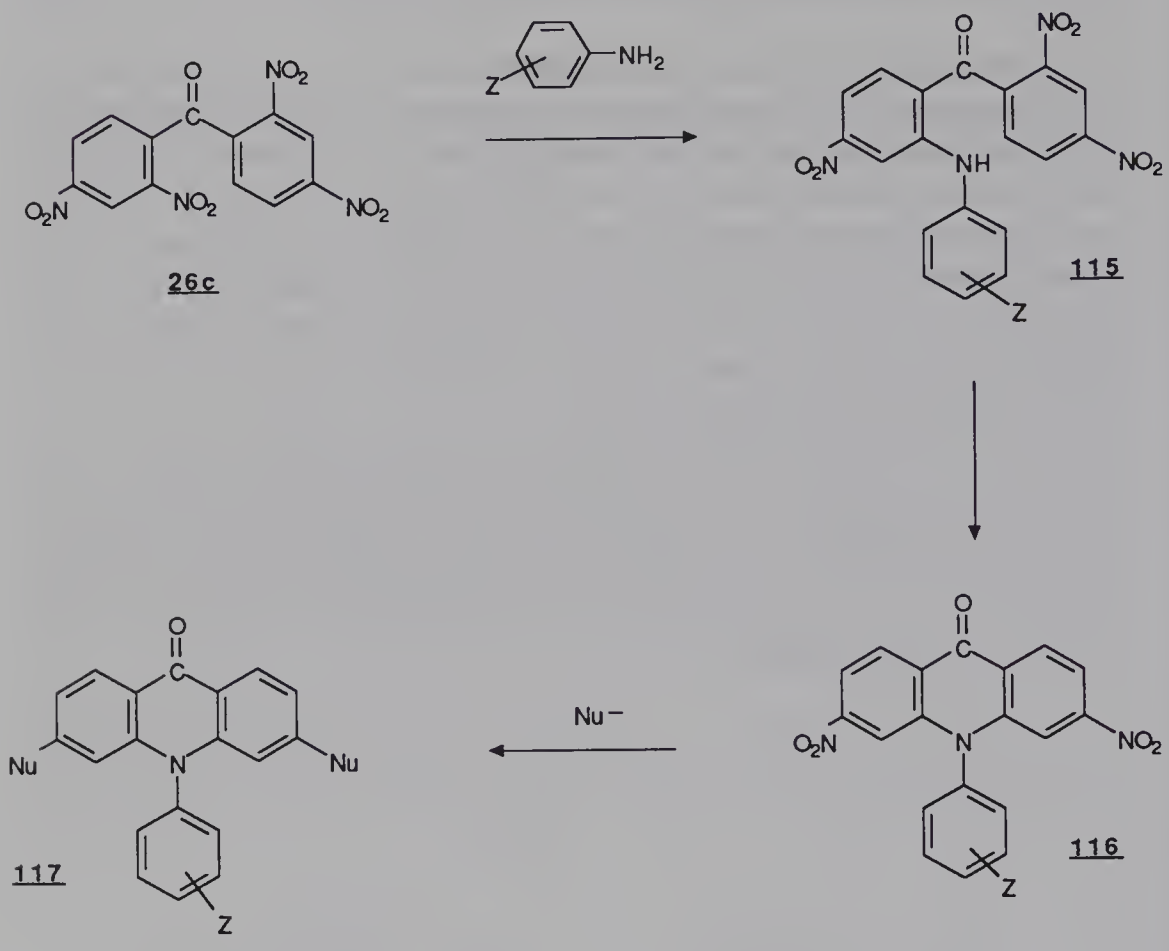
113a R = CH_3

113b R = C_2H_5



114

Substitutions of 2,2′,4,4′-tetranitrobenzophenone (**26c**) by alkoxide ions and aromatic amines, follow a different pattern.[46] While RO^- ions displace *p*-nitro groups preferentially (see Section 3.2.2), primary anilines react with

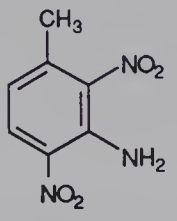


Scheme 3.7.

26c in DMSO to form the 2-anilino-2′,4,4′-trinitrobenzophenones **115**, which cyclize to the 10-aryl-3,6-dinitro-9-acridones **116** through intramolecular S_NAr displacement of the second *o*-nitro group (Scheme 3.7). Replacing the remaining *p*-nitro groups by other nucleophiles [CH_3O^-, $C_6H_5O^-$, $(C_2H_5)_2NCH_2CH_2O^-$, $(CH_3)_2NCH_2CH_2S^-$] leads to 10-aryl 3,6-disubstituted acridones **117** with the original substitution patterns.[46]

S_NAr reactions of ammonia with isomeric trinitroluenes offer an interesting synthetic route to aminodinitrotoluenes.[90] With the exception of symmetrical 2,4,6-trinitrotoluene, where all nitro groups are meta oriented, the other isomeric trinitrotoluenes suffer displacement of only the one nitro group that is ortho or para to another nitro group, upon treatment with excess ethanolic

ammonia. Thus, 3-amino-2,4-dinitrotoluene (**118**) was prepared in 90–95% yield from 2,3,4-trinitrotoluene. Similarly, it was observed that 2,3,5-trinitrotoluene, 2,4,5-trinitrotoluene, and 3,4,5-trinitrotoluene yielded mainly 2-amino-3,5-dinitrotoluene (**119**), 5-amino-2,4-dinitrotoluene (**120**), and 4-amino-3,5-dinitrotoluene (**121**), respectively.[90] Exceptional behavior was found for 2,3,6-trinitrotoluene, which afforded a 1:1 mixture of 2-amino-3,6-dinitrotoluene **122** and 3-amino-2,6-dinitrotoluene **123**.[90]



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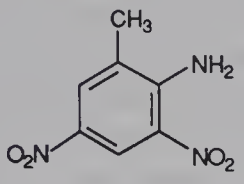

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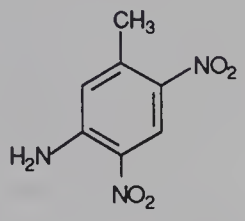
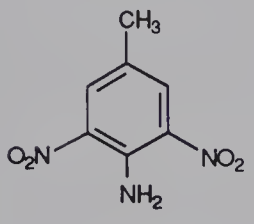
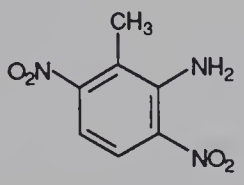


120



121



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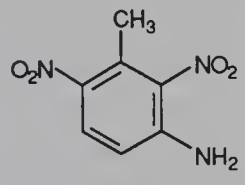
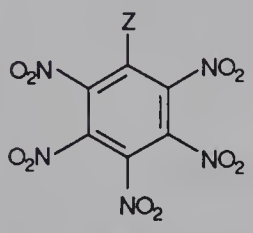
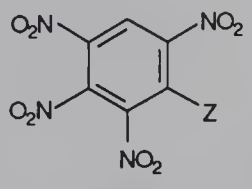


123

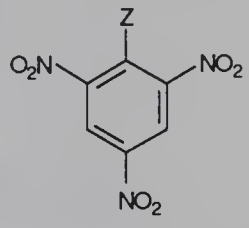
Hexanitrobenzene reacts with hydrogen halides (HCl, HBr, HI, but not HF) in benzene to produce high yields of the pentanitrohalobenzenes **124a–c**.[91]



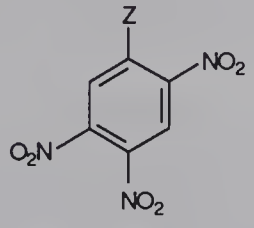
124a Z = Cl
124b Z = Br
124c Z = I



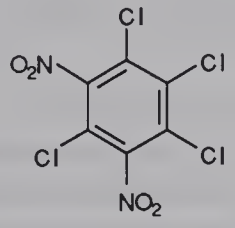
125a Z = Cl
125b Z = Br
125c Z = I



126a Z = Cl
126b Z = Br



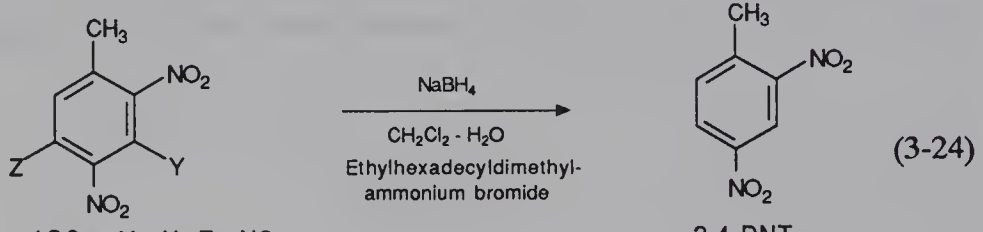
127a Z = Cl
127b Z= Br
127c Z = I



128

The reactions with pentanitrobenzene, 1,2,3,5-tetranitrobenzene, and 1,2,4,5-tetranitrobenzene proceed equally well and are regioselective. Halogen substitutions occur at a position meta to an existing hydrogen and ortho and para to nitro groups, leading exclusively to 2,3,4,6-tetranitrohalobenzenes **125a–c**, the picryl halides **126a,b**, and the 1-halo-2,4,5-trinitrobenzenes **127a–c**, respectively.[91] In all cases the substitution rates follow the nucleophilicity order of the halide anions: $I^- > Br > Cl^- >>> F^-$. Since substitution occurs only in acid media, the reactions probably involve halide ion attack on the starting aromatics activated by initial protonation at one of the nitro groups.[91] However, displacement of a nitro group of 1,3,5-trichloro-2,4,6-trinitrobenzene to give 1,2,3,5-tetrachloro-4,6-dinitrobenzene (**128**) has been reported to occur upon treatment with lithium chloride in acetone or 2-propanol.[92]

Unsymmetrical 2,4,5-trinitrotoluene (**129a**) and 2,3,4-trinitrotoluene (**129b**) have been subjected to reaction with sodium borohydride in the presence of a phase transfer catalyst.[93] Excellent yields of 2,4-dinitrotoluene, which is formed through a regioselective displacement of an NO_2 group by hydride ion, were obtained in both cases (eq. 3-24).[93] Under similar experimental conditions, 2,4,6-trinitrotoluene yielded ring reduction products.[93] Since 2,4-dinitrotoluene can readily be further nitrated to yield 2,4,6-trinitrotoluene, the reaction is of obvious interest for the conversion of unsymmetrical isomers that are formed as side products during the production of 2,4,6-trinitrotoluene.



129a Y = H, Z = NO_2
129b Y = NO_2, Z = H

2,4-DNT

(3-24)

3.3 Intermolecular Displacements of Halogen and Other Leaving Groups

S_NAr substitutions of moderately activated aromatic halides like chloro-, bromo-, and iodomononitrobenzenes proceed in general, with most amine reagents, at rates that are too low under common experimental conditions to be useful for synthetic purposes. However, it has recently been shown that high pressure conditions cause a marked acceleration of these reactions, which then become more feasible.[94] Some data for reaction 3-25, summarized in Table

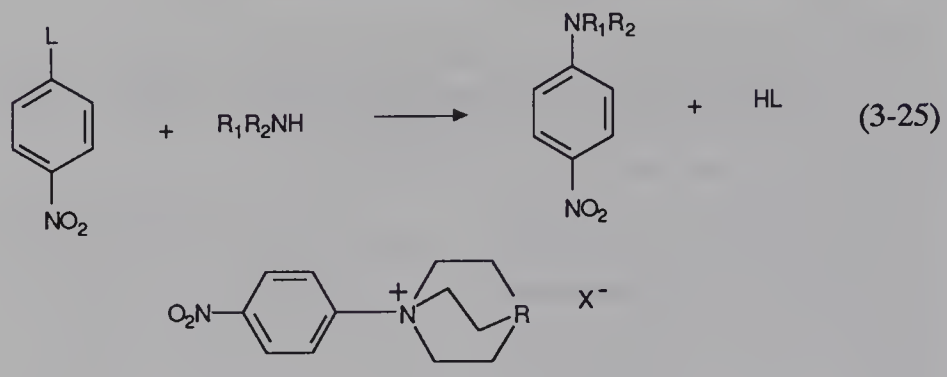
Table 3.3. Reactions of 4-Halonitrobenzenes with Primary and Secondary Amines Under High Pressure (eq. 3-25)[a]

Halide	Amine	Pressure (kbar)	*p*-Nitroaniline yield (%)[b]
Cl	*n*-Propylamine	7.2	93 (0)
	Isopropylamine		26 (0)
	n-Butylamine		76 (0)
	Isobutylamine		61 (0)
	tert-Butylamine		2 (0)
	n-Hexylamine		65 (0)
	Diethylamine		39 (0)
	Dipropylamine		24 (0)
	Morpholine	6	100 (3)
	Piperidine		100 (22)
	Pyrrolidine		100 (92)
Br	Pyrrolidine	12	100 (51)
I	Pyrrolidine	12	100 (14)

[a]All reactions were carried out in THF at 50°C for 20 hours; data reproduced with permission from ref. 94.

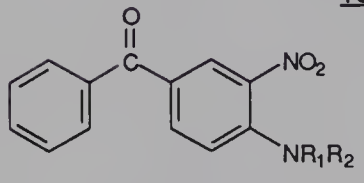
[b]Yields in parentheses refer to reections under 1 atm at 80°C.

3.3, show that unhindered primary amines and cyclic secondary amines exhibit a high reactivity.[94] Among tertiary amines, 1,4-diazabicyclo[2.2.2]octane and quinuclidine react with 4-halonitrobenzenes to give the corresponding ammonium halides **130a** and **130b** in quantitative yields.[94] Ayyangar *et al.* have similarly designed a new and convenient synthesis of the aminonitrobenzophenones **131** and **132**, which are useful starting materials in drug synthesis.[95] They displaced the methoxy group of 4-methoxy-3-nitrobenzophenone and 2-methoxy-5-nitrobenzophenone with aqueous ammonia or various primary or secondary amines upon heating the solutions in a closed pressure vessel at 120°C for 5 hours.[95] More activated 2,6-dihalo-4-nitrophenyl methyl and allyl ethers have been found to react readily with primary amines under smooth conditions in ethanol at room temperature, affording high yields of various 2,6-dihalo-4-nitro-*N*-alkylanilines.[96]

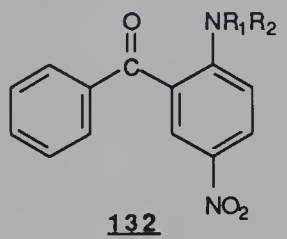


130a R = N , X = Cl , Br or I

130b R = CH , X = Cl



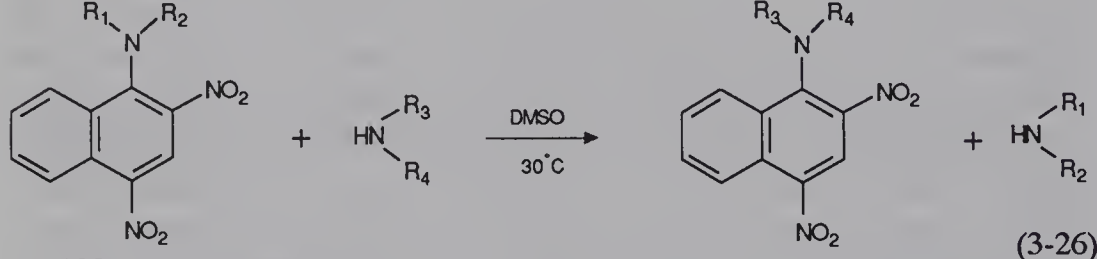
131



132

$R_1 = R_2 = H$; $R_1 = H$, $R_2 = CH_3$;
$R_1 = H$, $R_2 = C_2H_5$; $R_1 = H$, $R_2 = CH(CH_3)_2$;
$R_1 = H$, R_2 = n-C_4H_9 ; $R_1 = H$, R_2 = cyclohexylamino
$R_1 = R_2 = CH_3$

Various 1-dialkylamino-2,4-dinitronaphthalenes **133** undergo surprisingly facile amine–amine S_NAr exchange reactions upon simple addition of primary amines at 30°C in DMSO (eq. 3-26).[97] Despite the bulkiness of the dialkyl group in the starting materials, excellent yields in the substitution products **134** were obtained with methylamine, ethylamine, and 2-propylamine. Due to increased steric effects, the reactions with secondary amines (e.g., dimethylamine, diethylamine, piperidine) were not successful except in the case of pyrrolidine.[97]

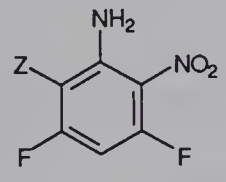


133 (3-26) **134**

(a) $R_1 = R_2 = CH_3$
(b) $R_1 = R_2 = C_2H_5$
(c) R_1 = n-C_4H_9, $R_2 = CH_3$
(d) R_1···· R_2 = piperidino

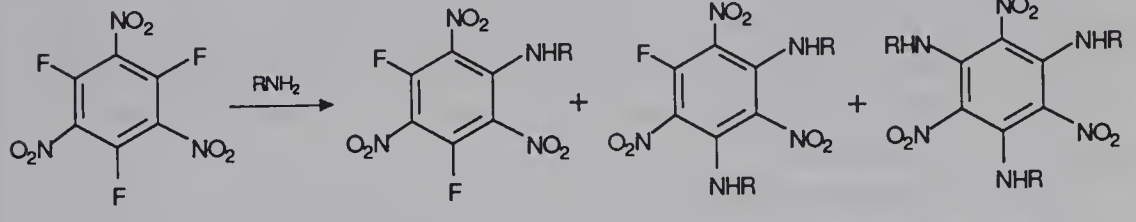
(a) $R_3 = H$, $R_4 = CH_3$
(b) $R_3 = H$, $R_4 = C_2H_5$
(c) $R_3 = H$, R_4 = i-C_3H_7
(d) R_3.....R_4 = pyrrolidino

A number of fluoronitroanilines that are useful reagents for analysis of amino acids and peptides have been prepared using the much higher ability of a fluorine atom, at a position ortho rather than para to nitro, to depart in S_NAr substitutions involving ammonia and amines.[1,2] Examples are the 3,5-difluoro-2-nitro- and 3,5-difluoro-2,6-dinitroanilines **135a** and **135b**, which have been readily obtained from treatment of 2,4,6-trifluoronitrobenzene and 1,3-dinitro-2,4,6-trifluorobenzene, respectively, with either ammonia or ammonium hydroxide in THF.[98] Similarly, the reactions of 2,3,4,6-tetrafluoronitrobenzene and 2,3,4,6-tetrafluoro-1,5-dinitrobenzene with ammonia in ether afforded the 2,3,5-trifluoronitroanilines **136a** and **136b** in yields exceeding 95%.[99] The reaction of 2,4,6-trifluorotrinitrobenzene **137** with ammonia in methylene chloride is so rapid that it affords a mixture of **138a**, **139a**, and **140a**, even at –70°C (eq. 3-27). *n*-Butylamine also reacts very rapidly with **137** to give 2,4,6-tris(butylamino)trinitrobenzene **140b** in 62% yield.[100] Hydrazino derivatives of type **139** and **140** (e.g., R = $NHCOCH_3$), which have explosive properties, have also been prepared.[100]



135a Z = H
135b Z = NO_2

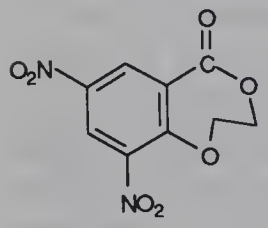
136a Z = H
136b Z = NO_2



137 **138** (a) R = H (b) R = n-C_4H_9 **139** **140** (3-27)

Jones and Rothenberger reported that treatment of the dinitrolactone **141** with aqueous ammonia does not result in formation of the expected salicylamide **142** but gives instead **143a** (90% yield), which is a potent anticoccidiosis agent known as "iramine."[101] Interestingly, the dinitroamide **142** was unchanged under similar ammonolysis conditions. This shows that the formation of **143a** is the result of two consecutive steps: (1) an S_NAr displacement of the alkoxy-type moiety of **141** to give **144**, which was not observed, and (2) amide formation from **144** with elimination of a β-

hydroxyethoxy group.[101] Similar reactions were observed with such aliphatic amines as methylamine and dimethylamine, giving **143b** and **143c**. The dinitroester **145** also led to **143a–c**, with initial S_NAr substitution of its β-hydroxyethoxy group by NH_3 or the amine, followed by conversion of the carbomethoxy group into the amide group.[101] Reactions of **141** and/or **145** with other nucleophiles (e.g., OH^-, $C_6H_5S^-$, aniline, CH_3O^-) afforded the free carboxylic acids **143d–g** by acidification of the resulting carboxylates.[101]



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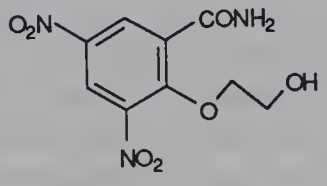

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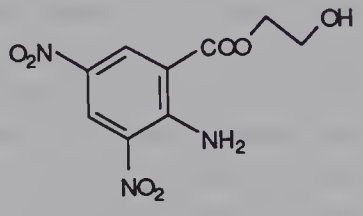

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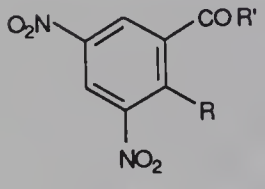
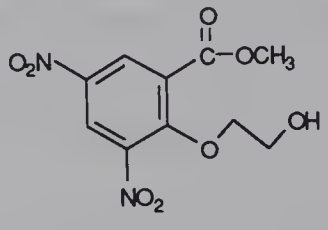


143

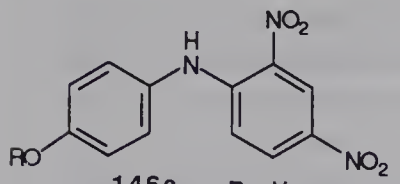
(a) R = R' = NH_2
(b) R = R' = $NHCH_3$
(c) R = R' = $N(CH_3)_2$
(d) R = R' = OH
(e) R = SC_6H_5 , R' = OH
(f) R = NHC_6H_5 , R' = OH
(g) R = OCH_3 , R' = OH



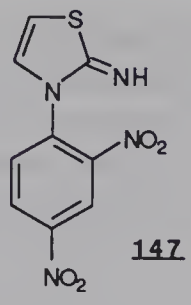
145

2,4-Dinitro-4′-hydroxydiphenylamine (**146a**) and 2,4-dinitro-4′-methoxydiphenylamine (**146b**) are formed in high yields via the S_NAr substitution of 1-chloro-2,4-dinitrobenzene with 4-hydroxyaniline and *p*-anisidine, respectively, in ethanol containing some sodium carbonate.[102] Such compounds are starting materials for a convenient synthesis of 3-cyanocarbazoles and pyrido[4,3-*b*]carbazoles.[102]

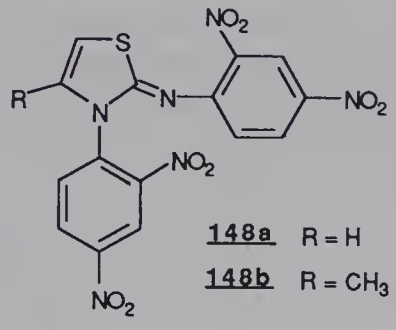
2-Aminothiazole and 4-methyl-2-aminothiazole act as ambident nucleophiles toward 1-fluoro-2,4-dinitrobenzene (DNFB) in DMSO. The reaction with 2-aminothiazole with an equal amount or a deficiency of DNFB gives the imino derivative **147** in 87% yield.[103] The same reaction in the presence of an excess DNFB affords the disubstituted product **148a** (90%). 4-Methyl-2-aminothiazole behaves differently, giving the 2-amino derivative **149** as the major product, even in the presence of excess DNFB. Only a small amount of the disubstituted product **148b** was obtained.[103] Besides their synthetic interest, the reactions show that in the absence of steric hindrance as in the 4-methyl derivative, the aza nitrogen of 2-aminothiazoles is a more efficient nucleophile than the amino nitrogen toward an aromatic sp^2 carbon.[103]



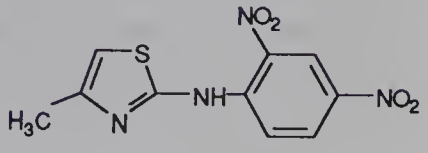
146a R = H
146b R = CH_3



147

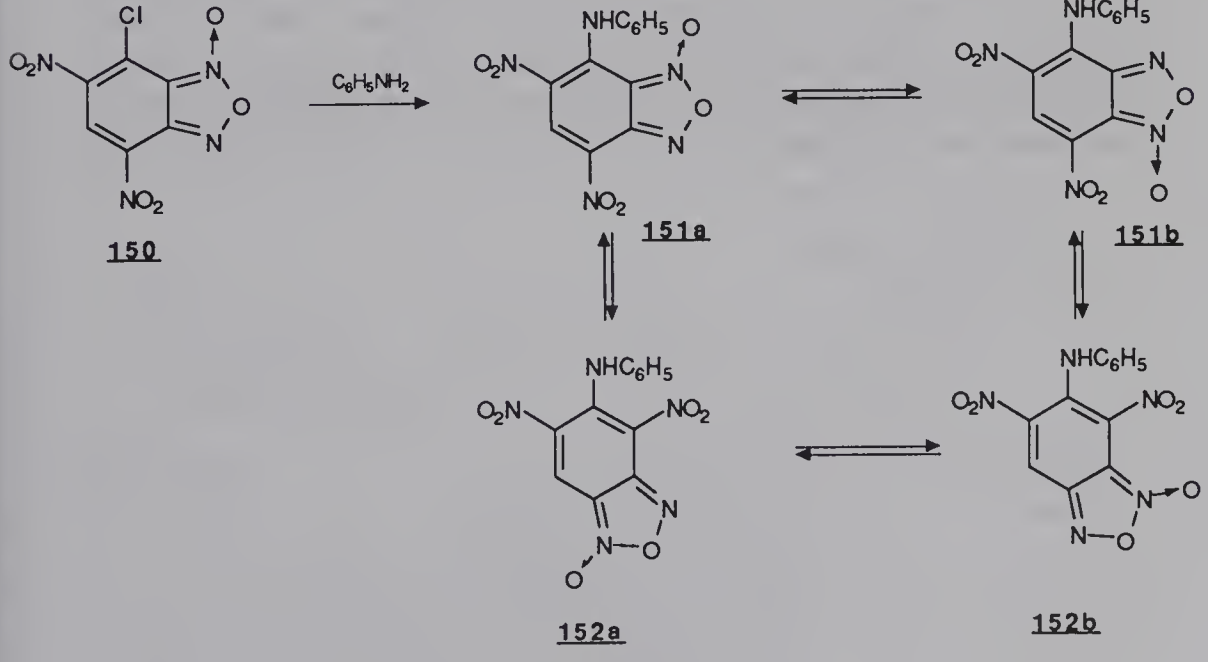


148a R = H
148b R = CH_3



149

In accord with the extremely high electrophilic character of a DNBF moiety, 7-chloro-4,6-dinitrobenzofuroxan (**150**) reacts under mild conditions in chloroform with a variety of aromatic amines, including those with deactivating substituents like *o*-nitroaniline. The 7-arylamino-4,6-dinitrobenzofuroxans **151** are formed in moderate to high yields together with some (10–15%) of the 5-arylamino isomers **152**. These arise from a partial conversion of the 7-isomers **151** via a *retro* Boulton–Katritzky rearrangement.[104]



150

151a

151b

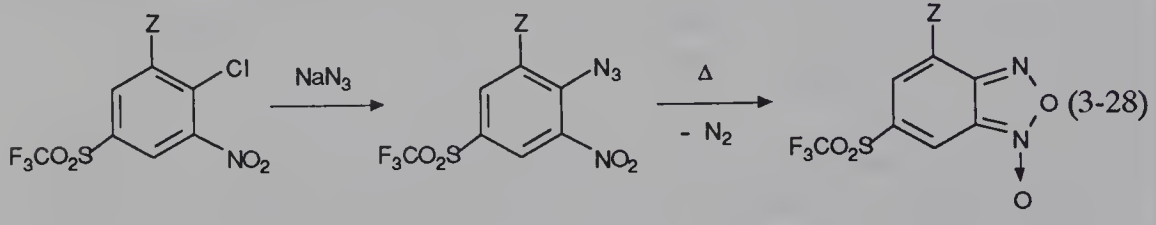
152a

152b

Scheme 3.8.

Compounds **151** and **152** are also subject to the tautomerism typical of the furoxan ring structure.[105] At room temperature, the 1-oxide structure **151a** predominates over the 3-oxide structure **151b** (Scheme 3.8). For **152**, the isomer **152a** would be most largely favored.[104]

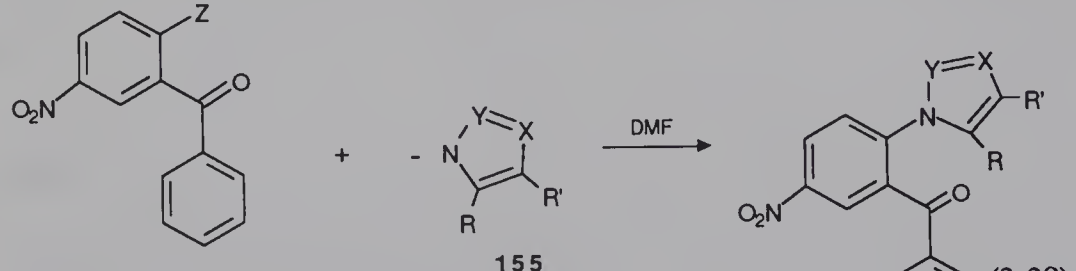
Pyrolysis of *o*-nitrophenyl azides is frequently used as a synthetic route to benzofuroxans.[105,106] Such azides are commonly obtained via S_NAr displacement of the halogen atom of *o*-nitrohalobenzenes by azide ion. A typical example is the recent synthesis of the superelectrophilic 4-nitro-6-trifluoromethylsulfonyl benzofuroxan **153a** and 4,6-bis(trifluoromethylsulfonyl) benzofuroxan **153b** according to eq. 3-28.[107]



153a Z = NO_2

153b Z = SO_2CF_3

Extensive work on the displacement of halogens in 2-halo-5-nitrobenzophenones **154a** and **154b** by the anions of various nitrogen heterocycles has been reported.[108] The chlorobenzophenone **154a** led to products **156a–d** when reacted with the sodium salts of imidazole (**155a**), 2-methylimidazole (**155b**), pyrrole (**155c**), and 3,5-diacetoxymethylpyrazole (**155d**), respectively, in DMF. The fluorobenzophenone **154b** also yielded **156b** and **156d** when treated with the appropriate heterocyclic anions (eq. 3-29). In contrast, only



154a Z= Cl

154b Z = F

155

(a) Y = CH , X = N , R = R' = H

(b) Y = C-CH_3 , X = N , R = R' = H

(c) Y = X = CH , R = R' = H

(d) Y = N , X = C-CH_2OCOCH_3 , R = CH_2OCOCH_3 , R' = H

(e) Y = C-CH_3 , X = N , R = R' = $CO_2C_2H_5$

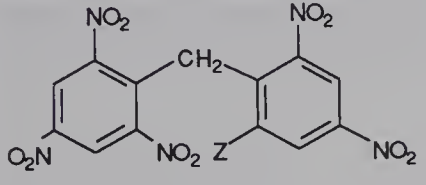
(f) Y = C-CO_2CH_3 , X = CH , R = R' = H

(g) Y = N , X = C-CO_2CH_3 , R = CO_2CH_3 , R' = H

156

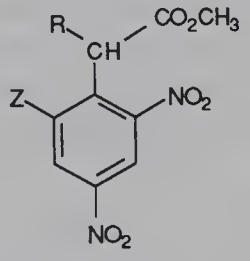
the fluorine atom in **154b** was readily displaced by anions of heterocyclic carboxylic esters like 2-methyl-4,5-imidazoledicarboxylic acid diethyl ester (**155e**), pyrrole-2-carboxylic acid methyl ester (**155f**), and pyrazole-3,5-dicarboxylic acid dimethyl ester (**155g**), to form products **156e–g** in satisfactory yields.[108] The imidazobenzophenone **156e** and the pyrazolobenzophenones **156d** and **156g** proved to be useful intermediates for the construction of the 1,4-benzodiazepine ring system.[109]

The synthetic utility of halogen S_NAr displacements by anionic or neutral carbon nucleophiles is well established. Treatment of picryl chloride and 2,4-dinitrofluorobenzene with 2,4,6-trinitrobenzyl anion in a mixed THF-DMSO solvent system afforded the hexa- and pentanitrodiphenylmethanes **157a** and **157b** in high yields.[110] Despite the occurrence of rapidly established side equilibria corresponding to σ-adduct formation at the 3- and/or 5-positions, the substitution of picryl chloride by dimethyl malonate anion to give **158a** proceeded satisfactorily in DMSO.[111] Similarly, the 2,4-dinitrophenyl compounds **158b**, **158c**, and **158d** and the 4-nitropyridine *N*-oxides **159a**, **159b**, and **159c** were obtained from treatment of 2,4-dinitrochlorobenzene and



157a Z = NO_2

157b Z = H

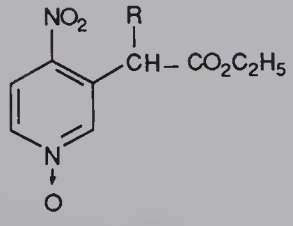


158a Z = NO_2, R = CO_2CH_3

158b Z = H, R = CO_2CH_3

158c Z = H, R = CN

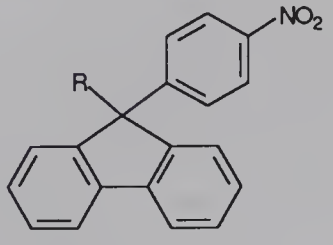
158d Z = H, R = $COCH_3$



159a R = $CO_2C_2H_5$

159b R = CN

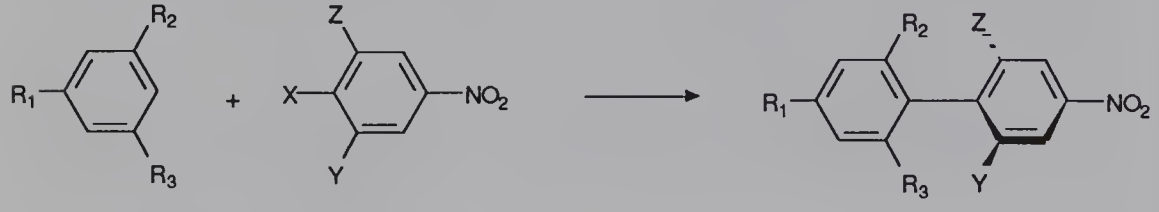
159c R = $COCH_3$



160 R = C_6H_5, R = $C_6H_5CH_2$, CH_3

3-bromo-4-nitropyridine *N*-oxide, respectively, by methyl or ethyl malonate, cyanoacetate, and acetoacetate anions in DMSO, diethyl carbonate, or pyridine.[112,113a] Interestingly, the acetoacetate derivative **159c** can undergo further cyclization to yield a furo[3,2-*c*]pyridine *N*-oxide derivative (see Chapter 4).[113] Bordwell and Hughes have synthesized a series of 9-substituted-9-(*p*-nitrophenyl) fluorenes **160** from the reaction of 9-substituted fluorenide carbanions with *p*-nitrohalobenzenes in DMSO.[114]

Picryl chloride reacts under smooth conditions (4 h reflux in an ethanol-chloroform mixture) with the bis- and tris(dialkylamino)benzenes **161a–f**, which all have a notable aryl carbon nucleophilicity, to afford the donor–acceptor substituted biphenyls **162a–f** (eq. 3-30).[115] In contrast, only the most reactive of the polyaminobenzenes employed (i.e., 1,3,5-tripyrrolidinobenzene, **161a**, reacts satisfactorily with 2,4-dinitrochlorobenzene to give **162g**. Use of 4-fluoro- instead of 4-chloro-3-(methoxycarbonyl) nitrobenzene has also allowed a facile synthesis of the tripyrrolidino biphenyl **162h**.[115] A crystal structure analysis of **162a** has been carried out. The dihedral angle between the two arene rings was found to be only 52.5°, despite the four bulky substituents in the *o*,*o*′-positions. This far-from-orthogonal torsional angle about the biphenyl linkage accounts for the finding that a strong intramolecular charge transfer from the π system of the donor into the π system of the acceptor arene ring occurs in **162a–g**.[115]

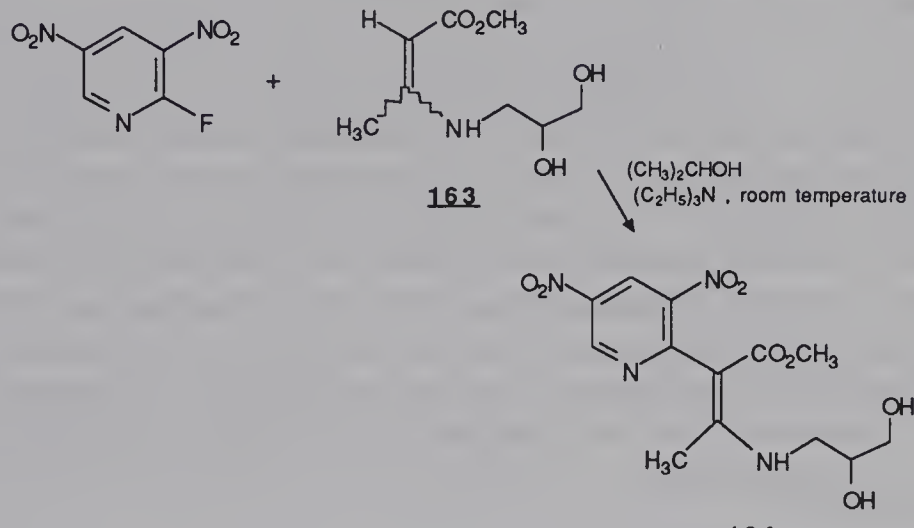


161 **162** (3-30)

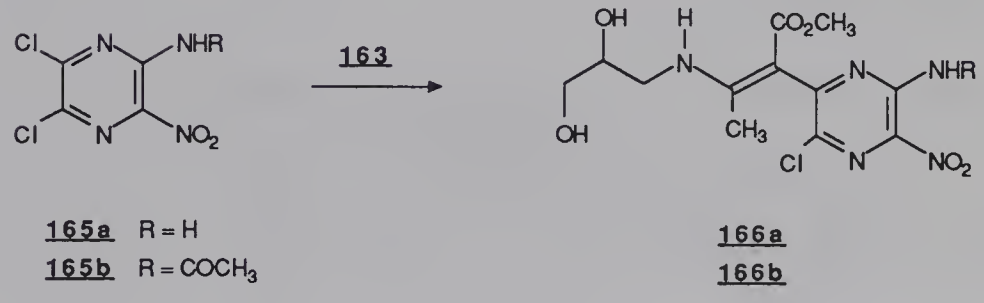
(a) $R_1 = R_2 = R_3$ = pyrrolidino , $Y = Z = NO_2$, X = Cl
(b) $R_1 = R_2 = R_3 = N(CH_3)_2$,
(c) $R_1 = R_2 = R_3$ = piperidino ,
(d) $R_1 = R_2 = R_3$ = morpholino ,
(e) R_3 = H , $R_1 = R_2$ = pyrrolidino
(f) R_3 = H , $R_1 = R_2$ = piperidino
(g) $R_1 = R_2 = R_3$ = pyrrolidino , $Y = NO_2$, Z =H , X = Cl
(h) $R_1 = R_2 = R_3$ = pyrrolidino , $Y = CO_2CH_3$, Z = H , X = F

3-Amino- and 3-(alkylamino)-2-butenoates react with nitroaromatics possessing readily displaceable halogens (F, Cl) to afford moderate yields of vinylogous amines as S_NAr products.[116] For example, treatment of 2-fluoro-3,5-dinitropyridine with methyl 3-[(2,3-dihydroxypropyl)amino]-2-butenoate (**163**) under the conditions depicted in eq. 3-31 affords **164** only as the Z isomer

in 52% yield. 3-Fluoro-4-nitropyridine *N*-oxide, 1-fluoro-2,4-dinitrobenzene, 5,6-dichloro-3-nitro-2-aminopyrazine (**165a**), and its corresponding acetamide **165b** undergo analogous nucleophilic attacks at C-2 of **163**, giving the expected products (e.g., **166a** and **166b**) as the Z isomers. In contrast, treatment of **165a** and **165b** with ethyl 3-amino-2-butenoate affords the substitution products **167a** and **167b** as a mixture composed predominantly of the Z isomer, but containing some amount (5–8%) of the E isomer.

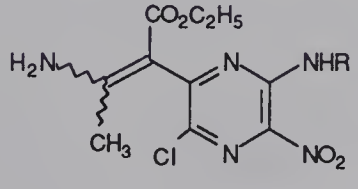


(3-31)



165a R = H
165b R = $COCH_3$

166a
166b

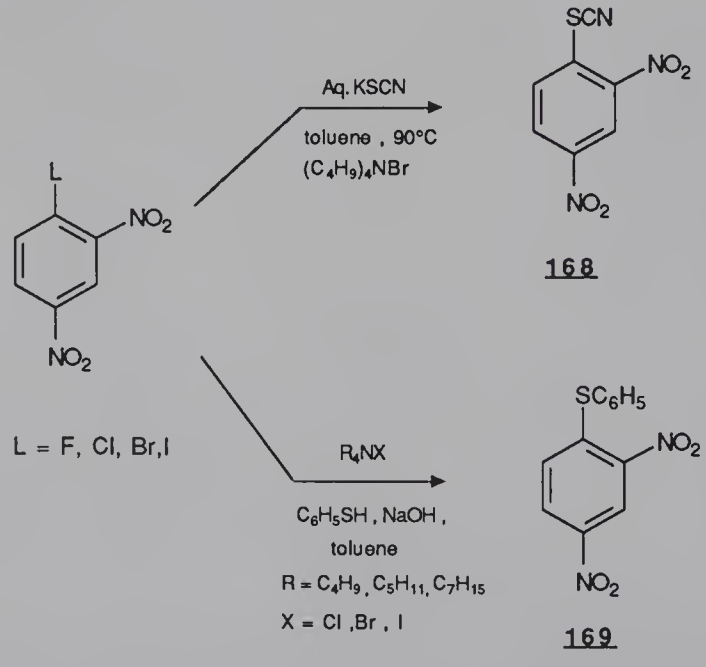


167a R = H
167b R = $COCH_3$

2,4,6-Trinitrophenylcellulose (picryl cellulose)—an interesting electrophilic polymer—was recently synthetized by S_NAr displacement of chloride from picryl chloride by sodium cellulosate in DMSO.[117] Two cel-

lulose ethers with different degrees of picrylation were obtained, which contained one picryl ring per approximately 6.5 glucosyl units (PC-6) and one picryl ring per 12 units (PC-12), respectively. In agreement with most of the substitution occurring at the primary hydroxyl function at C-6 of the glucosyl residues, picryl cellulose displays a thermal behavior characteristic of C-6 substituted cellulose ethers. Nitration of picryl cellulose to give picryl nitrocellulose has been reported.[118]

Phase transfer catalysis has been used to achieve some useful halogen displacements from halonitroaromatics by oxygen, sulfur, and nitrogen nucleophiles. Two noteworthy examples (eq. 3-32) are the conversions in near-quantitative yield of 1-halo-2,4-dinitrobenzenes into the thiocyanate **168** and the diarylsulfide **169**.[9,17] The use of protonated tertiary amines as phase transfer catalysts and of potassium disulfite ($K_2S_2O_5$) as the nucleophilic reagent has also allowed the efficient achievement of the sulfodechlorination of 1-chloro-2,4-dinitrobenzene in the CH_2Cl_2/H_2O two-phase system, resulting in pure 2,4-dinitrobenzenesulfonic acid in high yield.[10] Polyethers have been obtained via a phase-transfer-catalyzed nucleophilic substitution of bis(4-chloro-3-nitrophenyl)sulfone by phenoxide ions.[8,13] The effect of phase transfer catalysis on the ease of ammonolysis of nitroaryl halides is also remarkable.[119]



(3-32)

In conclusion, it is interesting to mention the recent finding by Brunelle and Singleton that *N*-alkyl-4-(*N*,*N*'-dialkylamino)pyridinium salts may be

more suitable phase transfer catalysts than ammonium and phosphonium salts for promoting S_NAr displacements with phenoxide and thiophenoxide salts.[120]

References

1. Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 271.
2. Miller, J. "*Aromatic Nucleophilic Substitution*". Elsevier: Amsterdam, 1968.
3. (a) Beck, J. R. *J. Org. Chem.* **1972**, *37*, 3224; (b) *ibid.* **1973**, *38*, 4086.
4. Beck, J. R.; Yahner, J. A. *J. Org. Chem.* **1974**, *39*, 3440.
5. Knudsen, R. D.; Snyder, H. R. *J. Org. Chem.* **1974**, *39*, 3343.
6. Kornblum, N.; Cheng, L.; Kerber, R. C.; Kestner, M. M.; Newton, B. N.; Pinnick, H. W.; Smith, R. G.; Wade, P. A. *J. Org. Chem.* **1976**, *41*, 1560.
7. Makosza, M. *Tetrahedron Lett.* **1969**, 673.
8. Imai, Y.; Veda, M.; Li, M. *J. Polymer. Sci., Polymer Lett. Ed.* **1979**, *17*, 85.
9. Reeves, W. P.; Simmons, A., Jr.; Keller, K. *Synth. Commun.* **1980**, *10*, 633.
10. Gisler, M.; Zollinger, H. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 203.
11. Soula, G. *J. Org. Chem.* **1985**, *50*, 3717.
12. Clark, J. H.; Macquarrie, D. J. *Tetrahedron Lett.* **1987**, *28*, 111.
13. Andrews, S. M.; Konstantinou, C.; Feld, W. A. *Synth. Commun.* **1987**, *17*, 1041.
14. Beck, J. R. *Tetrahedron*, **1978**, *34*, 2057.
15. Cogolli, P.; Testaferri, L; Tingoli, M.; Tiecco, M. *J. Org. Chem.* **1979**, *44*, 2636.
16. Beck, J. R.; Yahner, J. A. *J. Org. Chem.* **1978**, *43*, 2048.
17. Reeves, W. P.; Bothwell, J. C.; Rudis, J. A.; McClusky, J. V. *Synth. Commun.* **1982**, *12*, 1071.
18. Ferreira, J. T. B.; Simonelli, F.; Comasseto, J. V. *Synth. Commun.* **1986**, *16*, 1335.
19. Norris, R. K.; Randles, D. *Aust. J. Chem.* **1979**, *32*, 2413.
20. Burt, B. L.; Freeman, D. J.; Gray, P. G.; Norris, R. K.; Randles, D. *Tetrahedron Lett.* **1977**, 3063.

21. Nikolaeva, S. V.; Kukovitskii, D. M.; Zorin, V. V.; Rakhmankulov, D. L. *Zh. Obshch. Khim.* **1986**, *56*, 2804.
22. Iwasaki, G.; Saeki, S.; Hamana, M. *Chem. Lett.* **1986**, 31.
23. Hamana, M.; Iwasaki, G.; Saeki, S. *Heterocycles*, **1982**, *17*, 177.
24. Iwasaki, G.; Wada, K.; Saeki, S.; Hamana, M. *Heterocycles*, **1984**, *22*, 1811.
25. Ishikawa, N.; Kuroda, K. *Chem. Abstr.* **1971**, *75*, 63381u.
26. Pedersen, E. B.; Perregärd, J.; Lawesson, S. O. *Tetrahedron*, **1973**, *29*, 4211.
27. Gupton, J. T.; Idoux, J. P.; Baker, G. ; Colon, C.; Crews, A. D.; Jurss, C. D.; Rampi, R. C. *J. Org. Chem.* **1983**, *48*, 2933.
28. (a) Gorvin, J. H. *J. Chem. Soc., Chem. Commun.* **1985**, 238; (b) Gorvin, J. H. *J. Chem. Soc., Perkin Trans. 1*, **1988**, 1331.
29. Iida, H.; Yamazaki, M.; Takahashi, K.; Yamada, K. *Nippon Kagaku Kaishi*, **1976**, 138.
30. Cadogan, J. I. G.; Sears, D. J.; Smith, D. M. *J. Chem. Soc. C*, **1969**, 1314.
31. (a) Sammes, P. G.; Thetford, D.; Voyle, M. *J. Chem. Soc., Chem. Commun.* **1987**, 1373; (b) *J. Chem. Soc., Perkin Trans. 1*, **1988**, 3229.
32. Clark, J. H.; Owen, N. D. S. *Tetrahedron Lett.* **1987**, *28*, 3627.
33. (a) Attina, M.; Cacace, F.; Wolf, A. P. *J. Chem. Soc., Chem. Commun.* **1983**, 108. (b) Attina, M.; Cacace, F.; Wolf, A. P. *J. Lab. Comp. Radiopharm.* **1983**, *20*, 501. (c) Angelini, G.; Speranza, M.; Wolf, A. P.; Shiue, C. Y. *J. Fluoride Chem.* **1985**, *27*, 177. (d) Maeda, M.; Fukumura, T.; Kojima, M. *Chem. Pharm. Bull.* **1985**, *33*, 1301. (e) Rieux, C.; Langlois, B.; Gallo, R. *C.R. Acad. Sci. Paris, Ser. 2*, **1990**, *310*, 25.
34. Clark, J. H.; Smith, D. K. *Tetrahedron Lett.* **1985**, *26*, 2233.
35. Cacace, F.; Speranza, M.; Wolf, A. P.; Fowler, J. S. *J. Lab. Comp. Radiopharm.* **1981**, *18*, 1721.
36. Fowler, J. S.; Arnett, C. D.; Wolf, A. P.; MacGregor, R. R.; Norton, E. F.; Findley, A. M. *J. Nuclear Med.* **1982**, *23*, 437.
37. Montanari, F.; Pelosi, M.; Rolla, F. *Chem. Ind.* **1982**, 412.
38. Bartoli, G.; La Trofa, A.. Naso, F.; Todesco, P. E. *J. Chem. Soc., Perkin Trans. 1*, **1972**, 2671.
39. (a) Doddi, G.; Illuminati, G.; Mencarelli, P.; Stegel, F. *J. Org. Chem.* **1976**, *41*, 2824; (b) Di Lorenzo, A.; Mencarelli, P.; Stegel, F. *ibid.* **1986**, *51*, 2125.
40. Mencarelli, P.; Stegel, F. *J. Org. Chem.* **1977**, *42*, 3550.
41. Newcombe, P. J.; Norris, R. K. *Aust. J. Chem.* **1978**, *31*, 2463.

42. Mokrushin, V. S.; Belyaev, N. A.; Kolobov, M. Yu.; Fedotov, A. N. *Khim. Geterotsikl. Soedin.* **1983**, 808.

43. Logue, M. W.; Han, B. H. *J. Org. Chem.* **1981**, *46*, 1638.

44. Reinders, W.; Ringer, W. E. *Rec Trav. Chim. Pays-Bas*, **1899**, *18*, 326.

45. Gorvin, J. H. *Chem. Ind.* **1967**, 1525.

46. Gorvin, J. H.; Whalley, D. P. *J. Chem. Soc., Perkin Trans. 1*, **1979**, 1364.

47. Fischer, W.; Kvita, V. *Helv. Chim. Acta*, **1985**, *68*, 854.

48. Olivard, J.; Heotis, J. P. *J. Org. Chem.* **1968**, *33*, 2552.

49. Shimadzu, M.; Ishikawa, N.; Yamamoto, K.; Tanaka, A. *J. Heterocycl. Chem.* **1986**, *23*, 1179.

50. Idoux, J. P. ; Madenwald, M. L.; Garcia, B. S.; Chu, D. L. *J. Org. Chem.* **1985**, *50*, 1876.

51. Idoux, J. P.; Gupton, J. T.; McCurry, C. K.; Crews, A. D.; Jurss, C. D.; Colon, C..; Rampi, R. C. *J. Org. Chem.* **1983**, *48*, 3771.

52. (a) Gupton, J. T.; Idoux, J. P.; Decrescenzo, G.; Colon, C. *Synth. Commun.* **1984**, *14*, 621; (b) Gupton, J. T.; Idoux, J. P.; Colon, C.; Rampi, R. *ibid.* **1982**, *12*, 695.

53. (a) Lee, C. C.; Abd-el-Aziz, A. J.; Chowdhury, R. L.; Piorko, A.; Sutherland, R. G. *Synth. React. Inorg. Met.-Org. Chem.* **1986**, *16*, 541; (b) Chowdhury, R. L.; Lee, C. C.; Piorko, A.; Sutherland, R.G. *ibid.* **1985**, *15*, 2237.

54. Beck, J. R.; Suhr, R. G. *J. Heterocycl. Chem.* **1974**, *11*, 227.

55. Knudsen, R. D.; Morrice, A. G.; Snyder, H. R. *J. Org. Chem.* **1975**, *40*, 2878.

56. Baumann, J. B. *Synthesis*, **1975**, 782.

57. Mauleon, D.; Granados, R.; Minguillon, C. *J. Org. Chem.* **1983**, *48*, 3105.

58. (a) Heath, D. R.; Wirth, J. G. U.S. Pat. 3,763,210 (1973); *Chem. Abstr.* **1974**, *80*, 3246x. (b) Takekoshi, T.; Wirth, J. G.; Heath, D. R.; Kochanowski, J. E.; Manello, J.S.; Webber, M. J. *J. Polym. Sci. Polym. Chem. Ed.* **1980**, *18*, 3069, and patents therein.

59. Williams, F. J.; Donahue, P. E. *J. Org. Chem.* **1977**, *42*, 3414.

60. Williams, F. J.; Relles, H. M.; Manello, J. S.; Donahue, P. E. *J. Org. Chem.* **1977**, *42*, 3419.

61. Relles, H. M.; Johnson, D. S.; Manello, J. S. *J. Am. Chem. Soc.* **1977**, *99*, 6677.

62. Relles, H. M.; Johnson, D. S.; Dellacoletta, B. A. *J. Org. Chem.* **1980**, *45*, 1374.

63. Caswell, L. R.; Kao, J. L. *J. Heterocycl. Chem.* **1966**, *3*, 333.

64. Wirth, J. G.; Heath, D. R. U.S. Pat. 3,838,097 (1974); *Chem. Abstr.* **1975**, *82*, 17479d.

65. Radlmann, E.; Schmidt, W.; Nischk, G. E. *Makromol. Chem.* **1969**, *130*, 45.

66. Tanaka, A.; Usui, T.; Shimadzu, M. (a) *J. Heterocycl. Chem.* **1981**, *18*, 1241; (b) *Chem. Pharm. Bull.* **1980**, *28*, 2846.

67. Baumann, S. *J. Org. Chem.* **1971**, *36*, 396.

68. Beck, J. R. *J. Heterocycl. Chem.* **1978**, *15*, 513.

69. Teulade, J. C.; Grassy, G.; Escale, R.; Chapat, J. P. *J. Org. Chem.* **1981**, *46*, 1026.

70. (a) Beck, J. R.; Yahner, J. A. *J. Org. Chem.* **1973**, *38*, 2450; (b) *ibid.* **1978**, *43*, 1604.

71. (a) Williams, F. J.; Donahue, P. E. *J. Org. Chem.* **1978**, *43*, 250; (b) *ibid.* **1978**, *43*, 255.

72. (a) Markezich, R. L.; Zamek, O. S. *J. Org. Chem.* **1977**, *42*, 3431; (b) Markezich, R. L.; Zamek, O. S.; Donahue, P. E.; Williams, F. J. *ibid.* **1977**, *42*, 3435.

73. Fischer, W.; Kvita, V. *Helv. Chim. Acta* **1985**, *68*, 846.

74. Kirillov, I. T.; Kukovitskii, O. M.; Zorin, V. V.; Plakhtinskii, V. V.; Rakhmankulov, D. L. *Zh. Org. Khim.* **1987**, *23*, 444.

75. Makosza, M.; Jagusztyn-Grochowska, M.; Ludwikow, M.; Jawdosiuk, M. *Tetrahedron* **1974**, *30*, 3723.

76. Iwasaki, G.; Saeki, S.; Hamana, M. *Chem. Lett.* **1986**, 173.

77. Gill, U. S. *Inorg. Chim. Acta*, **1986**, *114*, 25.

78. Moriarty, R. M.; Gill, U. S. *Organometallics*, **1986**, *5*, 253.

79. Ishikawa, N.; Tanabe, T.; Hayashi, D. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 359.

80. Bailey, D. M.; Wood, D. *J. Heterocycl. Chem.* **1974**, *11*, 229.

81. (a) Hwang, D. R.; Moerlein, S. M.; Lang, L; Welch, M. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1799; (b) Berridge, M. S.; Crouzel, C.; Comar, D. *J. Lab. Comp. Radiopharm.* **1985**, *22*, 687.

82. Beck, J. R.; Yahner, J. A. *J. Org. Chem.* **1978**, *43*, 2052.

83. Beck, J. R.; Sobczak, R. L; Suhr, R. G. ; Yahner, J. A. *J. Org. Chem.* **1974**, *39*, 1839.

84. Benedetti, F.; Marshall, D. R.; Stirling, C. J. M.; Leng, J. L. *J. Chem. Soc., Chem. Commun.* **1982**, 918.

85. Biggi, G.; Pietra, F. *J. Chem. Soc., Perkin Trans. 1*, **1973**, 1980.

86. Kozikowski, A. P.; Greco, M. N. *J. Am. Chem. Soc.* **1980**, *102*, 1165.

87. Ishikawa, N.; Inoue, Y.; Kitagawa, K. *Nippon Kagaku Zasshi*, **1970**, *91*, 742.

88. Holmes, C. W. N.; Loudon, J. D. *J. Chem. Soc.* **1940**, 1521.

89. De Munno, A.; Bertini, V.; Denti, G. *Int. J. Sulfur Chem. A*, **1972**, *2*, 25.

90. Nielsen, A. T.; Henry, R. A.; Norris, W. P.; Atkins, R. L.; Moore, D. W.; Coon, C. L.; Spanggord, R. J.; Son, D. V. H. *J. Org. Chem.* **1979**, *44*, 2499.

91. Nielsen, A. T.; Chafin, A. P.; Christian, S. L. *J. Org. Chem.* **1984**, *49*, 4575.

92. Gore, P. H.; Hammond, S. D.; Morris, D. F. C. *Tetrahedron Lett.* **1970**, 2747.

93. Okamoto, Y.; Attarwala, S. T. *J. Org. Chem.* **1979**, *44*, 3269.

94. Ibata, T.; Isogami, Y.; Toyoda, J. *Chem. Lett.* **1987**, 1187.

95. Ayyangar, N. R.; Lahoti, R. J.; Srinivasan, K. V.; Daniel, T. *Org. Prep. Proced. Int.* **1987**, *19*, 167.

96. Pilichowski, J. F.; Gramain, J. C. *Synth. Commun.* **1984**, *14*, 1247.

97. (a) Sekiguchi, S.; Horie, T.; Suzuki, T. *J. Chem. Soc., Chem. Commun.* **1988**, 698; (b) Sekiguchi, S.; Suzuki, T.; Hosokawa, M. *J. Chem. Soc., Perkin Trans. 2*, **1989**, 1783.

98. Sitzmann, M. E. *J. Org. Chem.* **1978**, *43*, 1241.

99. Burdon, J.; Fischer, D.; Parsons, I. W.; Tatlow, J. C. *J. Fluoride Chem.* **1981**, *18*, 507.

100. Koppes, W. M.; Lawrence, G. W.; Sitzmann, M. E.; Adolph, H. G. *J. Chem. Soc., Perkin 1*, **1981**, 1815.

101. Jones, P. R.; Rothenberger, S. D. *J. Org. Chem.* **1986**, *51*, 3016.

102. Henichart, J. P.; Bernier, J. L; Vaccher, C.; Houssin, R.; Warin, V.; Baert, F. (a) *Tetrahedron Lett.* **1979**, 945; (b) *Tetrahedron*, **1980**, *36*, 3535.

103. Forlani, L; De Maria, P.; Foresti, E.; Pradella, G. *J. Org. Chem.* **1981**, *46*, 3178.

104. Read, R. W.; Norris, W. P. *Aust. J. Chem.* **1985**, *38*, 435.

105. (a) Boulton, A. J.; Ghosh, P. B. *Adv. Heterocyclic Chem.* **1969**, *10*, 1; (b) Gasco, A.; Boulton, A. J. *ibid.* **1981**, *29*, 251.

106. Boyer, J. H. *Chem. Rev.* **1980**, *80*, 495.

107. Yagupolskii, L. M.; Gogoman, I. V.; Shchupak, G. M. ; Boiko, V. N. *Zh. Org. Khim.* **1986**, *22*, 743 (*J. Org. Chem. USSR*, **1986**, *22*, 664).

108. Gilman, N. W.; Holland, B. C.; Walsh, G. R.; Fryer, R. I. *J. Heterocycl. Chem.* **1977**, *14*, 1157.

109. (a) Gilman, N. W.; Holland, B. C.; Fryer, R. I. *J. Heterocycl. Chem.* **1977**, *14*, 1163; (b) Gilman, N. W.; Fryer, R. I. *ibid.* **1977**, *14*, 1171.

110. Shipp, K. G.; Kaplan, L. A.; Sitzmann, M. E. *J. Org. Chem.* **1972**, *37*, 1966.

111. (a) Kavalek, J.; Machacek, V.; Pastrnek, M.; Sterba, V. *Collect. Czech. Chem. Commun.* **1977**, *42*, 2928; (b) Kavalek, J.; Pastrnek, M.; Sterba, V. *ibid.* **1978**, *43*, 1401.

112. Kavalek, J.; Machacek, V.; Lycka, A.; Sterba, V. *Collect. Czech. Chem. Commun.* **1976**, *41*, 590.

113. Matsumura, E.; Ariga, M. (a) *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3144; (b) *ibid.* **1977**, *50*, 237.

114. Bordwell, F. G.; Hughes, D. L. *J. Am. Chem. Soc.* **1986**, *108*, 5991.

115. Effenberger, F.; Agster, W.; Fischer, P.; Jogun, K. H.; Stezowski. J. J. ; Daltrozzo, E.; Kollmannsberger-von Nell, G. *J. Org. Chem.* **1983**, *48*, 4649.

116. Hartman, G. D.; Hartman, R. D.; Cochran, D. W. *J. Org. Chem.* **1983**, *48*, 4119.

117. Strauss, M. J.; Torres, R.; Phelan, J.; Craft, A.; Pitner, B.; Nason, D.; Carignan, Y.; Dust, J. M.; Buncel, E. *Can. J. Chem.* **1987**, *65*, 1891.

118. Strauss, M. J.; Torres, R.; Carignan, Y.; Buncel, E. *Tetrahedron Lett.* **1987**, *28*, 159.

119. Barak, G.; Sasson, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1267.

120. Brunelle, D. J.; Singleton, D. A. *Tetrahedron Lett.* **1984**, *25*, 3383.

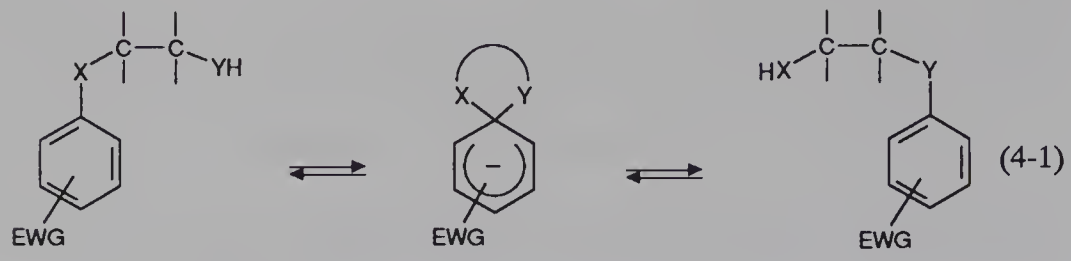
CHAPTER 4.
Intramolecular S_NAr Reactions

4.1 Introduction

It was pointed out in Chapter 3 that an activated aromatic nitro group is especially susceptible to intermolecular S_NAr displacement when there are other groups in close proximity that prevent its coplanarity with the aromatic ring. When one of these groups is a side chain containing a potential and appropriately located nucleophilic site, structural conditions required for an intramolecular S_NAr displacement of such sterically hindered nitro groups exist. Section 4.2 describes a variety of reactions that demonstrate the utility of the process for the synthesis of many heterocyclic ring systems. A few systems involving intramolecular displacement of other leaving groups also are mentioned.

Cyclization reactions through intramolecular nitro group displacement are part of synthetic methods involving neighboring group interaction in ortho-substituted nitroarene derivatives. This general area has been reviewed by Preston and Tennant in 1972.[1] A shorter review appeared in 1982.[2]

Section 4.3 deals with intramolecular rearrangements of the type shown in eq. 4-1, which are known as Smiles rearrangements.[3–8] The nitro group is especially efficient as an electron-withdrawing group (EWG) providing the activation for such intramolecular S_NAr substitutions, which proceed through formation of the intermediate spiro complex 1. In eq. 4-1, X and Y represent various combinations of heteroatoms (O, S, N—R) and the carbon chain joining X and Y may be saturated or part of an aromatic system. On the other hand, depending on the nature of YH, a proton transfer may precede (Y = O, S) or follow (Y = NR) the formation of 1; this may or may not require the presence of an external base.



(4-1)

1

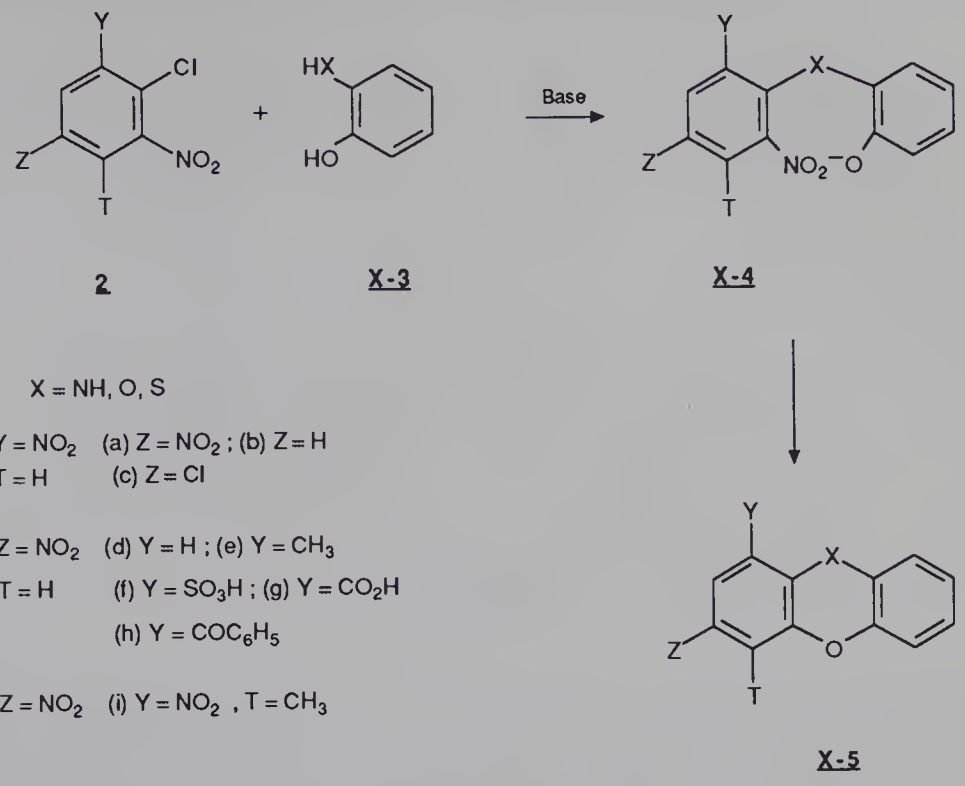
4.2 Intramolecular Nitro Group Displacements

4.2.1 Displacements by Oxygen Nucleophiles

Intramolecular S_NAr displacements of a nitro group by a phenolic oxygen are involved in the synthesis of a number of oxygen-containing heterocycles. A long-known prototype reaction is the Turpin reaction in which *o*-chloronitrobenzenes (**2**) are condensed with *o*-aminophenol (**NH-3**) or related derivatives under basic conditions.[1] As shown in Scheme 4.1, the interaction consists of an initial intermolecular S_NAr substitution of the chlorine atom of **2** by the amino group of **NH-3** to give the 2-hydroxy-2′-nitrodiphenylamines **NH-4**. These amines subsequently cyclize to the phenoxazines **NH-5** via intramolecular substitution of an *o*-nitro group by the remaining phenoxide functionality. Many examples of this reaction have been quoted in reviews.[1,2,9]

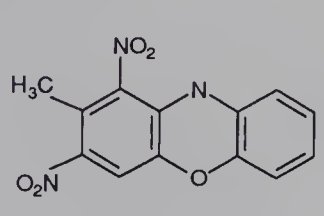
Analogous nucleophilic substitution reactions of some *o*-chloronitrobenzenes (**2**) with pyrocatechol (**O-3**) and thiopyrocatechol (**S-3**) have been used for the synthesis of phenodioxins **O-5** and phenoxathiins **S-5**, respectively.[1,2] Most of these reactions obey Scheme 4.1; that is, they occur via direct cyclization of initially formed diphenyl ethers **O-4** or diphenyl sulfides **S-4**.[1,2,10–12] However, examples are given in Section 4.3 of syntheses of phenoxazines, phenodioxins, and phenoxathiins in which the S_NAr substitution of the chlorine atom of **2** gives rise to an intermediate that undergoes a Smiles rearrangement prior to cyclization.

Steric effects are important in determining the course of the reactions presented in Scheme 4.1. For example, treatment of **NH-3** with 3-chloro-2,4,6-trinitrotoluene (**2i**) gives only the phenoxazine **NH-5i**.[1] No trace of the isomeric phenoxazine **NH-6i** could be found. This shows that the cyclization of the intermediate diphenylamine **NH-4i** takes place exclusively via displace-

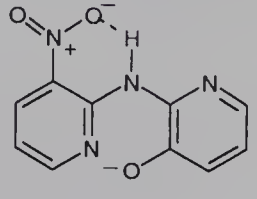


Scheme 4.1.

ment of the most sterically hindered nitro group. A similar regioselectivity was observed in many intermolecular nitro substitutions (see Chapter 3, Section 3.2.3).

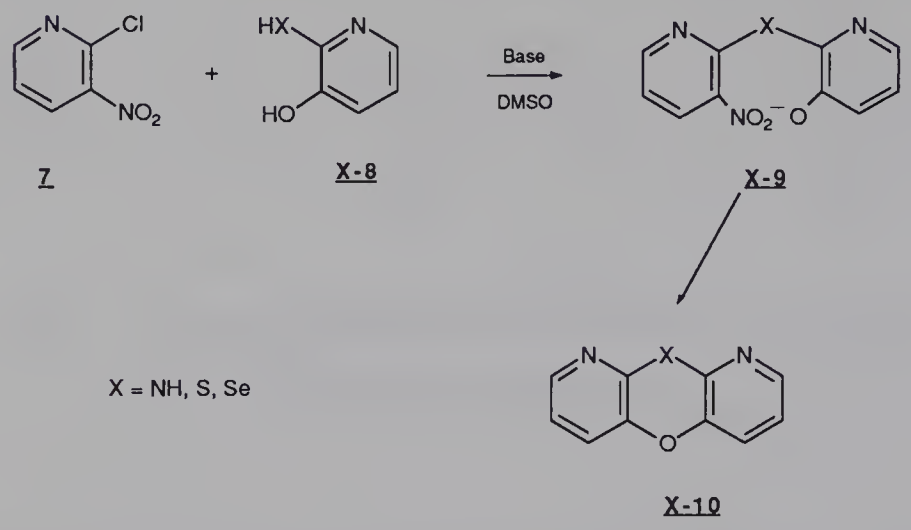


NH-6I



11

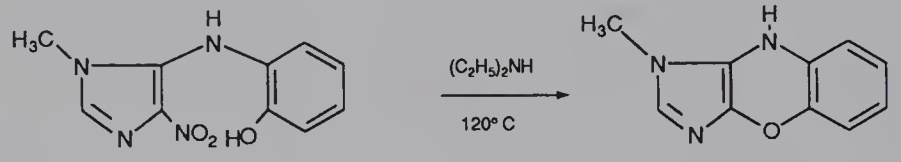
In a search for new biologically active heterocycles, efforts have been directed toward the synthesis of monoaza and diaza derivatives.[13–23] The synthesis of 1,9-diazaphenoxazine (**NH-10**) from 2-chloro-3-nitropyridine (**7**) and 2-aminopyridin-3-ol (**NH-8**) is a representative example (Scheme 4.2).[14a] In this instance, the intermediate dipyridylamine **NH-9** is susceptible to strong stabilization through intramolecular hydrogen bonding, as shown in structure **11**, and it fails to cyclize in aqueous or alcoholic base. Hydrogen bonding, as



7 X-8 X-9 X-10

Scheme 4.2.

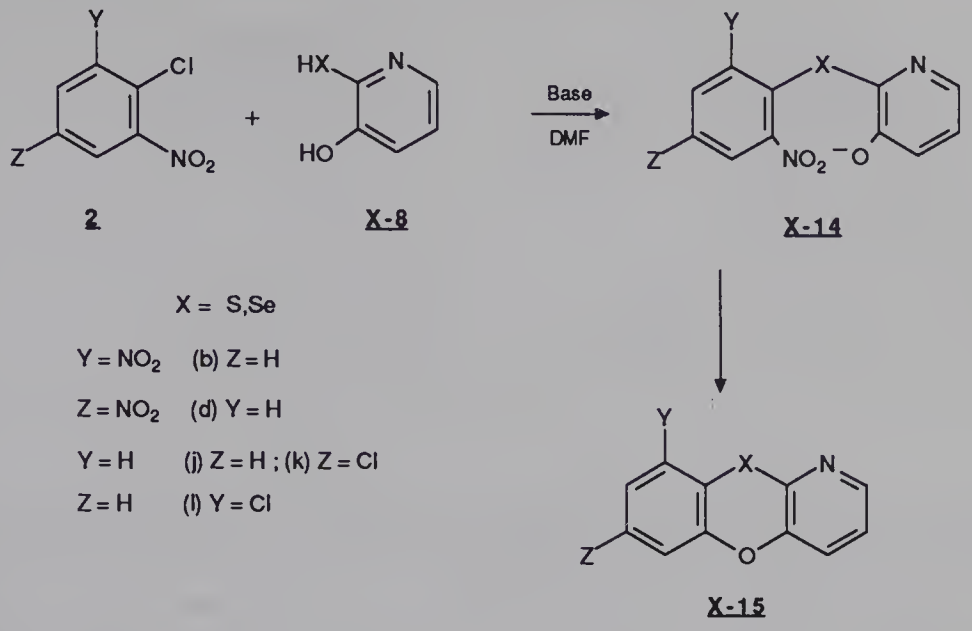
depicted in **11**, is a common situation in many *o*-nitrodiphenylamines, including the 2-hydroxy-2′-nitrodiphenylamines **NH-4** involved in Scheme 4.1.[2,14,24] However, breaking of the hydrogen bond occurs in dipolar aprotic solvents like DMSO—a strong hydrogen bond acceptor—and this allows the cyclization of **NH-9** (= **11**) to **NH-10** to be achieved.[14a] Upon treatment of **NH-3** with 5-chloro-4-nitro-1-methylimidazole in the presence of sodium acetate in ethanol, the amine **12** is obtained, which upon heating in diethylamine, affords the imidazolobenzoxazine **13** in 25% yield (eq. 4-2).[25] Subsequent oxidation of **13** readily occurs to give free radicals for which an azyl or azhydrin structure has been proposed.



(4-2)

12 13

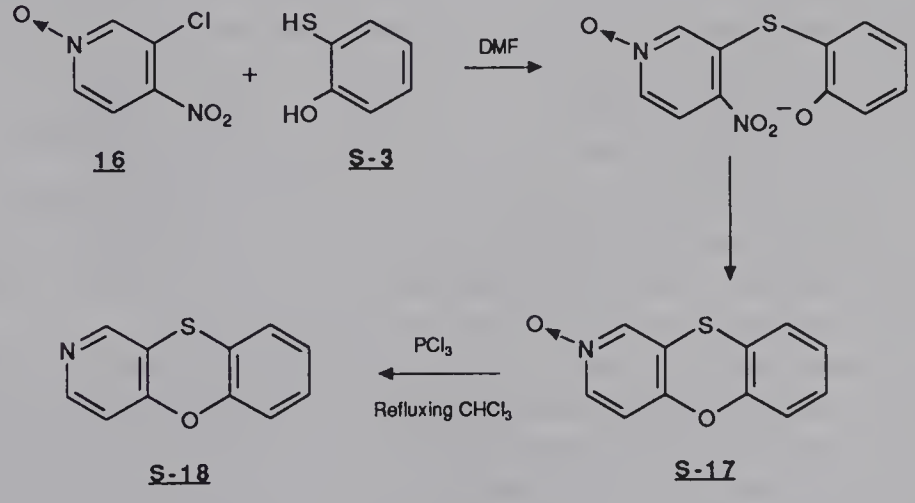
Martin and coworkers have reported the synthesis of several monoaza- and diazaphenoxathiins.[15–20] Condensation of the disodium salt of 3-hydroxypyridine-2-thiol (**S-8**) with *o*-chloronitrobenzenes (**2**) in DMF at or below room temperature gave the sulfides **S-14** which, without isolation, afforded upon heating moderate yields of the 7- and 9- nitro- or -chloro-1-azaphenoxathiins **S-15 b,d,k,l** as well as the parent unsubstituted derivative **S-15j** (Scheme 4.3).[15,16] A number of related 1-azaphenoxaselenines (**Se-15**)



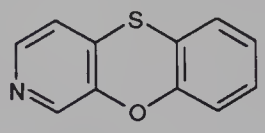
Scheme 4.3.

have recently been synthesized in a similar way using the dianion of 3-hydroxypyridine-2-selol (**Se-8**) as the nucleophile precursor; yields are in the range of 50–70% (Scheme 4.3).[22]

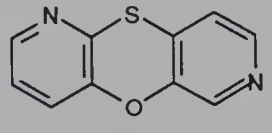
2-Azaphenoxathiin (**S-18**) was obtained from the reaction of 3-chloro-4-nitropyridine 1-oxide (**16**) with thiopyrocatechol (**S-3**) and the reduction of the resulting 2-azaphenoxathiin 2-oxide (**S-17**: 20% overall yield; Scheme 4.4). Activation by the *N*-oxide group in **16** promotes a more efficient initial S_NAr



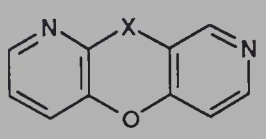
Scheme 4.4.



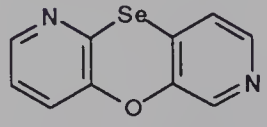
S-19



S-20



X-21

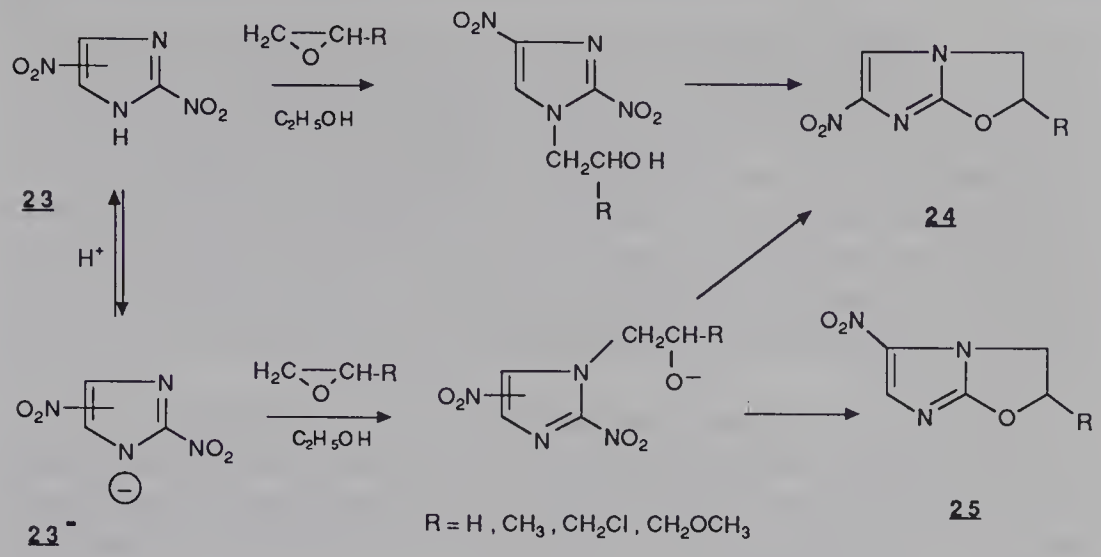


Se-22

displacement of the chlorine atom, thereby facilitating the overall synthesis of **S-18**.[17] The displacement by **S-3** of the chlorine atom of 4-chloro-3-nitropyridine, which is activated by both an *o*-nitro group and a *p*-aza functionality, was found to take place more readily, yielding a sulfide whose cyclization afforded 3-azaphenoxathiin (**S-19**) as the final product (60% yield).[18]

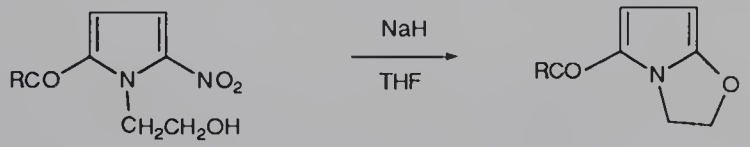
Condensation of the dianions of the 3-hydroxypyridine-2-thiol and -selol (**S-8** and **Se-8**) with 2-chloro-3-nitropyridine (**7**) in DMF according to Scheme 4.2 gave the desired 1,9-diazaphenoxathiin and -selenine (**S-10** and **Se-10**) in 79 and 25% yield, respectively.[19,23] The formation of **S-10** was also achieved in DMSO.[21] The low yield of **Se-10** is the consequence of the predominance of a competitive Smiles rearrangement process in the selenium system.[23] Under the same conditions as those described in Scheme 4.2, 4-chloro-3-nitropyridine reacts with **S-8** to give 1,7-diazaphenoxathiin (**S-20**) in 58% yield.[19] Using the method described for the synthesis of **S-18**, 1,8-diazaphenoxathiin (**S-21**: overall yield, 65%) and 1,8-diazaphenoxaselenine (**Se-21**: overall yield, 43%) were obtained upon treatment of 3-chloro-4-nitropyridine 1-oxide (**16**) with **S-8** and **Se-8** according to Scheme 4.4.[20,23] Interestingly, the reactions also afforded a minor amount of 1,7-diazaphenoxathiin (**S-20**) and 1,7-diazaphenoxaselenine (**Se-22**).[20,23] The formation of **S-20** and **Se-22** indicates that a reaction pathway consisting of an initial displacement of the nitro group **16** by the thiolate or selenide functions of **S-8** and **Se-8**, followed by intramolecular substitution of the remaining chlorine atom, competes with that depicted in Scheme 4.4.

Intramolecular ortho-nitro substitutions by the alcoholic oxygen of a suitably located 2-hydroxyalkyl substituent afforded compounds with an oxygen-containing five-membered ring. Agrawal *et al.* reported the preparation of the isomeric 2,3-dihydroimidazo[2,1-*b*]oxazoles **24** (35–75% yield) and **25** (25% yield) from the reaction of 2,4(5)-dinitroimidazole (**23**) with

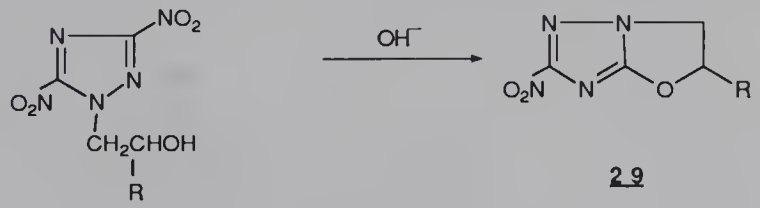


Scheme 4.5.

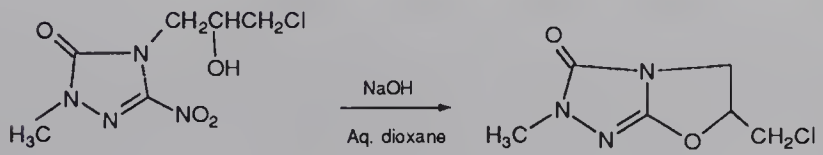
various oxiranes at 40–80°C in ethanol.[26,27] As shown in Scheme 4.5, isomers **24** and **25** would form from the initial reaction of the oxiranes with the nonionized and ionized fractions of the parent imidazole. Similar intramolecular displacements occur in the base-catalyzed cyclizations of 2-acyl-



(4-3)



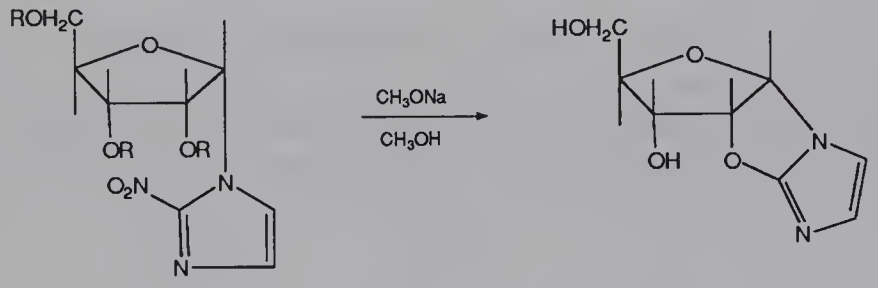
(4-4)



(4-5)

1-(β-hydroxyethyl)-5-nitropyrroles **26** (eq. 4-3) and 1-(β-hydroxy alkyl)-3,5-dinitro-1,2,4-triazoles **28** (eq. 4-4), which gave good yields of 5-acyl-2,3-dihydropyrrolo [2,1-b] oxazoles **27** and 2-nitro-5,6-dihydrooxazolo[3,2-*b*] [1,2,4]triazole derivatives **29**, respectively.[28,29] Compounds **26** and **28** were previously obtained from the reaction of 2-acyl-5-nitropyrroles or 3,5-dinitro-1,2,4-triazole with the appropriate oxirane. This cyclization process has been extended to a triazolone derivative **30**, which forms, in basic media, 2-methyl-3-oxo-6-chloromethyl-5,6-dihydrooxazolo[3,2-*b*] [1,2,4]-triazole (**31**) in 52% yield (eq. 4-5).[30]

Verheyden *et al.* have reported that treatment of 1-(α-D-ribofuranosyl)-2-nitroimidazole **32** with methanolic sodium methoxide produced in low yield the 2,2′-anhydronucleoside **33**.[31] This product resulted from intramolecular displacement of the 2-nitro function by the cis-oriented 2′-hydroxy group that is formed in the solvolysis process (eq. 4-6).

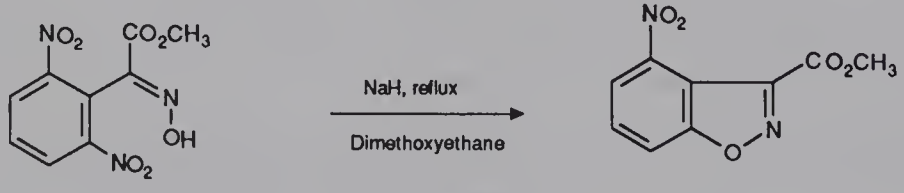


(4-6)

32 R = COC_6H_5

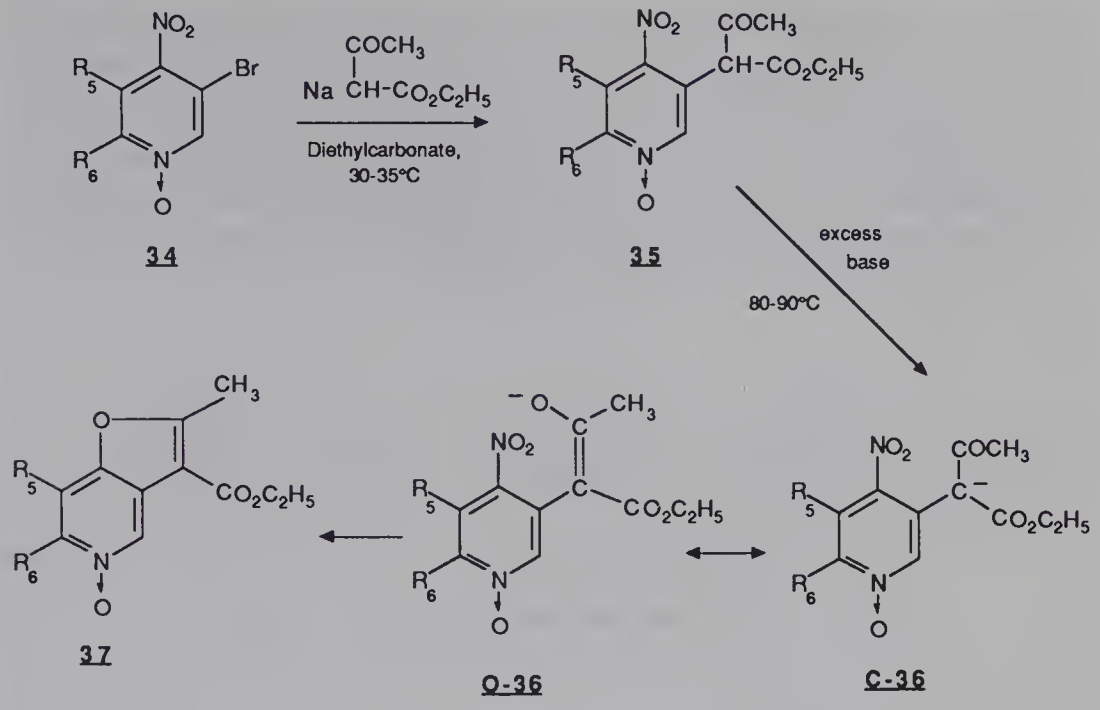
33

Nitro substitution by an oxime function is a well-known procedure leading to benzisoxazoles.[1,2,32] In most reported cases, the cyclization is favored by the presence of another activating group (e.g., a second NO_2 group). Equation 4-7 shows a representative reaction.[33]



(4-7)

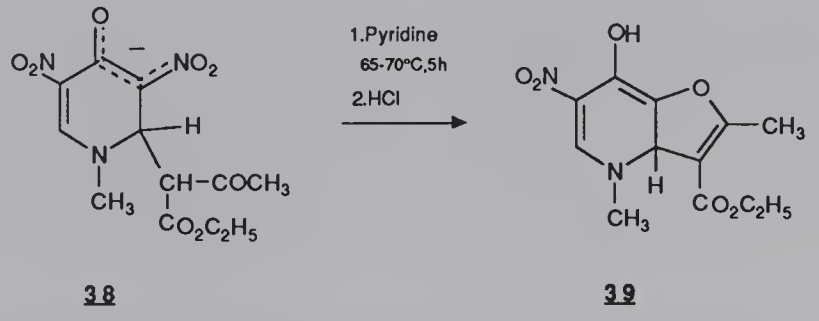
Several cyclizations occur via S_NAr substitution of a nitro group by an enolic oxygen. Reactions of 3-bromo-4-nitropyridine 1-oxides (**34**) with ethyl acetoacetate anion afford the C-substituted S_NAr products **35**, which can sometimes be isolated (e.g., **35a** and **35b**). With excess base, compounds **35** readily lose a methine proton to give the enolate anions **36**. Subsequent intramolecular displacement of the 4-nitro group by the nucleophilic oxygen



(a) $R_5 = R_6 = H$; (b) $R_5 = H$, $R_6 = CH_3$; (c) $R_5 = Br$, $R_6 = H$

Scheme 4.6.

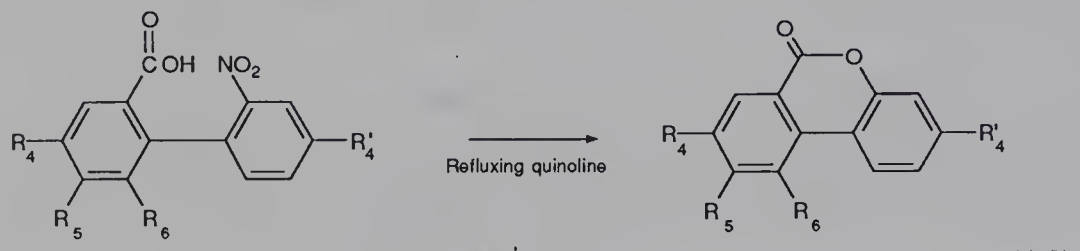
affords furo[3,2-*c*]pyridine *N*-oxides **37** in high yields (Scheme 4.6).[34] Similar displacement occurs within the σ-type adduct **38**, which is initially formed in the reaction of 3,5-dinitro-1-methyl-4-pyridone with ethyl acetoacetate anion. The final product in this instance is **39** (eq. 4-8).[35]



(4-8)

Facile intramolecular displacement of the nitro group by the carboxylate group commonly occurs in 2'-nitrobiphenyl-2-carboxylic acids (**40**) on refluxing solutions of these compounds in solvents of appreciable basicity like quinoline, DMF, or DMSO or in the presence of an external base, in solvents

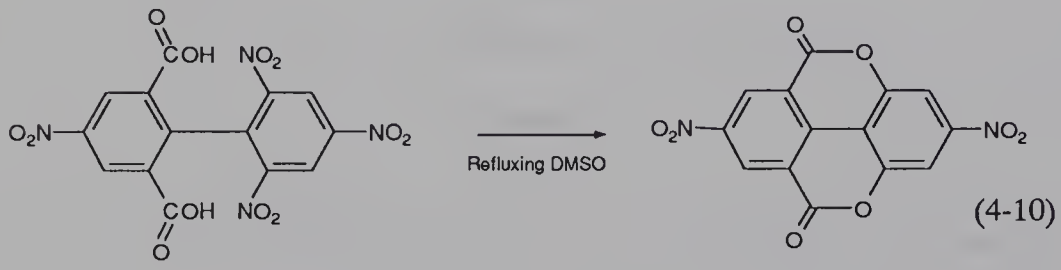
like xylene or tetralin.[36,37] Excellent yields of the benzocoumarins **41** (eq. 4-9) are obtained. The juxtaposition of the nitro and carboxyl groups is especially favorable in the 2,6-dicarboxylic acids (**42**), which readily cyclize to **43** (90% yield) in DMSO (eq. 4-10).[38] Cyclization of 2,2′-dicarboxylic acids also occurs but is made more difficult by a possible stabilization of the intermediate carboxylate anions via intramolecular hydrogen bonding, as shown in **44**.[39,40]



(a) $R_4 = R_5 = R_6 = R'_4 = H$
(b) $R_4 = NO_2$; $R_5 = R_6 = R'_4 = H$
(c) $R_4 = R_5 = R_6 = R'_4 = OCH_3$

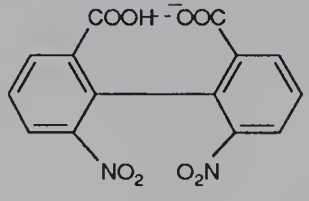
(4-9)

40 **41**



(4-10)

42 **43**

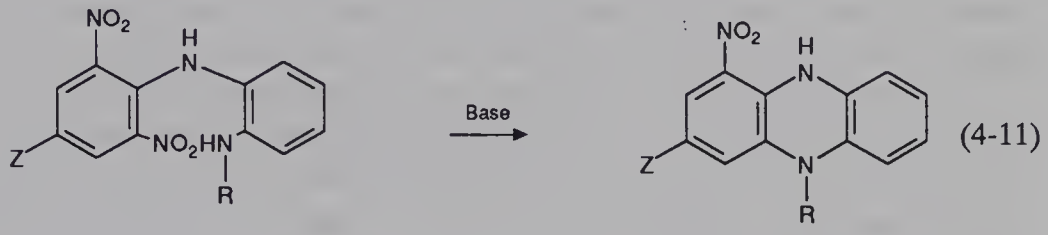


44

4.2.2 Displacements by Nitrogen Nucleophiles

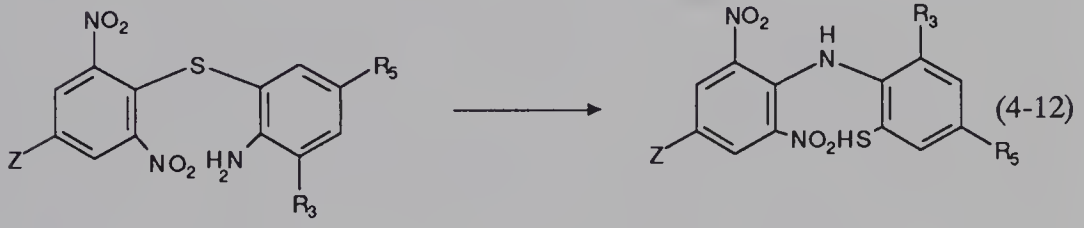
Intramolecular nitro group substitution by an arylamine nitrogen is the key step in the synthesis of nitrophenazines (**46**) from polynitrodiphenylamines (**45**) (eq. 4-11).[1,2] The same holds for the synthesis of related aza derivatives.[1]

On the other hand, base-catalyzed cyclization of the *o*-aminodiaryl sulfides **47**, which result from the reactions of *o*-mercaptoaniline derivatives with various *o*-chloronitrobenzenes, generally have failed.[1,2] In this case, Smiles rearrangement of **47** to the corresponding *o*-mercaptodiphenylamines **48** occurs first (eq. 4-12), and cyclization to phenothiazines takes place via nitro displacement by a thiolate function.[1,2] Reactions leading to phenothiazines and related aza derivatives are therefore detailed later: (Section 4.3.4: Scheme 4.24).



(4-11)

45 R = H, CH_3, C_2H_5, $CH_2C_6H_5$, C_6H_5; Z = NO_2, H **46**



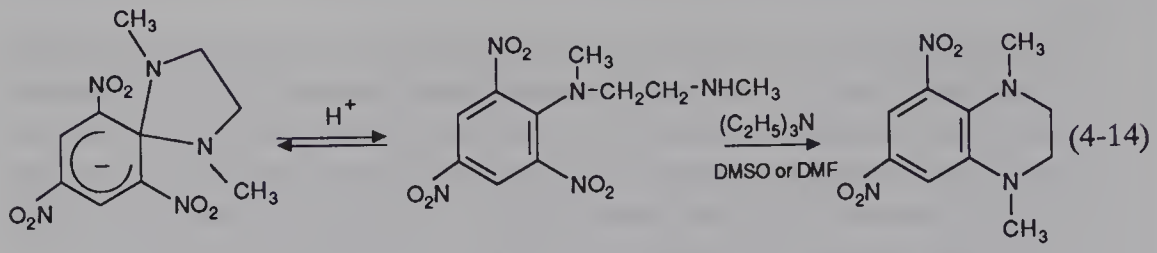
(4-12)

47 Z = NO_2, Cl, H ; R_3 = H, CH_3, OCH_3, Cl ; R_5 = H, OC_2H_5 **48**

Contrasting with arylamines, aliphatic amines have nucleophilicities comparable to those of thiolate anions. Because of this, experimental conditions could be found in which a compound like 1-[β-(*N*-methylamino)ethylthio]-2,4,6-trinitrobenzene (**49a**) did not undergo appreciable rearrangement to the corresponding sulfide,[41,42] allowing the preparation of the benzothiazine **50a** (86% yield) via intramolecular nitro substitution by the dialkylamino group (eq. 4-13).[41,42] However, the mechanistic aspects of the reaction are more appropriately discussed in Section 4.3.4, in connection with Scheme 4.23. Despite a rapid and thermodynamically favored initial conversion to the spiro

(4-13)

49a **50a**

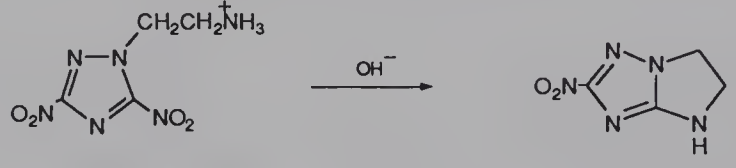


(4-14)

52 51 53

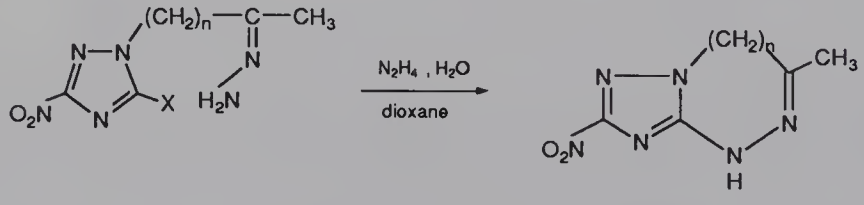
complex **52**, *N,N'*-dimethyl-*N*-picrylethylenediamine (**51**) reacts with triethylamine in DMSO or DMF to produce finally **53** (the product of nitro substitution) in high yield (≈ 65%) (eq. 4-14).[43]

Kofman *et al.* have reported the base-catalyzed cyclization of 1-(β-aminoethyl)-3,5-dinitro-1,2,4-triazole(**54**) to **55**(51% yield) via nitro substitution by the alkylamino group (eq. 4-15).[44] Related reactions are the conversions of the hydrazones **56** to either the triazolo[3,2-*c*][1,2,4]triazines **57a,b** or -triazepine **57c** (eq. 4-16).[45]



(4-15)

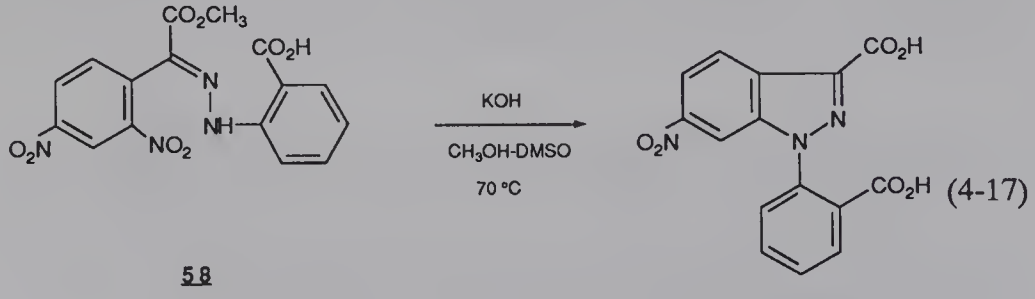
54 55



(4-16)

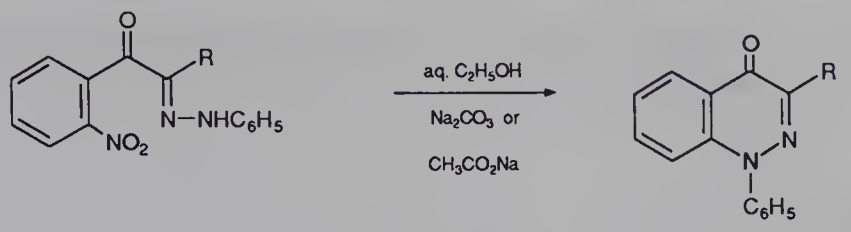
56 (a) X = Br, n=1 ; (b) X= NO_2, n= 1; (c) X= NO_2, n= 2; 57

Nitro substitution by a hydrazone functionality provides a well-known route to indazoles.[1,2,9] A representative example is the synthesis in 96% yield



(4-17)

58 59

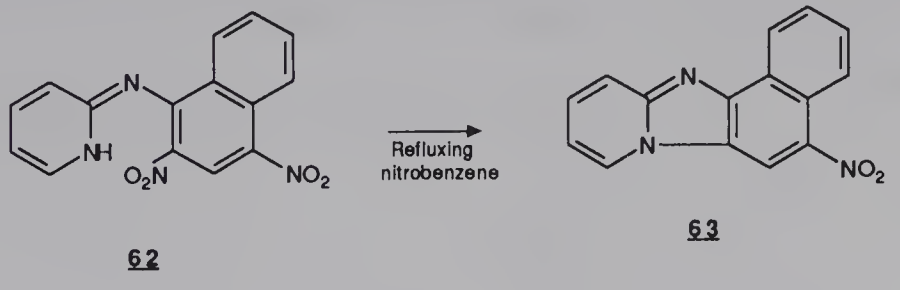


(4-18)

60 R = $COCH_3$, $CONH_2$, $CO_2C_2H_5$, CN, $SO_2C_6H_5$, NO_2, OH, OC_6H_5, C_6H_5 61

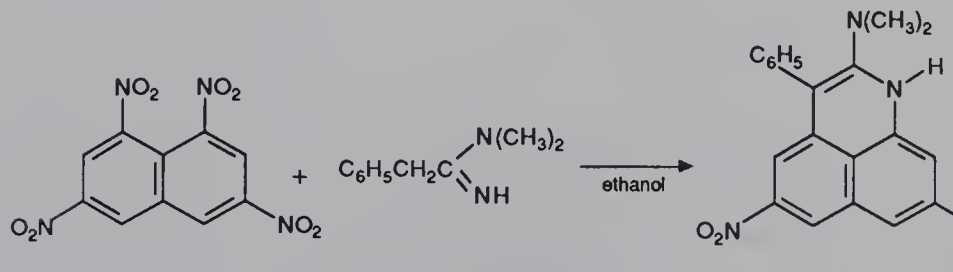
of **59** from **58** as shown in eq. 4-17.[46] Excellent yields of 1-phenylcinnolin-4(1*H*)-ones **61** have also been obtained on cyclization of the hydrazones **60** in aqueous alcohol containing sodium carbonate or sodium acetate (eq. 4-18).[47]

Cyclization via intramolecular nucleophilic attack by an amidine nitrogen has been reported. 2-Aminopyridine readily displaces the chlorine atom of strongly activated *o*-chloronitroarenes like picryl chloride (**2a**), 2,4-dinitrochlorobenzene (**2d**), and 2,4-dinitro-1-chloronaphthalene to give amidine-type intermediates such as **62**, which are prone to cyclization upon heating in nitrobenzene, yielding polycyclic compounds such as **63** (eq. 4-19).[48,49] Similar condensations involving 2-aminoquinoline, 9-aminophenanthridine, or 2-aminopyrimidine as the base precursors have been described.[2,48] Bard and Strauss found that the reaction of 1,3,6,8-tetranitronaphthalene (**64**) with α-phenyl-*N*,*N*-dimethylacetamidine (**65**) afforded the benzoquinoline **66** in 41% yield.[50] The formation of **66** (eq. 4-20) implies a double nitro S_NAr substitution by the carbon and nitrogen nucleophilic sites of the amidine moiety of **65**.[50] The benzimidazolium nitrite



(4-19)

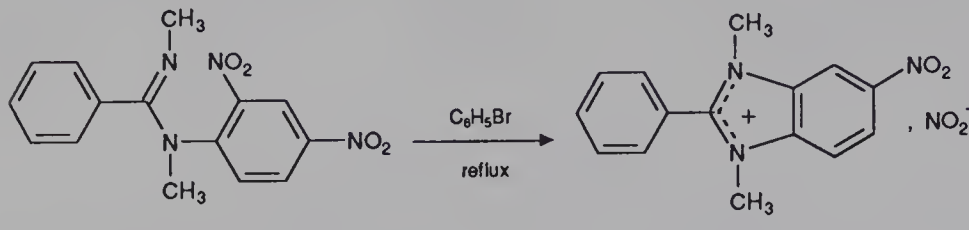
62 63



(4-20)

64 65 66

salt **68** was obtained quantitatively from the thermal cyclization of the *o*-nitrobenzamidine **67** (eq. 4-21).[51]

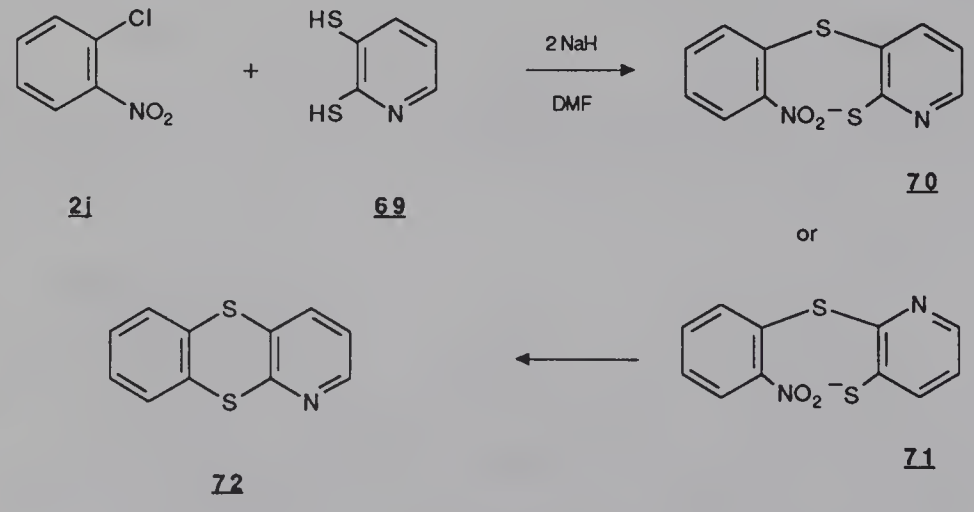


(4-21)

67 **68**

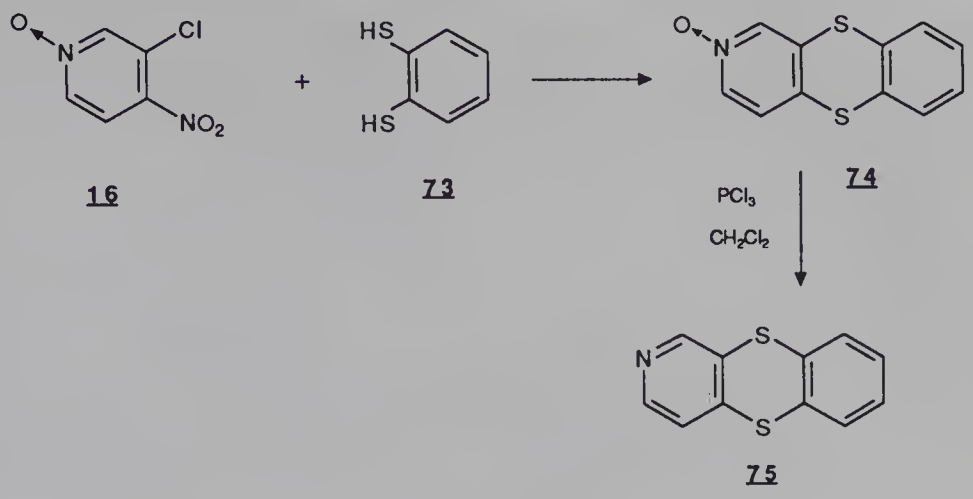
4.2.3 Displacements by Sulfur Nucleophiles

Various thianthrenes and azathianthrenes have been obtained by condensation of dithiopyrocatechol (**73**) or 2,3-pyridinedithiol (**69**) with *o*-chloronitrobenzenes and/or *o*-chloronitropyridines.[2,11,52,53] The reactions are analogous to processes described in Schemes 4.1 to 4.3 for the synthesis of pheno- or azaphenoxazines, -dioxins or -xathiins, but they involve intramolecular nitro group displacement by a thiolate instead of an aryloxyde function in the cyclization step. Among recent reports,[52,53] the synthesis of 1-azathianthrene (**72**; 45% yield) according to Scheme 4.7, which involves two possible intermediates, **70** and **71**, is noteworthy.[52] Also recently described was the synthesis of 2-azathianthrene (**75**)—the second possible monoazathianthrene system.[53] This synthesis was achieved in an overall 49% yield via the reaction of **73** with 3-chloro-4-nitropyridine 1-oxide (**16**) and reduction of the resulting 2-azathianthrene 2-oxide **74** (Scheme 4.8).[53] In



2j **69** **70** **71** **72**

Scheme 4.7

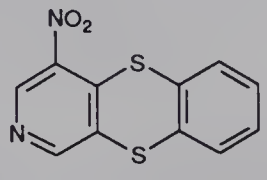


Scheme 4.8.

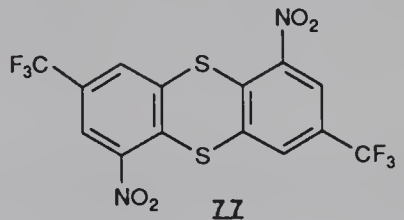
contrast, direct condensation of 73 with 4-chloro-3,5-dinitropyridine was successful, giving the corresponding 4-nitro-2-azathianthrene 76 in 92% yield.[53]

2,7-Dinitrothianthrene has been prepared in 62% yield by a simple base-catalyzed cyclization of 2-chloro-5-nitrobenzenethiol in HMPA at room temperature. This compound was used as a versatile starting point for the preparation of various 2,7-disubstituted thianthrenes.[54]

The reactions of potassium ethyl or isopropyldithiocarbonate with 4-chloro-3,5-dinitrobenzotrifluoride in DMF at 80–90°C afforded 1,6-dinitro-3,8-bis(trifluoromethyl)thianthrene 77 in 34% yield.[55a] A complex multistep sequence involving cyclization of a 2-mercapto-2′-nitrodiphenyl sulfide in a final step was proposed to account for the formation of 77, whose structure has been established by X-ray crystallography.[55a]

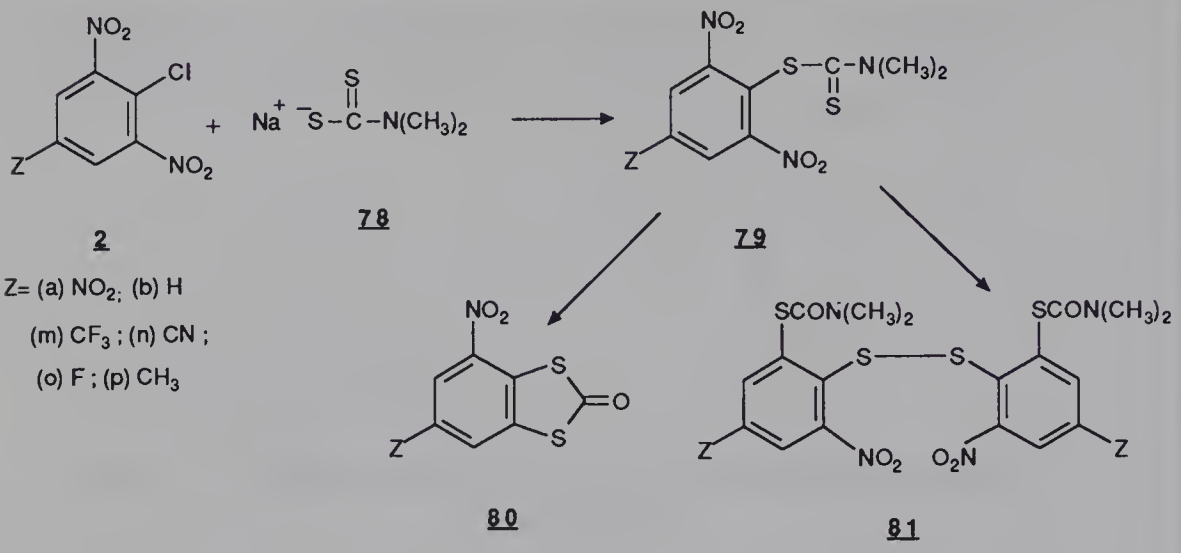


76



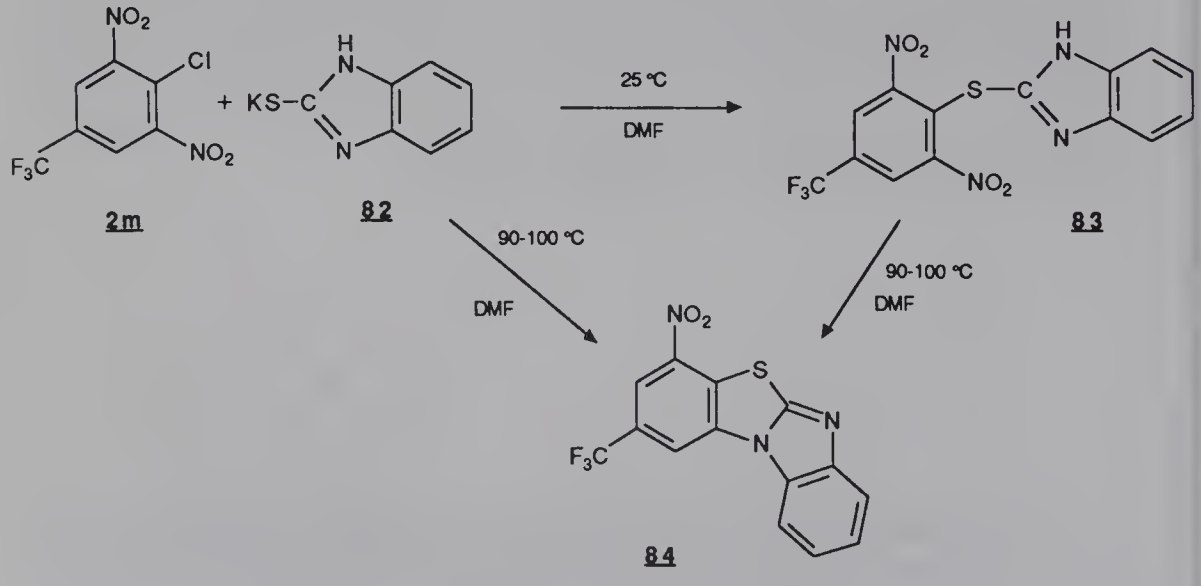
77

The reactions of various substituted 4-Z-2,6-dinitrochlorobenzenes (2) with the sodium salt of dimethyldithiocarbamic acid (78) in DMSO or acetone at room temperature produced the expected dithiocarbamates 79, which upon heating underwent intramolecular nitro displacement to afford the otherwise

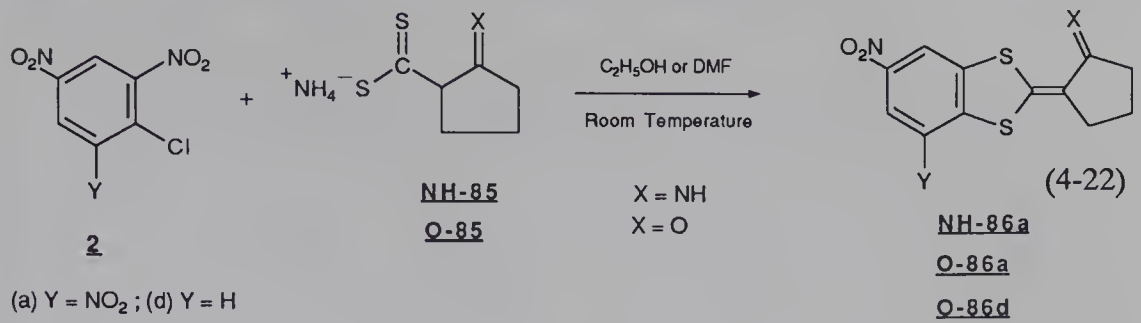


Scheme 4.9

hardly accessible substituted 1,3-benzodithiol-2-ones **80** in interesting yields (~ 40%).[56] Scheme 4.9 provides a facile synthetic route to these heterocycles, but in a few cases the disulfides **81** were also isolated in relatively important amounts.[55b,56] A relevant cyclization process was reported by d'Amico *et al.*, who studied the reaction of **2m** with the potassium salt of 2-mercaptobenzimidazole (**82**) in DMF.[57] As shown in Scheme 4.10, the desired 2-(2,6-dinitro-4-trifluoromethylphenylthio)benzimidazole (**83**) was obtained at room



Scheme 4.10.



2

(a) Y = NO_2 ; (d) Y = H

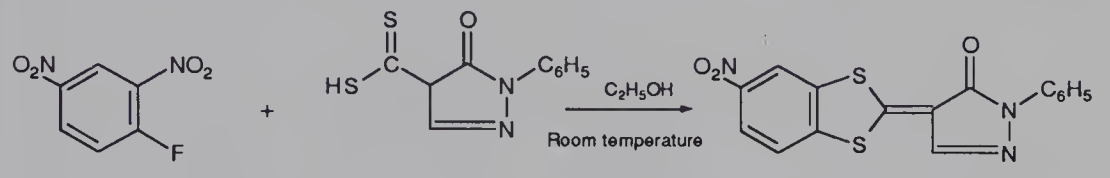
NH-85

O-85

NH-86a

O-86a

O-86d



O-87

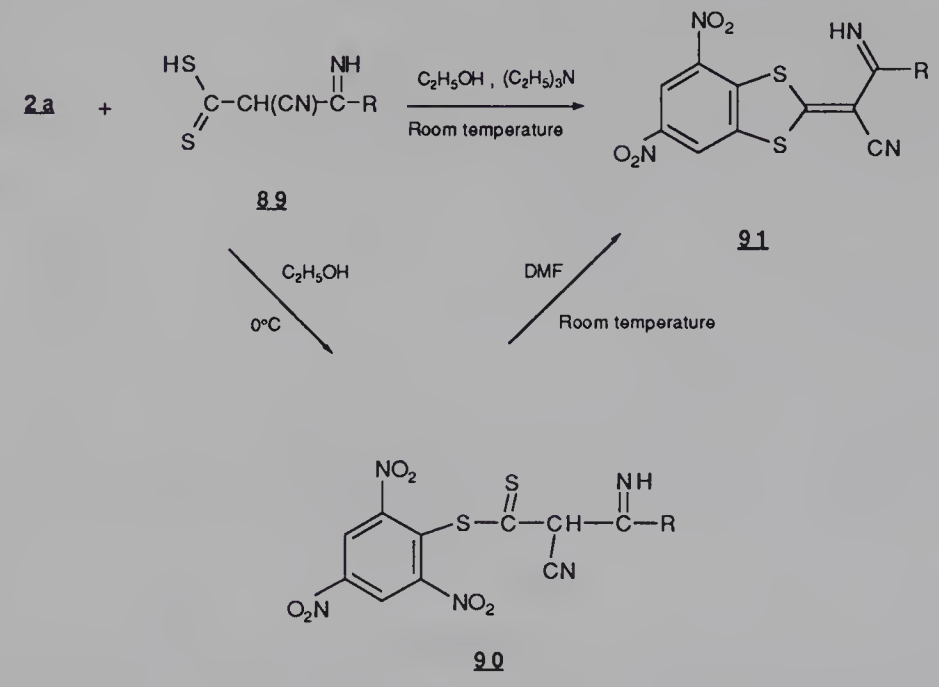
O-88

temperature (94% yield), but it is the cyclized product **84**, resulting from substitution of the nitro group by the imidazolic nitrogen of **83**, which was isolated at 90–100°C (86% yield).[57]

Treatment of picryl chloride (**2a**) with the ammonium salt of 2-iminocyclopentanedithiocarboxylic acid (**NH-85**) in ethanol at room temperature afforded 2-(2-iminocyclopentylidene)-4,6-dinitro-1,3-benzodithiole (**NH-86a**) in 62% yield (eq. 4-22).[58] In a similar fashion, the dithiocarboxylic acids **O-85** and **O-87** gave the benzodithioles **O-86a** (39% yield), **O-86d** (50% yield), and **O-88** (81% yield) (eq. 4-23), when treated with **2a**, 2,4-dinitrochlorobenzene (**2d**), or 2,4-dinitrofluorobenzene in DMF or ethanol.[59] Also studied were the reactions of ammonium salts of 2-cyano-3-iminodithiocarboxylic acids **89** with **2a**, which gave the benzodithioles **91** in good yields (Scheme 4.11).[60] Interestingly, the intermediate esters **90a–c** were isolated by performing the corresponding reactions at 0°C. This supports the idea that all above-cited benzodithioles are formed via initial intermolecular S_NAr displacement of chlorine or fluorine, followed by intramolecular S_NAr nitro substitution.

4.2.4 Displacements by Carbon Nucleophiles

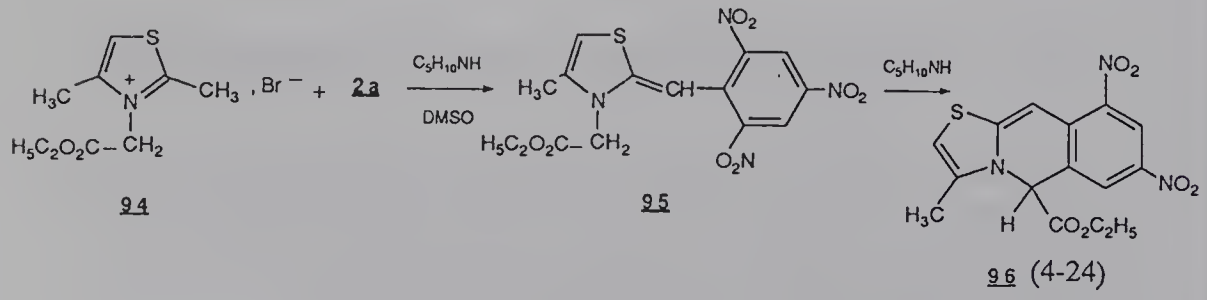
Kröhnke *et al.* have reported the synthesis of benz[*a*]indolizines and related compounds from the reactions of quaternary pyridinium, quinolinium, isoquinolinium, benzimidazolium, and thiazolium salts with *o*-nitrohaloaromatics like **2a**, 1-chloro-2,4-dinitronaphthalene, or methyl 4-

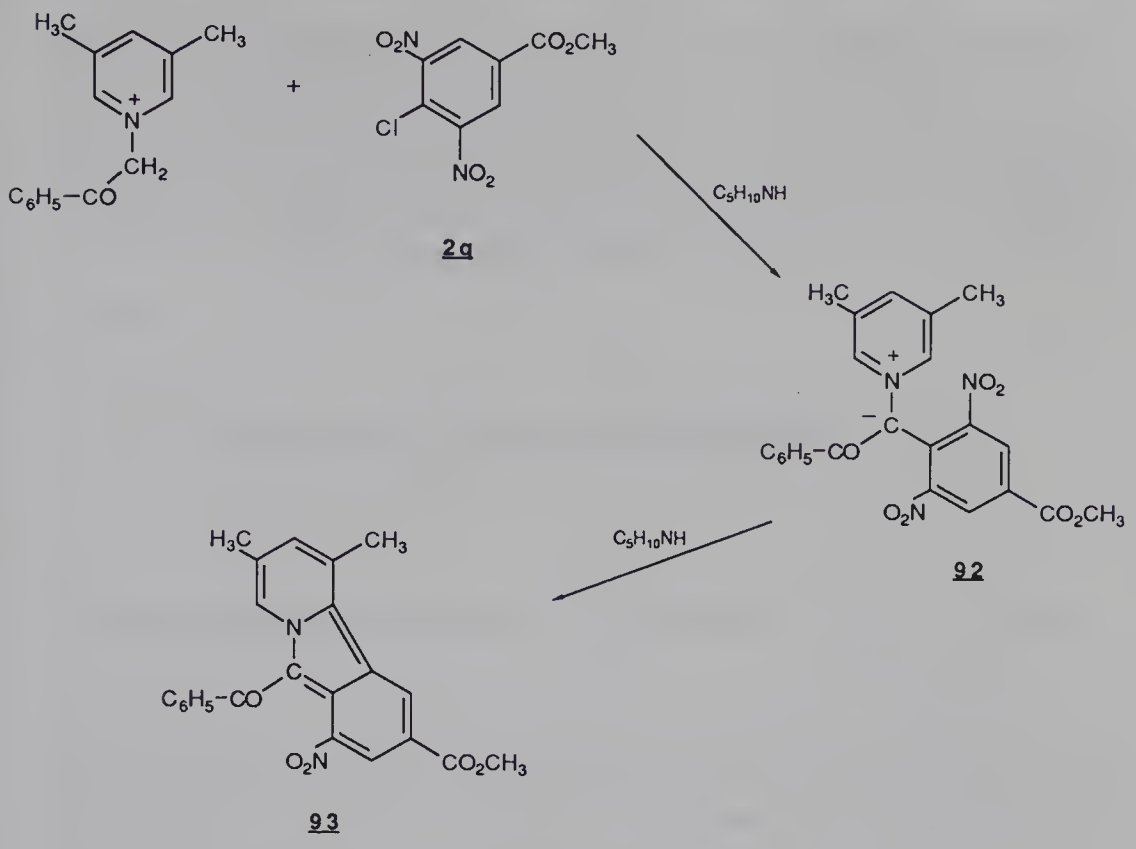


(a) R = C_6H_5 ; (b) R = 4-$CH_3C_6H_4$; (c) R = 3-$CH_3C_6H_4$; (d) R = CH_3 ;
(e) R = 4-$CH_3OC_6H_4$; (f) R = ß-naphthyl

Scheme 4.11.

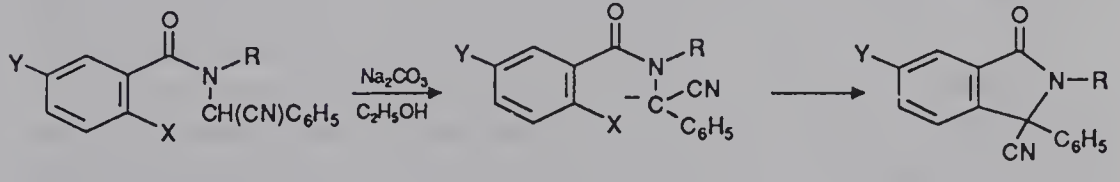
chloro-3,5-dinitrobenzoate (**2q**).[61,62] Scheme 4.12 is illustrative of such cyclizations, which generally proceed in excellent yield by treatment of the appropriate substrates in DMSO at room temperature with a base such as piperidine. As can be seen, the formation of the tricyclic system **93** occurs via an intramolecular S_NAr displacement of a nitro group by nucleophilic carbon in the enol betaine intermediate **92**. Similar reactions leading to condensed isoquinoline derivatives have been carried out using 2-methylcyclimonium salts.[62] For example, **2a** reacts with the thiazolium bromide **94** to give the trinitrobenzylidene intermediate **95**, which cyclizes to 7,9-dinitro-3-methyl-5-ethoxycarbonyl-5*H*-thiazolo[3,2-*b*]isoquinoline (**96**) (eq. 4-24); the overall yield for the formation of **96** from **94** is 60%.[62]





Scheme 4.12.

Another remarkable example of intramolecular nitro displacement with a carbon nucleophile was described by Spence and Tennant.[63] Treatment of the *N,N*-disubstituted *o*-nitrobenzamides **97a–c** with hot ethanolic sodium carbonate afforded the isoindolinones **99a–c** in good yields. The formation of **99a–c** is readily accomplished by the ionization of the exocyclic CH group, followed by nucleophilic substitution of the ortho nitro group by the cyanobenzyl carbanion **98** generated in the side chain (eq. 4-25).[63] Interestingly, no cyclization occurred when the nitro group in **97c** was replaced by a less



97 **98** **99** (4-25)

(a) R = CH_3, X = NO_2, Y = H; (b) R = $C_6H_5CH_2$, X = NO_2, Y = H;
(c) R = C_6H_5, X = NO_2, Y = H; (d) R = C_6H_5, X = Cl, Y = NO_2

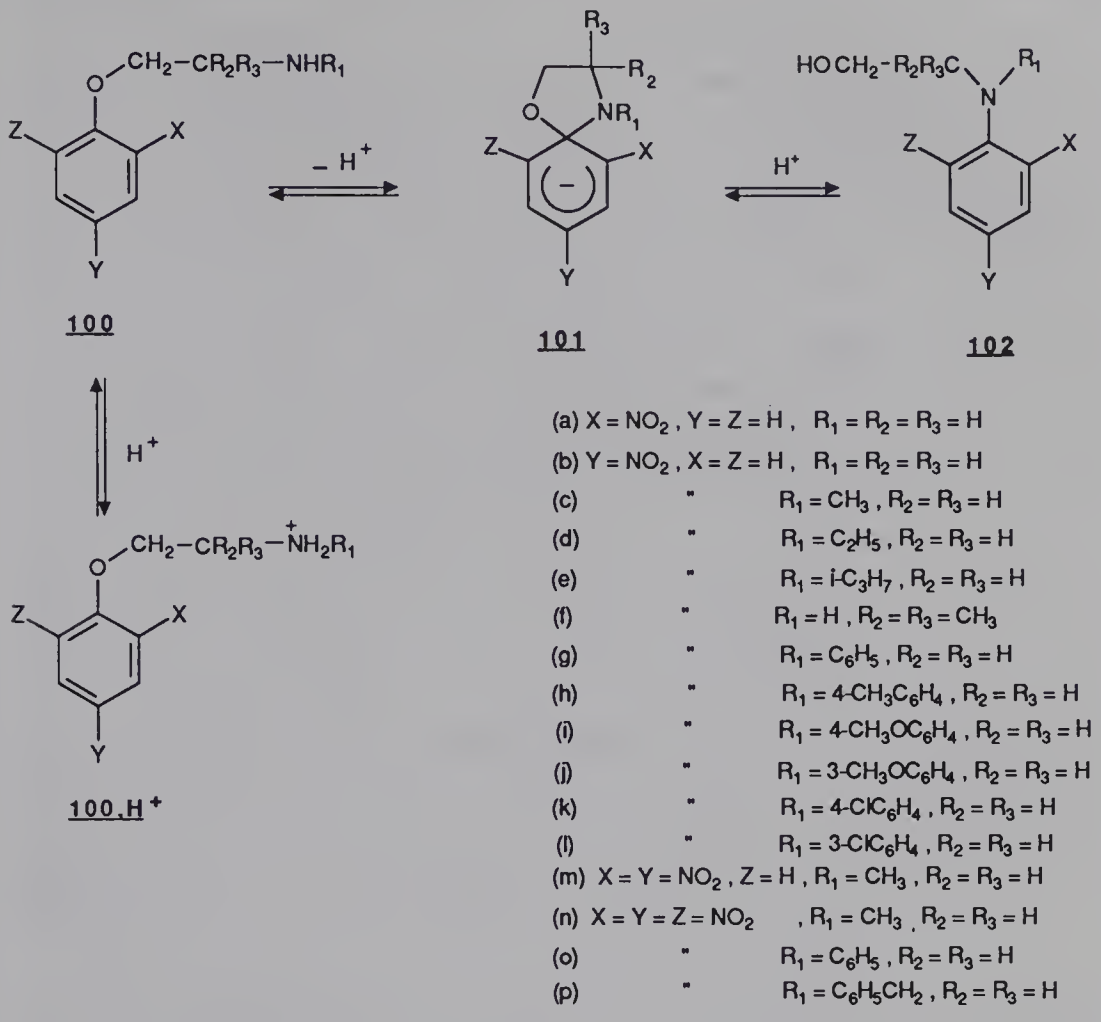
nucleofugal leaving group like a chloro or a methoxy group. In contrast, the 2-chloro-5-nitro derivative **97d**, in which the electron deficiency of the ortho-position is suitably enhanced by a para nitro group, was found to cyclize to **99d** under the same conditions as **97a–c**. These observations clearly show that significant activation of the ortho position of the benzamide precursor is a prerequisite for a successful cyclization to compounds **99**.[63]

4.3 Smiles Rearrangements

4.3.1 O → N and N → O Rearrangements

Scheme 4.13 describes the Smiles rearrangement of a series of β-aminoethyl nitro-activated aryl ethers **100** into the corresponding β-hydroxyethylnitroarylamines **102**.[64–68] Consistent with the observation that intermocular S_NAr displacements of oxygen bases with amines readily occur,[6] the process of Scheme 4.13 is strongly favored thermodynamically when the activation of the aromatic ring is provided by at least one ortho or para nitro group. Wubbels *et al.* reported that the 2- and 4-nitrophenyl ethers **100a** and **100b** undergo slow but clean rearrangements to **102a** and **102b** in aqueous sodium hydroxide.[68] Knipe *et al.* have made similar observations with **100b** and the related *N*-methyl, *N*-ethyl, and *N*-isopropyl derivatives **100c–e**, while Bernasconi, Drozd, *et al.* reported the rearrangement of the more activated 2,4-dinitro- and 2,4,6-trinitrophenyl ethers **100m**, **100n**, and **100o** as well as that of the 2,4-dinitronaphthyl analogue **103** (Scheme 4.14).[64–67] Extensive kinetic studies of the processes have shown that in all cases the rearrangement occurs via the formation of the intermediate spiro adducts **101** or **104**.[65,66] Interestingly, the picryl and 2,4-dinitronaphthyl adducts **101n**, **101o**, and **104** exhibit a high thermodynamic stability relative to the corresponding arylamines **102** or **105**.[65,67] This allows the isolation of these complexes as crystalline alkali salts on addition of a strong base to an alcoholic solution of **102n**, **102o**, or **105**.[65,67,69] Other functionalities (e.g., a quaternary nitrogen atom) are as effective as a nitro group in promoting rearrangements of the type shown in Scheme 4.13.[70]

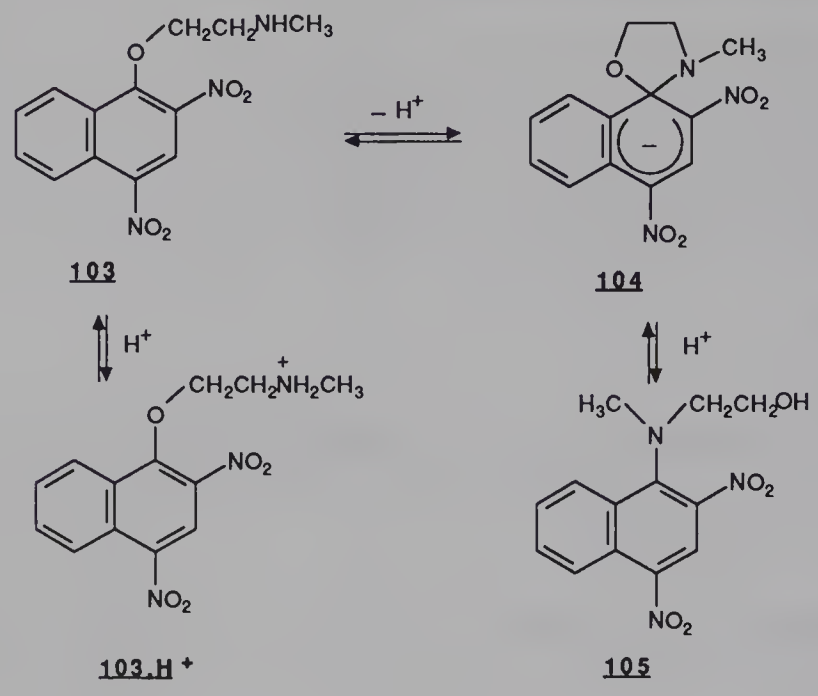
The facile rearrangements shown in Schemes 4.13 and 4.14 have long been a drawback for the isolation of ethers **100** and **103**.[7,71,72] Scheme 4.15 features



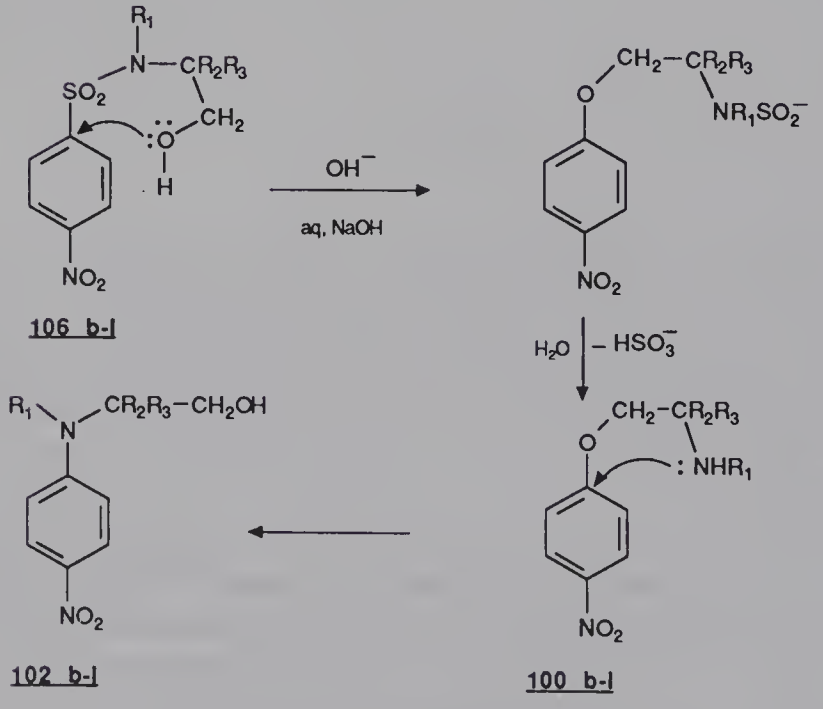
Scheme 4.13.

the well-known conversion of *N*-alkyl-*N*-(β-hydroxyethyl)-4-nitrobenzenesulfonamides **106** into the corresponding arylamines **102** upon reaction in aqueous sodium hydroxide.[7] Although kinetic studies have confirmed that this conversion is the result of the two depicted Smiles rearrangements, the intermediate ethers **100** could not be isolated from the sulfonamides **106** because they rearrange readily to **102** under the conditions initially employed.[7,71a]

It is only recently that successful syntheses of ethers **100** and **103** have been developed. Kinetic investigations of Scheme 4.13 have shown that dipolar aprotic solvents exert some rate-retarding effect on the rearrangement of **100** to **102**.[71b] This observation has been used to advantage by Knipe *et al.*, who were able to obtain satisfactory yields (40–72%) of the *N*-alkyl-β-aminoethyl 4-nitrophenyl ethers **100b–f** by carrying out a direct S_NAr substitu-



Scheme 4.14.



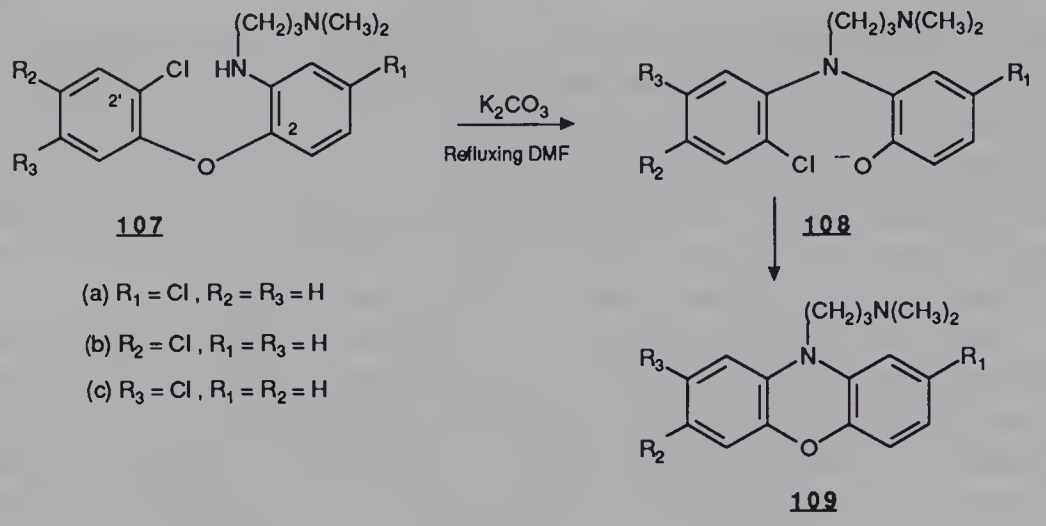
Scheme 4.15.

tion of *p*-chloronitrobenzene with the appropriate aminoethoxide ion in DMSO.[71b] These authors found also that the rate of the second rearrangement in Scheme 4.15 (see Scheme 4.13 for the significance of R_1, R_2, and R_3) is considerably reduced, even in aqueous solution, upon substitution of an *N*-aryl for an *N*-alkyl substituent in **106**. Thus, fair to good yields (37–79%) of **100g–l** were obtained upon treatment of the sulfonamides **106g–l** at 60°C in aqueous sodium hydroxide solutions containing 30% acetone (v/v).[71b]

The finding by Bernasconi that the picryl and 2,4-dinitronaphthyl spiro adducts **101n** and **104** exhibit a high thermodynamic stability relative to the corresponding arylamines **102n** and **105** has provided the basis for an original synthesis of the ethers **100n** and **103**.[64,65] These have been obtained in good yields by rapid acidification of **101n** and **104**, which were initially produced upon addition of a strong base to ethanolic or aqueous DMSO solutions of **102n** and **105**.[64] Under these experimental conditions, it turned out that the spiro ring opening of **101n** and **104** to **100n** and **103**, respectively, via C—N bond breaking, is strongly favored *kinetically* compared to that leading to the recovery of **102n** and **105** via C—O bond breaking. *Thus, the Smiles rearrangements of Schemes 4.13 and 4.14 are reversed* and the aryl ethers **100n** and **103** can be isolated as their ammonium salts **100n,H$^+$** and **103,H$^+$**.[64] The procedure has also been applied to the synthesis of the 2,4-dinitrophenyl ether **100m** from the dinitroaniline **102m**.[64] Synthetic methods that do not involve S_NAr processes have been designed to prepare **100a** and **100b**.[68]

Smiles rearrangements involving displacement of an aryloxide group by an aniline functionality in diaryl ethers derivatives are very common and occur in either the presence or absence of activation by a nitro group.[1,2,73,74] An illustrative example is the synthesis in high yields (69–95%) of phenoxazines **109** from *N,N*-dimethyl-*N'*-[2-(2'-chlorophenoxy)phenyl]-1,3-propanediamines (**107**).[73] In this instance, the halogen-activated Smiles rearrangement of **107** to **108** is followed by intramolecular S_NAr substitution of the 2'-chlorine atom by the phenoxide functionality in **108** (Scheme 4.16).

Considerable work has been reported on the Smiles rearrangements of the nitro-activated β-(acetylamino)ethyl phenyl, and β-(acetylamino)ethyl pyridyl ethers **110**.[72,75–79] In DMSO, these ethers undergo a base-catalyzed rearrangement with simultaneous migration of the acetyl group to give the aniline derivatives **112** in 75–80% yields (Scheme 4.17). Small amounts of the hydrolysis products of **112** (i.e., **113**) are also formed. Most compounds **110** yielded detectable spiro complex intermediates **111** in an initial and rapid step. Kinetic studies of Scheme 4.17 in aqueous DMSO have revealed that the rearrangement rates are strongly dependent on steric factors in the ortho positions.[76b,78,79] The 4-nitropyridyl and 4-nitrophenyl ethers **110h** and **110e**



107

(a) $R_1 = Cl$, $R_2 = R_3 = H$

(b) $R_2 = Cl$, $R_1 = R_3 = H$

(c) $R_3 = Cl$, $R_1 = R_2 = H$

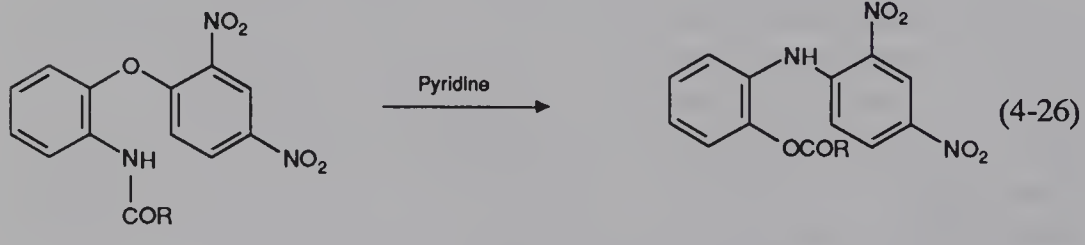
108

109

Scheme 4.16.

rearrange the most rapidly, while the 2,6-disubstituted ethers **110f** and **110g** rearrange the most slowly. The conversion of the diaryl ether **114** to the diarylamine **115** (eq. 4-26) falls into the category depicted in Scheme 4.17.[80]

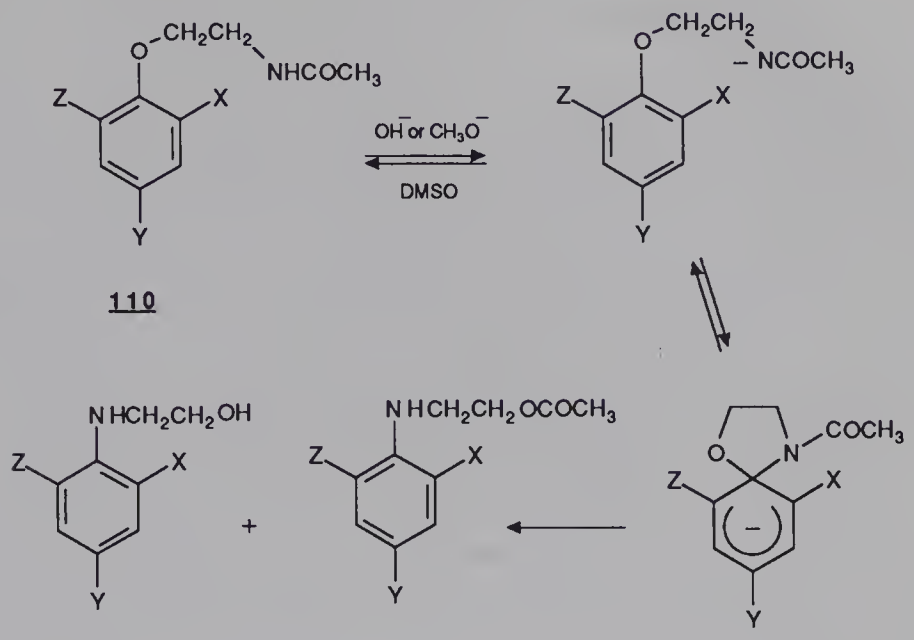
Turner *et al.* have described the Smiles rearrangement of 2-aryloxy-2-



(4-26)

114 **115**

methylpropanamides **116a–c** to **118a–c** via the spiro adducts **117a–c** (Scheme 4.18).[81] The reactions were conveniently carried out in dioxane at 100°C or in DMF at room temperature, affording compounds **118a–c** in 60% yields, approximately. When *N*-alkylated amides were used (e.g., **116c**), the rearrangement rate was considerably reduced.[81a] A similar rate retardation occurred when the α-methyl groups were replaced by hydrogen. Thus, 2-(4-nitrophenoxy)ethanamide (**116d**) underwent rearrangement to **118d** only when heated at 50°C in DMF.[81a] A remarkable feature is that 2-aryloxy-2-methylpropanamides, which possess nonactivated [i.e., **116e** (Y = Z = H)] or



(a) X = Y = NO_2 , Z = H ; (b) X = Br , Y = NO_2 , Z = H ; (c) X = CN , Y = NO_2 , Z = H ;

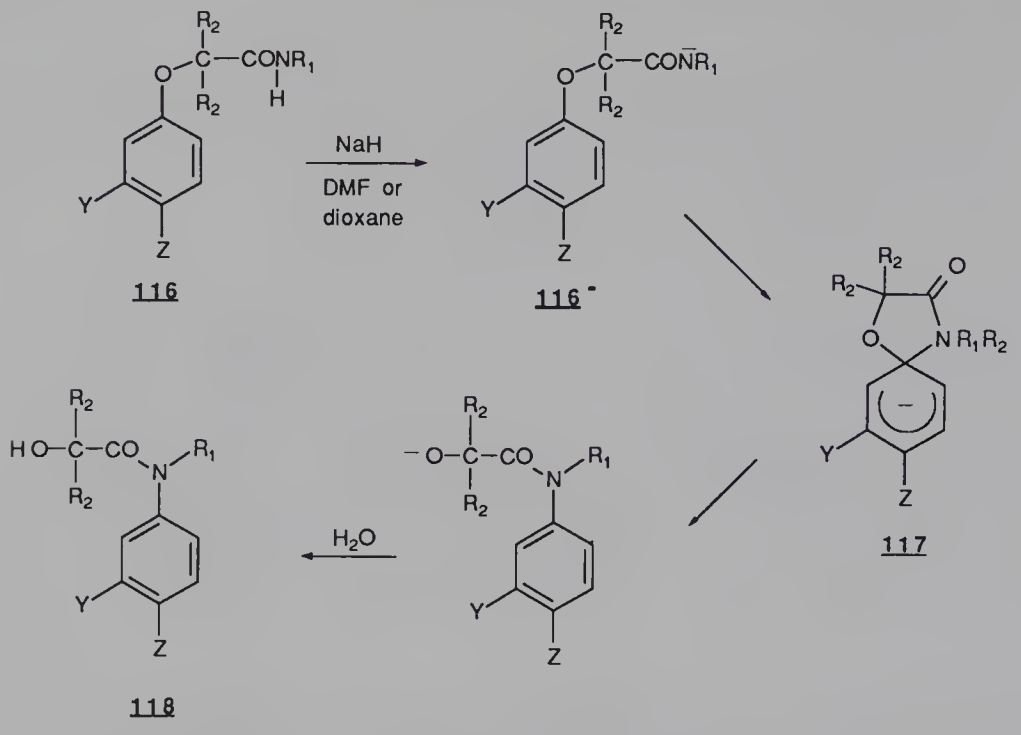
(d) X = CH_3 , Y = NO_2 , Z = H ; (e) X = Z = H , Y = NO_2 ; (f) X = Z = NO_2 , Y = H ;

(g) X = Y = NO_2 , Z = CH_3 ; (h) X = ring nitrogen , Y = NO_2 , Z = H

Scheme 4.17.

deactivated [i.e., **116f** (Z = 4-OCH_3, Y = H)], benzene rings could be readily rearranged to the corresponding anilides **118**.[81b] In these instances, the reactions were carried out either in HMPA or in the presence of crown ethers in acetonitrile—that is, under experimental conditions that favor the formation of and increase the reactivity of the intermediate propanamide ions **116**$^-$.[81b]

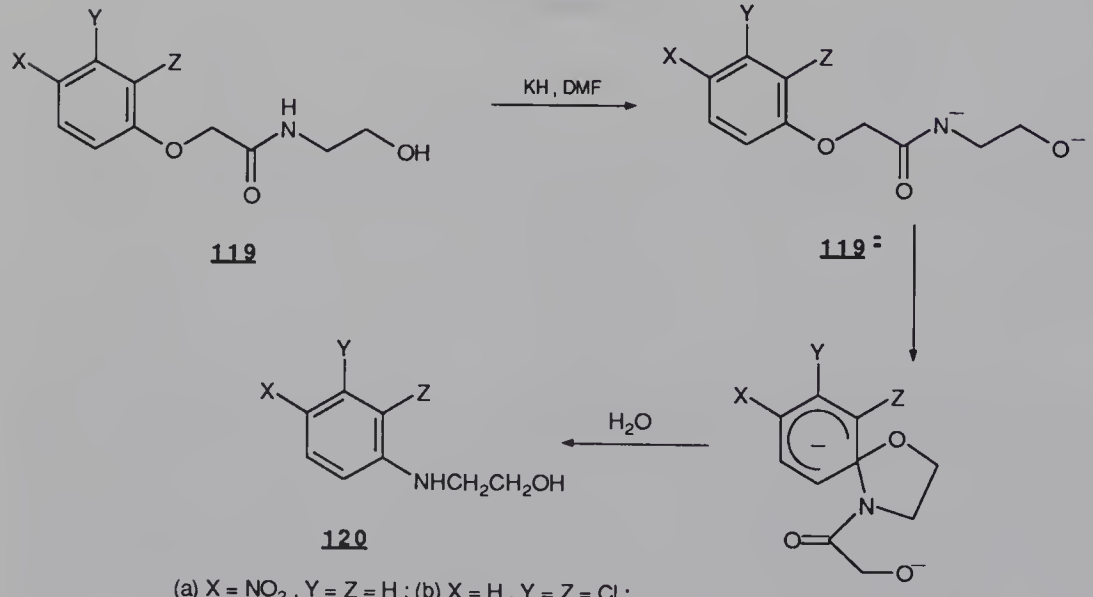
A reaction related to Scheme 4.18 is the rapid and exothermic rearrangement of substituted *N*-(2-hydroxyethyl)aryloxyacetamides **119** in the presence of potassium hydride in DMF or in THF containing 18-crown-6.[82] The reaction produces useful yields of the *N*-(β-hydroxyethyl)anilines **120**. The mechanism shown in Scheme 4.19 assumes that the rearrangement is accompanied by a transfer of the acyl group.[82] Also, the destabilization of the intermediate dianion **119**$^{2-}$ through Coulombic repulsion between the alkoxide and amide anionic centers is considered to be an important force driving the reaction.[82]



116 116⁻ 117 118

(a) Z = NO_2, Y = R_1 = H, R_2 = CH_3; (b) Z = NO_2, Y = CF_3, R_1 = H, R_2 = CH_3;
(c) Z = NO_2, Y = H, R_1 = R_2 = CH_3; (d) Z = NO_2, Y = R_1 = R_2 = H;
(e) Z = Y = R_1 = H, R_2 = CH_3; (f) Z = OCH_3, Y = R_1 = H, R_2 = CH_3

Scheme 4.18.



119 119⁻ 120

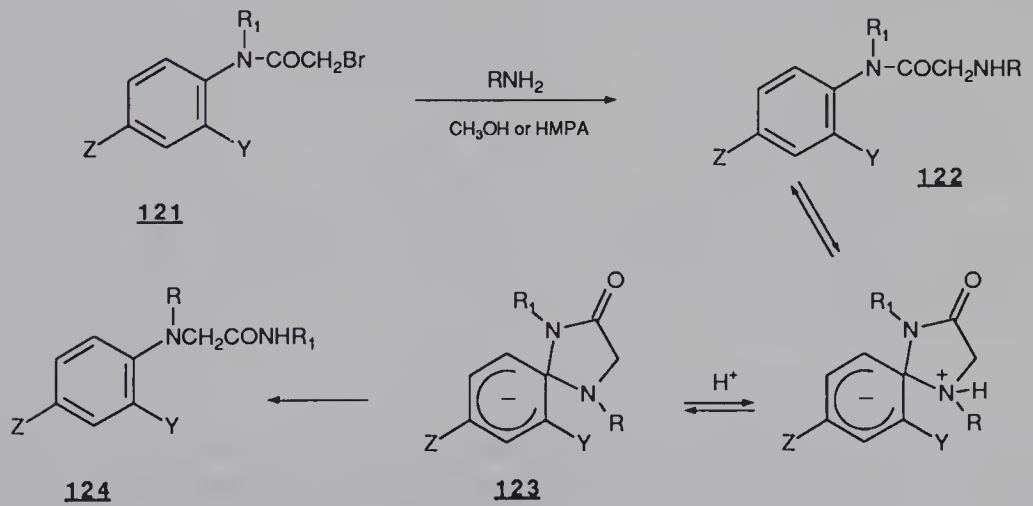
(a) X = NO_2, Y = Z = H; (b) X = H, Y = Z = Cl;
(c) X = Cl, Y = Z = H; (d) X = Y = Z = H;
(e) X = CH_3, Y = Z = H; (f) X = OCH_3, Y = Z = H

Scheme 4.19.

4.3.2 N → N Rearrangements

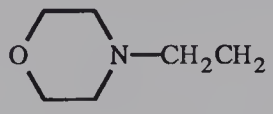
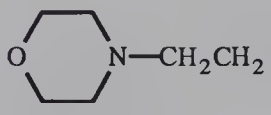
When suitably located in a side chain, an unhindered amine nitrogen can displace intramolecularly a weakly basic aromatic amide group. Gilman *et al.* found that a variety of tertiary 2-bromoacetanilides **121** react with many primary aliphatic amines in methanol or HMPA at room temperature to yield the glycinamides **124** in excellent yields.[83] The proposed mechanism (Scheme 4.20) involves the formation of the undetected free amine **122** and the intermediate spiro adducts **123**. Activation of the aromatic ring by an ortho or a para nitro group is especially effective in promoting the rearrangement, but a carbonyl group like C_6H_5CO is also very efficient.[83] Interestingly, the rearrangement did not occur when sterically hindered primary amines (e.g., *t*-butylamine) or secondary amines were used. In the latter case, the reaction is believed to go through formation of a zwitterionic intermediate (e.g. **125**), which cannot lose a proton and reverts back to the corresponding unrearranged compound because of the high nucleofugality of a protonated amine nitrogen (see Chapter 1). The behavior of secondary bromoacetanilides of type **121** (R_1 = H) with primary amines was also investigated, but in no case were rearrangements observed.[83]

Table 4.1 illustrates the synthetic utility of Scheme 4.20 for the preparation



Scheme 4.20.

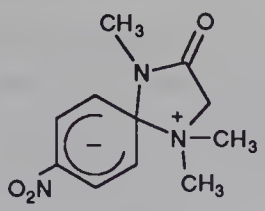
Table 4.1. Synthesis of *N*-Substituted Phenylglycinamides 124 from the Treatment of Tertiary 2-Bromoacetanilides 121 with Various Primary Aliphatic Amines (RNH_2) According to Scheme 4.20[a]

Y	Z	R_1	R	Product yield (%)
H	NO_2	CH_3	H	68
			CH_3	75
			C_6H_5	94
			$CH_2{=}CH{-}CH_2$	85
			$(CH_3)_2NCH_2CH_2$	59
				69
			CH_3O	38
C_6H_5CO	NO_2	$(CH_3)_3C$	H	84
			CH_3	76
			C_6H_5	82
			$CH_2{=}CH{-}CH_2$	92
			$(CH_3)_2N{-}CH_2CH_2$	76
			$(CH_3)_2N$	47
NO_2	H	CH_3	H	93
				66
C_6H_5CO	H	CH_3	H	32
C_6H_5CO	Cl	$(CH_3)_3C$	H	77

[a]Data from ref. 83.

of *N*-substituted phenylglycinamides 124. The essentially complete rearrangement of DL-2-aminododecanoic acid *N*-methyl-*p*-nitroanilide (126) to DL-2-(*p*-nitrophenyl) aminododecanoic acid *N*-methylamide (127) (eq. 4-27) and the conversion of the nitrobenzophenone 128 to 129 in the presence of hexamine (eq. 4-28; 52% yield) provide additional illustrations for Scheme 4.20.[84,85]

Machacek, Sterba, and coworkers have studied reactions of the type shown



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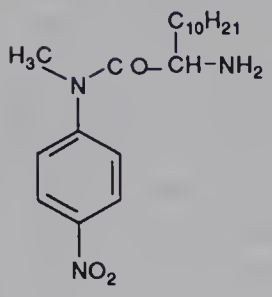
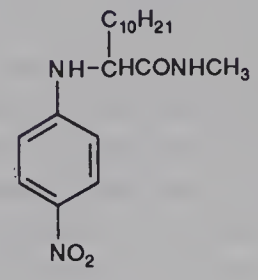


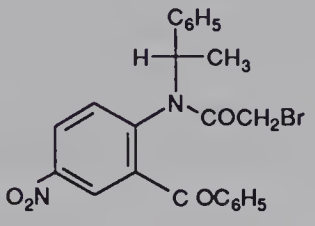
126



127

aq. C_2H_5OH
NaOH, 25°C

(4-27)



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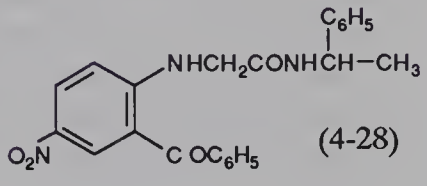
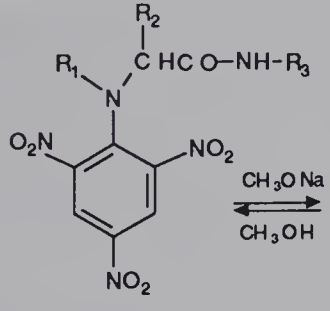


129

Hexamethylenetetramine
refluxing ethanol

(4-28)

in Scheme 4.20, in the reverse direction.[86–88] *N,N'*-Dimethyl-*N*-(2,4,6-trinitrophenyl) glycinamide (**130a**), *N'*-methyl-*N*-(2,4,6-trinitrophenyl)-alaninamide (**130b**), and *N*-methyl-*N*-(2,4,6-trinitrophenyl)aminoacetanilide (**130c**) readily cyclize to the stable and isolable spiro adducts **131a–c** upon addition of



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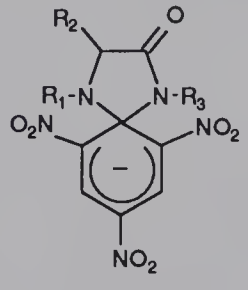

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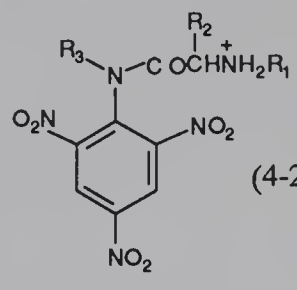
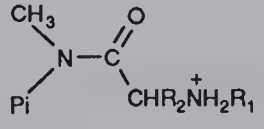


132

CH_3OH

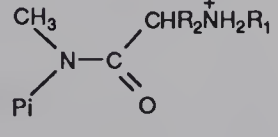
Acid

(4-29)



E-132

Pi=2,4,6-trinitrophenyl

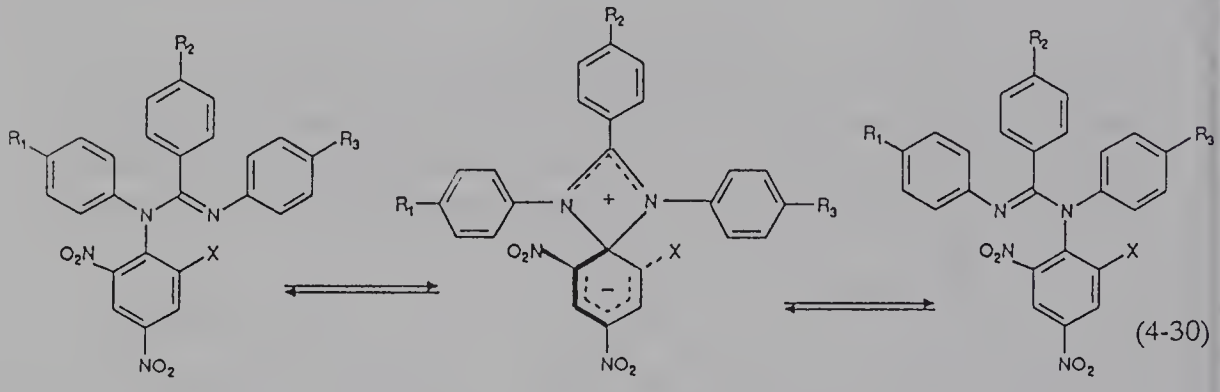


Z-132

(a) $R_1 = R_3 = CH_3$, $R_2 = H$; (b) $R_2 = R_3 = CH_3$, $R_1 = H$; (c) $R_1 = CH_3$, $R_2 = H$, $R_3 = C_6H_5$

sodium methoxide in methanol. However, rapid acidification of **131a–c** affords the amides **132a–c**, which have been isolated in high yields as their ammonium salts (eq. 4-29). Both **132a** and **132b** formed as a mixture of the Z and E isomers (Z-**132** and E-**132**).[86,87] Upon dissolution of **132c** in anilinium–aniline buffers in methanol, a slow conversion to the starting acetanilide **130c** occurs.[86] This indicates that the rearrangement of eq. 4-29 is in fact thermodynamically favored in the same direction as that of Scheme 4.20 and that the experimental conditions allowing the isolation of **132a–c** are reminiscent of those involved in the preparation of the ethers **100** in Scheme 4.13. It is only because the acid decomposition of the adducts **131** to **132** is kinetically favored compared to that leading to **130** that the isolation of the amides **132** is possible.

Reactions related to Smiles rearrangements are the *N,N*-transfers of 2,4-dinitrophenyl and picryl moieties that occur in the benzamidine derivatives **133** (eq. 4-30).[89,90] For similar substituents R_1–R_3, the 1,3-migration of the picryl ring is much faster than that of the 2,4-dinitrophenyl ring. Direct evidence for the formation of the intermediate spiro complex **134** has not been obtained but is supported by the observation of related dioxolane species in tropolone systems (Section 4.3.3).



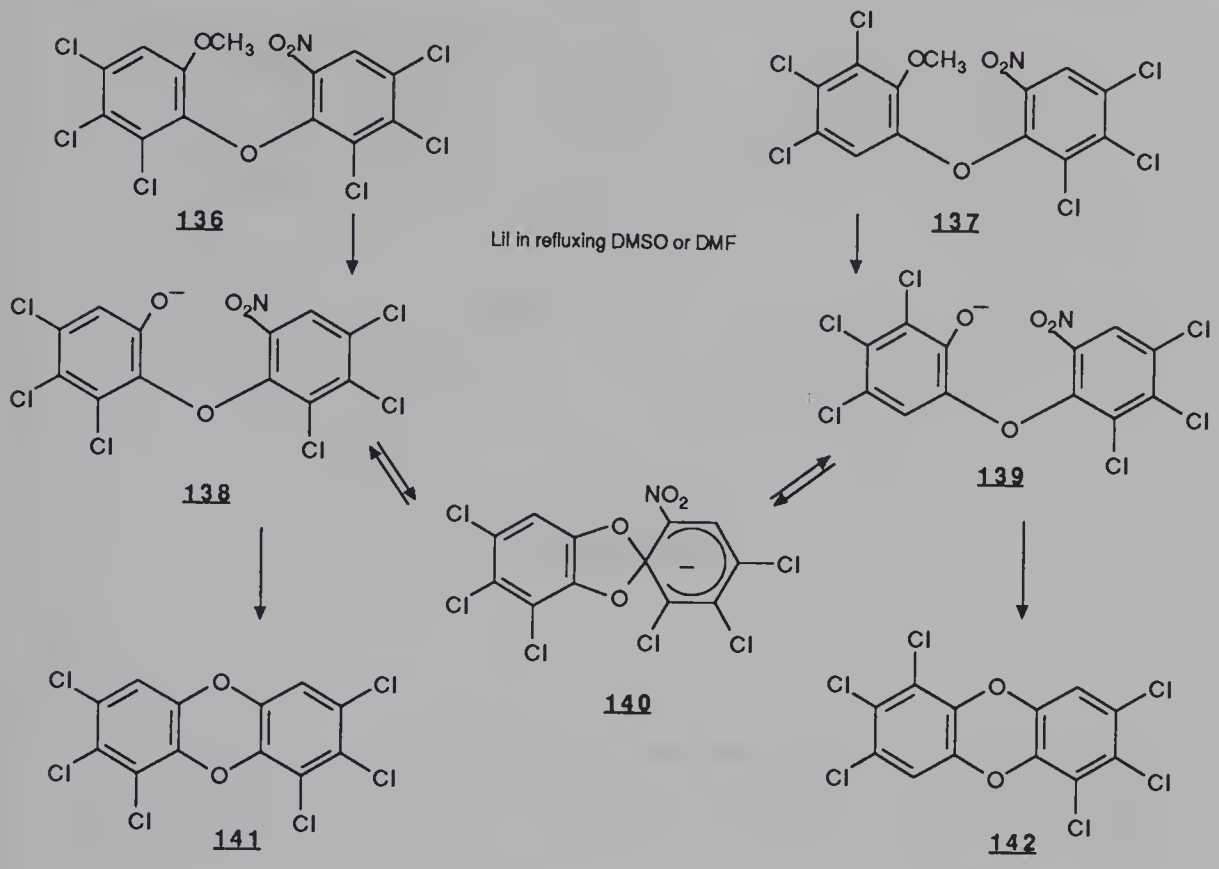
(4-30)

133 X = H, NO_2; R_2 = H; R_1 = R_3 = CH_3
R_1 = CH_3, R_3 = H
R_1 = R_3 = OCH_3

134 **135**

4.3.3 O → O Rearrangements

Kende and de Camp have reported the formation of both hexachlorodioxin isomers **141** and **142** in the same 2.5:1 ratio on treatment by lithium iodide of

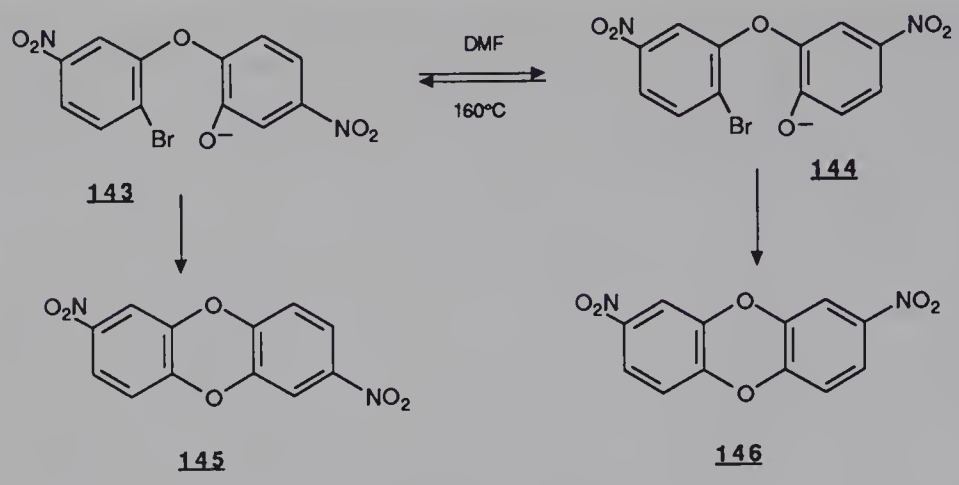


136 137 138 139 140 141 142

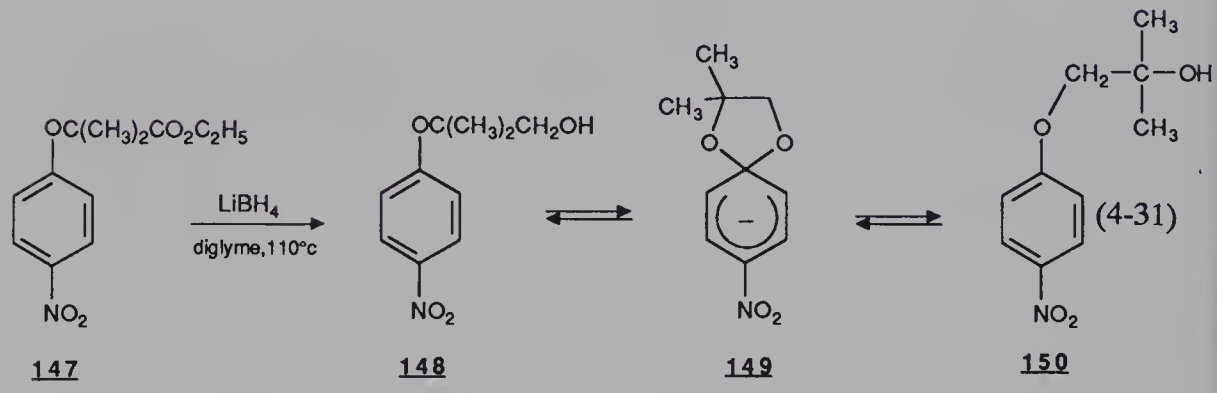
Scheme 4.21.

each of the two nitrodiphenyl ether precursors **136** and **137** in DMF or DMSO.[91] Scheme 4.21 assumes a rapid Smiles interconversion of the phenoxide intermediates **138** and **139** via the σ-complex **140** and cyclization of these species to **141** and **142**, respectively, via S_NAr substitution of the nitro group. In a similar way, Ramsden found that thermolysis of potassium 2-bromo-5-nitrophenoxide in refluxing DMF afforded a mixture of the 2,7- and 2,8-dinitrodibenzo-*p*-dioxins **145** and **146** in a 2:3 ratio, approximately.[92] This implies that the cyclization step is preceded by a partial rearrangement of the initially formed diaryl ether **143** to its isomer **144** (Scheme 4.22).[92] Smiles rearrangements were also found to occur in the formation of dioxins from diaryl ethers activated only by halogen atoms.[93]

Upon treatment of ethyl 2-methyl-2-(4-nitrophenoxy) propionate (**147**) with lithium borohydride in diglyme, the reduction of the ester function takes place normally, but the resulting primary alcohol **148** rapidly rearranges to the tertiary alcohol **150** (70% yield) via the spiro adduct **149** (eq. 4-31).[94]

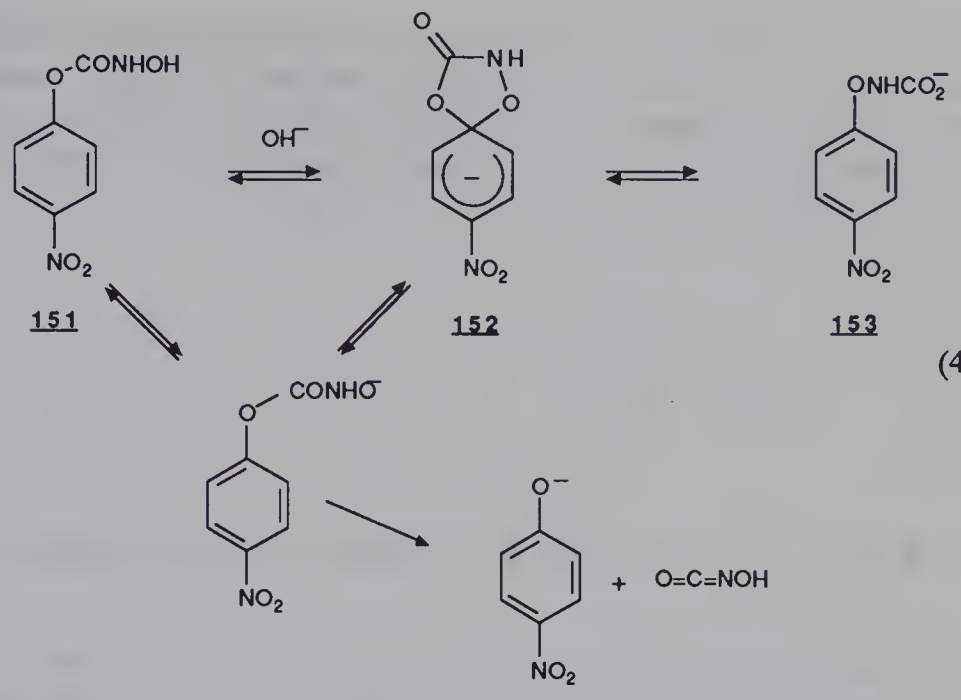


Scheme 4.22.



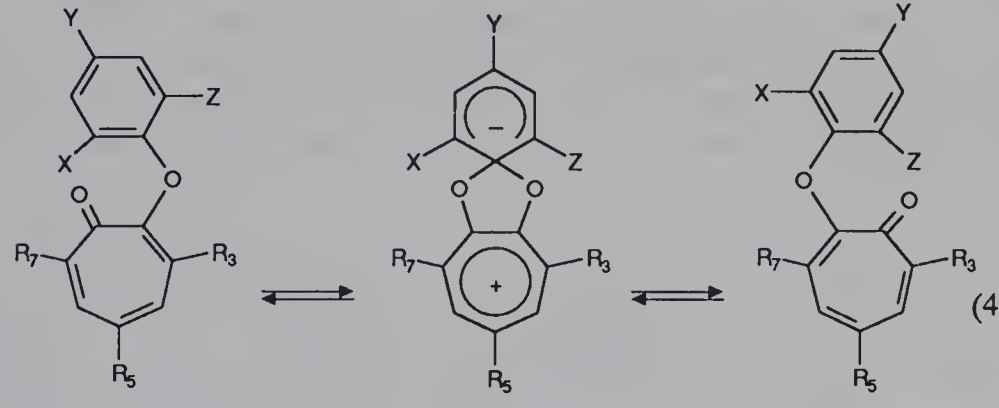
In aqueous alkali solution, rearrangement of 4-nitrophenyl *N*-hydroxycarbamate (**151**) to *N*-carboxy-4-nitrophenoxyamine (**153**) occurs in competition with an elimination process leading to 4-nitrophenoxide ion and *N*-hydroxycyanic acid.[95] The yield of **153** appears to be pH-dependent, being maximal at pH 12. Compelling kinetic evidence for the intermediacy of the mononitro spiro adduct **152** in the rearrangement has been obtained (eq. 4-32).[95] Participation of carboxy groups in Smiles rearrangements of diaryl ethers not bearing nitro groups has been reported, especially in the chemistry of depsides.[96–98]

Analogous to the *N,N*-transfers of eq. 4-30 is the migration of nitrophenyl moieties in the various tropolone ethers **154** (eq. 4-33).[99] While the tautomeric rearrangement of the 4-nitrophenyl derivative **154a** required high temperatures (> 170°C) as observed by ^1H and ^{13}C NMR (coalescence of the 3- and 7-methyl groups), it occurred at a very high rate, even at –100°C, for the 2,6-dinitrophenyl derivative **154b**. For the picryl system **154c** with $R_3 = R_5 = R_7$



(4-32)

= CH_3, the dipolar spiro adduct **155c** has such a high thermodynamic stability that its isolation is very facile.[100] Interestingly, both the closed and open forms **155d** and **154d** (= **156d**) exist at equilibrium in solutions of the unsubstituted analog ($R_3 = R_5 = R_7 = H$) in DMF.[101]



(4-33)

(a) X = Z = H , Y = NO_2 ; $R_3 = R_5 = R_7 = CH_3$

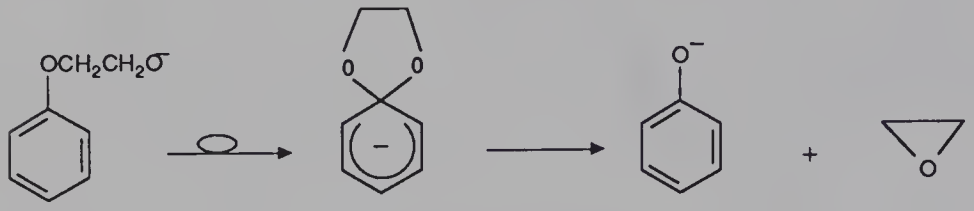
(b) X = Z = NO_2 , Y = H ; $R_3 = R_5 = R_7 = CH_3$

(c) X = Y = Z = NO_2 ; $R_3 = R_5 = R_7 = CH_3$

(d) X = Y = Z = NO_2 ; $R_3 = R_5 = R_7 = H$

Heavy atom (^{13}C, ^{18}O) labeling studies have provided evidence that the

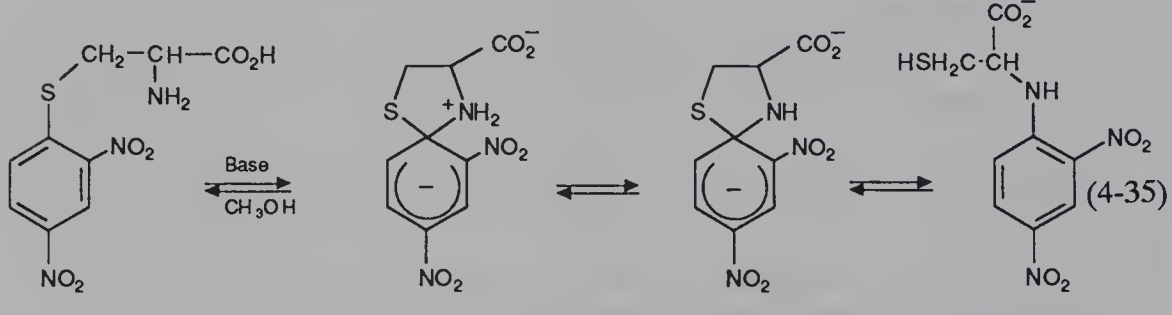
collisional activation of 2-phenoxyethoxide ion in the gas phase produces phenoxide ion through the intermediacy of a dioxolane spiro adduct, as shown in eq. 4-34. This suggests that gas phase Smiles rearrangements do not necessarily require the activation of the benzene ring by an ortho or para electron-withdrawing group such as an NO_2 group (see Chapter 1, Section 1.8).[102]



(4-34)

4.3.4 N → S and S → N Rearrangements

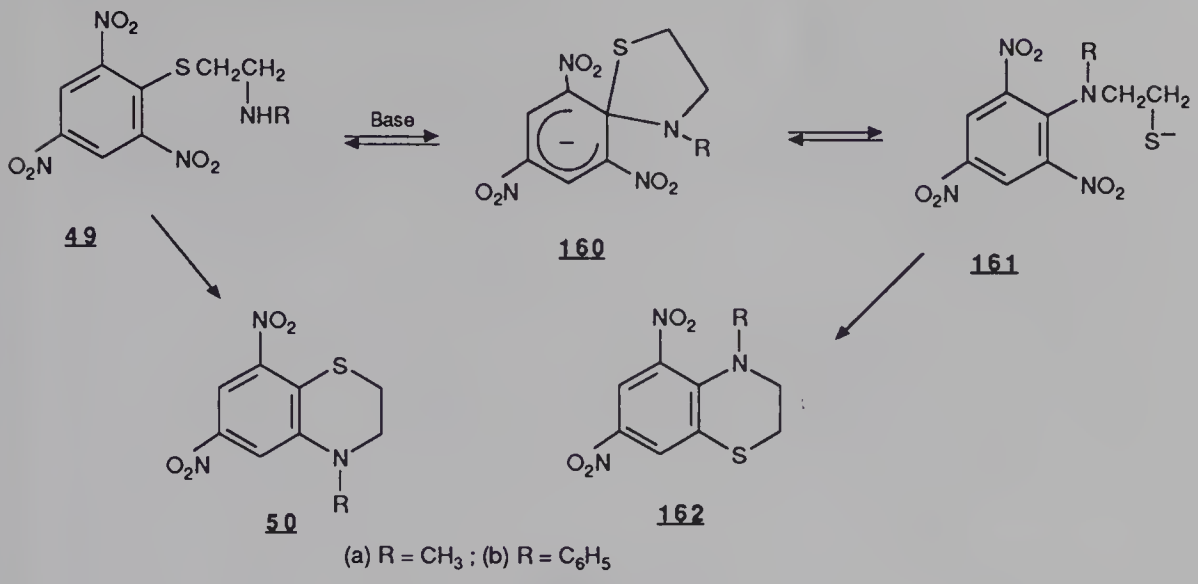
The base-catalyzed conversion of *S*-(2,4-dinitrophenyl)cysteine (**157**) occurs under mild conditions in methanol or DMF,[103] but a noteworthy feature is the evidence that the neighboring carboxy group in **157** plays an essential role in promoting the reaction (eq. 4-35).[103a] In methanol, the rearrangement from **157** to **159** via the σ-adduct **158** goes essentially to completion, while in the presence of a strong base (e.g., DBU), capable of ionizing the SH group of **159** in DMF, the reverse rearrangement becomes effective, giving an equilibrium mixture of **157** and **159** in a 5:95 ratio.[103a] Such behavior is in accord with the similar nucleophilicity of thiolate ions and aliphatic amines in many S_NAr reactions (Section 4.2.2 and Chapter 1). Other noteworthy S → N rearrangements involving a cysteine moiety are rearrangements of 6- and 8-*S*-cysteinylflavins into the corresponding 6- and 8-*N*-cysteinylflavins.[104]



(4-35)

157 **158** **159**

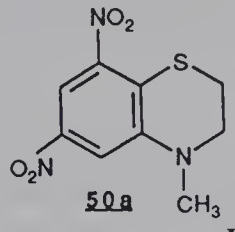
1-[β-(*N*-Methylamino)ethylthio]-2,4,6-trinitrobenzene(**49a**) slowly cyclizes in basic media to form both isomeric 6,8- and 5,7-dinitro-4-methyl-2,3-



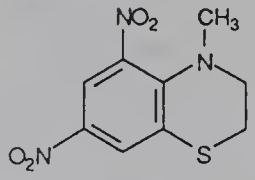
Scheme 4.23.

dihydro-1,4-benzothiazines (**50a**) and (**162a**).[41,42] This suggests the mechanism of Scheme 4.23, which involves a partial rearrangement of **49a** to the sulfide **161a** via **160a**, followed by intramolecular S_NAr displacement of an *o*-nitro group in each picryl moiety, allowing one to obtain **50a** and **162a**, respectively.[41,42] As shown in Table 4.2, use of strong bases in dipolar aprotic

Table 4.2. Effect of Base and Solvent on the Formation of the Isomeric Benzothiazines 50a and 162a[a]



50a

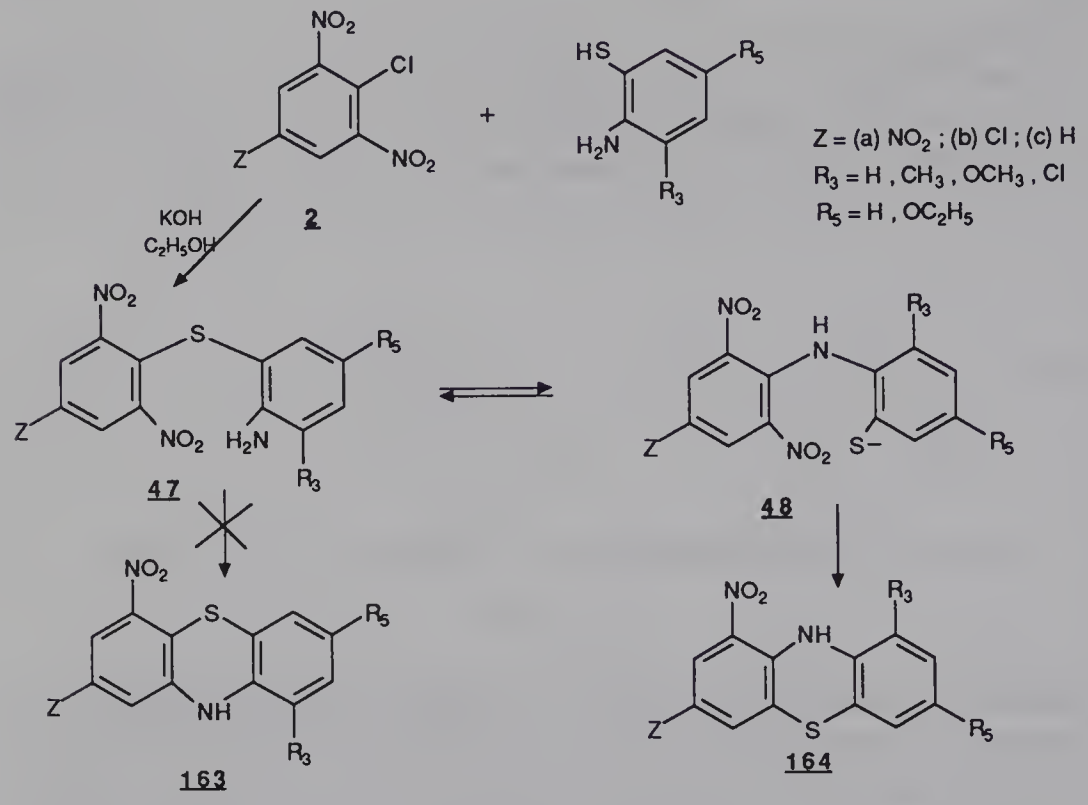


162a

Solvent:	Ratio of 50a to 162 a[b] HMPA	DMSO	DMF	$(CH_3)_3COH$	CH_3OH	THF
Base						
$(CH_3)_3COK$		100:0	100:0 (86)	86:14 (16)		0:100 (32)
$(C_2H_5)_3N$	68:32 (13)		67:33 (80)	30:70 (19)	24:76 (20)	
Pyridine			0:100 (53)	0:100 (44)	4:96 (82)	0:100 (17)

[a] Refs. 41 and 42.

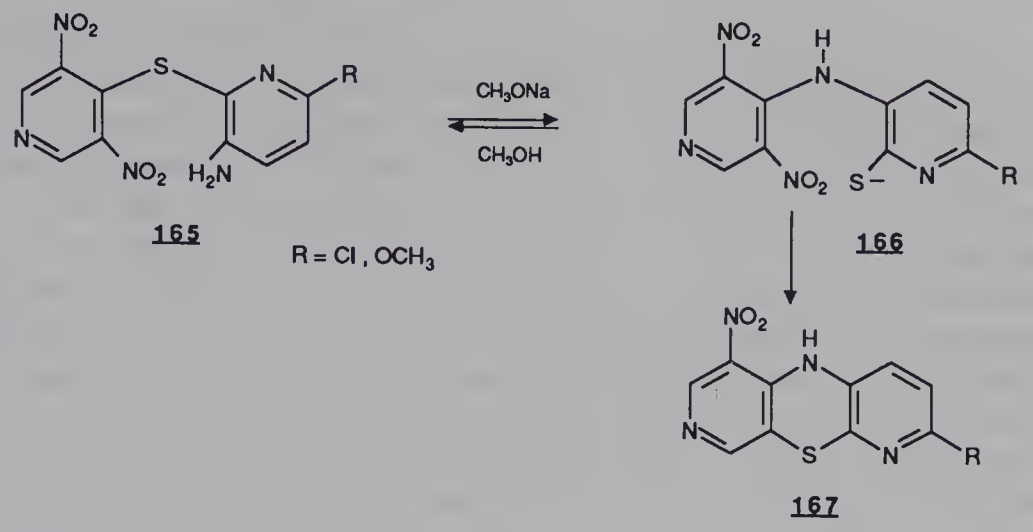
[b] Yield (%) given in parentheses.



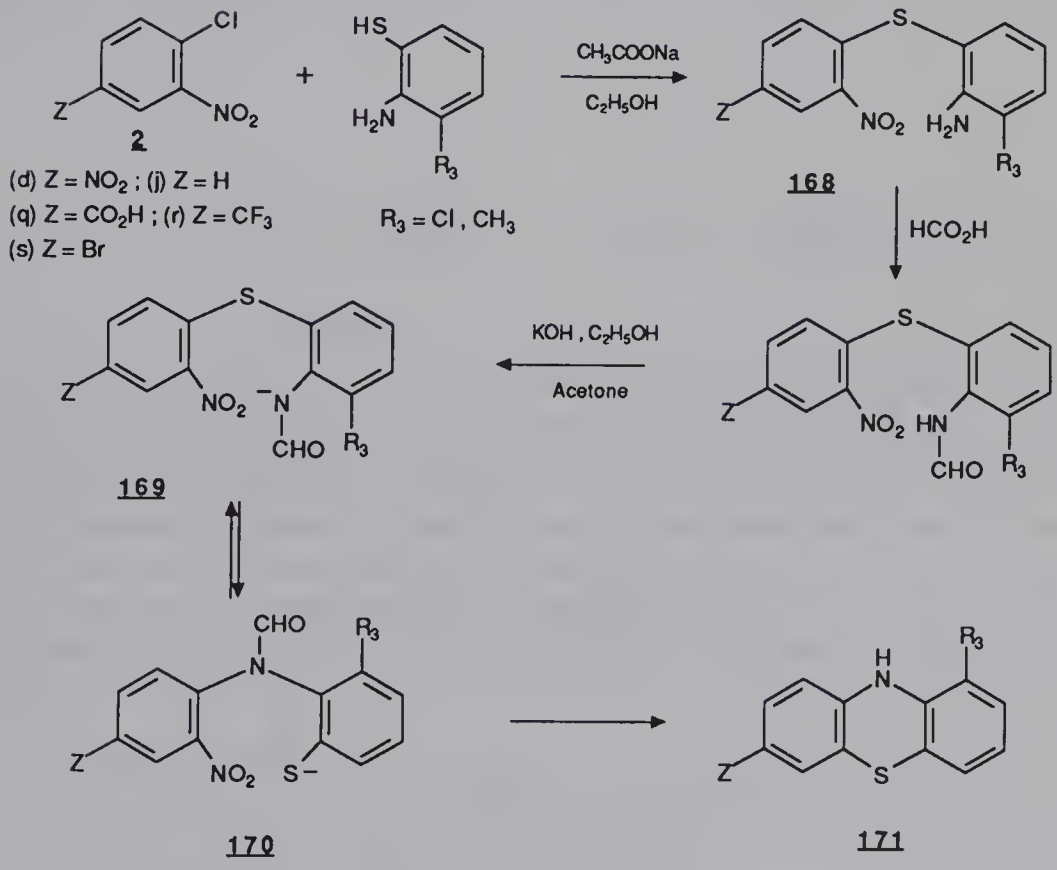
Scheme 4.24.

solvents like DMSO or DMF allows one to obtain **50a** in high yields, while use of weak bases like pyridine affords exclusively **162a** in all solvents employed. In contrast with **49a**, 1-[β-(*N*-phenylamino)ethylthio]-2,4,6-trinitrobenzene (**49b**) undergoes almost exclusive conversion to the benzothiazine **162b**.[42]

Smiles rearrangements are a key step in most reaction sequences leading to phenothiazines.[105–108] Scheme 4.24 exemplifies the one-pot synthesis of some 1-nitrophenothiazines **164** (60–80% yield) via direct condensation of various 2-mercaptoanilines with 1-chloro-2,6-dinitrobenzenes **2a**, **2b**, and **2c** in ethanolic sodium hydroxide.[106,107] The reactions involve rapid Smiles rearrangement of the diaryl sulfide intermediates **47** to the diarylamines **48** and cyclization of these amines to **164** via nitro displacement. No appreciable amount of the isomeric nitrophenothiazines (**163**) was found. Similarly, the condensation of substituted 3-amino-2-mercaptopyridines with 4-chloro-3,5-dinitropyridine in methanolic methoxide afforded the dipyridyl sulfides **165**, which rearranged to the dipyridylamines **166**. Cyclization of **166** yielded the 1-nitro-3,6-diazaphenothiazines **167** in good yields (Scheme 4.25).[109]

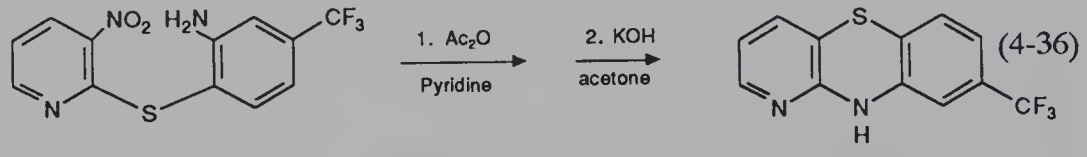


Scheme 4.25.



Scheme 4.26.

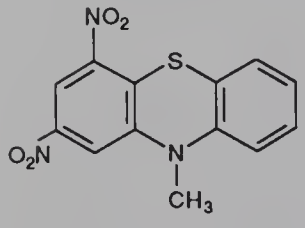
Phenothiazines not containing a nitro group at the 1-position were prepared according to Scheme 4.26, since the lower activation of the haloaromatic precursors **2d**, **2i**, and **2q–2s** used does not make the resulting diarylsulfides **168** very prone to undergo further S_NAr processes.[107,108] In these instances, formylation of the amino group followed by ionization of the resulting formamido group in strong base afforded the reactive amide ions **169**, which led exclusively to the phenothiazines **171** (60–70% yield). This indicates that rapid rearrangement of **169** to **170** occurs prior to S_NAr cyclization.[107,108] Activation of the amino group of the sulfide **172** by an acetyl group was similarly used to synthesize the 1-azaphenothiazine **173** in 45% yield (eq. 4-36).[110] In contrast to the examples above, 1-[*o*-(*N*-methylamino)phenylthio]-2,4,6-trinitrobenzene cyclized both with and without preliminary rearrangement in the presence of triethylamine in DMSO to give a 1:1 mixture of the isomeric phenothiazines **174** and **175**; the overall yield of the cyclization is 64%.



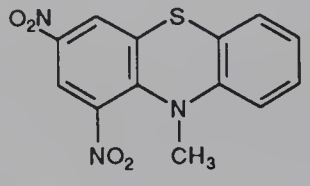
(4-36)

172

173 (45%)

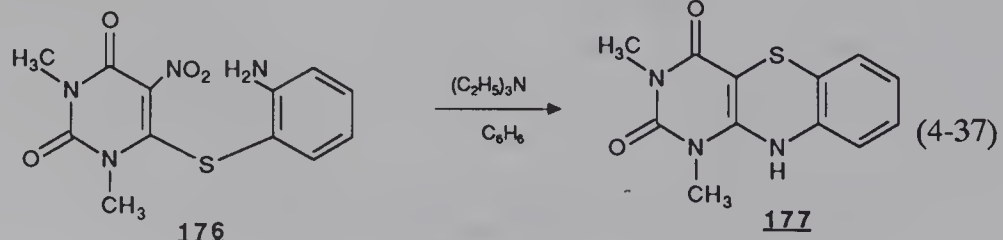


174



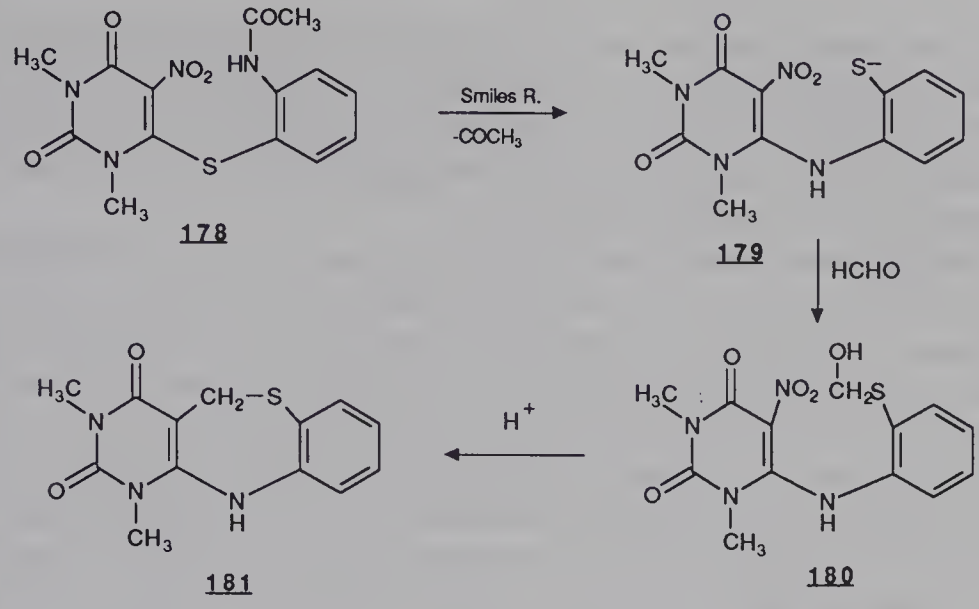
175

S → N Smiles rearrangements occur in uracil derivatives.[111] Thus, condensation of 1,3-dimethyl-5-nitro-6-chlorouracil with 2-mercaptoaniline in benzene containing triethylamine gave the benzothiazine **177**, indicating that rearrangement of the sulfide **176** precedes the cyclization step (eq. 4-37).[111a] The pyrimido[5,4-*c*][1,5]benzothiazepine **181** was obtained in high yield by rearrangement of the sulfide **178**, trapping of the resulting thiolate anion **179**



(4-37)

176 **177**



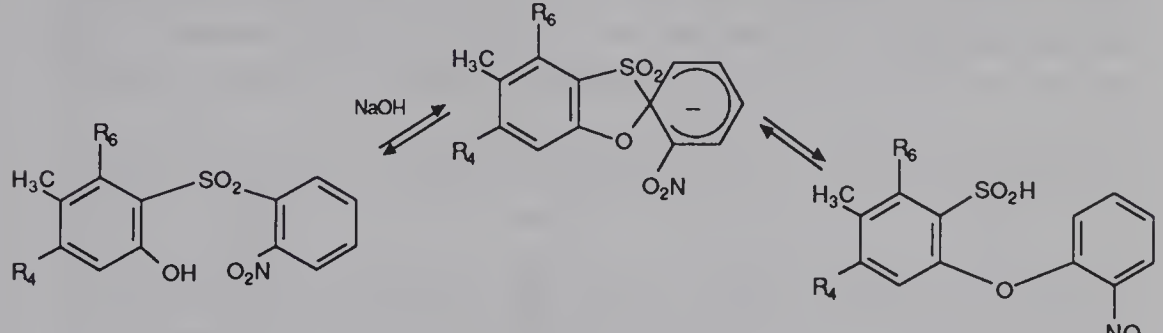
178 179 180 181

Scheme 4.27.

with formaldehyde, and acid-catalyzed cyclization of the hydroxymethylthio derivative **180** (Scheme 4.27).[111b]

4.3.5 S → O and Se → O Rearrangements

Since many original Smiles rearrangements were of the S → O type, a number of examples of such reactions were quoted in early reviews.[4,112] The conversion of the nitrobenzenesulfonamides **106** to the nitrophenyl ethers **100** (Scheme 4.15), as discussed in Section 4.3.1, exemplifies the displacement of

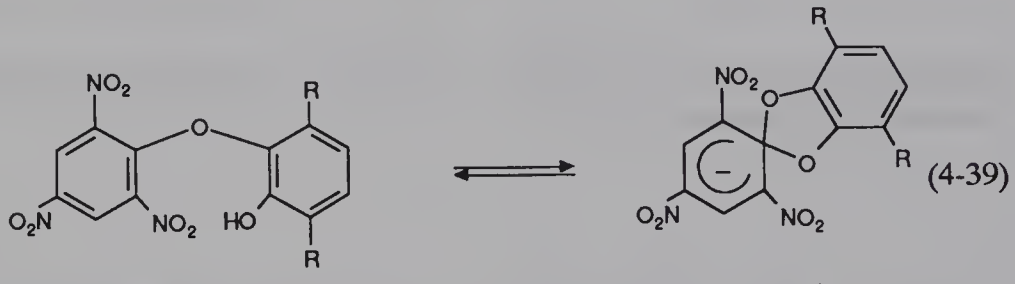


182 $R_6 = H, R_4 = H, CH_3, Cl, Br$ **183**

184 $R_4 = H, R_6 = H, CH_3, Cl, Br$ **185** (4-38)

a sulfinyl group by an alkoxide ion.[7,71a] Substitution of a sulfinyl functionality by an aryloxide ion also occurs, as shown in eq. 4-38, which describes the facile conversion of various 4- and 6-substituted 2-hydroxy-5-methyl-2′-nitrodiphenylsulfones (**182** and **184**) to the corresponding 2-(*o*-nitrophenoxy)-benzenesulfinic acids (**183** and **185**).[113,114]

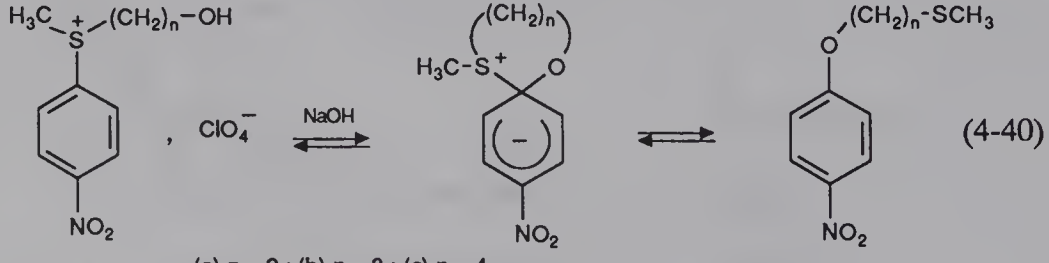
Besides their synthetic interest, these reactions are worth mentioning for mechanistic reasons. All sulfones **182** that lack a 6-substituent were found to rearrange considerably more slowly than the isomeric sulfones **184**, which contain a 6-substituent. On the other hand, both the electron-releasing 6-methyl group and the electron-withdrawing 6-bromo and 6-chloro groups cause similar tremendous increases (~ 500,000-fold) in the rearrangement rate.[114] This suggests that the origin of the acceleration is steric and not electronic.[114] A recent study by Bernasconi and Fairchild of the cyclization of the catechol ethers **186a** and **186b** to the stable spiro adducts **187a** and **187b** (eq. 4-39) has revealed a similar steric acceleration by the methyl groups in **186b**.[115]



(4-39)

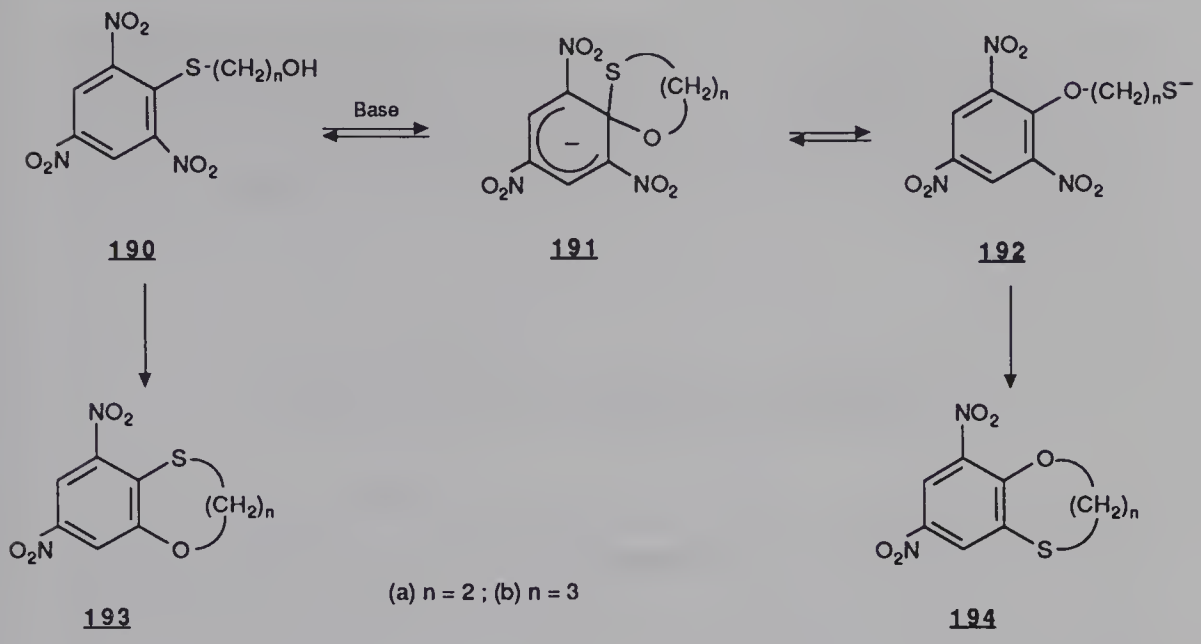
186 (a) R = H ; (b) R = CH_3 **187**

Displacement of a labile sulfonium group by an alkoxide ion is very facile. As an example, the rearrangement of the *p*-nitrophenylsulfonium perchlorate **188b** proceeded readily in aqueous sodium hydroxide to give a quantitative yield of the ether **189b** (eq. 4-40).[116] However, the ease of rearrangement depends on the size of the side chain. The conversion of the 2-hydroxyethyl derivative **188a** afforded the corresponding ether **189a** in only about 40% yield while that of the 4-hydroxy-*n*-butyl analogue **188c** did not proceed at all.[116]



(4-40)

188 (a) n = 2 ; (b) n = 3 ; (c) n = 4 **189**

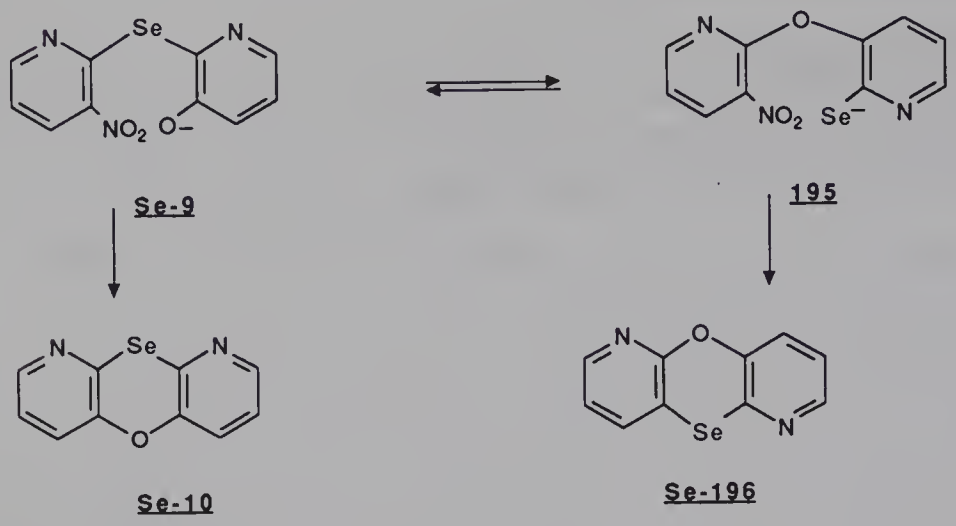


Scheme 4.28.

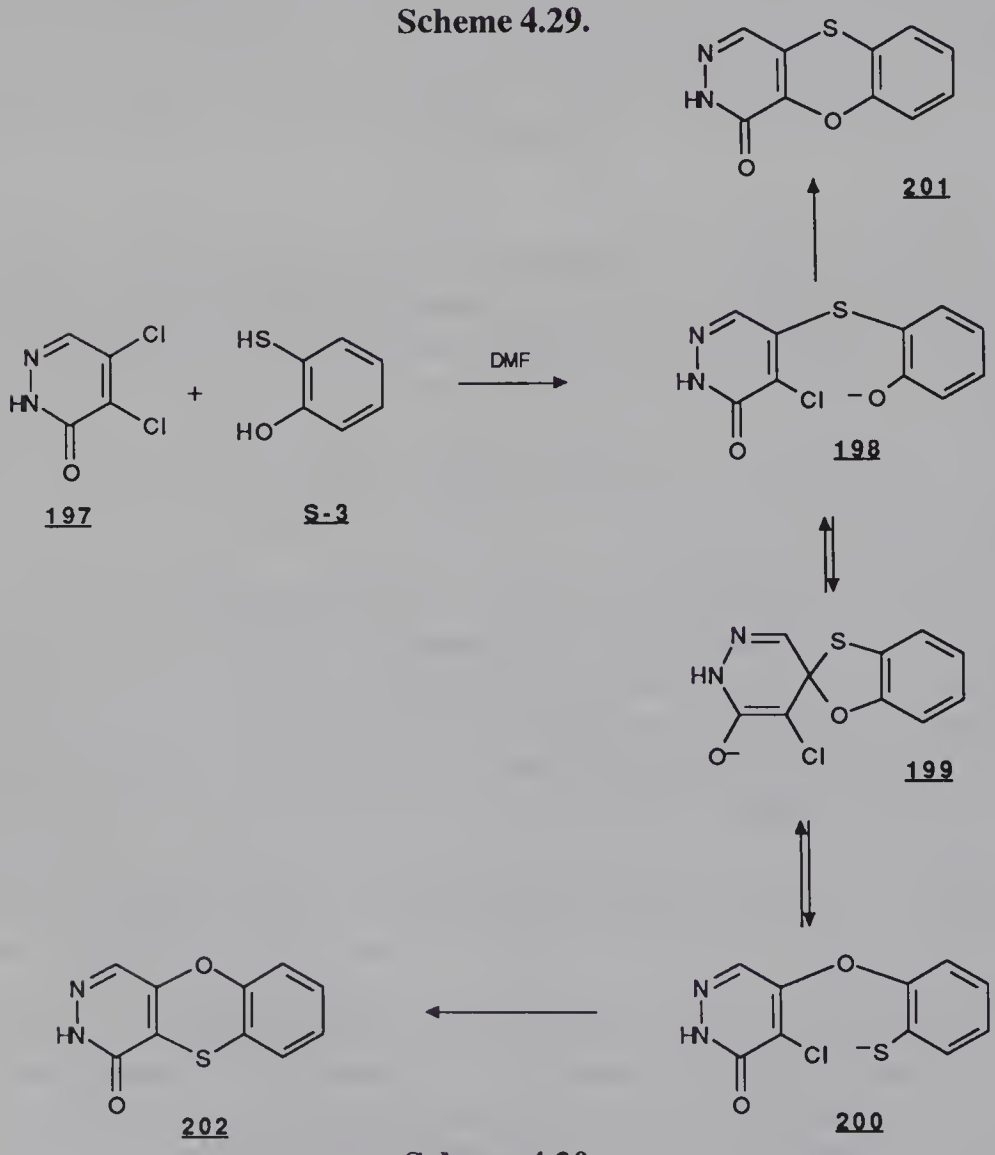
In basic media, 1-(γ-hydroxypropylthio)-2,4,6-trinitrobenzene (**190b**) afforded a 95:5 mixture of the benzoxathiepins **193b** and **194b** while the 1-(β-hydroxyethylthio) analogue **190a** decomposed very rapidly to picrate ion and ethylene sulfide.[11,117,118] Obviously, an S → O rearrangement of **190** to **192** via the σ-adducts **191** occurred in the two systems (Scheme 4.28). That none of the isomeric benzoxathiins **193a** and **194a** form upon treatment of **190a** is simply the consequence of the rapid decomposition of the rearranged ether **192a** to picrate ion.[11,118]

In contrast with the situation for the benzoxathiine series, Smiles rearrangements do not in general occur in the phenoxathiine series (Section 4.2.1). It is therefore a remarkable result that the reaction of 2-chloro-3-nitropyridine (**7**) with the dianion of 3-hydroxypyridine-2-selol (**Se-8**) was recently found not to proceed regiospecifically in DMF.[23] In this case, a rapid and partial rearrangement of the initially formed dipyridyl selenide **Se-9** to the dipyridyl ether **195** accounts for the formation of the isomeric 1,9- and 1,6-diazaphenoxaselenines **Se-10** and **Se-196** (Scheme 4.29).[23] There is as yet no definitive explanation for the marked difference between the sulfur and selenium series.

Scheme 4.30 describes the only example of the occurrence of a Smiles rearrangement during the synthesis of a phenoxathiin.[119] Condensation in DMF of the disodium salt of thiopyrocatechol **S-3** with 4,5-dichloro-6(1*H*)-pyridazinone **197** gives the phenolate sulfide intermediate **198**, which rapidly



Scheme 4.29.

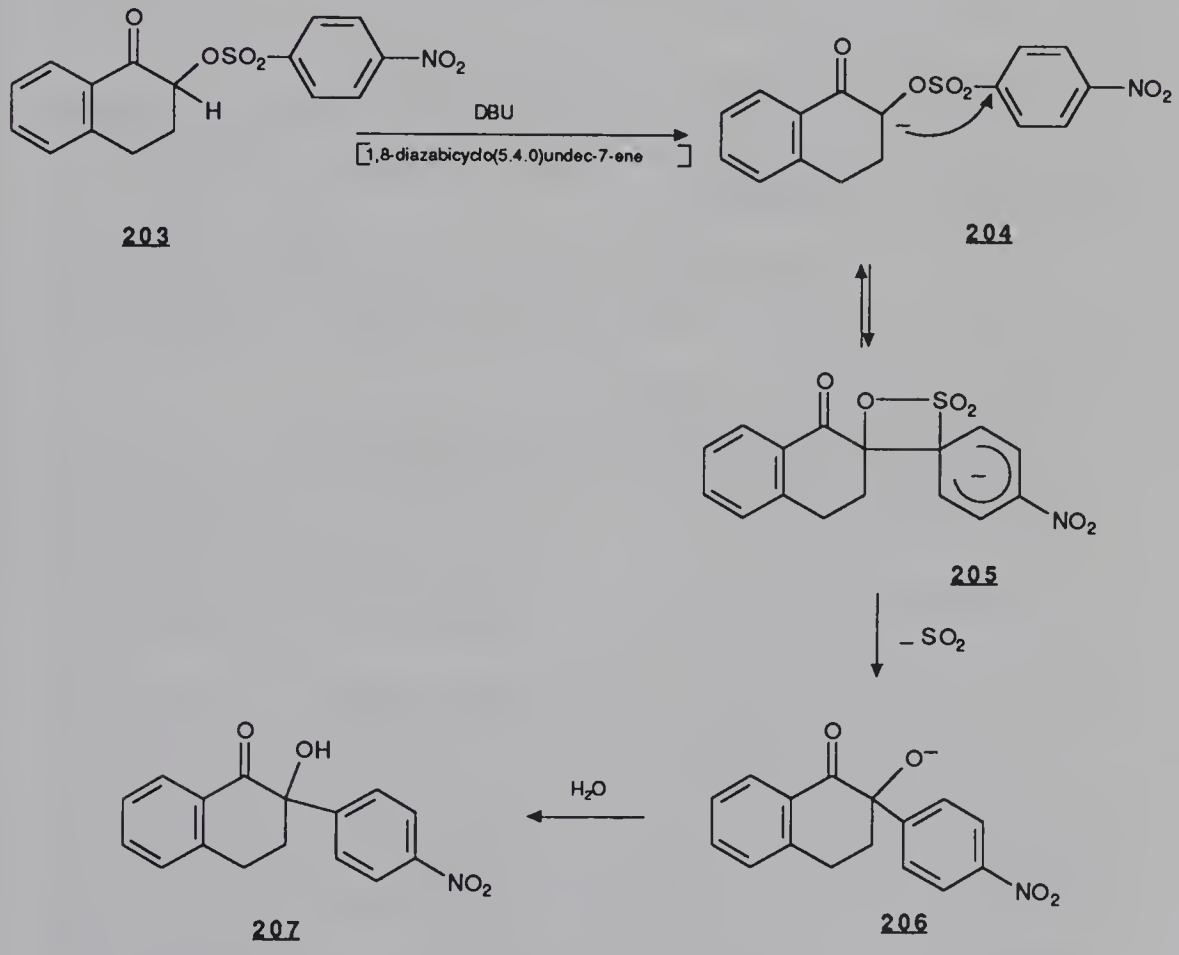


Scheme 4.30.

rearranges to the thiolate ether **200**. Subsequently, cyclizations of **198** and **200** compete to afford a mixture of the two isomeric benzoxathiinopyridazinones **201** and **202**. In this instance, the carbonyl group of **198** must act similarly to a nitro group, facilitating the formation of the spiro complex intermediate **199**. (Scheme 4.30).[119]

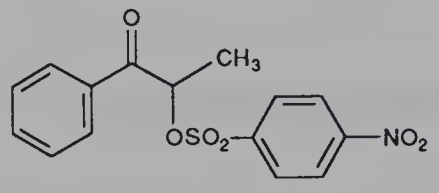
4.3.6 C → S Rearrangements

A novel intramolecular substitution that may be formally considered to involve a C → S Smiles rearrangement has recently been reported.[120] Ketones like **203** with an α-(*p*-nitrophenyl)sulfonoxy group have a relatively acidic α-proton. In the presence of sterically hindered bases (DBU, DBN), which do

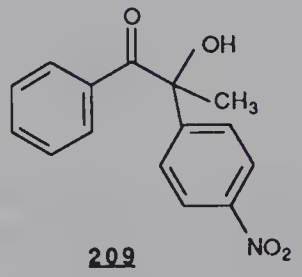


Scheme 4.31.

not add to the carbonyl group, α-proton removal to the enolate **204** is followed by intramolecular attack by the nucleophilic carbon to form the intermediate spiro adduct **205** (Scheme 4.31). Opening of the four-membered ring of **205** then occurs, with breaking of the C—S bond and concomitant loss of SO_2 to give **206**, which, upon reaction with water, affords the ketol **207** (78% yield). Similar reactivity was seen for **208**, which gave ketol **209** in 45% yield.[120]



208



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References

1. Preston, P. N.; Tennant, G. *Chem. Rev.* **1972**, *72*, 627.
2. Migachev, G. I.; Danilenko, V. A. *Khim. Geterotsikl. Soedin.* **1982**, 867.
3. (a) Warren, L. A.; Smiles, S. *J. Chem. Soc.* **1930**, 956; (b) Evans, W. J.; Smiles, S. *ibid.* **1935**, 181.
4. Truce, W. E.; Kreider, E. M.; Brand, W. W. *Org. React.* **1970**, *18*, 99.
5. Shine, H. J., "*Aromatic Rearrangements*". Elsevier: Amsterdam, 1967, p. 307.
6. Terrier, F. *Chem. Rev.* **1982**, *82*, 77.
7. Kleb, K. G. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 291.
8. Knyazev, V. N.; Drozd, V. N. *Izv. Sib. Otd. Akad. Nauk SSR, Ser. Khim. Nauk*, **1983**, *4*, 43.
9. Pearson, D. E.; Brockman, R. W.; Cole, W. E.; Greer, C. M.; Sigal, M. V. In "*Heterocyclic Compounds*", Vol. 6, Elderfield, R. C., ed. Wiley: New York, 1957, p. 686.
10. Breslow, D. S.; Skolnik, H. "*Multisulfur and Sulfur and Oxygen Five- and Six-Membered Ring Heterocycles*", Part II. Wiley-Interscience: New York, 1966, pp. 864–997.
11. Knyazev, V. N; Klimov, A. A.; Drozd, V. N. *Zh. Org. Khim.* 1975, 11, 1440.
12. Knyazev, V. N.; Drozd, V. N.; Mozhaeva, T. Ya. *Zh. Org. Khim.* **1980**, *16*, 876.
13. Takahashi, T.; Yoneda, F. *Chem. Pharm. Bull.* **1958**, *6*, 46, 378.

14. Okafor, C. O. (a) *J. Chem. Soc., Chem. Commun.* **1974**, 878; (b) *Int. J. Sulfur Chem.* **1971**, *B*, 345.
15. (a) Martin, G. E.; Turley, J. C.; Williams, L.; Steenberg, M. L.; Bockley, J. P. *J. Heterocycl. Chem.* **1977**, *14*, 1067; (b) Martin, G. E.; Turley, J. C.; Williams, L. *ibid.* **1977**, *14*, 1249.
16. Martin, G. E.; Turley, J. C. *J. Heterocycl. Chem.* **1978**, *15*, 609.
17. Caldwell, J. R., Martin, G. E. *J. Heterocycl. Chem.* **1980**, *17*, 989.
18. Caldwell, J. R.; Martin, G. E.; Simonsen, S. H.; Inners, R. R.; Willcott, M. R. *J. Heterocycl. Chem.* **1981**, *18*, 479.
19. Caldwell, J. R.; Turley, J. C.; Martin, G. E. *J. Heterocycl. Chem.*, **1980**, *17*, 1153.
20. Lindsy, C. M.; Smith, K.; Martin, G. E. *J. Heterocycl. Chem.* **1987**, *24*, 211.
21. Davies, J. S.; Smith, K.; Turner, J. R.; Gymer, G. *TetrahedronLett.* **1979**, 5035.
22. Smith, K.; Matthews, J.; Hulme, N. M.; Martin, G. E. *J. Chem. Soc., Perkin Trans. 1*, **1986**, 2075.
23. Smith, K.; Matthews, J.; Martin, G. E. *J. Chem. Soc., Perkin Trans. 1*, **1987**, 2839.
24. Balasubramanian, A.; Capindale, J. B.; Forbes, W. F. *Can. J. Chem.* **1964**, *42*, 2674.
25. Berg, S. S.; Petrov, V. *J. Chem. Soc.* **1952**, 784.
26. Agrawal, K. C.; Bears, K. B.; Sehgal, R. V.; Brown, J. N.; Rist, P. E. *J. Med. Chem.* **1979**, *22*, 583.
27. Sehgal, R. K.; Agrawal, K. C. *J. Heterocycl. Chem.* **1979**, *16*, 1499.
28. Vecchietti, V.; Dradi, E.; Lauria, F. *J. Chem. Soc. C*, **1971**, 2554.
29. Kofman, T. P.; Manuilova, V. I.; Pevzner, M. S.; Timofeeva, T. N. *Khim. Geterotsikl. Soedin.* **1975**, 705.
30. Kofman, T. P.; Vasil'eva, I. V.; Pevzner, M. S. *Khim. Geterotsikl. Soedin.* **1977**, 1407.
31. Prisbe, E. J.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1978**, *43*, 4784.
32. Wunsch, K. H.; Boulton, A. J. *Adv. Heterocycl. Chem.* **1967**, *8*, 277.
33. Kemp, D. S.; Cox, D. D.; Paul, K. G. *J. Am. Chem. Soc.* **1975**, *97*, 7312.
34. (a) Matsumura, E.; Ariga, M. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3144; (b) *ibid.*, **1977**, *50*, 237.
35. Matsumura, E.; Ariga, M.; Tohda, Y. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2891.

36. (a) Collington, D. M.; Hey, D. H.; Rees, C. W. *J. Chem. Soc. C*, **1968**, 1030; (b) Hey, D. H.; Leonard, J. A.; Rees, C. W. *ibid.* **1962**, 4579.
37. Mathur, K. B. L.; Sarbhai, K. P. *Tetrahedron Lett.* **1964**, 1743.
38. Migachev, G. I.; Eremenko, L. V.; Dokunikhin, N. S.; Dyumaev, K. M. *Zh. Org. Khim.* **1978**, *14*, 668.
39. Migachev, G. I.; Rodionova, G. N. *Zh. Vses. Khim. Ova.* **1980**, *25*, 237.
40. Migachev, G. I.; Andrievskii, A. M.; Dokunikhin, N. S. *Zh. Org. Khim.* **1977**, *13*, 463.
41. Knyazev, V. N.; Drozd, V. N.; Minov, V. M. *Tetrahedron Lett.* **1976**, 4825.
42. Knyazev, V. N.; Drozd, V. N.; Minov, V. M.; Akimova, N. P. *Zh. Org. Khim.* **1977**, *13*, 1255.
43. Buncel, E.; Hamaguchi, M.; Norris, A. R. *J. Chem. Soc., Perkin Trans. 1*, **1980**, 2205.
44. Kofman, T. P.; Medvedeva, N. Yu.; Uspenskaya, T. L.; Pevzner, M. S. *Khim. Geterotsikl. Soedin.* **1977**, 1271.
45. Kofman, T. P.; Zirpenko, Z. V.; Pevzner, M. S. *Khim. Geterotsikl. Soedin.* **1982**, 1113.
46. Schimmelschmidt, K.; Hoffman, H. *Justus Liebigs Ann. Chem.* **1964**, *677*, 157.
47. Sandison, A. A.; Tennant, G. *J. Chem. Soc., Chem. Commun.* **1974**, 752.
48. Kost, A. A. *Khim. Geterotsikl. Soedin.* **1980**, 1200.
49. (a) Morgan, G.; Stewart, J. *J. Chem. Soc.* **1938**, 1292; (b) *ibid.* **1939**, 1057.
50. Bard, R. R.; Strauss, M. J. *J. Org. Chem.* **1977**, *42*, 435.
51. Wolff, H. M.; Hartke, K. *Tetrahedron Lett.* **1977**, 3453.
52. Puig-Torres, S.; Martin, G. E.; Ford, J. J.; Willcott, M. R.; Smith, K. *J. Heterocycl. Chem.* **1982**, *19*, 1441.
53. Lam, W. W.; Martin, G. E.; Lynch, V. M.; Simonsen, S. H.; Lindsay, C. M.; Smith, K. *J. Heterocycl. Chem.* **1986**, *23*, 785.
54. Still, I. W. J.; Sayeed, V. A. *Synth. Commun.* **1983**, *13*, 1181.
55. D'Amico, J. J.; Tung, C. C.; Dahl, W. E.; Dahm, D. J. (a) *J. Org. Chem.* **1977**, *42*, 2896 ; (b) *ibid.*, **1976**, *41*, 3564.
56. Rasheed, K.; Warkentin, J. D. *J. Org. Chem.* **1977**, *42*, 1265.
57. D'amico, J. J.; Tung, C. C.; Dahl, W. E. *J. Org. Chem.* **1977**, *42*, 600.
58. Takeshima, T.; Miyauchi, T.; Fukada, N.; Koshizawa, S. *J. Chem. Soc., Perkin Trans. 1*, **1973**, 1009.

59. Takeshima, T.; Fukada, N.; Okabe, E.; Mineshima, F.; Muraoka, M. *J. Chem. Soc. Perkin Trans. 1*, **1975**, 1277.
60. Muraoka, M.; Yamamoto, T.; Yamaguchi, S.; Tonosaki, F.; Takeshima, T.; Fukada, N. *J. Chem. Soc., Perkin Trans. 1*, **1977**, 1273.
61. Augstein, W.; Kröhnke, F. *Justus Liebigs Ann. Chem.* **1966**, *697*, 158.
62. Reuschling, D. B.; Kröhnke, F. *Chem. Ber.* **1971**, *104*, 2103, 2110.
63. Spence, T. W. M.; Tennant, G. *J. Chem. Soc., Perkin Trans. 1*, **1972**, 835.
64. Bernasconi, C. F.; de Rossi, R. H.; Gehriger, C. L. *J. Org. Chem.* **1973**, *98*, 2838.
65. Bernasconi, C. F.; Gehriger, C. L.; de Rossi, R. H. *J. Am. Chem. Soc.* **1976**, *98*, 8451.
66. (a) Knipe, A. C.; Sridhar, N. ; Lound-Keast, J. *Tetrahedron Lett.* **1979**, 2541; (b) Knipe, A. C.; Lound-Keast, J.; Sridhar, N. *J. Chem. Soc., Perkin Trans. 2*, **1984**, 1885; (c) Knipe, A. C.; Sridhar, N.; Lound-Keast, J. *ibid.* **1984**, 1893.
67. Drozd, V. N.; Knyazev, V. N.; Minov, V. M. *Zh. Org. Khim.* **1977**, *13*, 396.
68. Wubbels, G. A.; Halverson, A. M.; Oxman, J. D.; De Bruyn, V. H. *J. Org. Chem.* **1985**, *50*, 4499.
69. Sekiguchi, S.; Shiojima, T. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 693.
70. Mizuta, H.; Naruto, S.; Nishimura, H. *Chem. Pharm. Bull.* **1987**, *35*, 2238.
71. (a) Knipe, A. C.; Sridhar, N. *Synthesis,* **1976**, 606. (b) Knipe, A.C.; Sridhar, N.; Lound-Keast, J. *J. Chem. Soc., Perkin Trans. 1*, **1977**, 581.
72. Skarzewski, J.; Skrowaczenska, Z. *Tetrahedron*, **1976**, *32*, 1221.
73. Schmidt, D. M.; Bonvicino, G. E. *J. Org. Chem.* **1984**, *49*, 1664.
74. Radinov, R.; Haimova, M.; Simova, S.; Simova, E. *Justus Liebigs Ann. Chem.* **1988**, 231.
75. Sekiguchi, S.; Okada, K. *J. Org. Chem.* **1975**, *40*, 2782.
76. (a) Okada, K.; Matsui, K.; Sekiguchi, S. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2601. (b) Okada, K.; Sekiguchi, S. *J. Org. Chem.* **1978**, *43*, 441.
77. Sekiguchi, S.; Hoshino, O.; Hirai, M.; Okada, K. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2173.
78. Sekiguchi, S.; Hirai, M.; Tomoto, N. *J. Org. Chem.* **1984**, *49*, 2378.
79. Sekiguchi, S.; Ohtsuka, I.; Okada, K. *J. Org. Chem.* **1979**, *44*, 2556.
80. Roberts, V. C.; de Worms, C. G.; Clark, H. B. *J. Chem. Soc.* **1935**, 196.
81. Bayles, R.; Johnson, M. C.; Maisey, R. F.; Turner, R. W. (a) Synthesis, **1977**, 31; (b) *ibid.* **1977**, 33.

82. Baker, W. R. *J. Org. Chem.* **1983**, *48*, 5140.

83. Gilman, N. W.; Levitan, P.; Sternbach, L. H. (a) *Tetrahedron Lett.* **1970**, 4121; (b) *ibid. J. Org. Chem.* **1973**, *38*, 373.

84. Sunamoto, J.; Kondo, H.; Yanase, F.; Okamoto, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1361.

85. Sunjic, V.; Oklobdzija, M.; Lisini, A.; Sega, A.; Kajfez, F.; Srzic, D.; Klasinic, L. *Tetrahedron*, **1979**, *35*, 2531.

86. Machacek, V.; Hassanien, M. M. M.; Sterba, V. *J. Chem. Soc., Perkin Trans. 2*, **1986**, 813.

87. Machacek, V.; Hassanien, M. M. M.; Sterba, V.; Lycka, A. *Collect. Czech. Chem. Commun.* **1986**, *51*, 1972.

88. Machacek, V.; Hassanien, M. M. M.; Sterba, V. *Collect. Czech. Chem. Commun.* **1987**, *52*, 2225.

89. Minkin, V. I.; Olekhnovich, L. P.; Zhdanov, Yu. A.; Mikhailov, I. E.; Metlushenko, V. P.; Ivanchenko, N. M. *Zh. Org. Khim.* **1976**, *12*, 1271.

90. Minkin, V. I.; Olekhnovich, L. P.; Zhdanov, Yu. A. *Acc. Chem. Res.* **1981**, *14*, 210.

91. Kende, A. S.; de Camp, M. R. *Tetrahedron Lett.* **1975**, 2877.

92. Ramsden, C. A. *J. Chem. Soc., Perkin Trans. 1*, **1981**, 2456.

93. Gray, A. P.; Cepa, S. P.; Cantrell, J. S. *Tetrahedron Lett.* **1975**, 2873.

94. Harfenist, M.; Thom, E. *J. Org. Chem.* **1971**, *36*, 1171.

95. (a) Blakeley, R. L.; Zerner, B. *Chem. Ind. (London)* **1973**, 133. (b) Fitzgerald, L. R.; Blakeley, R. L.; Zerner, B. *Chem. Lett.* **1984**, 29.

96. Pfister, J. R. *J. Heterocycl. Chem.* **1982**, *19*, 1255.

97. Elix, J. A.; Jones, A. J.; Lajide, L.; Copins, B. J.; James, P. W. *Aust. J. Chem.* **1984**, *7*, 2349.

98. Elix, J. A.; Jenie, U. A.; Parker, J. L. *Aust. J. Chem.* **1987**, *40*, 1451.

99. (a) Minkin, V. I.; Olekhnovich, L. P.; Zhdanov, Yu. A.; Budarina, Z. N.; Metlushenko, V. P.; Orenstein, I. B. *Zh. Org. Khim.* **1977**, *13*, 777. (b) Minkin, V. I.; Olekhnovich, L. P.; Zhdanov, Yu. A.; Mikhailov, I. E.; Budarina, Z. N.; Ivanchenko, N. M. *Dokl. Akad. Nauk. SSSR*, **1974**, *219*, 357.

100. Furmanova, N. G.; Struchkov, Yu. T.; Kompan, O. E.; Budarina, Z. N.; Olekhnovich, L. P.; Minkin, V. I. *Zh. Strukt. Khim.* **1980**, *21*, 83.

101. Oleknovich, L. P.; Furmanova, N. G.; Minkin, V. I.; Struchkov, Yu. T.; Kompan, O. E.; Budarina, Z. N.; Yudilevich, I. A.; Eruzheva, O. V. *Zh. Org. Khim.* **1982**, *18*, 465.

102. Eichinger, P. C. H.; Bowie, J. H.; Hayes, N. R. *J. Am. Chem. Soc.* **1989**, *111*, 4224.

103. (a) Kondo, H. ; Moriuchi, F.; Sunamoto, J. *J. Org. Chem.* **1981**, *46*, 1333; (b) Wallenfel, S. K.; Streffer, C. *Biochem. Z.* **1966**, *346*, 119.

104. Ghisla, S.; Kenney, W. C.; Knappe, W. R.; McIntire, W.; Singer, T. P. *Biochemistry* **1980**, *19*, 2537.

105. Knyazev, V. N.; Drozd, V. N.; Mozhaeva, T. Ya. *Zh. Org. Khim.* **1979**, *15*, 2561.

106. Ojha, K. G.; Jain, S. K.; Gupta, R. R. *Synth. Commun.* **1979**, *9*, 457.

107. Gupta, R. R.; Kalwania, G. S.; Kumar, M. (a) *Heterocycles*, **1981**, *16*, 1527; (b) *J. Heterocycl. Chem.* **1984**, *21*, 893.

108. (a) Gupta, R. R.; Jain, S. K.; Gosmami, N. V.; Kalwania, G. S. *Heterocycles*, **1980**, *14*, 831; (b) Gupta, R. R.; Kumar, R. *ibid.* **1984**, *22*, 1169.

109. Okafor, C. O. *J. Org. Chem.* **1967**, *32*, 2006.

110. Agrawal, R.; Oberol, G. K.; Jain, D. C.; Mital, R. I. *Rev. Roum. Chim.* **1987**, *32*, 37.

111. (a) Maki, Y.; Hiramitsu, T.; Suzuki, M. (a) *Chem. Pharm. Bull.* **1974**, *22*, 1265; (b) *Tetrahedron*, **1980**, *36*, 2097.

112. Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 369.

113. McClement, C. S. ; Smiles, S. *J. Chem. Soc.* **1937**, 1016.

114. (a) Okamoto, T.; Bunnett, J. F. *J. Am. Chem. Soc.* **1956**, *78*, 5357; (b) Bunnett, J. F.; Okamoto, T. *ibid.* **1956**, *78*, 5363.

115. Bernasconi, C. F.; Fairchild, D. E. *J. Am. Chem. Soc.* **1988**, *110*, 5498.

116. Irie, T.; Tanida, H. *J. Org. Chem.* **1980**, *45*, 4961.

117. Knyazev, V. N.; Drozd, V. N.; Minov, V. M. *Zh. Org. Khim.* **1978**, *14*, 105.

118. Crampton, M. R.; Willison, M. J. *J. Chem. Soc., Perkin Trans. 2*, **1976**, 901.

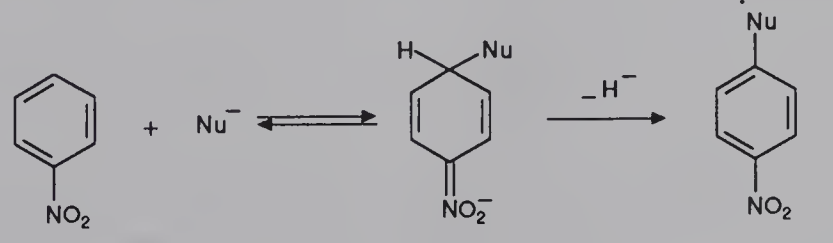
119. Womack, C. H.; Martin, L. M.; Martin, G. E.; Smith, K. *J. Heterocycl. Chem.* **1982**, *19*, 1447.

120. Hoffman, R. V.; Jankowski, B. C.; Carr, C. S.; Duesler, E. N. *J. Org. Chem.* **1986**, *51*, 130.

CHAPTER 5.
Nucleophilic Aromatic Substitutions of Hydrogen

5.1 Introduction

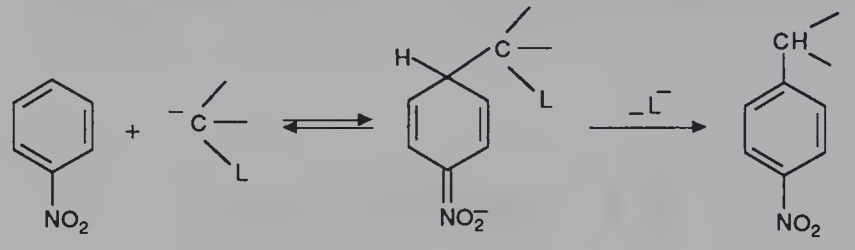
As discussed in Chapter 1, nucleophilic substitution of a nuclear hydrogen of an electron-deficient aromatic via an S_NAr mechanism is not a common process, since the hydride anion has a very low stability and is therefore a very poor leaving group.[1–4] Reactions in which an aromatic hydrogen atom is replaced by a nucleophile are known, however. Like the common S_NAr reactions, they generally occur via initial addition of the nucleophile to the ring, with formation of σ-complex-type intermediates.[1–4] These subsequently decompose in various "oxidation" pathways, which formally lead to nucleophilic aromatic substitution of hydrogen in the aromatic ring, as exemplified in eq. 5-1. This chapter focuses on these reactions, which will be referred to as S_NAr^H reactions for simplicity, and which are often of considerable interest for functionalization of nitroarene systems.



(5-1)

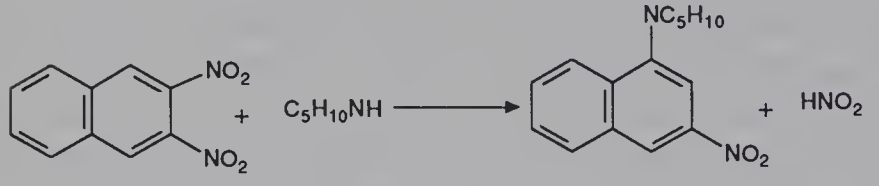
In the following discussion, we offer first a detailed consideration of processes in which the rearomatization step is undoubtedly the result of an oxidation of the σ-complex intermediate. Then we examine systems in which

the intermediate is rearomatized via a series of chemical transformations that do not generally involve an oxidation step. In this context, an important class of reactions are the (so-called) vicarious nucleophilic substitutions of hydrogen in which the driving force for the rearomatization of the intermediate is the elimination of a nucleofugal group initially present at the reactive center of the incoming nucleophile.[5,6] Such reactions are illustrated in eq. 5-2, which refers to carbanionic nucleophiles bearing a leaving group L at the anionic carbon atom. A second interesting class of reactions includes those in which the rearomatization requires departure of both a ring hydrogen atom and a ring substituent. Reactions classified as *cine* and *tele* substitutions usually fall into this category as shown in eq. 5-3.[7,8]



(5-2)

L = Cl, Br, CH_3O, C_6H_5O
C_6H_5S, $(CH_3)_2NC(S)S$



(5-3)

5.2 Reactions Involving Oxidation of σ-Complex-type Intermediates

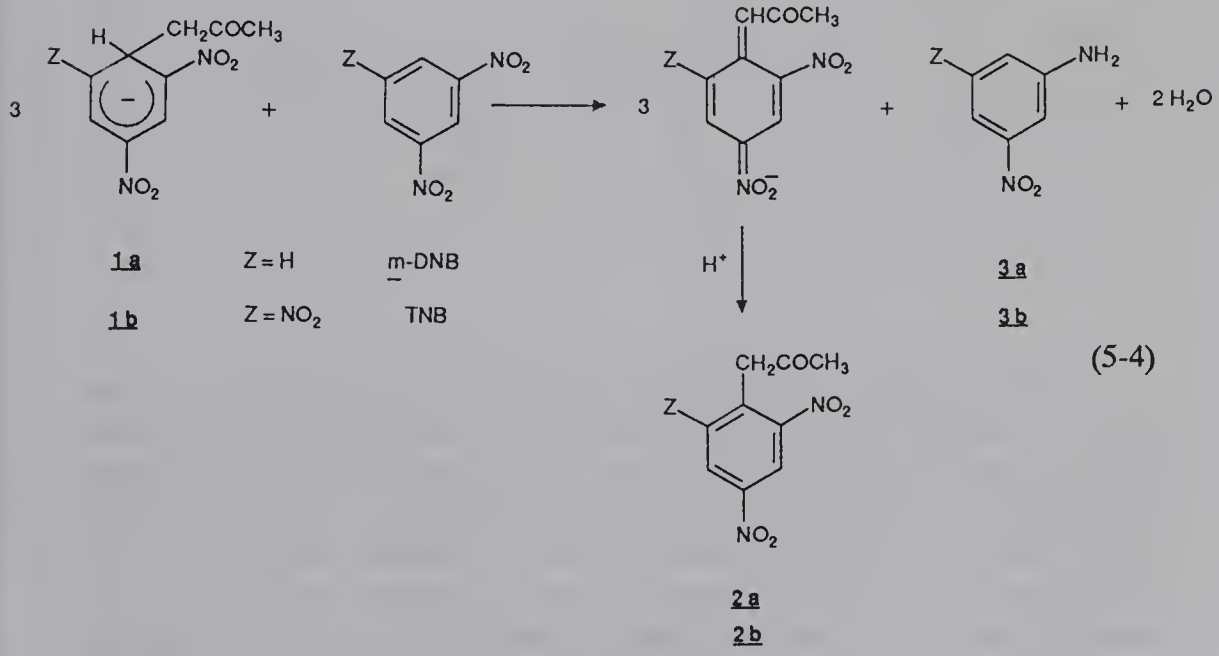
That nucleophilic displacement of hydrogen from aromatic nitro compounds can be achieved by oxidation of Meisenheimer or related complexes has long been known.[1–4] In most cases, the oxidation of the complexes occurs "spontaneously" (i.e., without addition of an oxidizing agent), but the presence of an oxidant favors the completion of the process. In other instances, an external oxidizing agent is necessary to oxidize the adducts. In general, the oxidation reactions take place under the basic conditions required for the formation of such intermediates. However, when the adducts are not susceptible to fast H^+-catalyzed decomposition to the starting materials (i.e., when they do not bear readily protonated leaving groups, or when they possess

leaving groups that undergo protonation at a center far removed from the bond to the anionic ring[2,9]), the oxidation can be carried out under acidic conditions. Regardless of the experimental conditions, the mechanistic details of the oxidation processes remain largely unanswered.

5.2.1 "Spontaneous Oxidations"

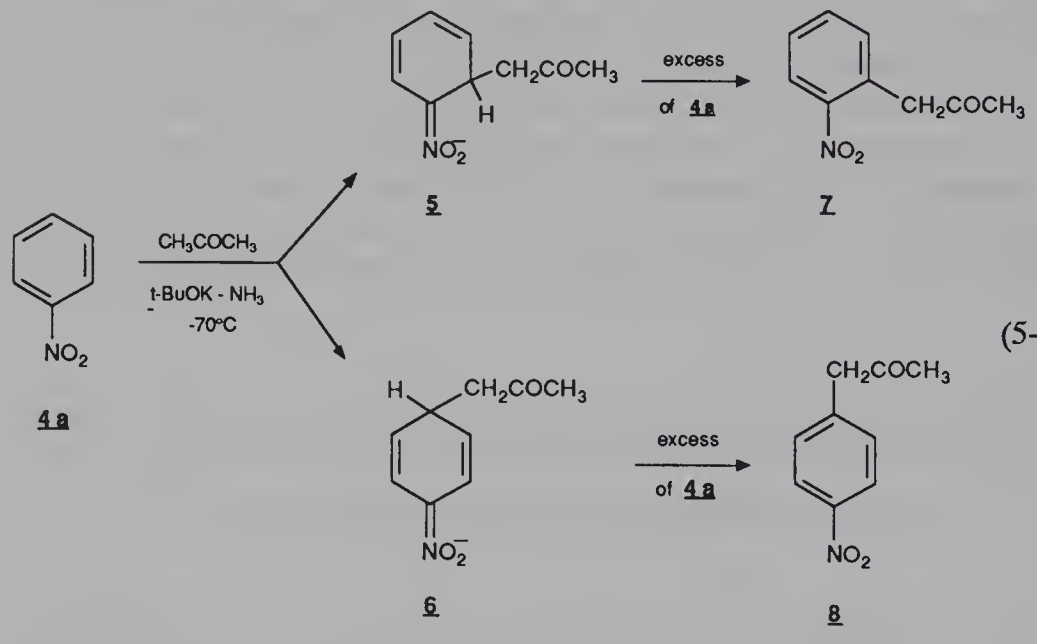
Because they are themselves oxidizing agents, nitroarenes presumably function as the oxidants in the "spontaneous" oxidation reactions.[1] A drawback of this behavior is that there is reduction of part of these compounds and therefore the oxidized products are formed in low to moderate yields.

The reduction of the nitroarene has been demonstrated in the Zimmermann reaction of meta-dinitrobenzene (*m*-DNB) with acetone in basic medium.[10–12] This reaction gives initially the acetonate σ-complex **1a**, which is sufficiently stable to be isolated as a crystalline alkali salt.[13,14] However, in the presence of an excess of *m*-DNB in solution, **1a** is oxidized to 2,4-dinitrophenylacetone (**2a**). The recovery of 3-nitroaniline (**3a**) from such solutions supports a mechanism in which conversion of **1a** to **2a** results from oxidation by free *m*-DNB (eq. 5-4).[11] One might argue that conversion of **1a** to **2a** results in part from simple air oxidation, but the stability of **1a** suggests that this latter process



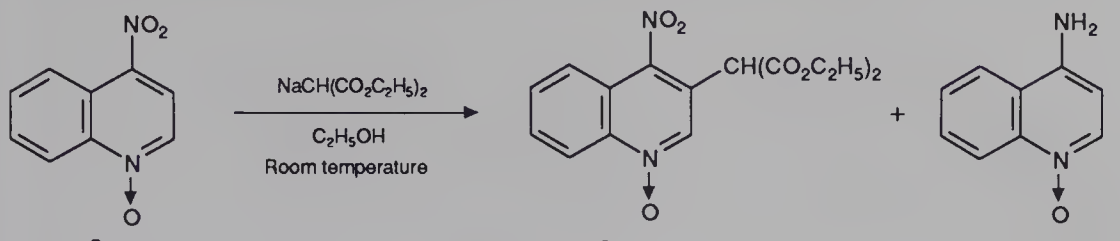
(5-4)

is slow compared to oxidation by *m*-DNB. In contrast to its dinitro analogue, the acetonate-TNB adduct **1b** is not readily oxidized under basic conditions, indicating that the redox potential for the analogous reaction that would produce picrylacetone (**2b**) and 3,5-dinitroaniline (**3b**) must be quite unfavorable.[2] In agreement with this conclusion, it was found that the oxidation potentials E° of the adducts **1a** and **1b**, measured by polarography in acetone, were 0.33 and 0.825 V, respectively, relative to a saturated calomel electrode.[15] On the other hand, the reaction of nitrobenzene (**4a**) with acetone in the presence of *t*-BuOK in liquid ammonia—a very basic medium—gives a mixture of the *o*- and *p*-nitrophenylacetones **7** and **8**, presumably through oxidation of the undetected adducts **5** and **6** (eq. 5-5).[16] *p*-Chloronitrobenzene (**4b**) reacts similarly with acetonate ion as well as other carbanions to give 2-substituted-4-chloronitrobenzenes in yields up to 50%. Significantly, no notable S_NAr displacement of the chlorine atom by acetonate ion to give *p*-nitrophenylacetone (**8**) occurs in this case.[16,17]



(5-5)

Another example in which there is good evidence that the substrate acts as the oxidizing agent in basic medium is the reaction of sodium diethyl malonate with 4-nitroquinoline *N*-oxide (**9**), which gives a mixture of the 3-substituted-4-nitroquinoline *N*-oxide (**10**) and the 4-aminoquinoline *N*-oxide (**11**) (eq. 5-6).[18] Also illustrative are the additions of various carbanions to 2-nitrophenazine *N*-oxide (**12**) that result in hydrogen substitution at the 1-position with concomitant reduction of the *N*-oxide function (eq. 5-7).[19] Also of interest are the additions of the carbanion of nitromethane to 1-nitronaph-



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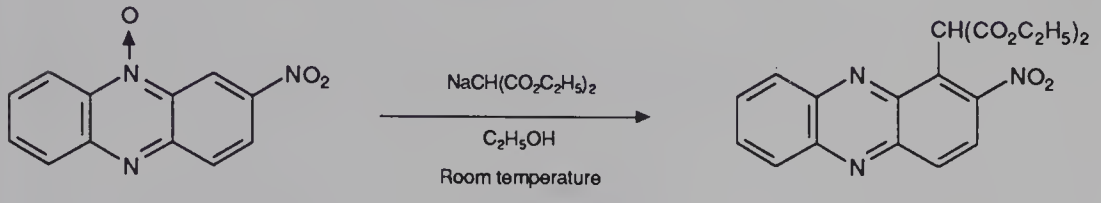
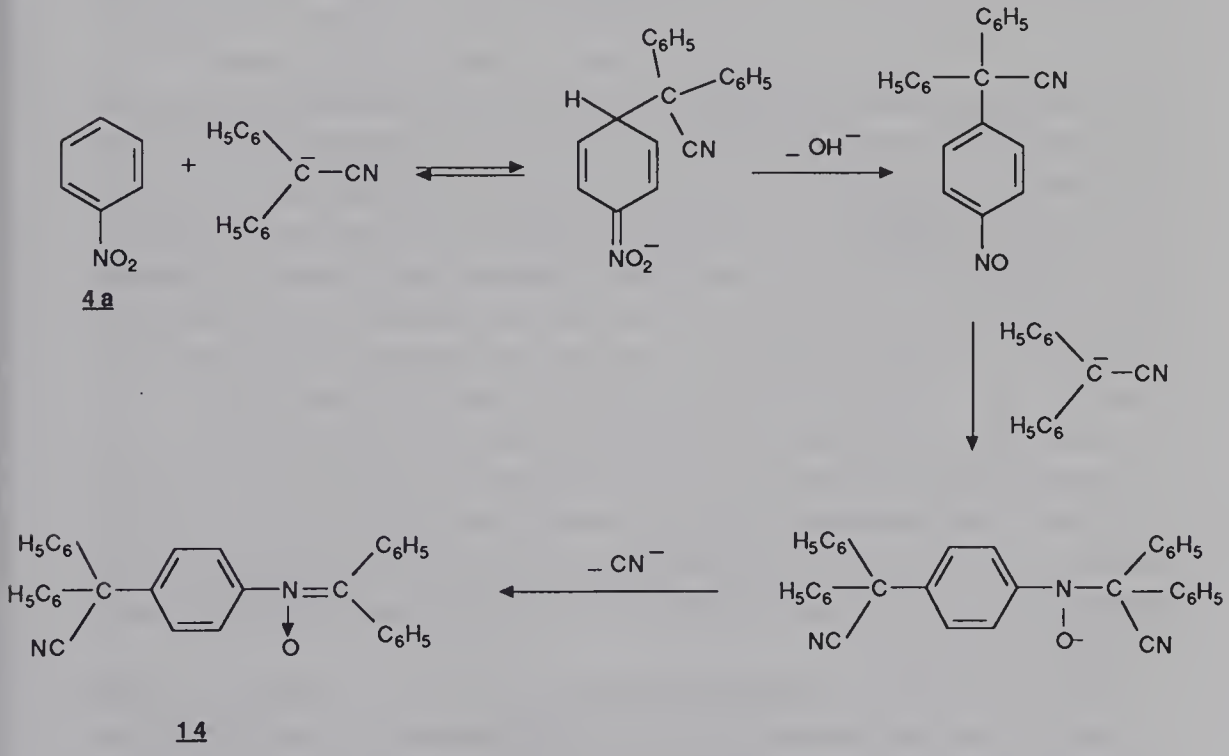


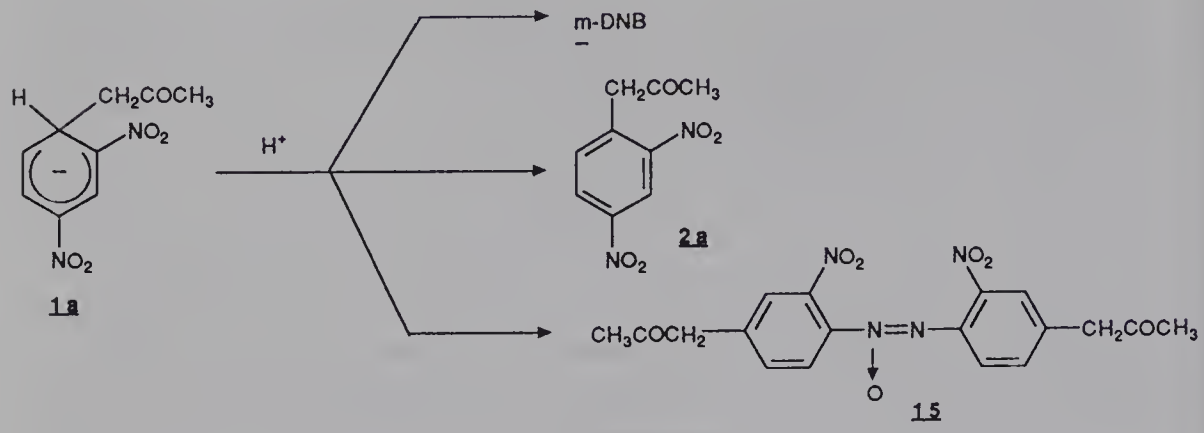
(5-7)

thalene to afford 1-nitro-2-nitromethylnaphthalene,[20a] and of the carbanion of diphenylacetonitrile to nitrobenzenes with a free para position to give nitrones (e.g., **14**), as shown in Scheme 5.1.[20b] Phenylalkylacetonitriles react in a similar way, but the nitrones obtained are not stable and further reactions occur.[20b]

Since they do not undergo instantaneous H^+-catalyzed decomposition to the precursor derivatives upon acidification[21] (a protonated ketone moiety is



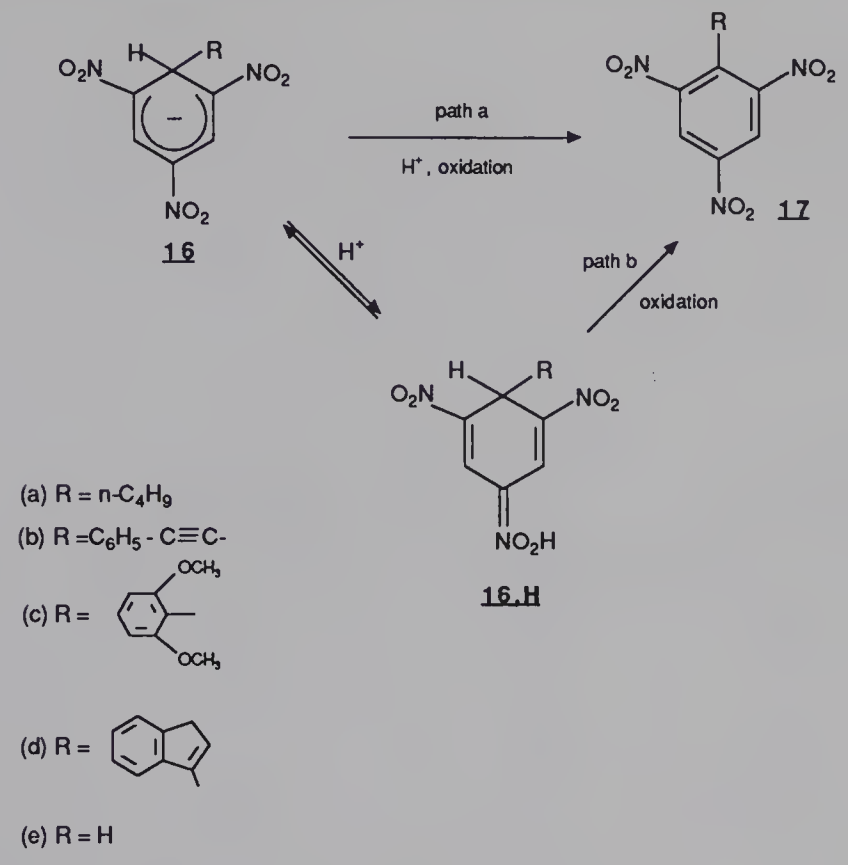
Scheme 5.1.



Scheme 5.2.

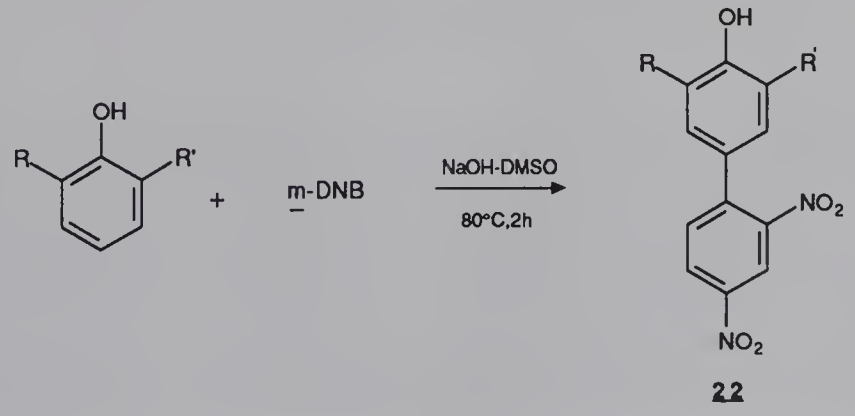
not a good leaving group), ketone adducts like **1a** and **1b** are susceptible to "spontaneous oxidation" under acidic conditions.[22–24] The reactions are complex, however, and in the case of the *m*-DNB adduct **1a**, there is apparently competition between the two processes, for some *m*-DNB is recovered in addition to 2,4-dinitrophenylacetone (**2a**) and 2,2′-dinitro-4,4′-diacetonylazoxybenzene (**15**) (Scheme 5.2).[22] Other C-bonded adducts that are especially less prone to undergo an H^+-catalyzed dissociation, and undergo oxidation upon acidification, are the adducts **16a–d**. These result from the reactions of TNB with *n*-butyllithium,[25] phenylethynyl copper,[26a] 2,6-dimethoxyphenyl/copper or silver reagents,[26b,27] and indene in the presence of silver oxide,[28a] respectively. While the only product reported to result from acidification of **16a** is *n*-butyl-2,4,6-trinitrobenzene (**17a**), **16b** gives 2,4,6-trinitrotolane (**17b**), which is subject to further cyclization to 4,6-dinitro-2-phenylisatogen.[25,26] On the other hand, addition of a strong acid to **16c** and **16d** results in the initial formation of the nitronic acids **16c,H** and **16d,H**.[26b,27,28a] Oxidation follows, however, to afford the 1-(2,6-dimethoxyphenyl)- and 1-(1-indenyl)-2,4,6-trinitrobenzenes (**17c**) and (**17d**).[26b,27,28a] Similarly, the TNB-hydride adduct **16e** is converted to **16e,H**, which slowly disappears with regeneration of TNB and formation of many other products.[28b] Whether in these instances the rearomatization occurs via direct H^+-catalyzed oxidation of the equilibrium amounts of the anionic adducts **16** (path a in Scheme 5.3) or via oxidation of the nitronic acid intermediates **16,H** (path b) is not established.

The addition of 1,3,5-trimethoxybenzene as well as various π-excessive five-membered ring heterocycles to 4,6-dinitrobenzofuroxan (DNBF) and 4,6-dinitrobenzofurazan (DNBZ) results in the formation of adducts in an acid



Scheme 5.3.

form (e.g., **18,H**)[29] Exchanging the H^+ counterion for an alkali or silver cation gives stable salts (**18,M**: M = Na, K, Ag) with high oxidation potentials (e.g., $E°$ ~ 0.87 V for **18,M**: Y = N → O) relative to a saturated calomel electrode.[30] On this ground, it is a remarkable feature that the acids **18,H** oxidize "spontaneously" at mild acidic conditions in DMSO and DMF, to give the corresponding 7-substituted derivatives **19** in 50% yield (Scheme 5.4).[30]



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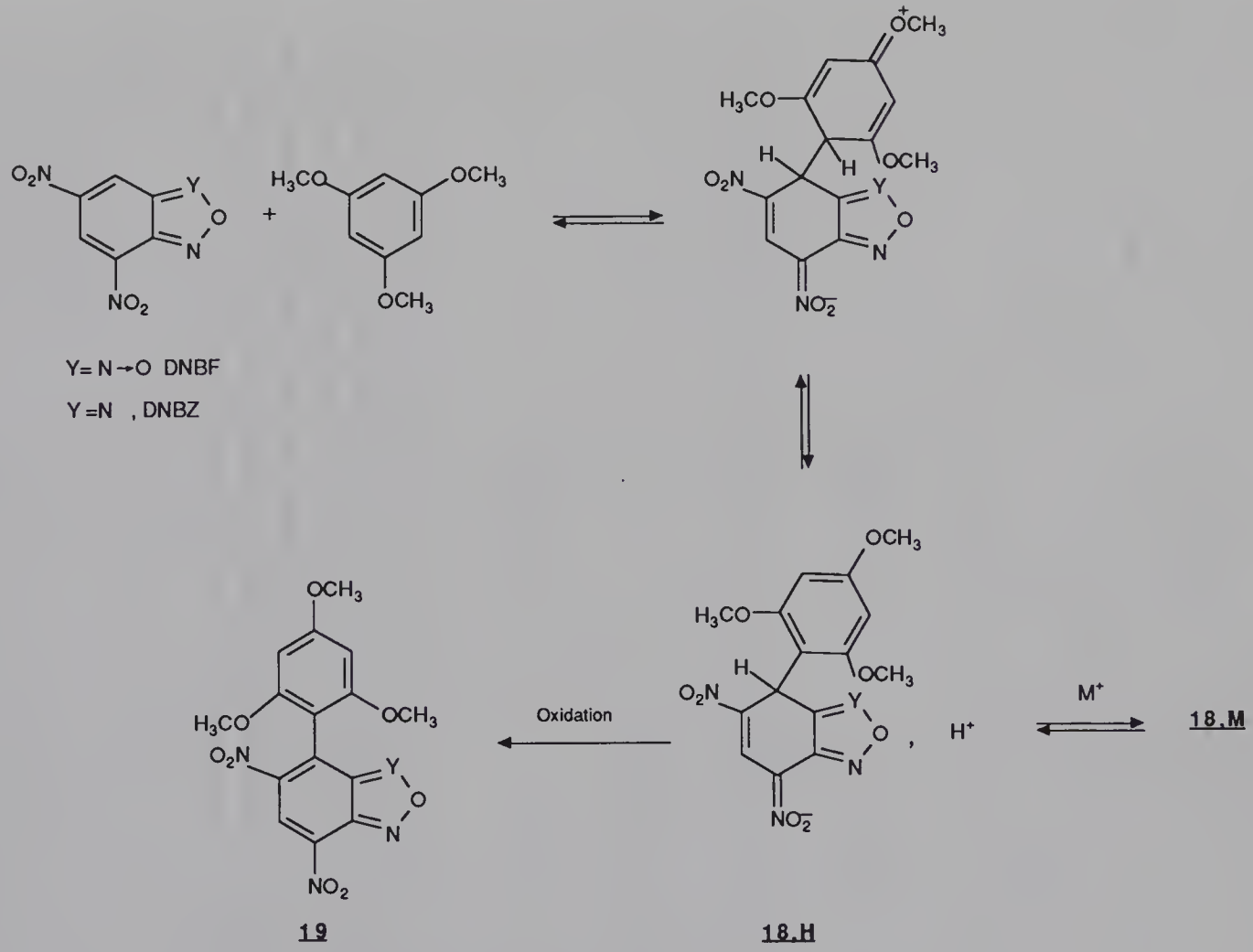
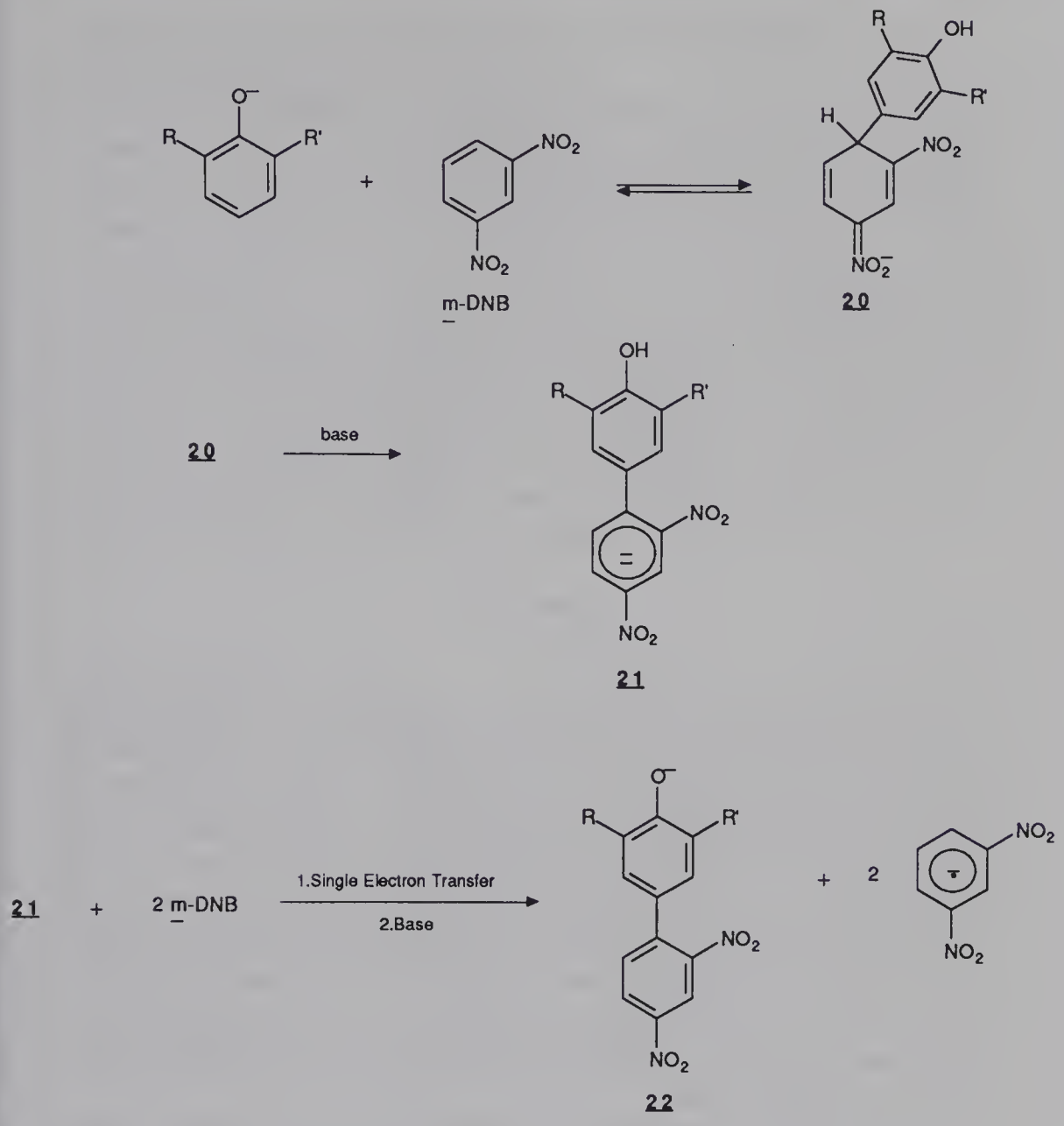
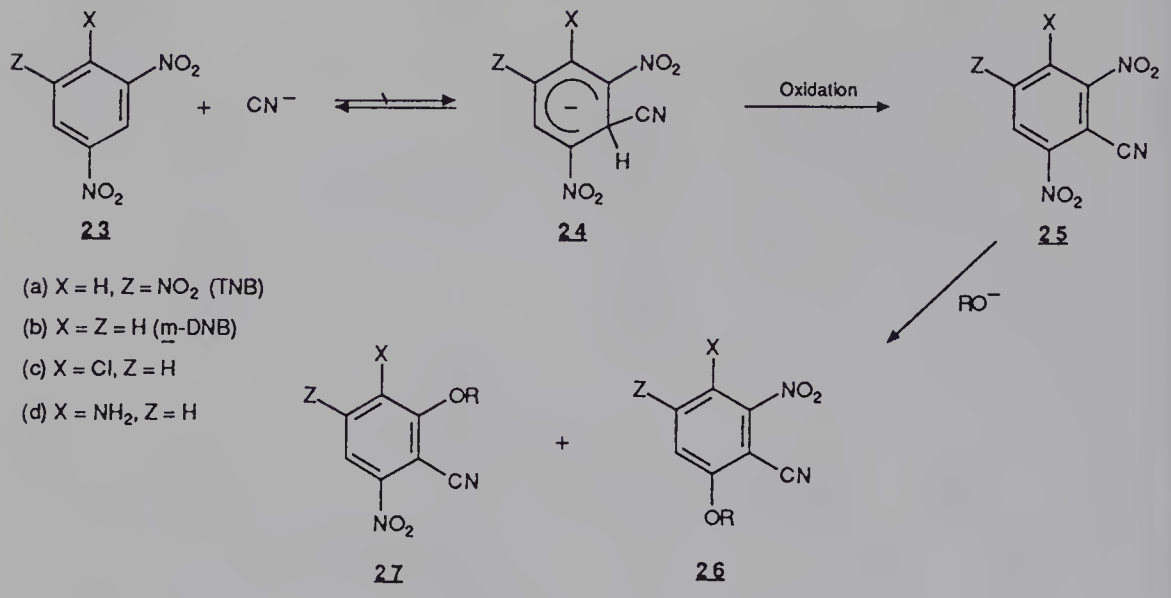


Scheme 5.4.



Scheme 5.5.

In a recent study, Stahly has reported a novel oxidative coupling process between phenols and some nitroarenes in the presence of powdered sodium hydroxide in DMSO at 80°C.[31] The reaction affords biphenyl derivatives by formal displacement of a hydrogen atom of the nitroaromatic ring, as depicted in eq. 5-8, for *m*-DNB systems. The results indicate that biphenyl formation is not particularly dependent on hindrance at the phenolic hydroxy group, since a greater yield is obtained with 2,6-di-*tert*-butylphenol (69%) than with



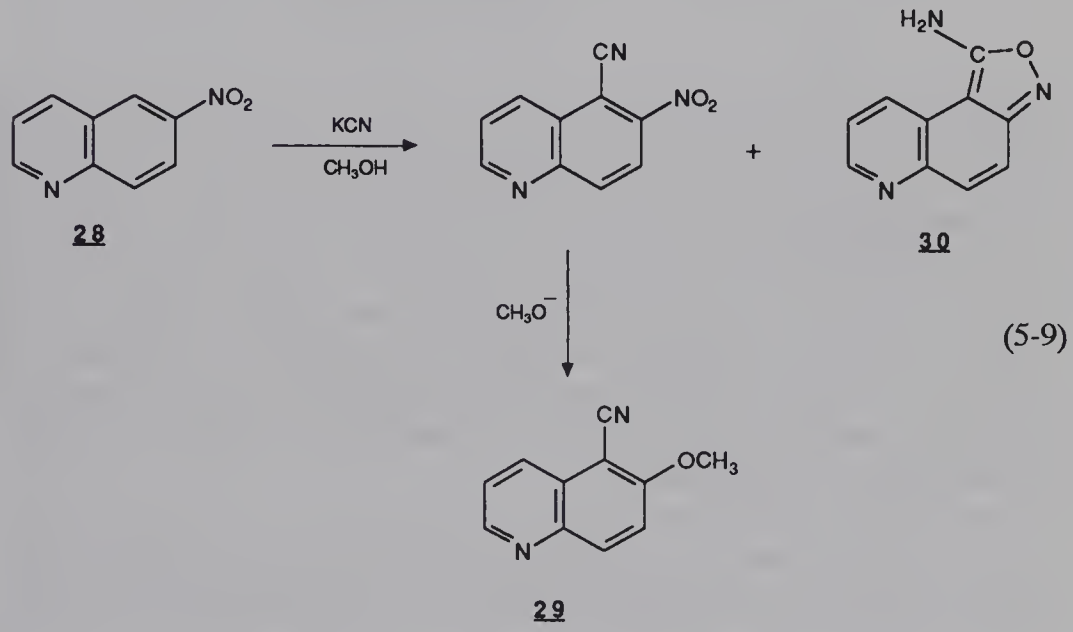
Scheme 5.6.

2,6-dimethylphenol (49%). The lower yield reported for the phenol/*m*-DNB system (17%) is due to a competition between the oxidative coupling and the S_NAr displacement of an NO_2 group by phenoxide ion. In accord with the well-known ability of phenoxide ions to act as carbon nucleophiles in σ-complex formation,[32–34] the reaction will proceed through initial formation of the C-adducts **20**. Based on the identification of some reduction products of *m*-DNB, and by analogy with a mechanism proposed by Guthrie and Nutter for the reaction of nitrobenzene and potassium *t*-butoxide (see below),[35] the reaction pathway shown in Scheme 5.5, and involving formation of the intermediate dianion **21** is suggested for the subsequent conversion of **20** into the biphenyl derivatives **22**.

Interesting S_NAr^H reactions, which are assumed to proceed via oxidation of intermediate σ-adducts, are those involving CN^- ion. This nucleophile has a high tendency to add to an activated nitroaromatic ring, and the trinitrobenzene as well as the dinitrobenzene cyanide adducts **24a** and **24b** have been structurally characterized.[2,9,14,36,37] In alcoholic solution, however, the reaction of *m*-DNB derivatives **23b–d** with CN^- ion gives the 6-alkoxy–2-nitrobenzonitriles **26b–d**, as shown in Scheme 5.6.[38–41] The reaction proceeds through the adducts **24b–d**, which are oxidized, presumably by other molecules of the nitroarenes, to give the dinitrobenzonitriles **25b–d**.[1] The alcoholysis of CN^-, which yields the corresponding lyate RO^- ion ($CN^- + ROH \rightleftharpoons HCN + RO^-$),

causes an S_NAr reaction of an NO_2 group with RO^- to occur to give the alkoxy derivatives **26** and/or **27**.[2,38–41]

Similar results have been obtained in the reaction of CN^- with heterocyclic derivatives like nitroquinolines and nitroquinoxalines.[42,43] Upon treatment with CN^- in methanol, 6-nitroquinoline (**28**) yields mainly **29**, but an appreciable amount of the isoxazole derivative **30** is also formed (eq. 5-9).[43b] On the other hand, there have been reports that nitrobenzenes, 1- and 2-nitronaphthalenes, and nitroquinolines react with various cyanocarbon acids like ethyl cyanoacetate in the presence of base (CN^-, OH^-) to give products like **31**, which formally result from an S_NAr^H displacement of a hydrogen atom by CN^- and a concomitant reduction of an NO_2 group (eq. 5-10). However, the mechanism of these reactions, which are of some synthetic interest, is totally unknown.[44,45] Subsequent hydrolysis of **31** by hydrochloric acid affords the corresponding 6-amino 5-cyano quinoline in good yield.[45]



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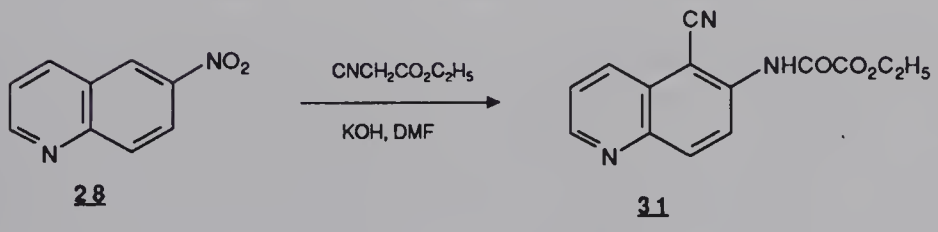
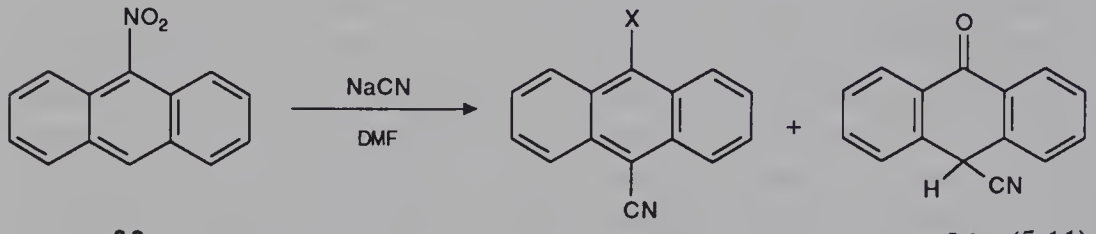


(5-10)

Cyanide adducts of some nitroaromatics also undergo oxidation in dipolar aprotic solvents. Two reactions have been studied in detail. The first is the reaction of 9-nitroanthracene (**32**) with sodium cyanide at room temperature

in DMF; this gives a solution exhibiting an electron paramagnetic resonance (EPR) signal and results in the formation of a series of products that were identified as 9-cyano-10-nitroanthracene (**33a**), 9-amino-10-cyanoanthracene (**33b**), 9,10-dicyanoanthracene (**33c**), 9-cyano-10-anthranol (**33d**) and 9-cyanoanthrone (**34**) (eq. 5-11).[46] The formation of **33a** and **33b**, which represent products of oxidation and reduction of the cyanide complex **35**, was



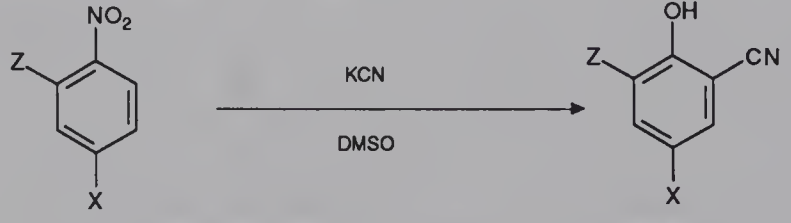
32 **33** **34** (5-11)

(a) X = NO_2; (b) = NH_2

(c) X = CN; (d) X = OH

explained in terms of Scheme 5-7. Electron transfer between the adduct **35** and 9-nitroanthracene (**32**) yields the anion radical **37** and the radical **36**, which then undergoes a disproportionation reaction with formation of 9-cyano-10-nitroanthracene (**33a**) and 9-cyano-10-nitrosoanthracene (**38**). The latter is the precursor of the amino derivative **33b**. Competitive S_NAr reactions involving CN^- and OH^- ions would account for the formation of **33c** and **33d**, as well as of **34**, which is the tautomer of **33d**. The hydroxide ion effecting the nucleophilic displacement was assumed to be formed from water present in the solvent and/or reagent, or to be produced in the oxidation–reduction occurring in the overall process.

The second reaction deals with the direct conversion of nitrobenzenes to *o*-cyanophenols by the action of CN^- ion in DMSO, as shown in eq. 5-12 for a series of nitrobenzenes **39** carrying an electron-withdrawing substituent in the ortho or para positions.[47,48] A thorough study of this reaction has been made

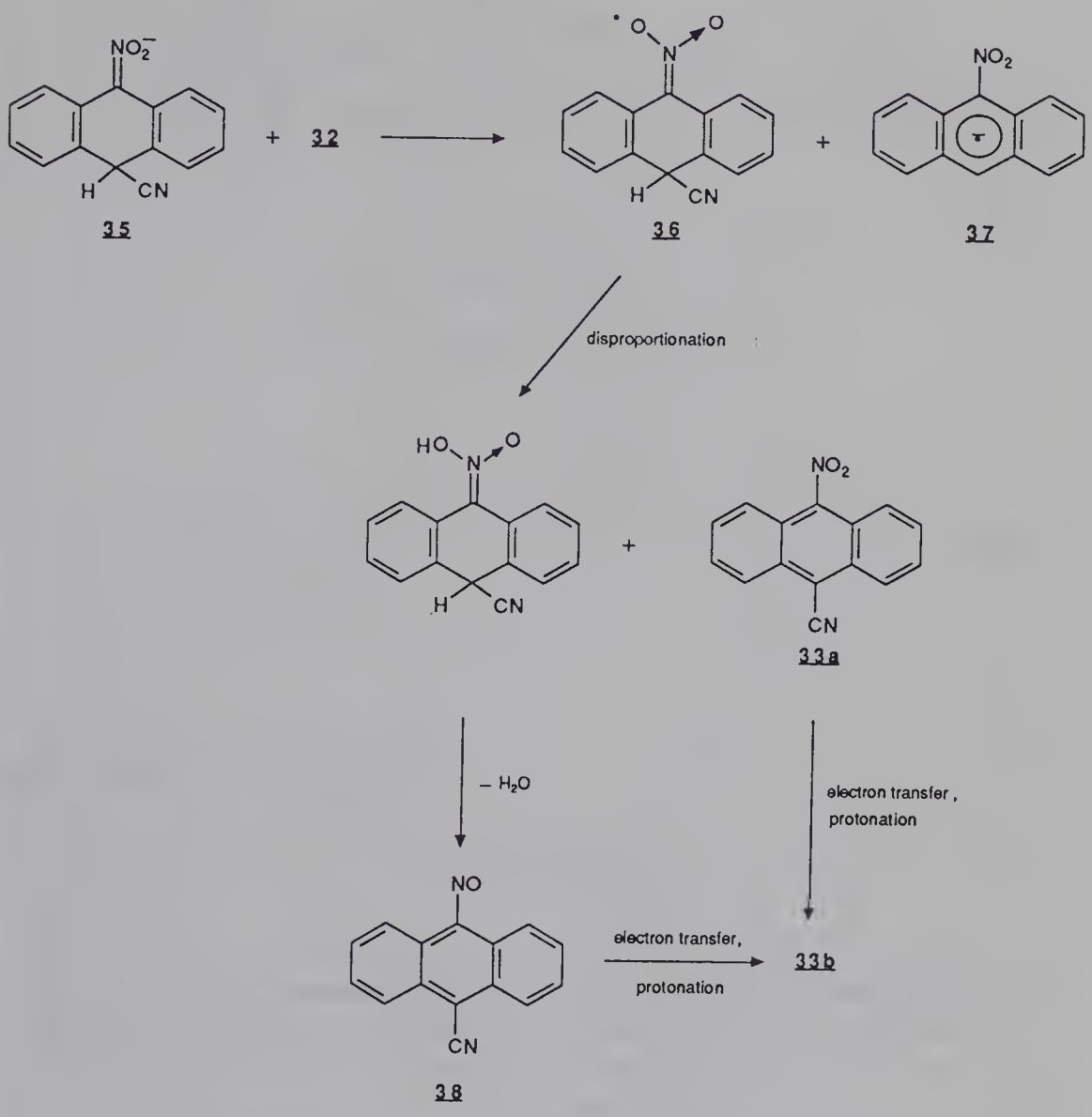


(5-12)

39 (a) X = H, Z = CN; (b) X = CN, Z = H **40**

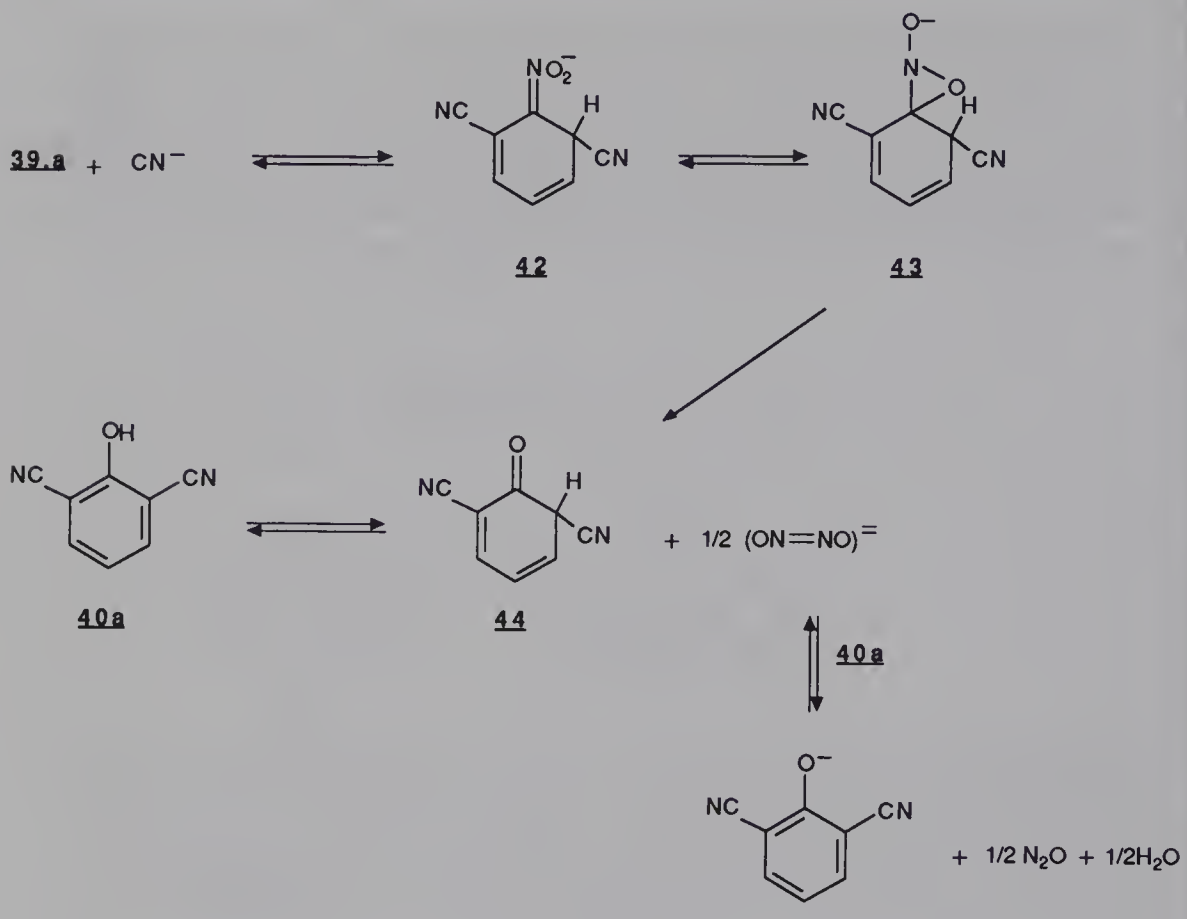
(c) X = COC_6H_5, Z = H; (d) X = $SO_2C_6H_5$, Z = H;

(e) X = $CO_2C_2H_5$, Z = H



Scheme 5.7.

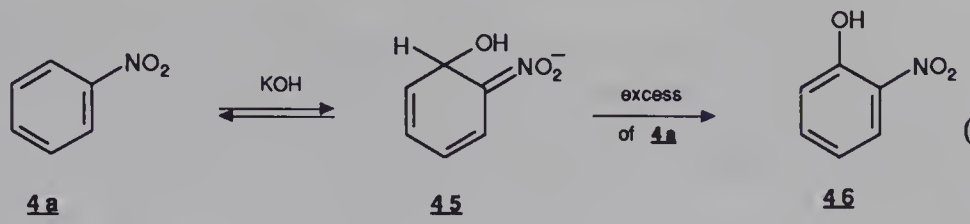
by Snyder *et al.* in the case of *o*-and *p*-nitrobenzonitriles **39a** and **39b**.[47] These investigators found that the solutions give no detectable EPR signal, while the formation of the phenols **40** is accompanied by the evolution of nitrous oxide. On these grounds, they rejected Scheme 5.7 and suggested the mechanism of Scheme 5.8 to account for the formation of **40**. The key step of the reaction would be the isomerization of the σ-adduct **42** to the oxaziridine isomer **43**, which would decompose to **44**, the tautomeric form of **40a**, with loss of hyponitrite anion. Protonation of this anion by **40a** would produce nitrous



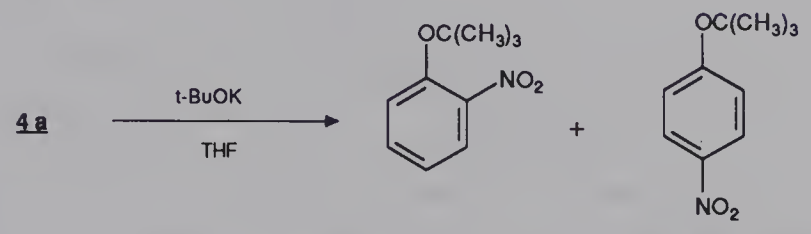
Scheme 5.8.

oxide. In the case of the reaction of *p*-nitrobenzophenone (**39c**), however, the formation of reduction by-products believed to be azo and azoxy compounds along with the corresponding phenol **40c**, suggests that the mechanisms of Schemes 5.7 and 5.8 are both operative.[47] Note that the reaction, shown in eq. 5-12, constitutes an example of the rare occurrence of a Nef-type process in a basic medium.[47]

"Spontaneous" oxidations of oxygen and nitrogen-based adducts of nitroaromatics are less common than those of carbon-base adducts. However the production of *o*-nitrophenol (**46**) by the action of finely divided dry KOH on nitrobenzene (**4a**) at 60–70°C is a long known example of the displacement of hydrogen by hydroxide ion.[49] Although Wohl was unable to isolate any reduction product, the reaction, which occurs even in a hydrogen atmosphere, probably proceeds via oxidation of the adduct **45** by **4a** (eq. 5-13). Support for this idea was provided by a detailed study by Guthrie and Nutter of the reaction of **4a** with *t*-BuO⁻ in tetrahydrofuran (THF).[35] In this instance, a mixture of

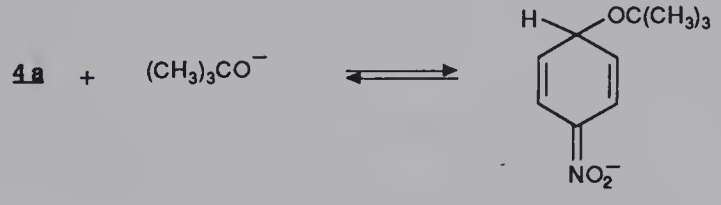


4a **45** **46** (5-13)

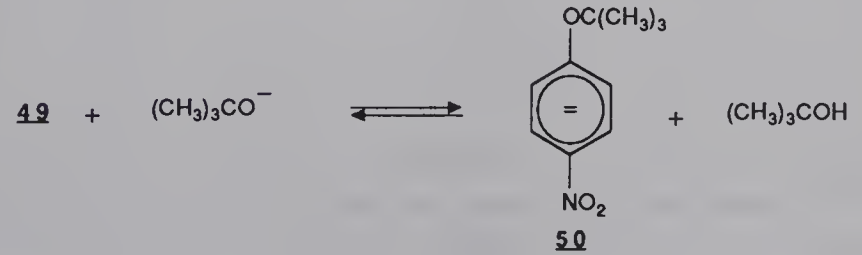


47 **48** (5-14)

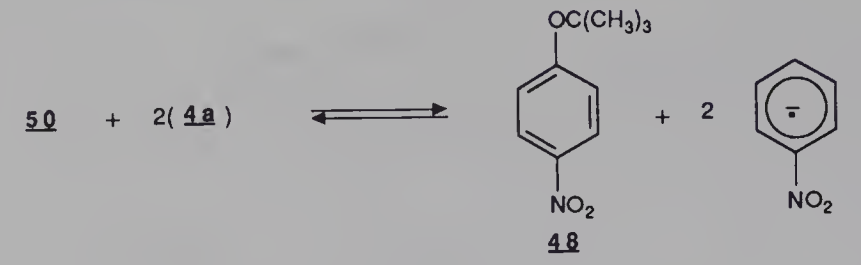
the *o*- and *p*-*tert*-butoxynitrobenzenes **47** and **48** is produced (eq. 5-14) and also the nitrobenzene radical anion $C_6H_5NO_2^{\bullet-}$ (a reduction product), which is formed in significant quantity. Interestingly, kinetic experiments carried out by using nitrobenzene-d_5 revealed that the reaction is subject to a sizable isotope effect: $k_H/k_D \approx 5$. This suggested that the substitution involves a hydrogen transfer step, as the rate-limiting step, and led the authors to propose the mechanism shown in eqs. 5-15 to 5-17. The key point in this mechanism is that the initially formed adduct **49** is regarded as being a negatively charged CH-type acid susceptible to deprotonation by a strong base like *t*-BuO^-. As is well known,[50,51] the ionization of carbon acids is not necessarily a very fast process and the formation of the dianion **50** (eq. 5-16) would in fact be rate limiting. The conversion of **50** to the observed product **48** is believed to proceed by two electron-transfer steps (eq. 5-17).[35] It is this mechanism that has served as a model for the mechanism presented in Scheme 5.5.[31]



49 (5-15)

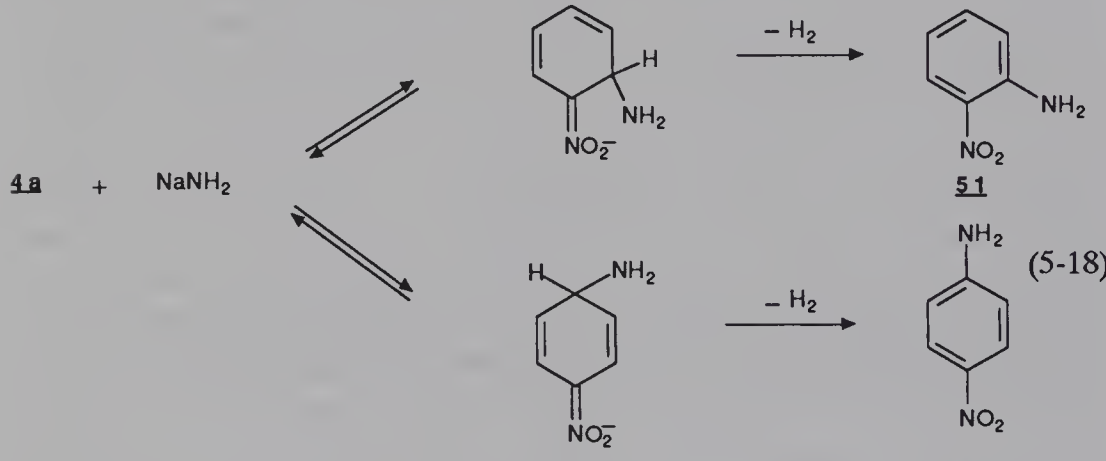


50 (5-16)

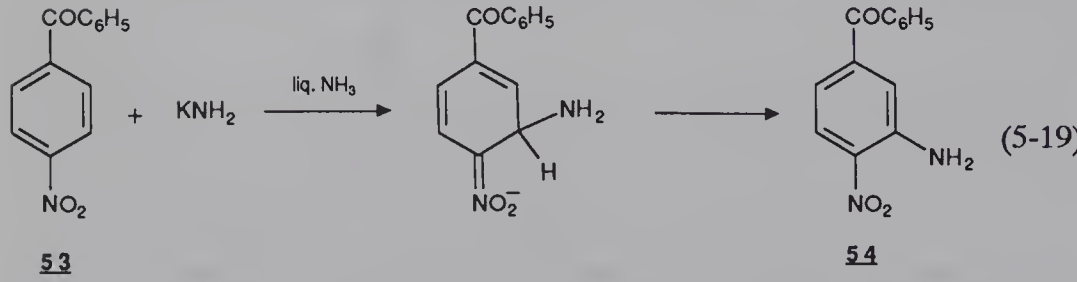


48 (5-17)

It is now well established that σ-complexes form as intermediates in the reactions of amide ion with azaaromatics.[2,52–55] By analogy with pyridine, one might have expected the action of alkali metal amides on **4a** to give *o*- and *p*-nitroanilines (**51** and **52**) through formation of intermediate σ-adducts, according to the mechanism generally accepted for the Chichibabin reaction (eq. 5-18).[56] A very complicated mixture of products was obtained, however, from which **51** and **52** could not be isolated.[57,58] In contrast, convincing evidence has been obtained that some 3-amino-4-nitrobenzophenone (**54**) is formed upon treatment of 4-nitrobenzophenone (**53**) with potassium amide in liquid ammonia (eq. 5-19).[59] Whether **54** is formed from the intermediate adduct via the Chichibabin mechanism or via oxidation by the nitroarene has not been established.



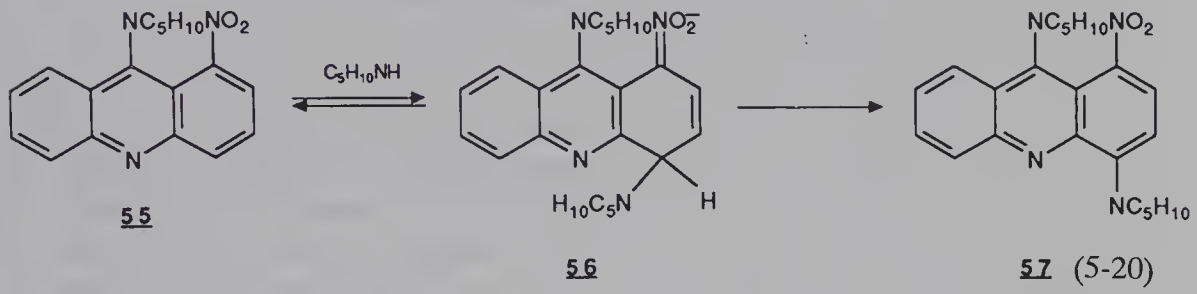
(5-18)



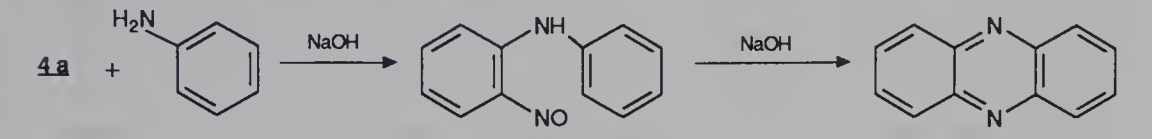
(5-19)

Amination reactions occur more readily with substituted amides. Thus **4a** reacts with potassium carbazole and with alkali metal piperidides or diphenylamides to give the expected substitution products, such as *N-p-*

nitrophenylcarbazole, *N-p-* and/or *N-o*-nitrophenylpiperidine, and *p*-nitrotriphenylamine, respectively.[57,60–62] Similar amination reactions of 1-nitronaphthalene and 8-nitroquinoline by sodium piperidide have been reported.[57] Recently, it has been shown that treatment of 1-nitro-9-piperidinoacridine (**55**) with piperidine in the presence of KOH results in the formation of 1-nitro-4,9-dipiperidinoacridine (**57**) (eq. 5-20). In all these cases, the intermediate adducts (e.g., **56**), appear to be oxidized by molecules of the starting nitro compounds.[63,64]



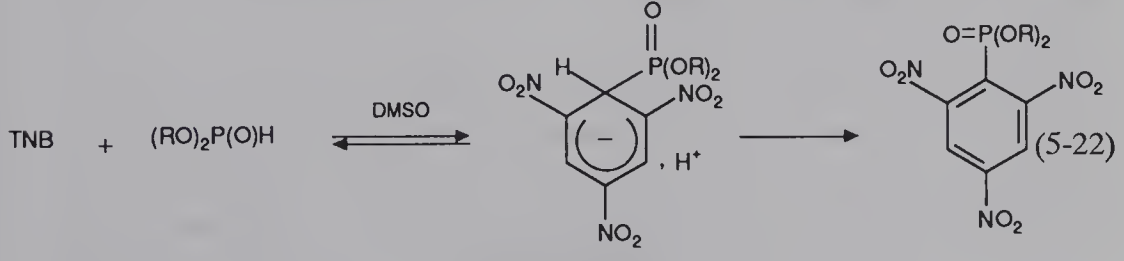
55 **56** **57** (5-20)



4a **58** **59** (5-21)

The formation of phenazine (**59**) from aniline and **4a** in the presence of sodium hydroxide is probably an example of an amination reaction in which the intermediate σ-adduct undergoes an intramolecular oxidation to give the *o*-nitrosodiphenylamine (**58**).[49, 61] Since it cyclizes rapidly to **59**, no trace of **58** could be detected, but a small amount of its *p*-nitroso isomer could be recovered from the reaction mixture (eq. 5-21).[65]

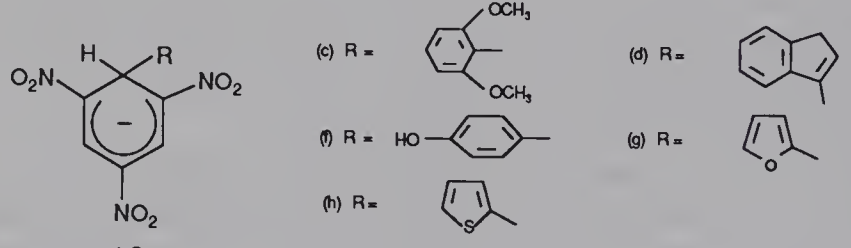
There are some recent reports that the adducts **60** resulting from the reaction of 1,3,5-trinitrobenzene (TNB) with dialkyl phosphites are subject to spontaneous oxidation in DMSO. The reactions afford the picrylphosphonates **61**, but whether they involve oxidation by TNB itself or atmospheric oxygen has not been established (eq. 5-22).[66a] THe phosphonates **61** were also obtained as the final products of the reactions of TNB with trialkylphosphites.[66b]



60 R = CH_3, C_2H_5 **61**

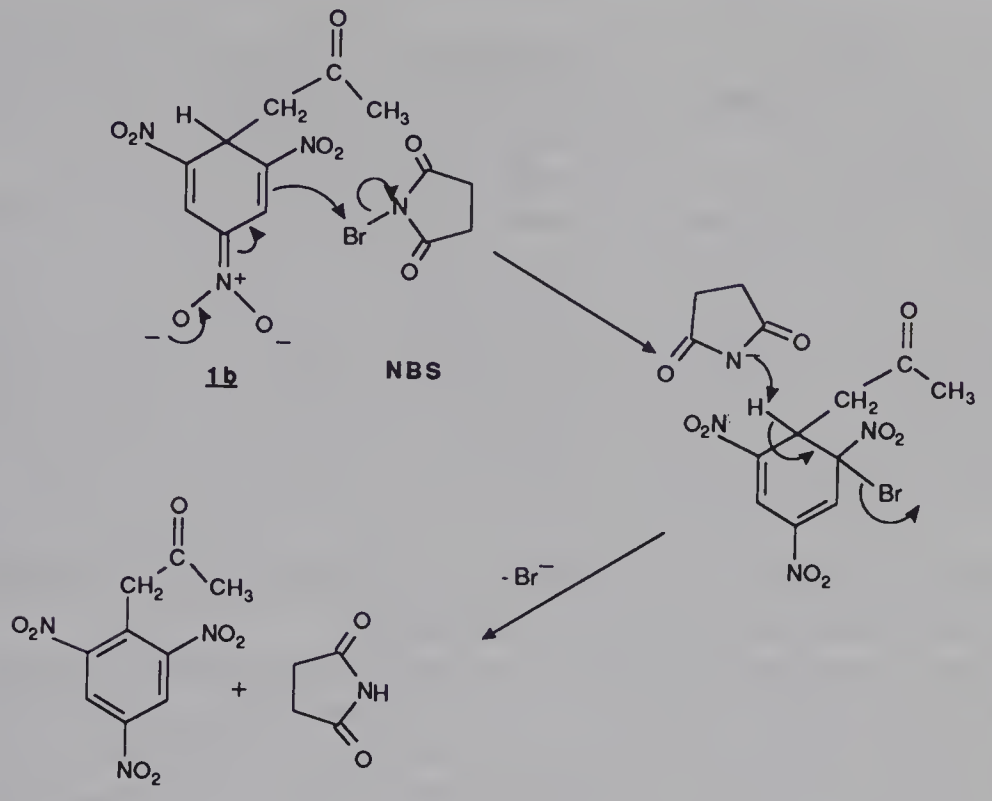
5.2.2 Reactions Involving an External Oxidizing Agent

The "spontaneous" oxidations described in the preceding section give generally poor yields of the expected oxidation products. It is therefore of interest for synthetic purposes that the feasibility of the oxidation processes is considerably increased when oxidizing reagents are added. A large variety of oxidants have been used to oxidize C-bonded adducts. For example, the picryl adduct of acetone **1b** undergoes conversion to picrylacetone (**2b**) in very high yield (~ 80%) in the presence of many inorganic [H_2O_2, halogens, hypohalite ions, $AgNO_3$, $Pb(OAc)_4$] as well as organic oxidants [chloranil, tropylium cation, and *N*-bromosuccinimide (NBS)].[2,67–69] Similarly, the oxidative rearomatization of the TNB-2,6-dimethoxybenzene, -phenol, -indene, -furan, and -thiophene adducts **16c–g** was successfully achieved by using *p*-benzoquinone, acidic H_2O_2, or CrO_3 under various experimental conditions.[27,28,70] The recovery of succinimide in the oxidation of **1b** as well as of other TNB-ketone adducts by NBS has suggested the mechanism shown in Scheme 5.9.[67] Support for this mechanism is provided by the observation of a "trapped" bromotrinitrocyclohexadiene **63** in the meta-bridged product **64** obtained from NBS oxidation of the TNB-amidine complex **62** (Scheme 5.10).[71]

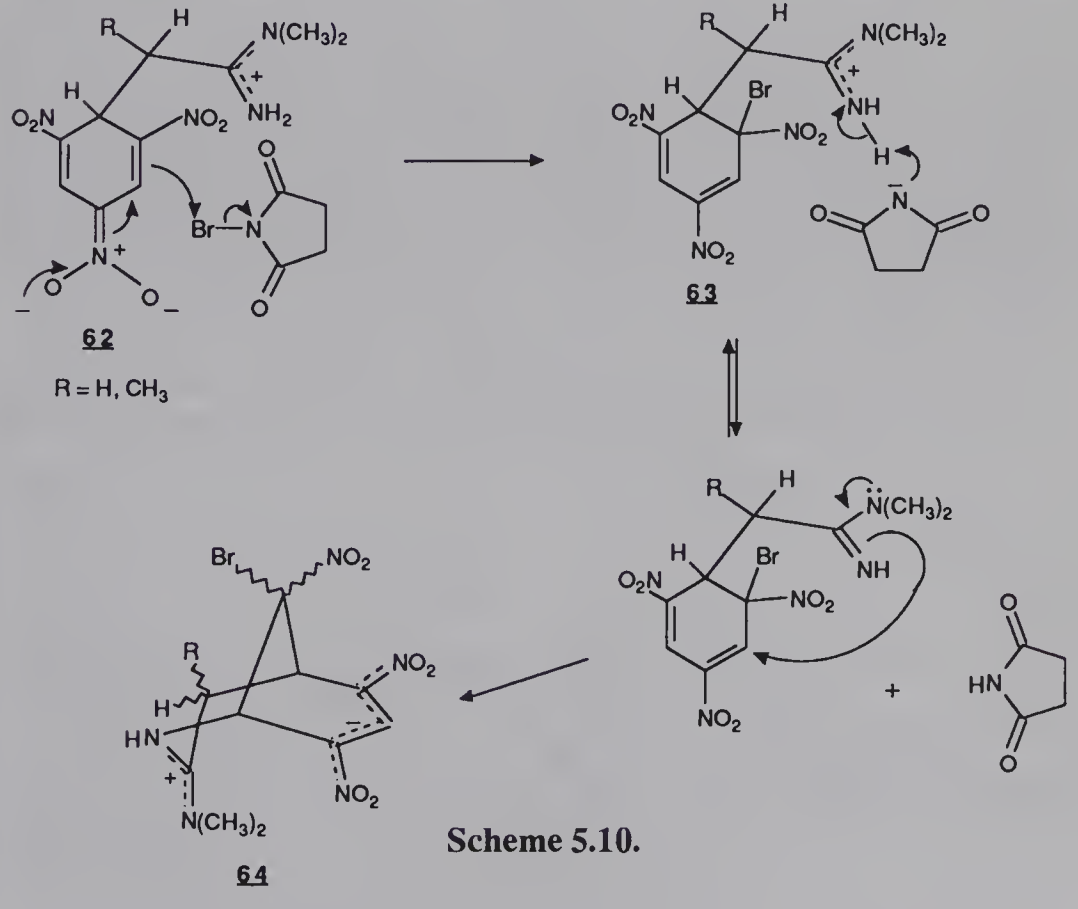


16

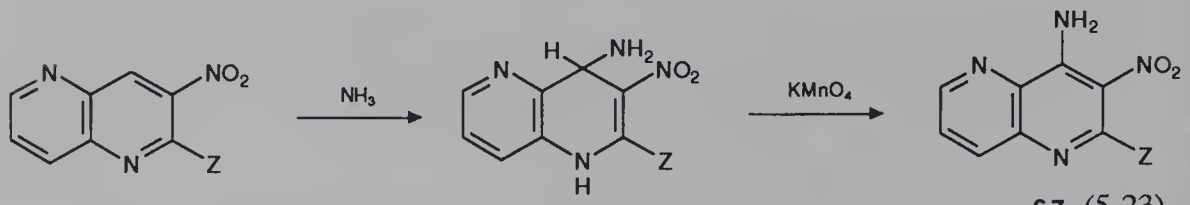
In the past few years, new and useful S_NArH reactions have been described which involve the *in situ* oxidation by an external oxidizing agent of the adducts initially formed by nucleophilic addition to a nitroaromatic ring. Van der Plas and coworkers have observed that 3-nitro-1,5-naphthyridine (**65**) and 3-nitro-1,8-naphthyridine (**68**) are sufficiently electrophilic to react with liquid ammonia, in the absence of any amide anion, to give the covalent amino adducts **66** and **69**, respectively, which have been characterized by NMR techniques.[72] When the reactions were performed in the presence of potassium permanganate, the intermediate adducts **66** and **69** were not observed because they



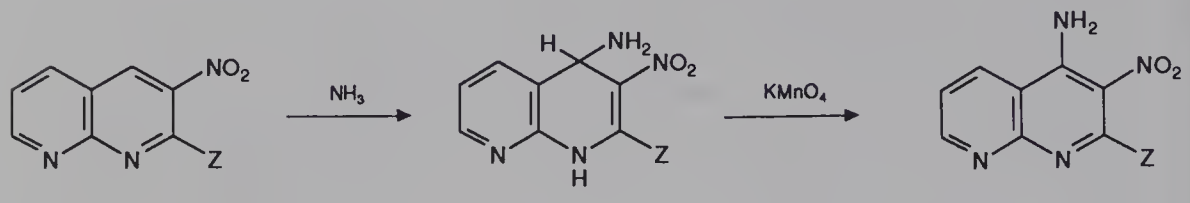
Scheme 5.9.



Scheme 5.10.



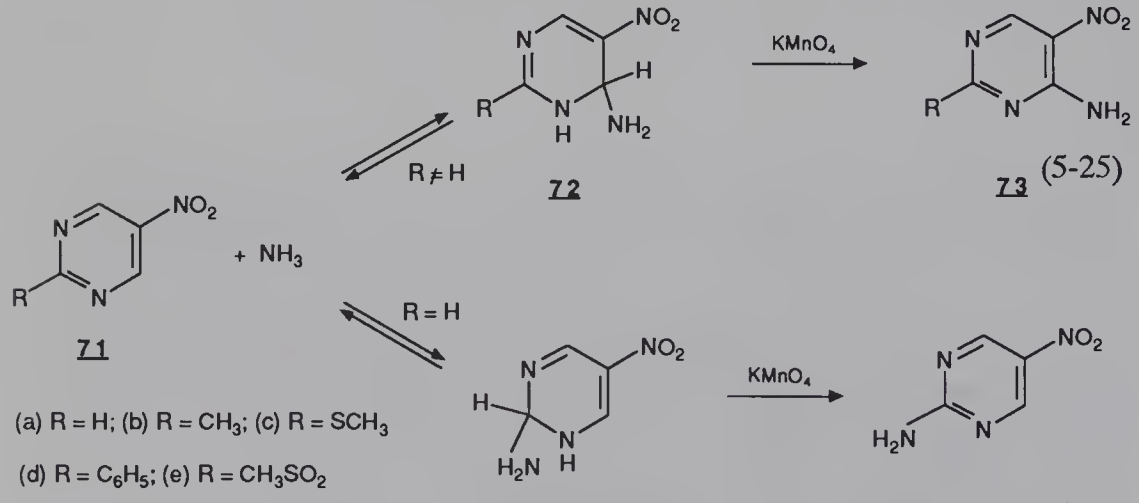
65 Z = H, Cl, OC_2H_5, OH, NH_2 66 67 (5-23)



68 Z = H, Cl, OC_2H_5, OH, NH_2 69 70 (5-24)

oxidized instantaneously to give the corresponding amination products **67** and **70** in moderate to good yields (eqs. 5-23 and 5-24).

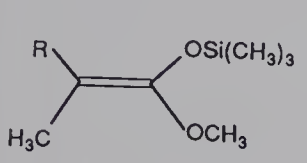
The 2-substituted-5-nitropyrimidines **71b–e** behave similarly, adding the amino group at the 4-position to give the adducts **72b–e** which undergo immediate conversion to 4-aminopyrimidines **73b–e** in good yields (eq. 5-25).[73] In the case of the unsubstituted 5-nitropyrimidine **71a**, the reaction pattern is different, since the formation of the 2-amino adduct **74a** precedes that of the thermodynamically more stable 4-amino isomer **72a**. However, in the presence of $KMnO_4$, the isomerization of **74a** to **72a** does not occur and only 2-amino-5-nitropyrimidine (**75**) is obtained, which is the amination product of **71a** (eq. 5-26). All attempts have failed to obtain 4-amino-5-nitropyrimidine (**73a**) by adding $KMnO_4$ to solutions in which conversion of **74a** to **72a** has been observed to occur.[73] This *in situ* amination reaction by liquid $NH_3/KMnO_4$ constitutes a very useful modification of the Chichibabin



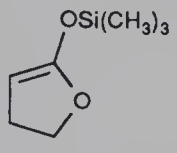
71 (a) R = H; (b) R = CH_3; (c) R = SCH_3 (d) R = C_6H_5; (e) R = CH_3SO_2 72 73 (5-25) 74 75 (5-26)

procedure. Nitroquinolines, nitropyridazine *N*-oxides, as well as highly electrophilic azines like pteridines, tetrazines, and quaternary pyrimidinium salts, have been readily aminated in this way.[54,55,74–76]

Oxidation of the adducts, formed upon fluorine-assisted addition of silyl enol ethers to aromatic nitro compounds, occurs when a stoichiometric amount of an oxidizing agent, for example bromine in cyclohexane or dicyanodichloro-*p*-benzoquinone (DDQ) in THF, is added to the solutions.[77,78] Scheme 5.11 describes the reactions of various nitrobenzenes with the silyl reagents **76a–e** in THF/CH_3CN in the presence of 1 equivalent of the Lewis base tris(dimethyl-amino)sulfonium difluorotrimethylsiliconate (TASF), to give **78** and **80**, the products of ortho and/or para substitution. The results obtained for **4a** are summarized in Table 5.1, which shows that para substitution predominates only when bulky silyl reagents (e.g., **76a**) are used. By employing the *in situ*



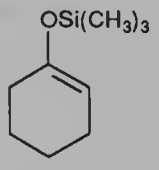
76a R = CH_3
76b R = H



76c

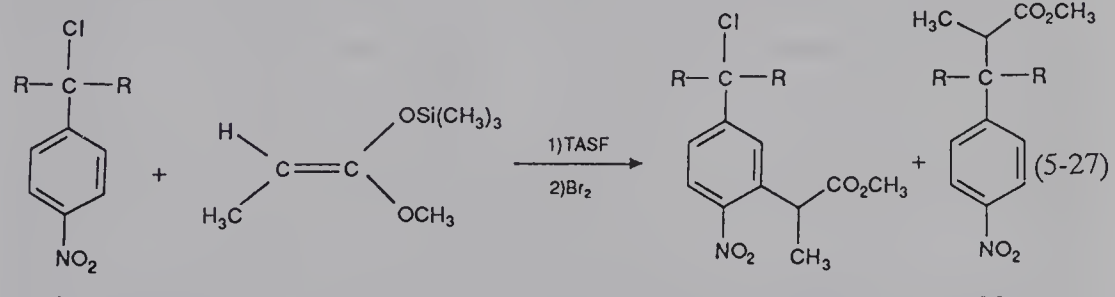
$(CH_3)_3SiCH_2CO_2CH_3$

76d



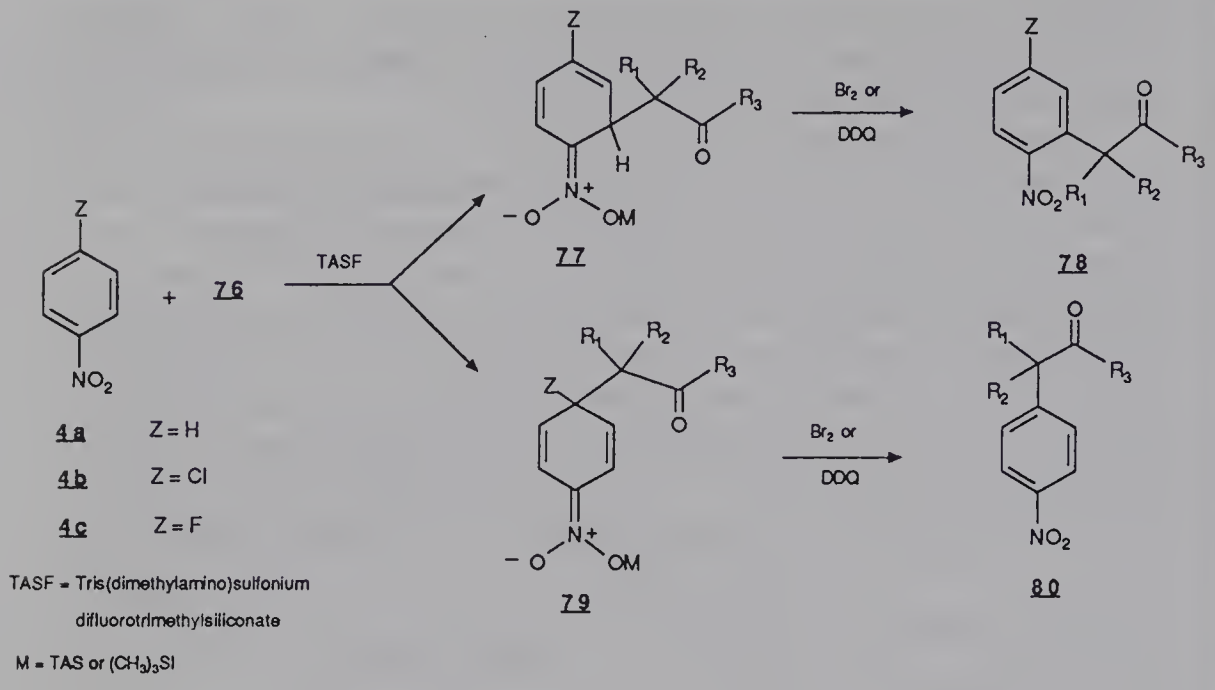
76e

oxidation procedure, various substituted nitrobenzenes have been converted into the corresponding α-nitroaryl carbonyl compounds **78** and/or **80**. Of special interest is the behavior of *p*-fluoro- and *p*-chloronitrobenzenes **4c** and **4b**, which react exclusively according to Scheme 5.11 to give the 2-substituted derivatives **78**; no trace of an S_NAr displacement of Cl or F to give **80** was observed. Another interesting result is that *p*-nitrocumyl chloride (**81a**: a typical $S_{RN}1$ substrate) reacts only via the S_NAr^H pathway (Scheme 5.11) to give **82a**. Under the reaction conditions employed, no trace of benzylation or dimerization of either the nitro compound or the enolate was observed.



81 **76b** **82** **83**

(a) R = CH_3; (b) R = H



Scheme 5.11.

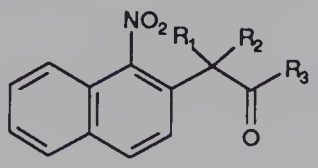
However, benzylic substitution was found to compete with addition to the ring when the unhindered *p*-nitrobenzyl chloride (**81b**) was used as the substrate (eq. 5-27).[78]

The mechanism presented in Scheme 5.11 is also applicable to heterocyclic and condensed nitroaromatic compounds. With 1-nitronaphthalene and 5-

Table 5.1. Addition of Silyl Reagents 76a–e to Nitrobenzene (4a) According to Scheme 5.11[a]

	Product			Yield (%)	
Silyl reagent	R1	R2	R3	78	80
76a	CH_3	CH_3	OCH_3		79
76b	H	CH_3	OCH_3	36	16
76c	H	—CH_2CH_2O—		32	14
76d	H	H	OCH_3	44	5
76e	H	—$CH_2CH_2CH_2CH_2$—		6	11

[a]Data reproduced with permission from ref. 77.



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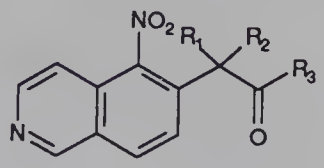

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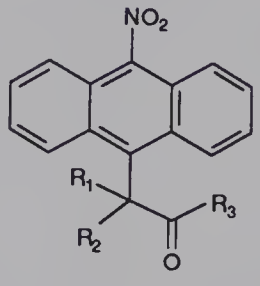

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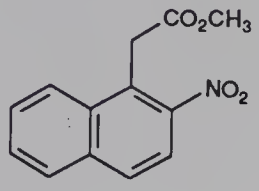

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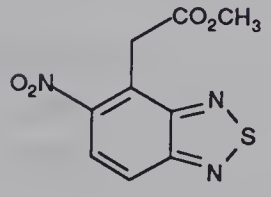

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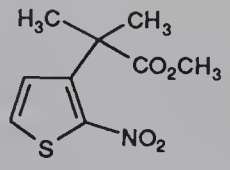
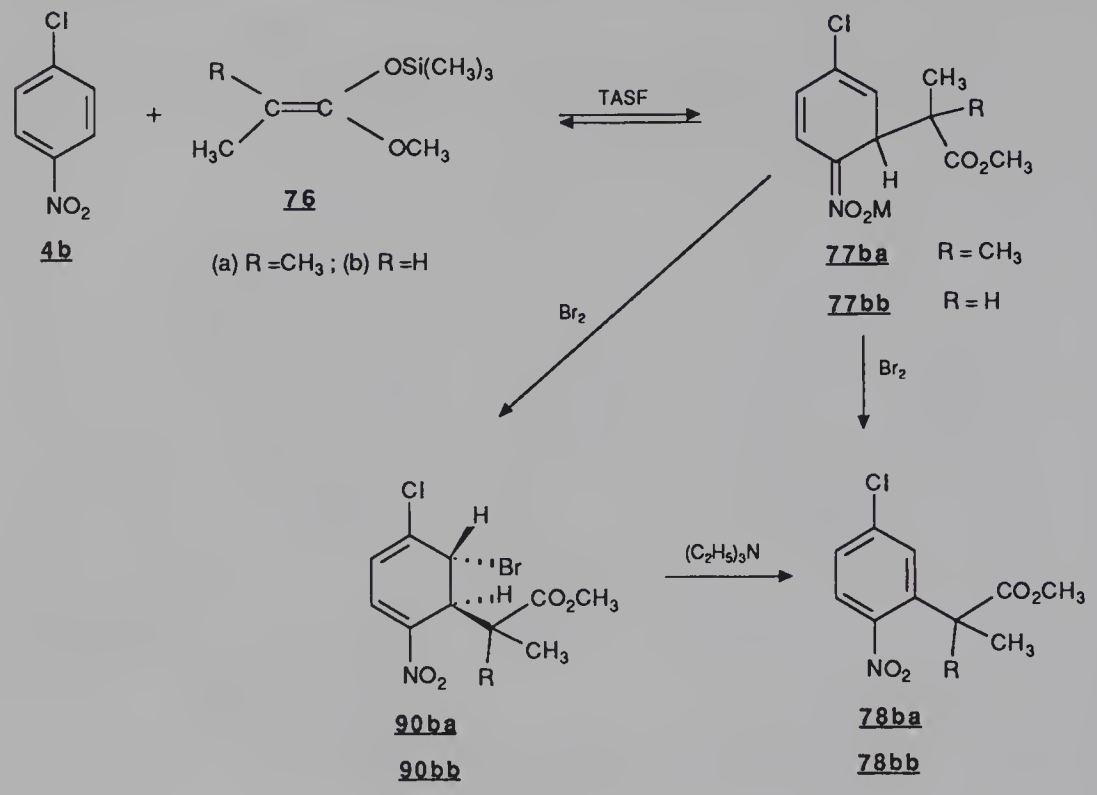


89

nitroquinoline, the addition occurs predominantly at the ortho position to give **84** and **85**, while with 9-nitroanthracene it occurs at the expected 10-position to give **86**.[77] Because the only position that can be alkylated without destroying the aromaticity of both rings is hindered, both 2-nitronaphthalene and 5-nitro-1,2,3-benzothiadiazole can react only with sterically undemanding silyl reagents like **76d** to give **87** and **88**. On the other hand, 2-nitrothiophene reacts at the 3-position with **76a** to give **89**.[77]

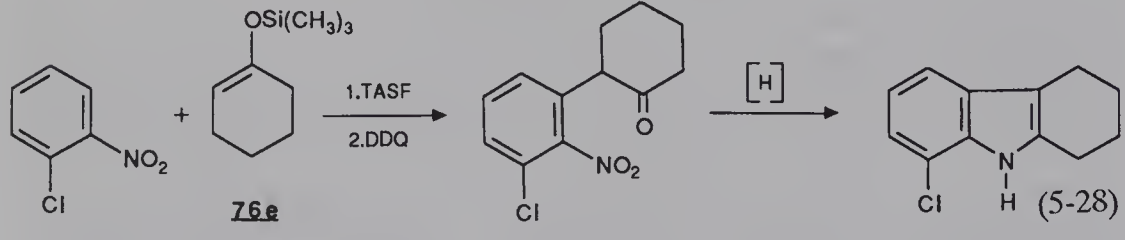
The mechanism of the oxidative coupling (Scheme 5.11), which allows a facile nitroarylation of carbonyl compounds, has been established with bromine as the oxidizing agent. As shown in Scheme 5.12, the initially formed nitronate adducts **77** are brominated to give the dihydroaromatic derivatives **90**, which rearomatize by elimination of HBr. Interestingly, the bromo intermediates **90** could be isolated in some instances. For example, the adducts **77ba** and **77bb** of 4-chloronitrobenzene (**4b**) with **76a** and **76b** yield **90ba** and **90bb** upon bromination. The doubling of CH_3CH doublets in the NMR spectrum of **90bb** clearly indicates diastereomerism at the newly created stereogenic centers.[77b] As in the case of the Grignard addition reactions (see below), the bromination is expected to take place from the side opposite to the



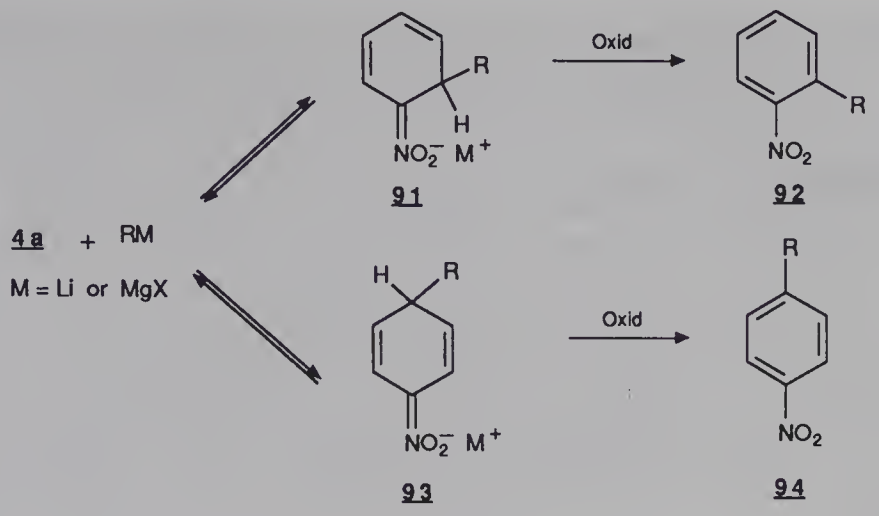
Scheme 5.12.

bulky alkyl ester side chain. Treatment of **90** with triethylamine catalyzes the conversion to the fully aromatic derivatives **78**.[77b]

It is interesting to point out that the α-nitroaryl or α-nitroheteroaryl carbonyl compounds (Scheme 5.11) are versatile intermediates that have been converted into indoles and indolinones by reductive cyclization, as illustrated in eq. 5-28.[78] In addition, the alkylation sequence of Scheme 5.11 has proved to be conveniently adapted to the synthesis of various arylacetic and arylpropionic acids with varied substitution patterns.[78]



Alkyllithium and alkyl Grignard reagents readily form ortho and/or para-alkylnitronate σ-type adducts on reaction with nitroaromatics in THF, ether or hexane.[79–82] This reaction is illustrated in Scheme 5.13, which refers to nitrobenzene-RLi or –RMgX systems. Like their trimethylsilyl analogues,



Scheme 5.13.

adducts **91** and **93** are converted to the corresponding nitroalkyl aromatics **92** and **94** through *in situ* oxidation.[80–82] Bromine and DDQ were initially used as the oxidizing agents,[80,81] but it has been recently shown that the most satisfactory yields in oxidation products are generally obtained when the solutions of the adducts are treated with an alkaline acetone–water solution of $KMnO_4$.[81] The use of $Pb(CH_3CO_2)_4$ is also recommended for polycyclic systems (e.g., anthracenes).[83] Thus, many substituted benzenes and naphthalenes as well as heterocycles like thiophenes, pyrroles, indoles, benzothiazoles, and benzoxazoles have been successfully alkylated.[81,82,84,85] Some results are summarized in Table 5.2. A remarkable feature is that the alkylation could be effected with compounds bearing electrophilic substituents like CO—R, CO_2CH_3, or CN groups, which are normally susceptible to nucleophilic attack by an organometallic reagent.[84] Such a preference for the alkylation of the ring is of considerable interest for synthetic purposes. The mechanism of the oxidations has been established in the case of bromine, for bromonitrocyclohexadienes have been isolated in some instances.[80,82] A typical example is compound **96**, which was isolated as an intermediate

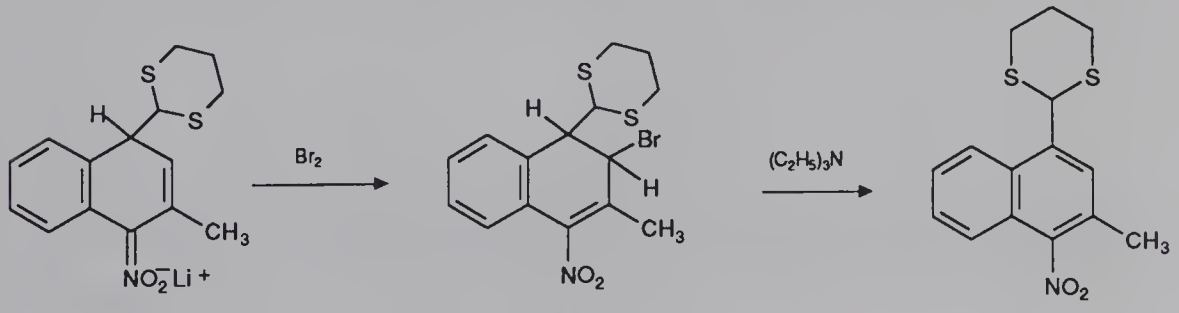
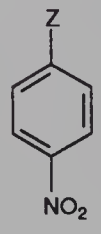
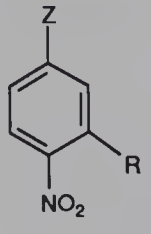
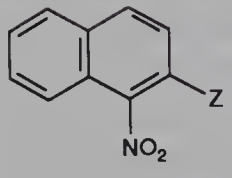
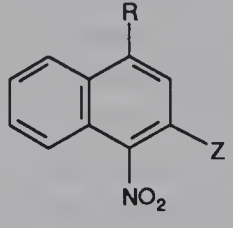
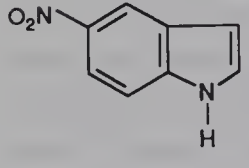
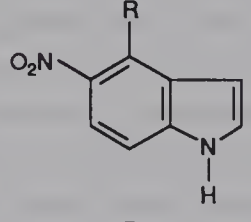
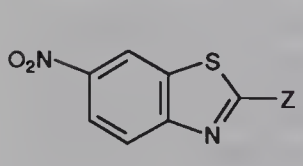
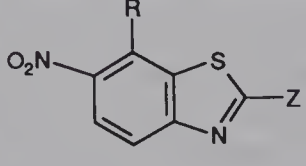
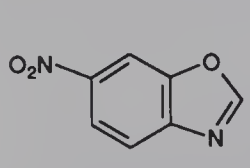
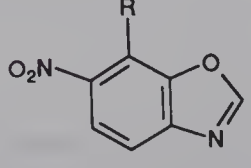


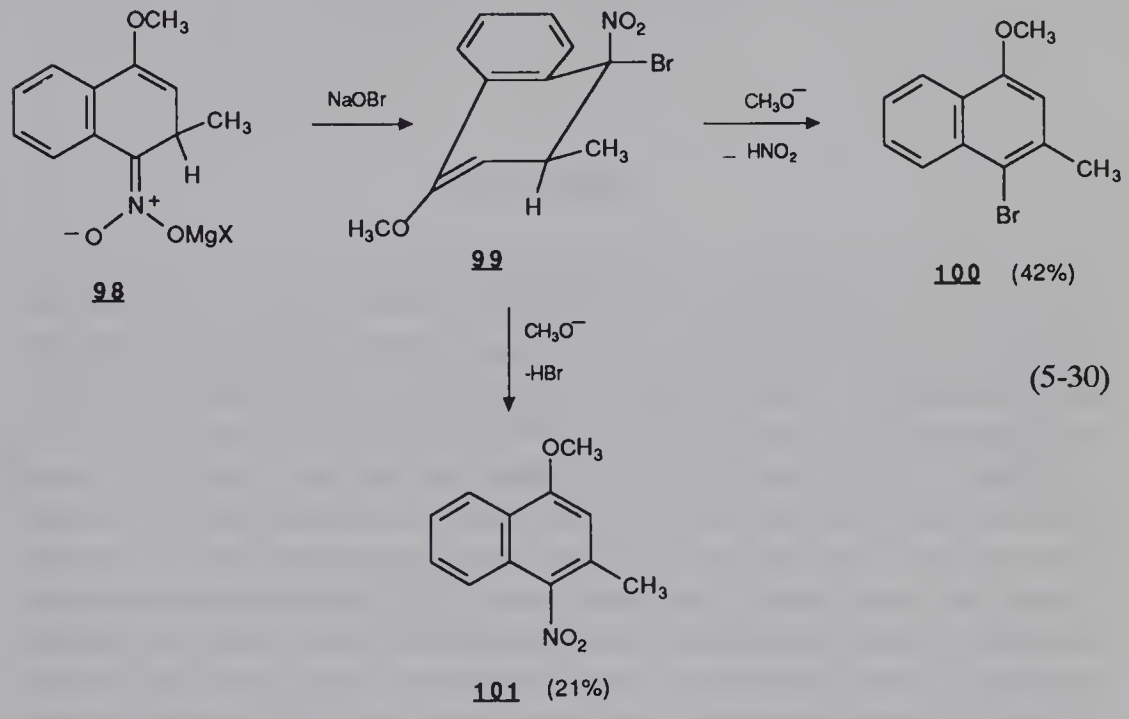
Table 5.2. Alkylation of Nitroaromatics via Addition to Alkyllithium or Alkylmagnesium Halides According to Scheme 5.13

Nitroaromatic	Product	Z	R	Yield (%)	Ref.
		H	CH_3	32–46[a]	82,84
		CH_2H_5	CH_3	52	82
		Cl	CH_3	56	81
			$C_6H_5CH_2CH_2$	36	81
		I	CH_3	74	84
		OCH_3	CH_3	56	81
			$C_6H_5CH_2CH_2$	62	81
		$COCH_3$	CH_3	51	84
		CO_2CH_3	CH_3	72	84
		CN	CH_3	70	84
		H	*n*-C_4H_9	48[a]	82
		CH_3	CH_3	66	82
		OCH_3	CH_3	62	81
		OCH_3	*n*-C_4H_9	75	81
			*n*-C_4H_9	66	81
			$C_6H_5CH_2CH_2$	68	81
		H	CH_3	75	81
			n-C_4H_9	68	81
		CH_3	CH_3	75	81
			CH_3	60	81
			$C_6H_5CH_2CH_2$	72	81

[a]Nitrobenzene and 1-nitronaphthalene are also alkylated in the positions para and ortho, respectively, to the NO_2 group.

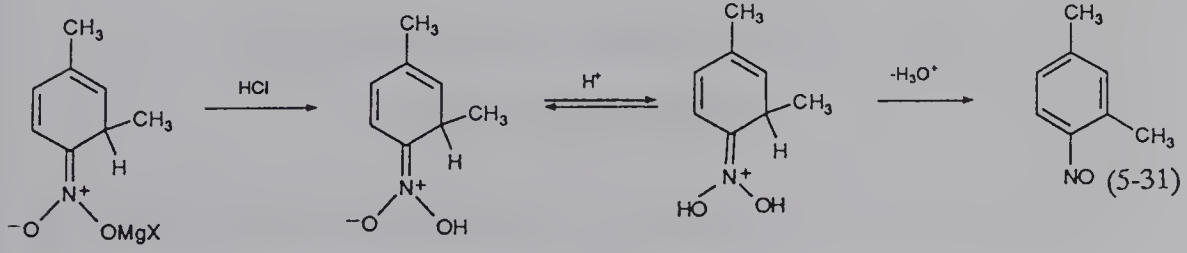
during the oxidation of adduct **95** of 1-nitro-2-methylnaphthalene and 1,3-dithianyllithium (eq. 5-29).[82]

Rearomatization also occurs when nitronate adducts are treated with alkaline sodium hypobromite.[80,86,87] In the case of adduct **98** of 4-methoxy-1--nitronaphthalene, the dihydro isomer **99**, in which the halogen atom and the methyl group are in a trans configuration, is immediately and exclusively formed.[86] It undergoes preferentially an E_2-type elimination of HNO_2 to yield 4-bromo-3-methyl-1-methoxynaphthalene (**100**); some elimination of HBr also occurs to give **101** (eq. 5-30). Similar oxidations with loss of the NO_2 group have been observed with 1- and 2-nitronaphthalenes, 6-nitroquinoline, and 6-nitrobenzothiazole under similar experimental conditions.[87]



(5-30)

Although they cannot be regarded as true oxidation reactions, it is relevant here to mention rearomatization processes, which occur in acidic media.[80] Two different reaction pathways have been identified, which are illustrated by eq. 5-31 and Scheme 5.14. The first process is very common and occurs in the presence of a strong acid like HCl. It involves the initial formation of a nitronic



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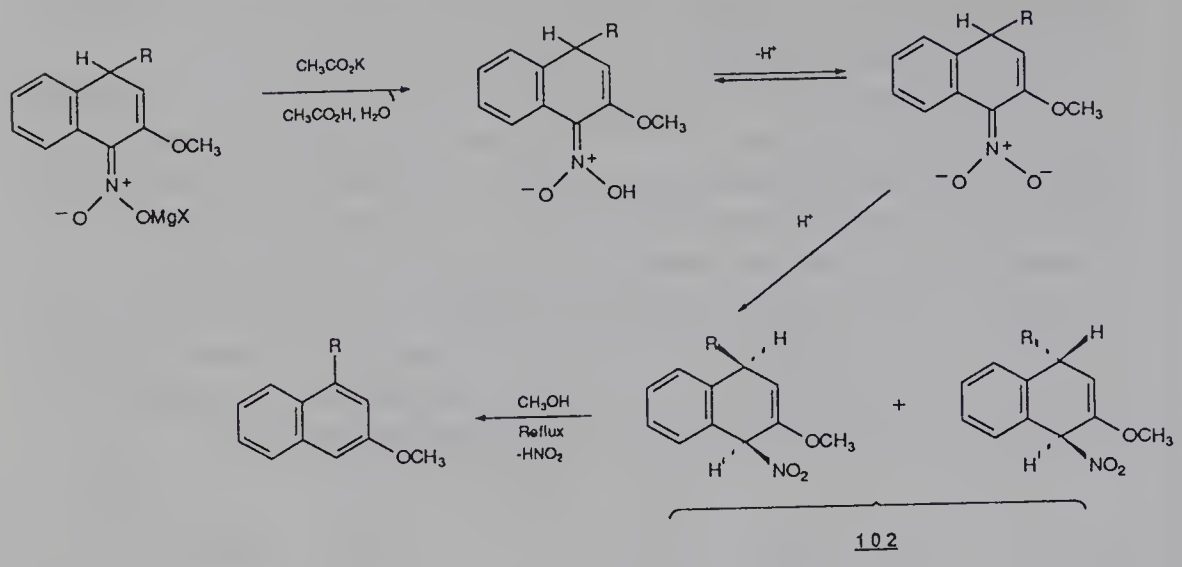


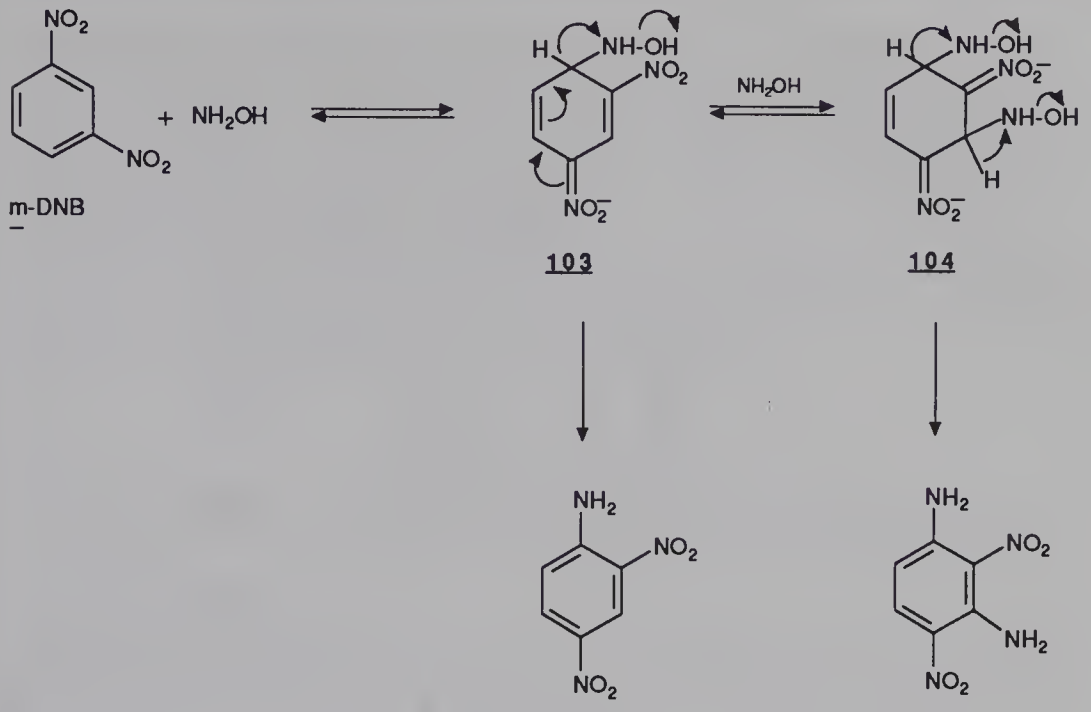
Scheme 5.14.

acid, which is susceptible to a H^+-catalyzed elimination of a water molecule, leading to a nitroso derivative.[80] In the second process, C-protonation competes favorably with protonation at the oxygen atom of the NO_2 group, and dihydro derivatives **102** are formed as cis and/or trans isomers. Heating methanolic solutions of **102** results in elimination of HNO_2 and formation of alkyl derivatives.[83,88]

Direct conjugate addition of a highly basic carbanion to the activated aromatic ring is the key step in the reactions of Grignard reagents with the nitroarenes discussed above. However, Bartoli and coworkers have recently shown that polar and single electron transfer (SET) pathways can compete in systems involving nitroarenes like *p*-dinitrobenzene, which are known to undergo facile electron transfer from carbon bases to give relatively stable radical anions.[89–91] Low temperatures, and weakly polar and highly viscous solvents, would favor the addition pathways, while steric hindrance in the carbanionic reagent would be a major factor favoring an SET mechanism.[91]

5.3 Vicarious Nucleophilic Substitutions

The so-called vicarious nucleophilic substitutions of hydrogen (VS_NAr^H)



Scheme 5.15.

are reactions in which the elimination of the hydrogen bonded to the sp^3 carbon atom of the intermediate adduct is promoted by the concomitant departure of part of the nucleophilic addend.[5] The long-known reactions of nitroaromatics like *m*-DNB with hydroxylamine to give aromatic amines is an example of this behavior.[92–94] As can be seen in Scheme 5.15, the departure of the hydroxy group of the NHOH residues of adducts **103** and **104** assists the departure of the hydrogen atoms; the hydroxy group acts as a vicarious leaving group in the overall process, which formally accomplishes the S_NAr substitution of a hydride anion. Although a comparative study of the behavior of *m*-DNB and d_4-*m*-DNB has revealed that there is migration of the leaving hydrogen(s) from the ring to the amino group(s) during the reaction, the exact mechanism of the rearomatization step(s) of Scheme 5.15 remains to be established.

Most VS_NAr^H reactions involve carbanionic nucleophiles and have been developed by Makosza and coworkers in the past 10 years. These authors have demonstrated that nitroarenes susceptible to undergoing nucleophilic attack at an unsubstituted ring position are readily alkylated by carbanions bearing a potential leaving group at the anionic carbon atom.[5] This behavior is depicted in Scheme 5.16, which refers to the interaction of nitrobenzene (**4a**) with the carbanion of chloromethyl phenyl sulfone (**105a**), in the presence of a strong base (B = KOH, NaOH, *t*-BuOK) in DMSO.[5,95,96] As can be seen, competitive nucleophilic addition of **105a** to the two activated positions para and ortho to

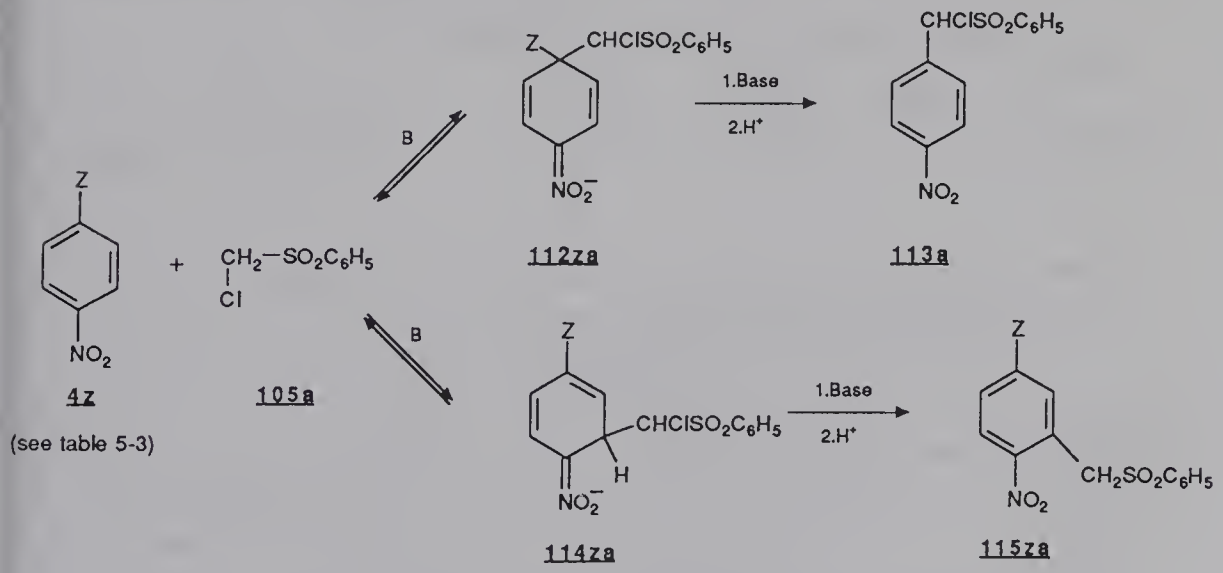
Scheme 5.16.

the NO_2 group initially occurs with formation of the adducts **106aa** and **109aa**. Then, the hydrogen bonded to the sp^3 carbon of these adducts departs concomitantly with the chlorine atom in a base-induced β-elimination step. Acidification of the resulting nitronate anions **107aa** and **110aa** gives the substitution products **108aa** and **111aa**.

Next we consider various VS_NAr^H reactions, which we describe by examining successively the influence of the structure of the nitroarene and of the carbanion on the feasibility of the substitution process.

5.3.1 Effect of the Structure of the Nitroarene

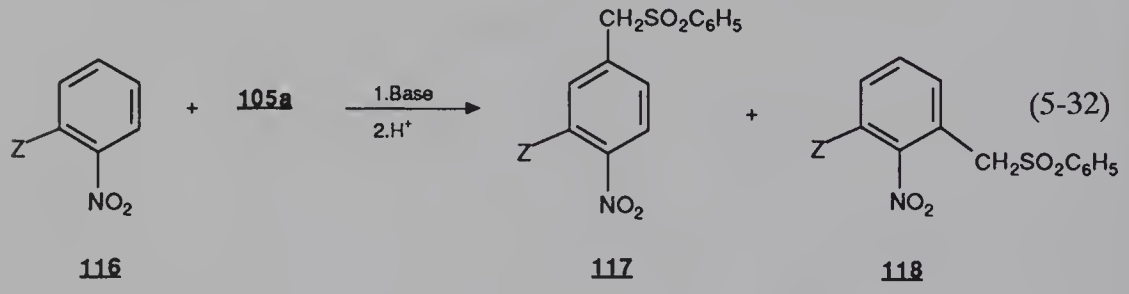
A major feature of Scheme 5.16 is that it is applicable to many substituted nitroarenes, including those that possess a good leaving group in an activated ring position and are therefore susceptible to undergoing an S_NAr process. 4-Chloro, 4-bromo, and 4-iodonitrobenzenes (**4b**, **4d**, and **4e**) thus react smoothly with the carbanion of **105a** to give exclusively the corresponding 3-halo-6-nitrobenzyl phenyl sulfones **115za** (Scheme 5.17).[97] No detectable amount of the sulfone, α-chloro-4-nitrobenzyl phenyl sulfone (**113a**), which would arise from an S_NAr substitution of the halogen atoms, could be found. This indicates that the overall vicarious substitution pathway proceeds at a



Scheme 5.17.

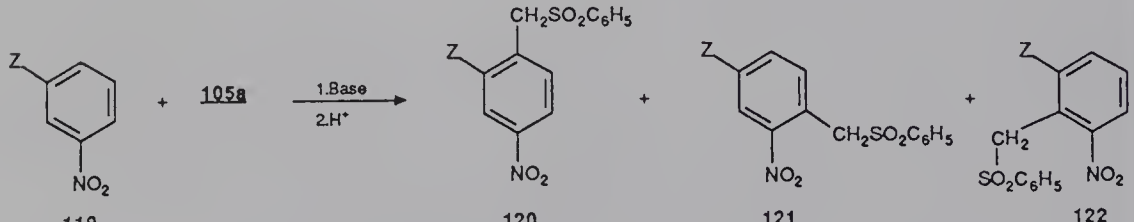
much faster rate than the conventional S_NAr substitution of the halogen atom. In contrast, but in accordance with the much higher leaving group ability of F and NO_2 relative to that of Cl, Br and I in S_NAr processes, both substitution pathways shown in Scheme 5.17 were found to compete when the carbanion was allowed to react with *p*-fluoronitro and *p*-dinitrobenzenes (**4c** and **4f**). In this regard, a significant result is that the formation of the product of the hydrogen substitution of **4c** (**115ca**), is very much favored when the reaction is carried out in the presence of excess base.[96] Since the S_NAr pathway is not expected to depend on this change in experimental conditions, this suggests that the rearomatization of the complexes **114za** as well as that of analogues like **106aa**, occur via a base-induced β-elimination step, as described in Scheme 5.16. Whether this process is an E_2 or E_1cB elimination has not been established so far.[96]

The entries in Table 5.3 show that most para-substituted nitrobenzenes (**4b-n**) are converted into the corresponding sulfones (**115za**) in satisfactory yields.[97] Similarly, ortho-substituted nitrobenzenes (**116**) readily undergo the VS_NAr^H substitution, but reactions occur at both the unsubstituted 4- and 6-positions to give the two isomeric sulfones **117** and **118** (eq. 5-32). Interestingly, the carbanion attacks preferentially the unhindered para position of **116** to give **117** when the reaction is carried out in the KOH/DMSO system but attacks almost exclusively the free ortho position of **116** to give **118** when the reaction is carried out in the *t*-BuOK-THF system.[98] On the other hand, meta-substituted nitrobenzenes **119** can lead to a mixture of the three sulfones



116 **117** **118** (5-32)

$Z = CH_3, Cl, OCH_3, OC_6H_5, N(CH_3)_2, CF_3, NO_2$



119 **120** **121** **122**

$Z = CH_3, Cl, Br, I, F, OCH_3, OC_6H_5, N(CH_3)_2, CF_3, SO_2CH_3, CN, NO_2$ (5-33)

Table 5.3. VS_NAr^H Substitutions of para-Substituted Nitrobenzenes 4z with the Carbanion of Chloromethyl Phenyl Sulfone (105a) According to Scheme 5.17[a]

Z	Starting nitrobenzene	Resulting sulfone	Yield (%)[b]
Cl	4b	115ba	69
F	4c	115ca	18[c]
Br	4d	115da	61
I	4e	115ea	74
NO_2	4f	115fa	13[c]
CN	4g	115ga	52
CF_3	4h	115ha	85
SO_2CH_3	4i	115ia	50
COO^-	4j	115ja	60[d]
OCH_3	4k	115ka	48
OC_6H_5	4l	115la	73
SCH_3	4m	115ma	72
$(CH_3)_3C$	4n	115na	71

[a]Data taken with permission from ref. 97. Experimental conditions: KOH/DMSO or KOH/NH_3.

[b]Yield of isolated sulfone.

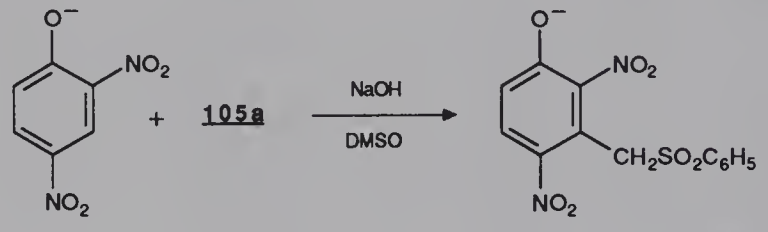
[c]α-Chloro-4-nitrobenzyl phenyl sulfone (113a) is also formed via the S_NAr pathway.

[d]See also ref. 103.

120, 121, and 122 (eq. 5-33). In this series, the orientation pattern is more complicated. In the presence of a strong base in DMSO, formation of the para isomer 120 is favored when Z is electron donating [CH_3, $N(CH_3)_2$, OCH_3, Cl, Br, I], while that of the less hindered ortho isomer 121 is favored when Z is electron withdrawing (CN, SO_2CH_3, CF_3). When the reaction is carried out with *t*-BuOK in THF, the substitution occurs mainly at the most sterically hindered ortho position, giving 122 as the major product.[98]

In a general way, it appears that the ability of para, ortho-, and meta-substituted nitrobenzenes to undergo the VS_NAr^H substitution is not strongly dependent on the electron-withdrawing or electron-donating nature of the

Z-substituent (see Table 5.3).[97] Nevertheless, there are a few noteworthy exceptions, like para-, ortho-, and meta-nitrophenols and para-nitrotoluenes, which react as the corresponding nitrophenoxide or nitrobenzyl anions in basic media.[97,99] In these anions, the strong delocalization of the negative charge onto the NO_2 group and/or the ring reduces the electrophilic character and therefore the susceptibility to nucleophilic attack of the ring. However, introduction of a second and a third nitro group into the aromatic ring provides a suitable activation, and dinitrophenols as well as picric acid readily add chloromethyl phenyl sulfone via the VS_NAr^H pathway in DMSO (eq. 5-34). Similarly, the dinitrobenzyl and trinitrobenzyl phenyl sulfones **123** and **124**, which are the primary products of the VS_NAr^H substitution of *m*-DNB and TNB with **105a**, further react in their anionic form to give the corresponding bis- and tris(phenylsulfonyl) methyl derivatives **125** and **126** (eq. 5-35).[99]



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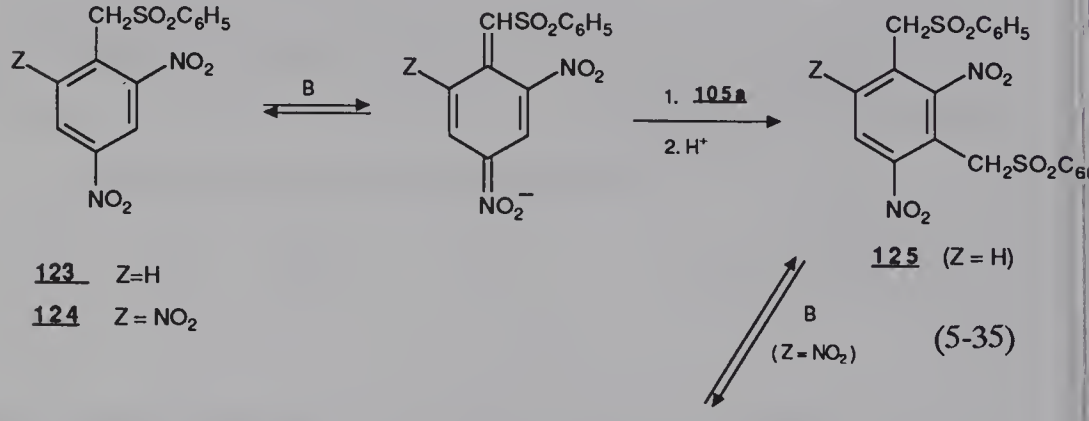
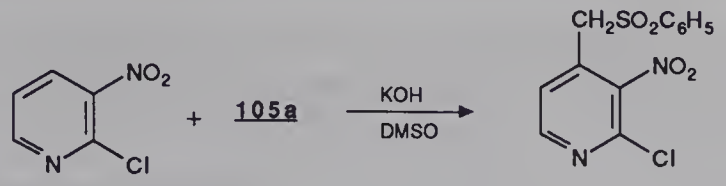


(5-35)

The examples above suggest that any aromatic ring capable of forming a σ-complex with a vicarious nucleophile may be expected to react via the VS_NAr^H pathway. In this regard, efficient substitutions have been achieved

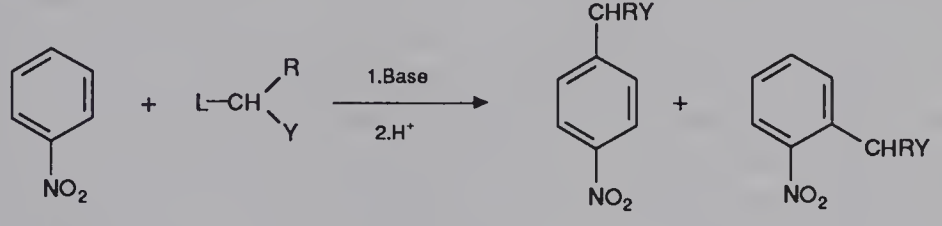


(5-36)

with naphthalene substrates.[100a] Experiments carried out with various π-deficient heterocycles have shown that pyridine and quinoline do not react unless they benefit from the additional activation of an NO_2 group (eq. 5-36),[100b,c] but more electrophilic heteroaromatics like 1,2,4-triazines or benzothiazoles exhibit the VS_NAr^H reactivity, even in the absence of activation by a nitro group.[5,101] Nitro-activated thiophenes, furans, and *N*-alkylpyrroles, as well as nitrobenzotriazoles, undergo efficient VS_NAr^H substitution upon treatment with **105a** in the presence of KOH in liquid ammonia, DMSO, or DMF.[102,103]

5.3.2 The Effect of the Structure of the Carbanion

Self-condensation between a CH-acid precursor and its carbanion is a common process in basic media when a displaceable group is attached to the ionizable carbon atom. Hence, only carbanions that are relatively reluctant to undergo this S_N2 process can be used to achieve a VS_NAr^H substitution.[5] These carbanions have the general structure $LYCR^-$ and have been designed by associating the presence of the leaving group L with that of a carbanion-stabilizing group Y (i.e., an electron-delocalizing substituent) at the anionic carbon center. In fact, combining the nature of L and Y and varying the nature of the R substituent has allowed the designing of a large variety of carbanions susceptible to reacting according to eq. 5-37.



(5-37)

4a

L=Cl, Br, CH_3O, C_6H_5O, CH_3S, C_6H_5S, $(CH_3)_2NC(S)S$

Y= $C_6H_5SO_2$, C_6H_5SO, CN, CO_2CH_3, C_6H_5S, Cl, $P(O)(OCH_3)_2$

R= H, alkyl, aryl, C_6H_5S, Cl

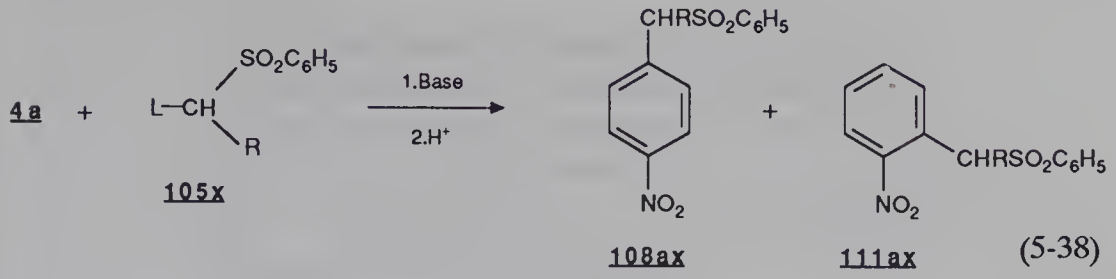
Table 5.4. VS_NAr^H Substitutions of Nitrobenzenes (4a) with the Carbanions of Various α-Haloalkyl Phenyl Sulfones 105x According to Equation 5-38.[a]

Sulfone 105x				Resulting sulfones: ratio of isomers	
x	L	R	Total yield (%)[b]	108ax	111ax
a	Cl	H	75	47	53
b	F	H	63	26	74
c	Br	H	40	65	35
d	I	H	20	85	15
e	Cl	C_2H_5	68	100	
f	Cl	C_6H_5	93	100	
g	Cl	Cl	35	100	

[a]Data reproduced with permission from ref. 97.

[b]Yield of isolated products.

In discussing the effect of the structure of the nitroarene on the reaction, it has been pointed out that α-chloromethyl phenyl sulfone is a suitable carbanion precursor. This shows that the phenylsulfonyl ($SO_2C_6H_5$) group is an efficient carbanion-stabilizing group. On this ground, the reaction of other α-haloalkyl phenyl sulfones **105x** (L = F, Cl, Br, I; R = H, C_2H_5, C_6H_5, Cl) with **4a** to give the isomeric nitrobenzyl sulfonyl derivatives **108ax** and **111ax** has been investigated (eq. 5-38).[97] The results are summarized in Table 5.4. They reveal that an increase in the steric demand of the carbanion does not impede the substitution, but favors the formation of the less hindered *p*-substituted product. Similarly, the reaction of α-halocarbanions stabilized by SO_2NR_2 groups as well as by some specific SO_2OR' groups [R' = C_6H_5 or $CH_2C(CH_3)_3$] has been studied.[5] Recently, it has been reported that 1-chloroalkanesulfonic esters and α-halosulfoxides are also convenient CH-acids for VS_NAr^H substitutions.[104] α-Chlorobenzyl phenyl sulfoxide thus reacts with **4a** and 2-chloronitrobenzene (**116b**) in the usual NaOH/DMSO system to give exclusively the corresponding 4-nitro- and 4-nitro-3-chlorobenzhydryl phenyl sulfoxides (**127a** and **127b**) in roughly 55% yield (eq. 5-39).[104b] Both these compounds form as a mixture of two diastereomers. These experimental conditions are not suitable for a weaker CH-acid like chloromethyl phenyl sulfoxide, but this compound does substitute the ortho and para positions of nitrobenzene and 1-nitronaphthalene in the presence of tetrabutylammonium hydroxide in *o*-dichlorobenzene. Under these conditions, dichloromethyl



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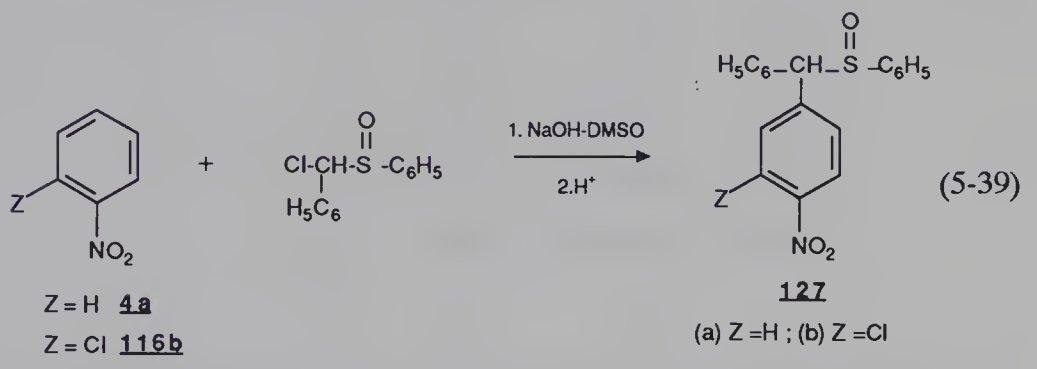
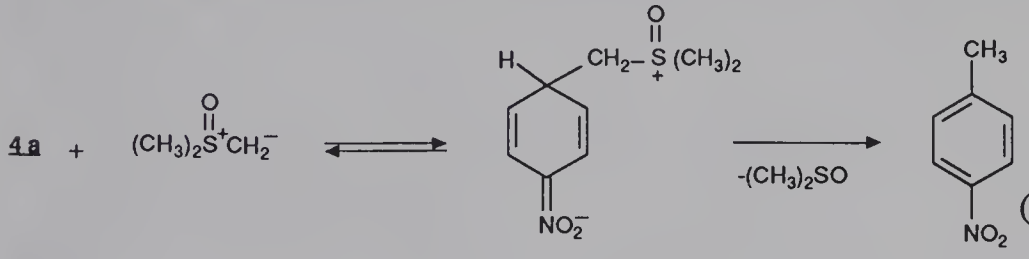


(5-39)

phenyl sulfoxide ($Cl_2CHSOC_6H_5$) also reacts with nitrobenzenes to yield preferentially the products of para-substitution.[104b]

With regard to the reactivity of sulfoxides, it is relevant to mention the methylation reactions of nitroaromatics using dimethylsulfoxonium methylide as the methylating agent.[105,106] As shown in eq. 5-40, this reaction may be regarded as a VS_NAr^H reaction in which dimethyl sulfoxide acts as the vicarious leaving group. Similarly, the methylation of nitrobenzenes upon treatment with the methylsulfinyl carbanion $CH_3SOCH_2^-$ in DMSO probably



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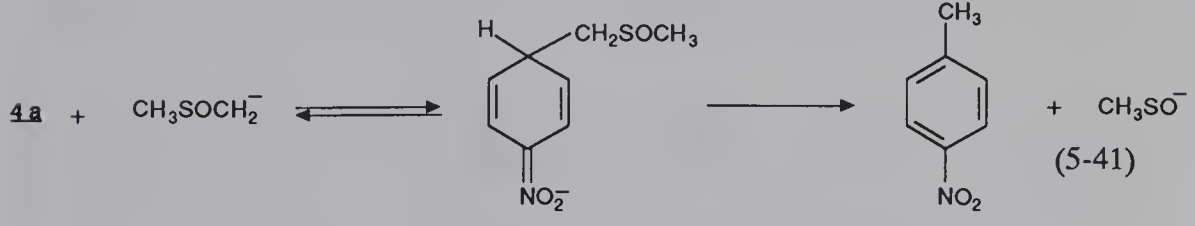


(5-41)

proceeds via the VS_NAr^H reaction described in eq. 5-41, rather than by formation of radical anion intermediates.[107]

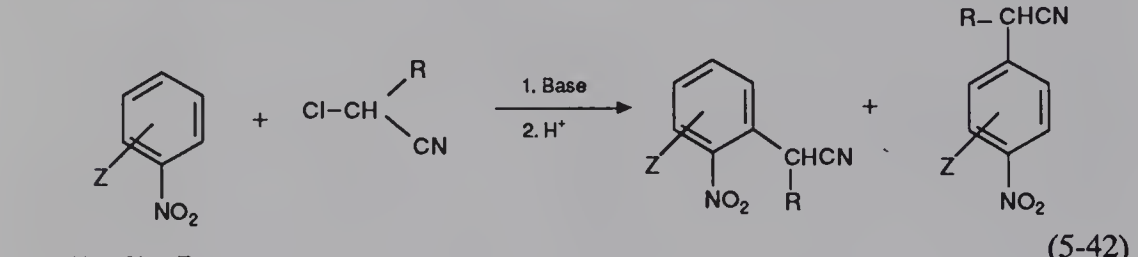
Table 5.5. VS_NAr^H Substitutions of 1-Nitronaphthalene with Carbanions of Various α-Substituted Nitriles According to Equation 5-43.[a]

Carbanion	Resulting nitriles	
L	Total yield (%)[b]	Ratio [130]/[131]
C_6H_5O	80	13
CH_3S	88	8
C_6H_5S	94	11

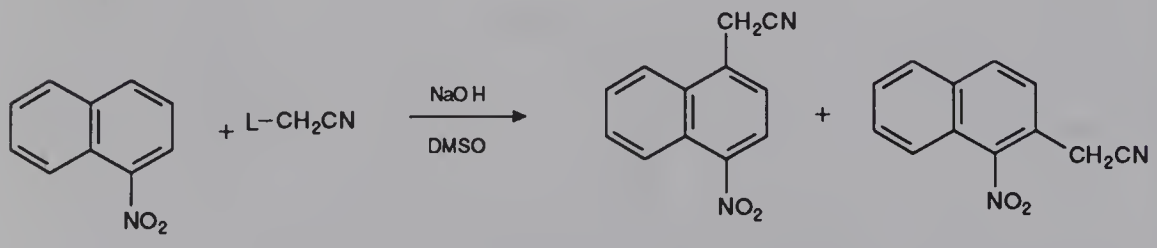
[a]Data from ref. 108.

[b]Yield of isolated nitriles.

α-Chloroacetonitrile derivatives have a notable tendency to undergo self-condensation in strongly basic media, and generally they react with nitrobenzenes in giving low to moderate yields of the expected ortho- and/or para-nitrophenylacetonitriles **128** and **129** (eq. 5-42).[108] The α-cyanoalkylation process occurs very nicely, however, when α-OR- and α-SR-substituted acetonitriles are used as the carbanion precursors. The reason for this is that RO substituents like CH_3O or C_6H_5O and RS substituents like CH_3S or C_6H_5S have a good nucleofugality in β-elimination reactions; but in contrast with halogen atoms, they do not readily depart in S_N2 processes, thus facilitating



Z = H, 2-Cl, 2-F, 3-Cl, 4-Cl R = H, CH_3, $CH(CH_3)_2$ **128** **129** (5-42)



L = C_6H_5O, CH_3S, C_6H_5S **130** **131** (5-43)

Table 5.6. VS_NAr^H Substitutions of 2-Substituted Nitrobenzenes with 2-Chloropropionate Esters According to Equation 5-44.[a]

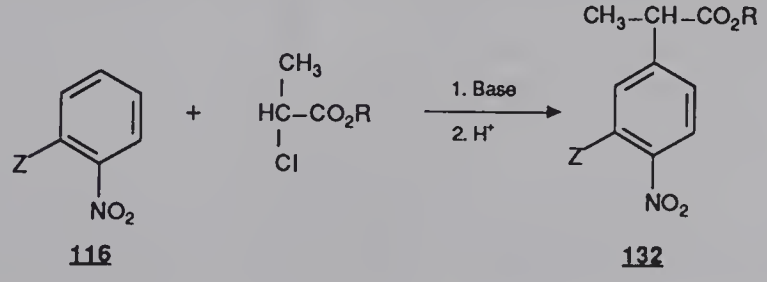
Z (116)	Ester, R	Base	Solvent[b]	Yield (%)
H	CH_3	NaH	DMF	66
H	C_2H_5	*t*-BuOK	DMF	80
Cl	CH_3	NaH	DMF	68
Cl	C_2H_5	*t*-BuONa	DMA	83
F	CH_3	NaH	DMF	58
		t-BuOK	DMF	55
F	C_2H_5	*t*-BuOK	DMF	75
F	$C(CH_3)_3$	*t*-BuOK	DMF	65
OC_6H_5	CH_3	*t*-BuOK	DMF	56

[a] Data reproduced with permission from ref. 109.

[b] Temperature in the range of –5 to 30°C.

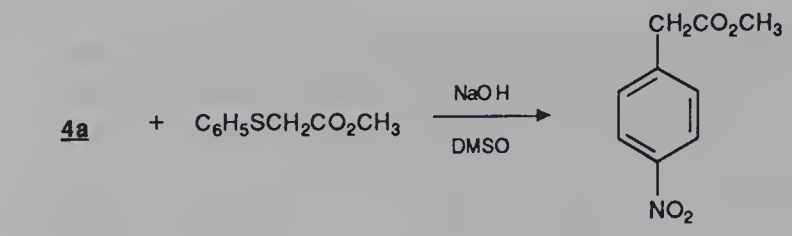
the course of vicarious substitution.[108] The results obtained in the α-cyanoalkylation of 1-nitronaphthalene (eq. 5-43) are given in Table 5.5.

α-Substituted carboxylic esters constitute another source of carbanions suitable for the VS_NAr^H substitution. The readily available 2-chloropropionate esters react with various *o*-substituted nitroarenes to form the 2-(4-nitrophenyl)propionates **132** in good yield (Table 5.6, eq. 5-44).[109,110] The reactions take place with high regioselectivity, not only because the carbanions are tertiary carbanions but also because of the greater bulkiness of a carboalkoxy group relative to a cyano group. A similar preference for carbanion addition at an unsubstituted para position has been observed in the reactions of esters of α-thiocarboxylic acids with various nitrobenzenes (eq. 5-45).[5] Because of the tendency of esters to undergo alkaline hydrolysis, the ex-



(5-44)

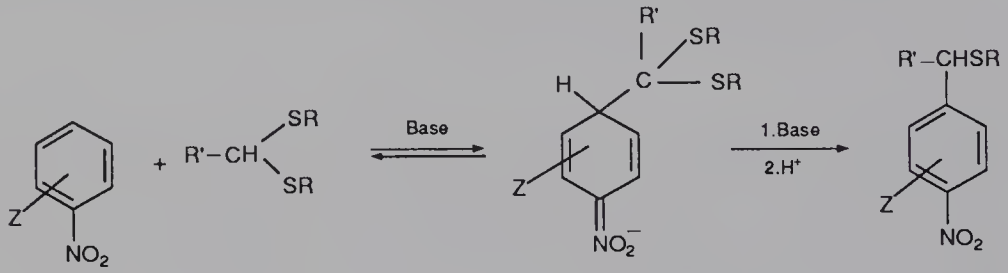
(see table 5-6)



(5-45)

perimental conditions most suitable for these VS_NAr^H substitutions have been carefully studied. For instance, the reactions with 2-chloropropionate esters do not work well in the systems commonly used (i.e., the KOH/ or NaOH/DMSO systems), but they proceed readily in DMF or DMA using NaH, *t*-BuOK, or *t*-BuONa as the base.[109] Carboalkoxymethylation of 2-nitrofuran via a VS_NAr^H-type mechanism has also been reported.[111]

Carbanions of dithioacetals of formaldehyde and benzaldehyde have been successfully used in VS_NAr^H reactions, allowing a direct introduction of thioalkyl substituents into a nitroaromatic ring (eq. 5-46). In these instances, the SR group acts simultaneously as a carbanion-stabilizing substituent and a vicarious leaving group.[112] Similarly, the use of carbanion-stabilizing, phos-

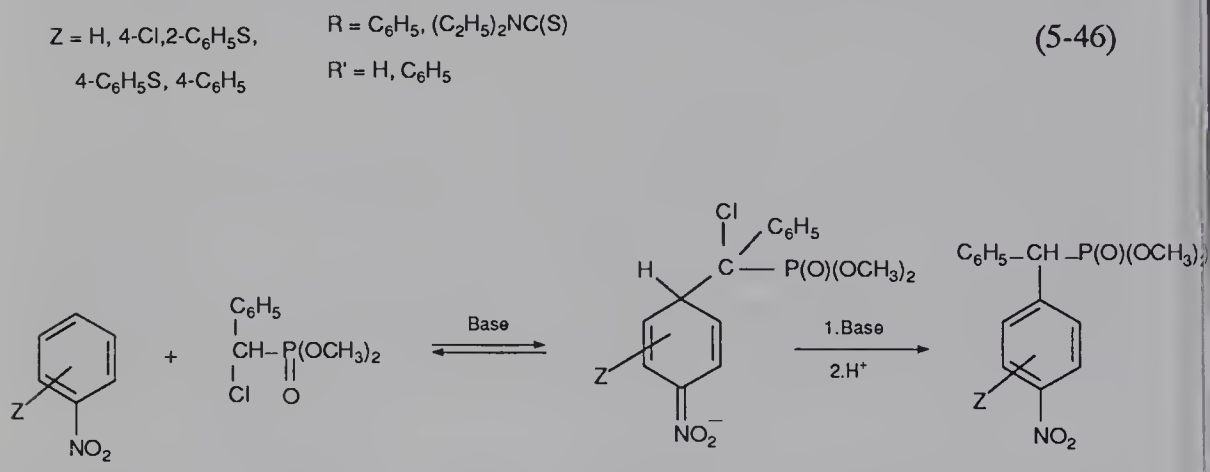


Z = H, 4-Cl,2-C_6H_5S, 4-C_6H_5S, 4-C_6H_5

R = C_6H_5, $(C_2H_5)_2NC(S)$

R' = H, C_6H_5

(5-46)

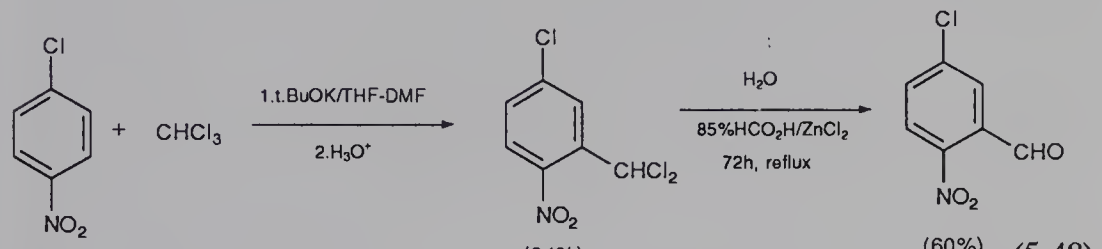


Z = H, 2-Cl, 3-Cl, 4-Cl, 4-Br

(5-47)

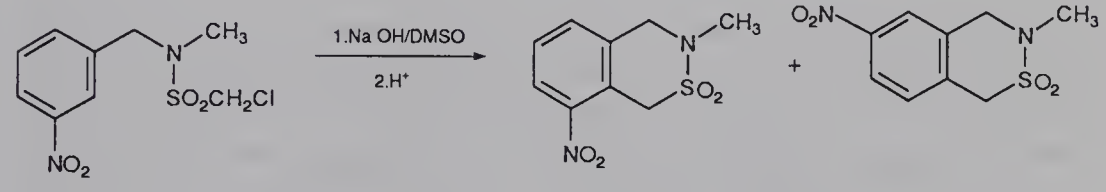
phorus-containing groups gives access to some nitroaromatic organophosphorus compounds (eq. 5-47).[113]

When generated by deprotonation of chloroform and bromoform with potassium *tert*-butoxide in a THF/DMF mixture at –70°C, the intrinsically unstable trichloromethyl and tribromomethyl carbanions exhibit typical vicarious behavior toward a variety of nitroaromatics and nitroheteroaromatics.[114] Equation 5-48 is representative of these reactions, which provide a facile access to dihalomethyl derivatives. Subsequent hydrolysis of these compounds affords the corresponding aldehydes in 50–90% yields.[114]



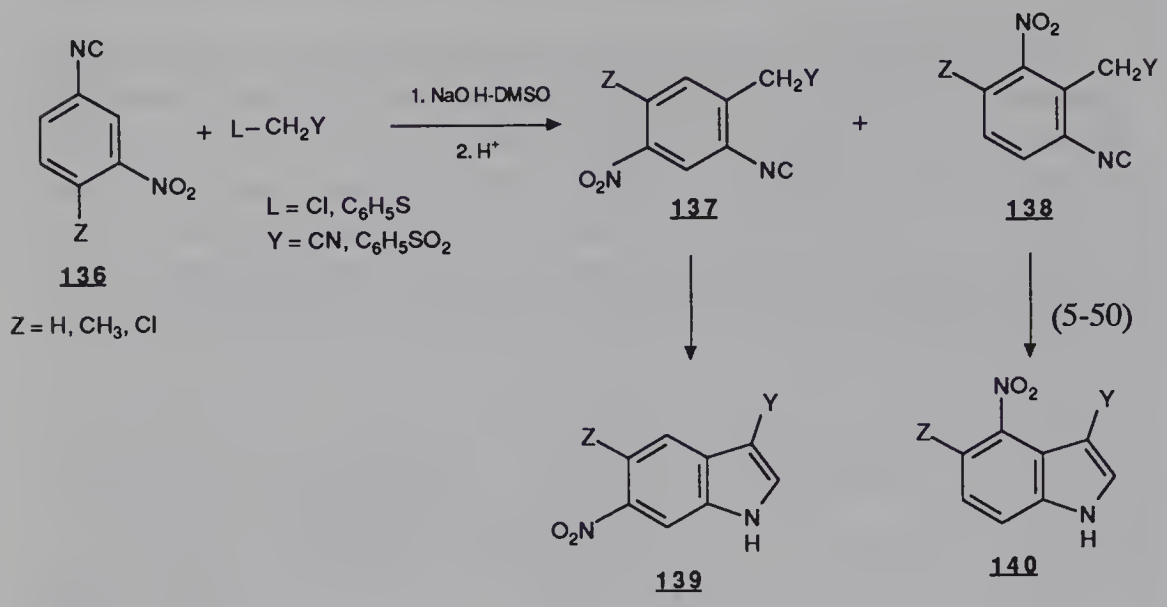
(5-48)

Intramolecular VS_NAr^H reactions are feasible, provided suitably substituted nitroaromatics are used. The process is exemplified by eq. 5-49, which refers to the cyclization of the *N*-methyl-*N*-*m*-nitrobenzyl chloromethyl sulfonamide **133**.[115] The resulting cyclized products **134** and **135** arise from hydrogen substitution at the positions ortho and para to the NO_2 group, respectively. Apparently the cyclization occurs in such a way that the β-elimination step of HCl, which requires an antiperiplanar orientation of the CH and CCl bonds, can be readily achieved.[5,115]



(5-49)

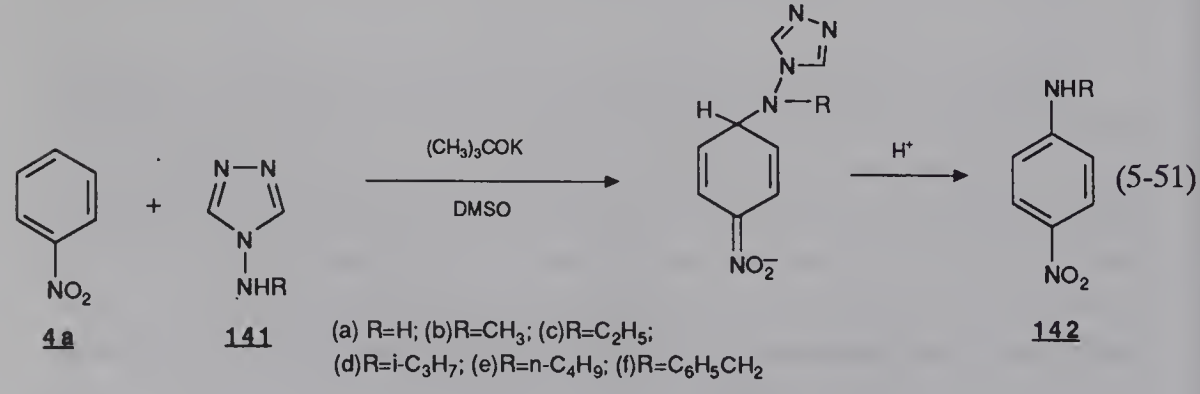
The various reactions discussed in this section clearly show that the VS_NAr^H substitution makes use of a variety of carbanions and is applicable to many nitrobenzenes as well as sufficiently activated aromatics or heteroaromatics. It is therefore an efficient and convenient method of introducing alkyl side chains bearing specific functional groups into the nitroaromatic ring. The resulting compounds can sometimes be engaged in additional transformations, which lead to more elaborate compounds whose synthesis by classical methods would be difficult. A nice example is the



recently reported indole synthesis shown in eq. 5-50.[116] In this instance, the vicarious substitution products **137** and **138**, which result from the addition of different carbanions to the *m*-nitrophenyl isocyanides **136**, cyclize readily to the substituted indoles **139** and **140**, as a result of a subsequent attack of the methylene group of **137** and **138** on the isocyano group.

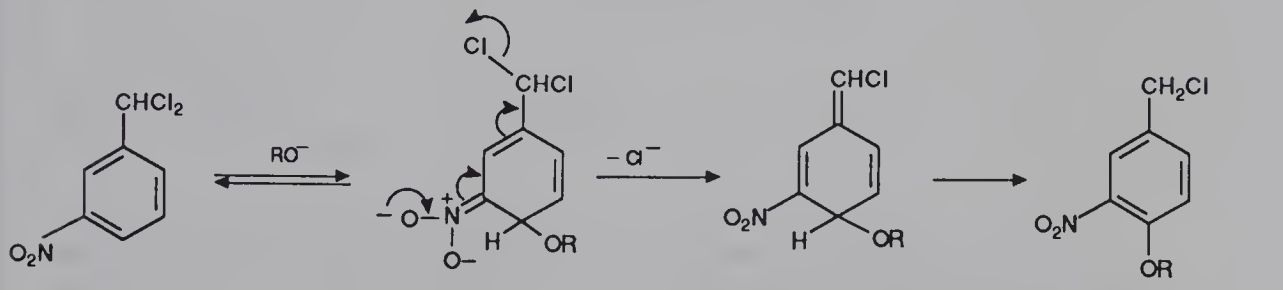
5.3.3 Related Reactions

Katritzky and Laurenzo have described vicarious nucleophilic substitutions involving 4-amino-1,2,4-triazole (**141a**) and related 4-alkylamino-1,2,4-triazoles such as **141b–f** as nitrogen nucleophiles.[117a,b] Equation 5-51 exemplifies these reactions, which in the case of nitrobenzene (**4a**), afforded the 4-nitroanilines **142a–f** in good yields, with no detectable ortho substitu-



tion. However, a similar amination of 1-nitronaphthalene, 2-nitronaphthalene, and 2-nitrothiophene was found to occur preferentially at the position ortho to the nitro group. Also of interest is a recent report that alkyl hydroperoxide anions behave as true vicarious nucleophiles when they react with a variety of nitroarenes in a *t*-BuOK/THF/liquid ammonia mixture. The reactions produce *o*- and/or *p*-nitrophenols in excellent yields.[117c]

An original S_NAr^H substitution, which is somewhat related to the VS_NAr^H reactions, was observed on treatment of 3-nitrobenzylidene dichlorides with alkoxide ions.[118,119] For example, the dichloride **143** reacts with methoxide and ethoxide ions to give the 4-alkoxybenzyl chlorides **145** whose formation has been accounted for in a way shown in eq. 5-52. As can be seen, the chlorine atom acts as a vicarious leaving group in the process. Its departure is necessary for inducing the rearomatization of the adduct **144**. However, the elimination of the hydrogen atom bonded at the sp^3 carbon of **144** occurs in a subsequent step. Similar behavior has been reported by Norris in a study of the reaction of **143** with propane-2-nitronate ion in DMSO.[120]



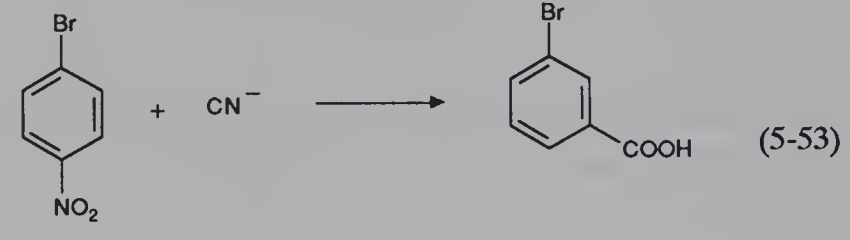
143 **144** R = CH_3, C_2H_5 **145** (5-52)

5.4 Cine and Tele Substitutions

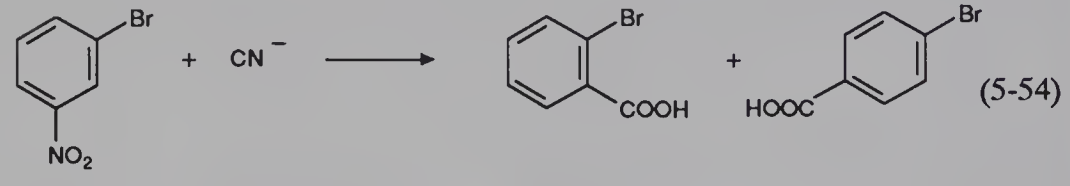
There are a number of aromatic nucleophilic substitutions in which the ring position taken by the entering group is not the same as that vacated by the displaced group. In accordance with IUPAC nomenclature,[121] these reactions, which often result in displacement of a ring hydrogen atom, are referred to as cine or tele substitutions, depending on whether the incoming group does or does not enter in an adjacent position to the leaving group. In the latter case, the position of entry can be separated by one or more atoms from that vacated by the leaving group.

5.4.1 The Von Richter Rearrangement

A long known example of a cine substitution is the Von Richter reaction, which is the conversion of a range of aromatic nitro compounds to carboxylic acids upon treatment with cyanide ion in aqueous alcoholic media.[1,3,122,123] Equations 5-53 and 5-54, which refer to the behavior of para- and meta-substituted nitrobenzenes, respectively, are illustrative of this reaction. It has been shown that the carboxyl group enters preferentially ortho to the position vacated by the NO_2 group.[123] In fact, most ortho-substituted nitro compounds do not react at conditions that are adequate for reaction by the meta and para isomers.[123]



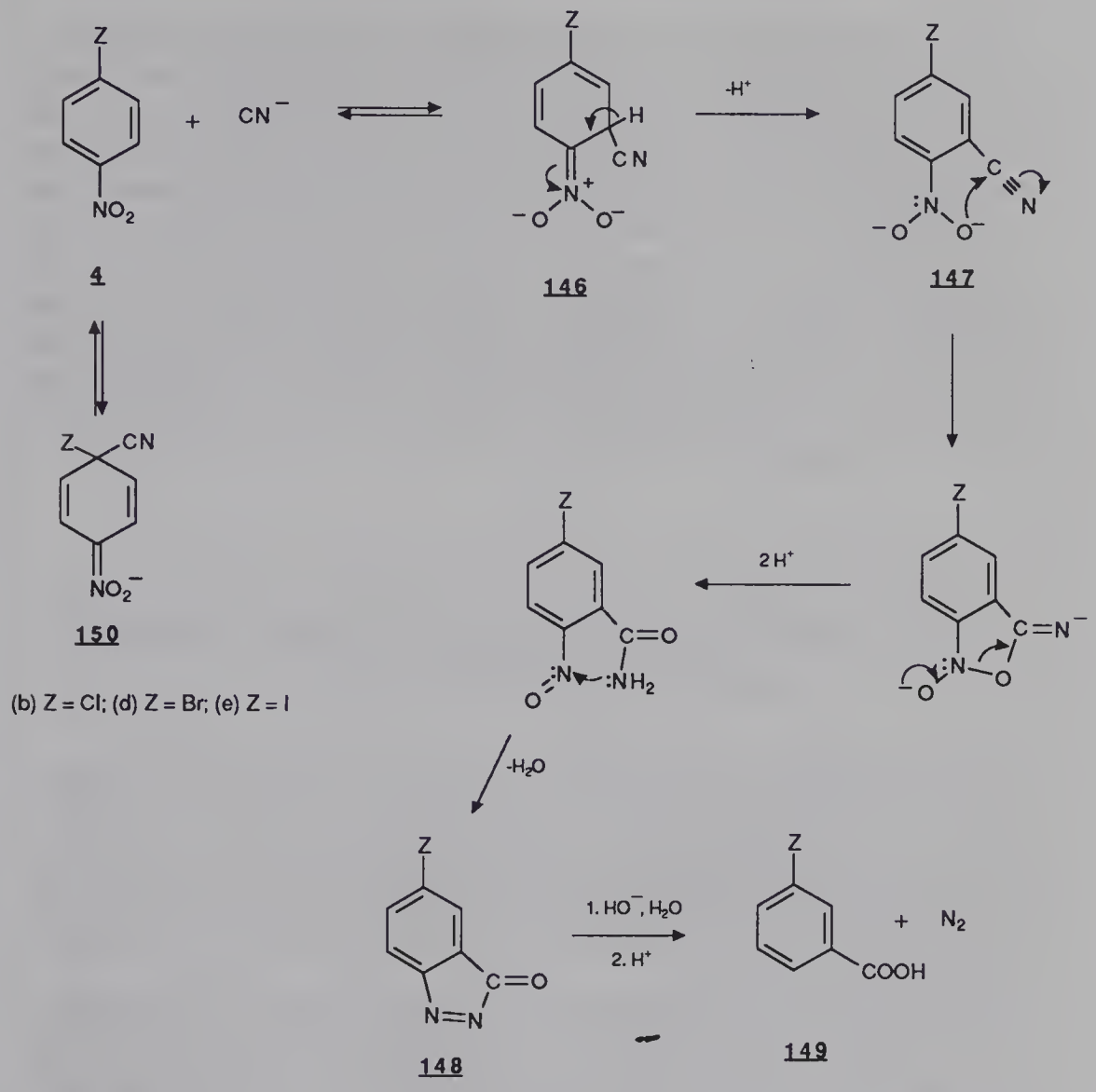
(5-53)



(5-54)

Studies by Bunnett, Rosenblum, and others have provided support for the mechanism depicted in Scheme 5.18.[123–128] Initial attack of CN^- ion at an unoccupied position ortho to the nitro group yields the σ-complex intermediate **146**. The presence of the adjacent CN group renders the hydrogen bonded to the sp^3 carbon of **146** relatively acidic; this permits its facile departure as a proton to form the dianion **147**. Subsequent intramolecular redox reactions can then occur, allowing intramolecular side-chain nucleophilic reactions and formation of the indazolone **148**. This compound undergoes facile hydrolysis to give the carboxylic acid **149**, with elimination of nitrogen. It should be noted that Scheme 5.18 is valid only for reactions carried out in protic solvents. In other solvents like DMSO, the course of the reaction is more complex and not understood.[129]

A noteworthy feature of the Von Richter reaction is that compounds like *p*-halonitrobenzenes, which have a good leaving group in a well-activated position, react preferentially via the overall 1,2-addition–elimination process of Scheme 5.18 rather than by the expected S_NAr mechanism.[123] However, it has been pointed out (see Chapter 2) that nucleophilic attack at an activated unsubstituted ring position generally occurs at a much faster rate than at a



Scheme 5.18.

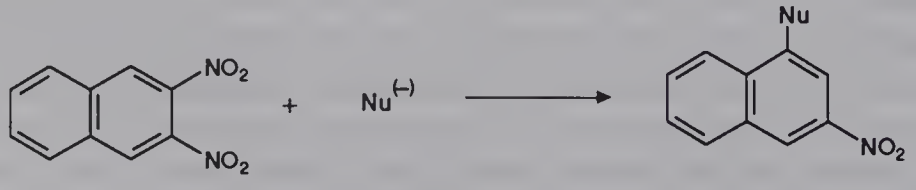
similarly activated substituted position. Accordingly, the adduct **146** may well be kinetically favored over its isomer **150** involved in the S_NAr pathway. The evolution of the reaction will depend only on the relative rates of rearrangement of **146** into **150**, with a predominance of the S_NAr process, or into **147**, with a preference for the abnormal substitution pathway leading to **149**. In this regard, the ease with which the proton departs from the negatively charged cyano "carbon acid" **146** is a major factor determining the course of the substitution. Thus, common nucleophiles such as alkoxide or thioalkoxide ions, or amines, fail to react with nitroarenes like the cyanide ion. The probable reason for this

is that, after entry ortho to the nitro group, they become alkoxy, thioalkoxy, or amino groups, which have no marked effect on the acidity of the geminal hydrogen atom.[123a] In this case, the S_NAr mechanism is generally favored. Note also that an increase in the activation of the ring (e.g., by an additional nitro group) increases the susceptibility of the arene to cyanide ion attack; but in general, neither the cine substitution nor the S_NAr pathway is favored. In most of these cases, hydrogen displacement still occurs under some experimental conditions in a position ortho to the NO_2 group but without elimination of this group. This type of S_NAr^H substitution has been discussed in connection with Scheme 5.6. However, a Von Richter rearrangement has been observed in the reaction of CN^- with a fairly activated heteroaromatic like 6-nitroquinoline.[130]

5.4.2 *o*-Dinitro Six-Membered Ring Aromatics and Related Derivatives

Even though the S_NAr mechanism remains the normal substitution pathway of most of these derivatives, the observation of a cine-substitution process is not uncommon in studies of the interaction of *o*-dinitroaromatics with some nucleophiles. Thus, 2,3-dinitronaphthalene (**151**) reacts with various alkoxide ions, amines as well as carbanions, to give essentially cine substitution products (eq 5-55).[7,8,44b,131]

A detailed kinetic study of the reaction of **151** with piperidine in benzene, which affords 1-piperidino-3-nitronaphthalene (**153**) in quantitative yield (eq. 5-56), has been made.[6,7] The reaction apparently involves initial and rate-determining addition—presumably in two or three steps—of a piperidine molecule to **151**, with formation of the dihydro intermediate **152**, which subsequently loses an HNO_2 molecule. In contrast with what is observed for **151**, S_NAr and cine-substitution processes compete when 6,7-dinitroquinoxaline (**154**) reacts with piperidine in ethanol, thus giving a mixture of **155** and **156** (eq. 5-57).[132]

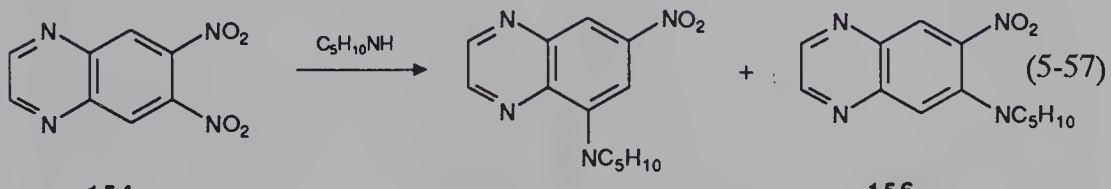


(5-55)

151

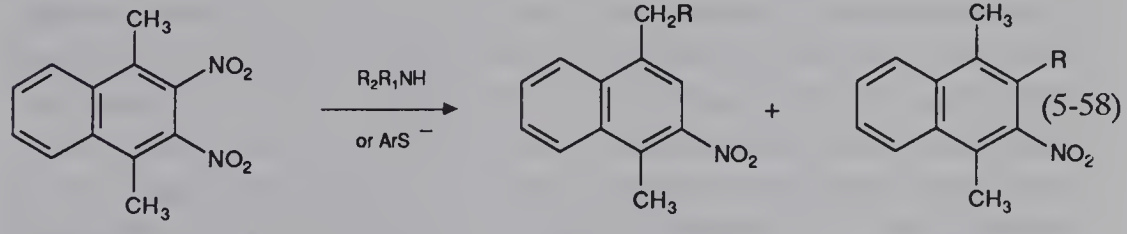
$Nu^{(-)} = CH_3O^-, C_2H_5O^-, CNCH^-CO_2C_2H_5, C_5H_{10}NH$

152 153



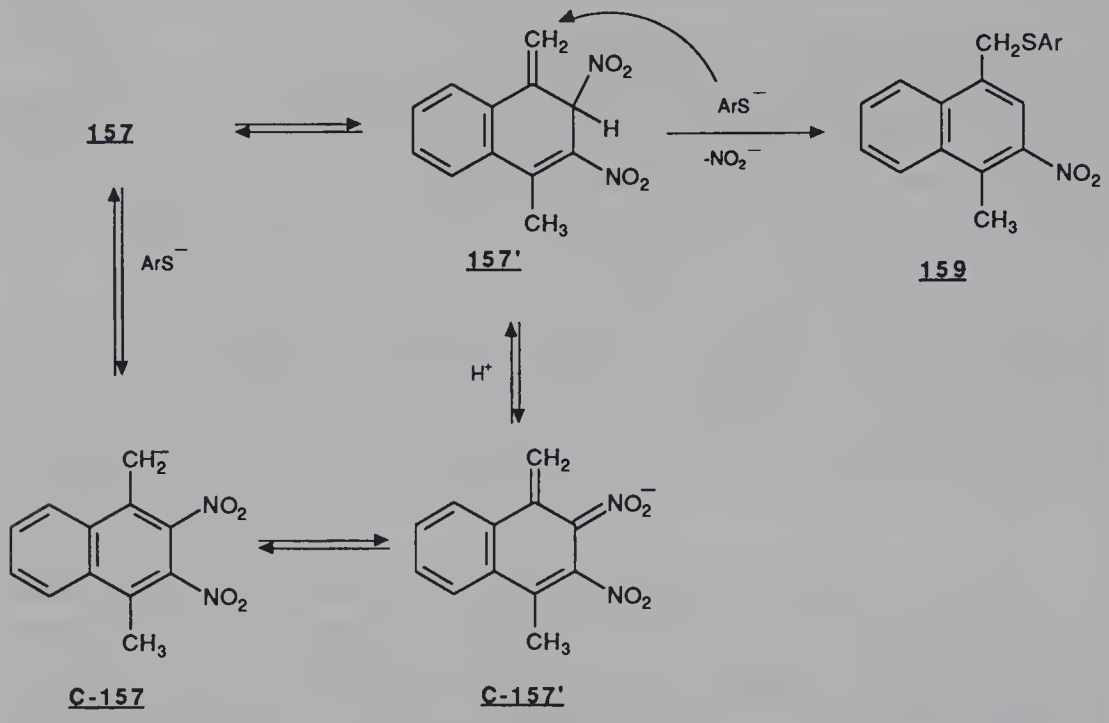
154 155 156

Of interest in the context of the unusual reactivity of *o*-dinitronaphthalenes is the behavior of 1,4-dimethyl-2,3-dinitronaphthalene (**157**), which reacts with secondary amines and arenethiolates (ArS^-) to give the 1-dialkylaminomethyl- or 1-arylthiomethyl-4-methyl-3-nitronaphthalenes **158** and **159** shown in eq. 5-58.[133,134] This reaction can be regarded as a nucleophilic tele substitution of a hydrogen atom of a side-chain α-carbon atom with departure of the nearest NO_2 group. Based on a detailed examination of the factors affecting the reaction of **157** with arenethiolates in DMSO, in which the formation of the tele-substitution products **159** competes with that of the normal substitution products **160**, the mechanism shown in Scheme 5.19 has been proposed. The methyl groups of **157** may be expected to have an appreciable acidity at the experimental conditions used, thus favoring the tautomerization of **157** into **157′** via the intermediate carbanions **C-157** and **C-157′**.[135] Then, formation of **159** would occur in a concerted process involving addition of the nucleophile to the methylene carbon of **157′** with concomitant expulsion of NO_2^-. Rearomatization of the aromatic ring would be the driving force for this process.[135] Similar tele substitutions were observed in the reactions of ArS- ions with 1,4-dimethyl-2-nitro-3-phenylsulfonyl- and



157 R_2R_1NH = Piperidine or Morpholine
ArS^- = $C_6H_5S^-$, 4-$CH_3C_6H_4S^-$
2,4,6-$(CH_3)_3C_6H_2S^-$

158 R = NR_1R_2
159 R = SAr
160

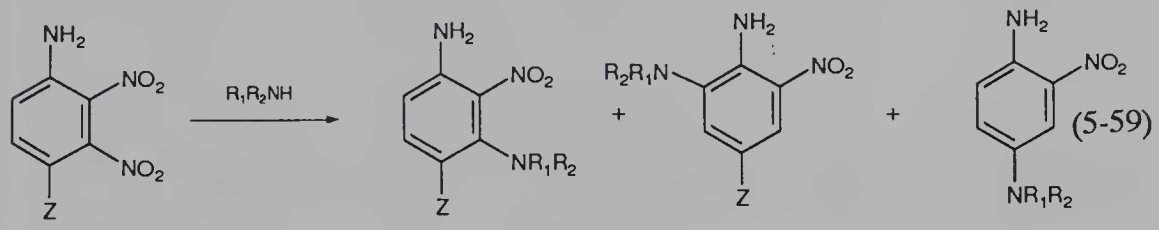


Scheme 5.19.

-2,3-bis phenylsulfonylnaphthalenes.[136] The results obtained emphasize that the phenylsulfonyl group is a much better nucleofugal group than the nitro group in such tele substitutions.[136] Naphthalenes with two meta-electron-withdrawing groups like 1,3-dimethyl-2,4-dinitro- and 1,3-dimethyl-2-nitro-4-phenylsulfonylnaphthalenes also undergo tele nucleophilic substitutions of a hydrogen atom at their methyl groups.[136]

In contrast to the *o*-dinitronaphthalene (**151**) and the *o*-dinitroquinoxaline (**154**), which have only unsubstituted positions ortho to the NO_2 groups, *o*-dinitrobenzene derivatives can have unsubstituted ring positions ortho, meta, or para to a nitro group. Accordingly, they can undergo nucleophilic displacement of hydrogen via cine- as well as tele-substitution pathways. Thus, 2,3-dinitroaniline (**161a**) reacts with cyclic secondary amines like piperidine, morpholine, or *N*-methylpiperazine to give the three substituted nitroanilines **162a**, **163a**, and **164a** (eq. 5-59).[137] While **162a** arises from normal S_NAr displacement of an activated NO_2 group by the amine, **163a** and **164a** result, respectively, from displacements in which the incoming amino group enters para and ortho to the outgoing NO_2 group; that is, tele and cine substitutions occur, respectively.[137] No detailed mechanism accounting for the observed products has been proposed, but the nature of the amine is of major importance in determining the course of the reactions, since primary amines react with

161a to give exclusively, normal substitution products. On the other hand, treatment of **161a** with a cyclic secondary amine like pyrrolidine, affords only the normal and cine substitution products **162a** and **164a**; no product arising from a tele substitution could be detected in this case. The anomalous behavior of pyrrolidine as compared with that of piperidine and morpholine has been noted in various instances.[138]



(5-59)

161

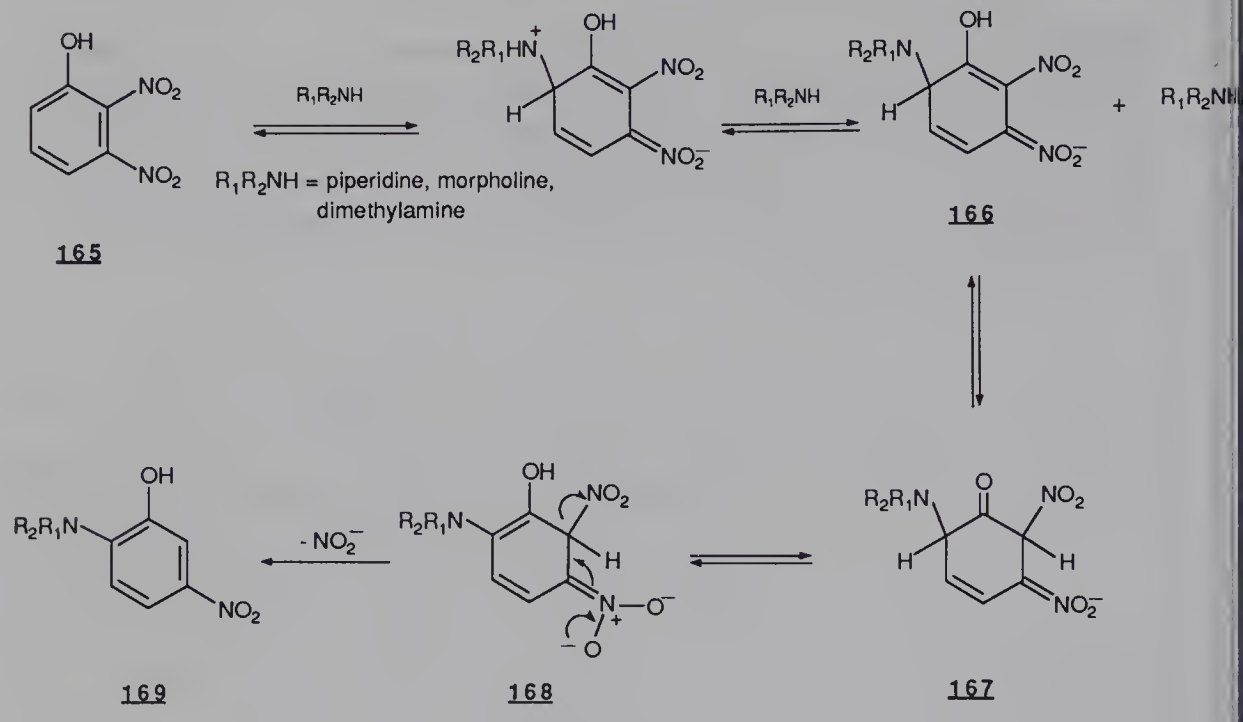
(a) Z = H; (b) Z = OCH_3

(c) Z = OC_2H_5

162 **163** **164**

Some other 2,3-dinitroaniline derivatives have also been studied. 4-Methoxy- and 4-ethoxy-2,3-dinitroanilines (**161b**) and (**161c**) react with piperidine and morpholine to give the tele-substitution products **163b** and **163c**; no cine substitution can occur in these 4-substituted compounds.[138] When similar reactions were carried out with the corresponding 4-alkoxy-2,3-dinitroacetanilides, only S_NAr displacements of the two NO_2 groups were observed.[139]

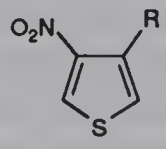
2,3-Dinitrophenol (**165**) undergoes tele substitution with secondary amines leading to 2-(*N*,*N*-dialkylamino)-5-nitrophenols **169**.[140] This tele substitution differs from that observed with the corresponding aniline **161a** in that the incoming amino group is situated meta and not para to the displaced NO_2 group. A possible mechanism is outlined in Scheme 5.20. Initial attack of the amine would occur at C-6 to give the intermediate σ-complex **166**, which benefits from the stabilizing influence of a *p*-NO_2 group. This adduct would undergo a 1,3-proton transfer via the oxo tautomer **167**. Subsequent loss of the 2-NO_2 group from **168** would lead to the final products **169**. Some support for the intermediacy of **167** is provided by the observation that 2,3-dinitrophenyl ethers do not undergo analogous "meta" tele substitution.[140] In fact, piperidine reacts with these ethers to give 3-nitro-5-piperidinophenyl ethers; that is, tele substitution occurs in the para position of the leaving NO_2 group, as observed for **161**.[140]



Scheme 5.20.

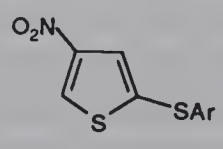
5.4.3 *o*-Dinitro Five-Membered Ring Heteroaromatics and Related Derivatives

Heteroaromatics having vicinal but weakly conjugated electron-withdrawing groups readily undergo cine substitutions. 3,4-Dinitrothiophene (**170a**) is a typical example of a compound that reacts with various sodium benzenethiolates (ArS^-) to give the 2-arylthio-4-nitrothiophenes **171** as the major final products.[141,142] 4-Nitro-3-thienyl phenyl sulfone (**170b**) reacts similarly to give **171** as well as **172**,—that is, the products of the cine substitutions of the NO_2 and $SO_2C_6H_5$ groups.[143] However, the reaction of **170a** with secondary amines does not afford cine substitution products. In this instance, there is

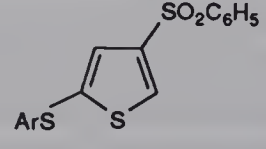


170a $R = NO_2$

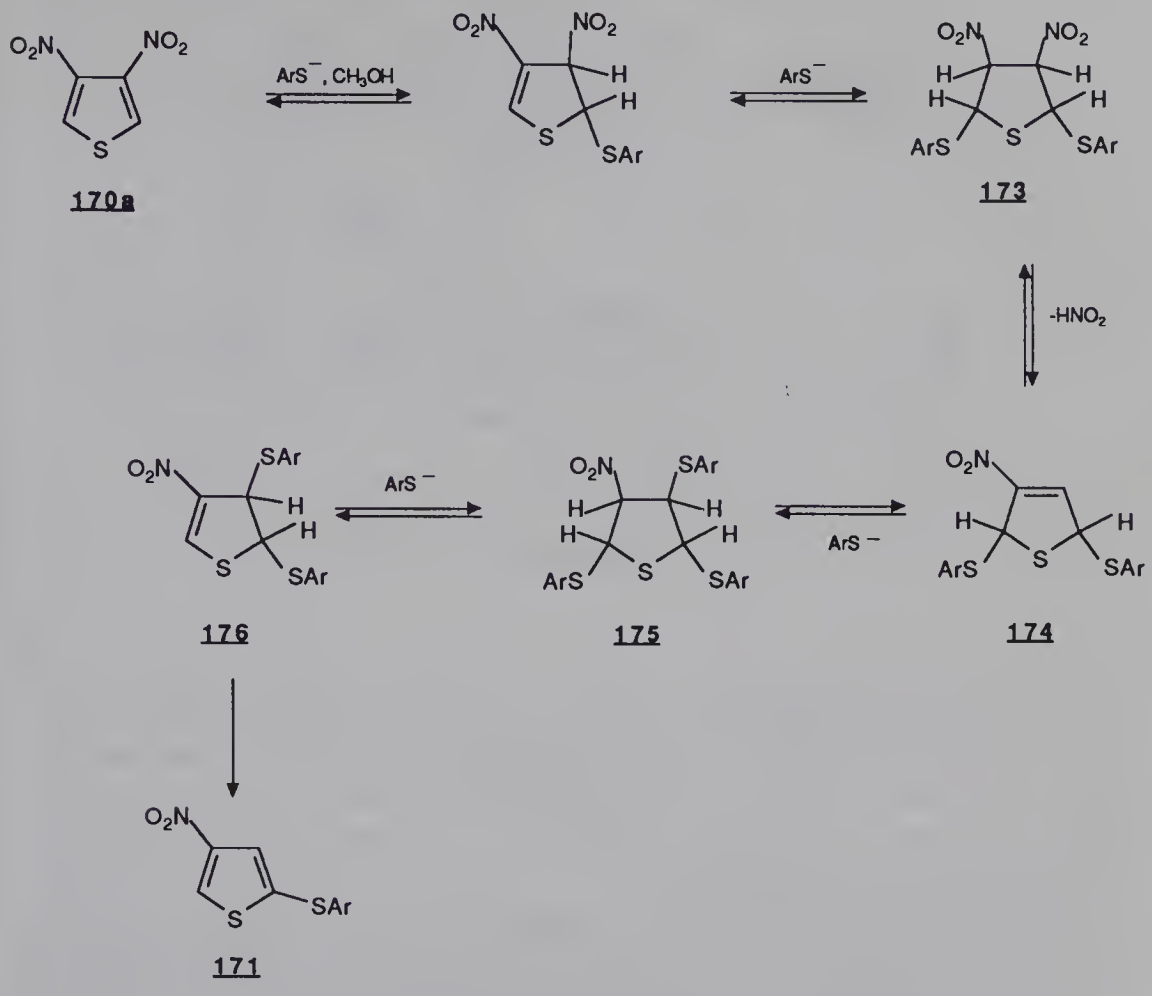
170b $R = SO_2C_6H_5$



171



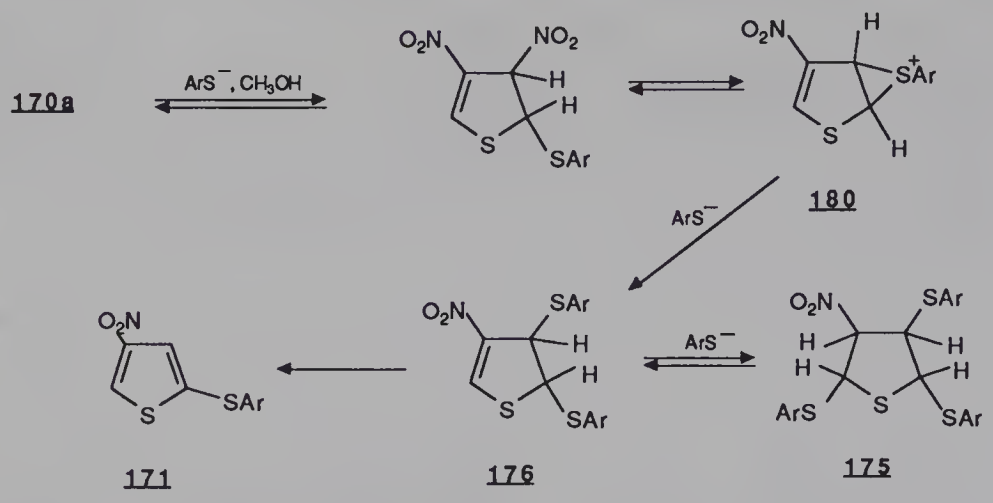
172



Scheme 5.21.

destruction of the ring, with formation of 1,4-dialkylamino-2,3-dinitrobutadienes and H_2S as the main products.[144]

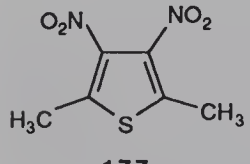
The mechanism for the conversion of **170a** into **171** is shown in Scheme 5.21. First, there is successive and reversible addition of two molecules of ArS^- to **170a** to give the tetrahydrothiophene intermediate **173**. This compound behaves as a vicinal dinitroalkane and undergoes irreversible elimination of nitrous acid to give the 2,5-dihydrothiophene **174**. Fast reversible addition of a third molecule of ArS^- to **174** then occurs, leading to the 4-nitro-2,3,5-tris(arylthio)tetrahydrothiophene **175**. Successive elimination of two molecules of ArS^- from **175** eventually occurs to form the resulting sulfide **171**. In the case of the 2,4,6-trimethylbenzenethiolate system, both the intermediates **175** and **176** were isolated as crystalline solids. While **175** was found to form as a mixture of two stereomers, **176** was shown by X-ray analysis to



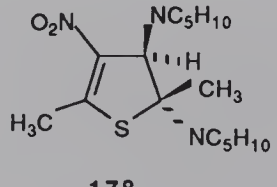
Scheme 5.22.

be the trans isomer. Interestingly, treatment of 2,5-dimethyl-3,4-dinitrothiophene (**177**) with secondary amines also affords isolable 2,3-dihydrothiophenes (**178**) in a trans configuration.[145] In contrast, the reaction of **177** with ArS^- ions yields the 2-arylthiomethyl-5-methyl-4-nitrothiophenes **179**, which are tele-substitution products, of the type observed with 1,4-dimethyl-2,3-dinitronaphthalene.[146,147]

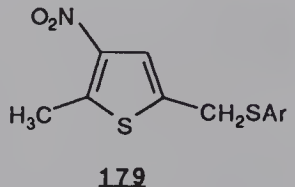
Quite recently, the alternative mechanism presented in Scheme 5.22 was proposed to account for the cine substitution leading from **170** to **171**.[148] It assumes the formation of an episulfonium ion **180**, which would be the direct precursor of **176**. The diastereomeric tetrahydrothiophenes **175** would form in a side equilibrium in this case.[148]



177

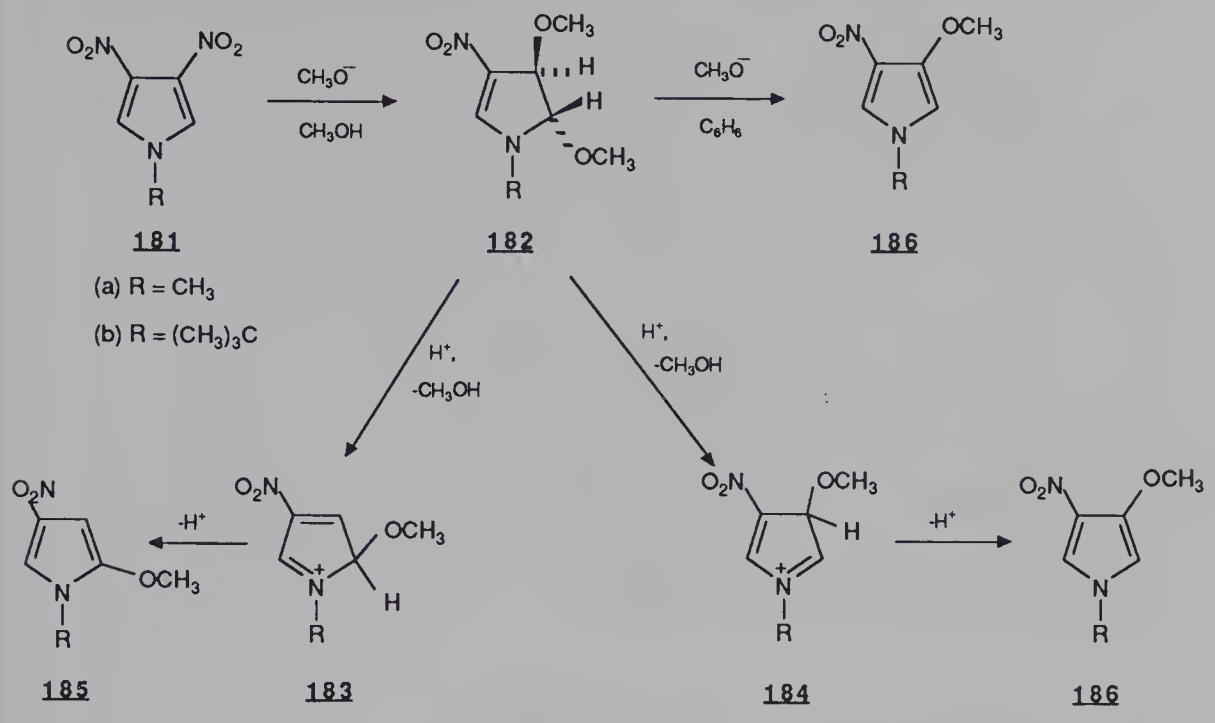


178



179

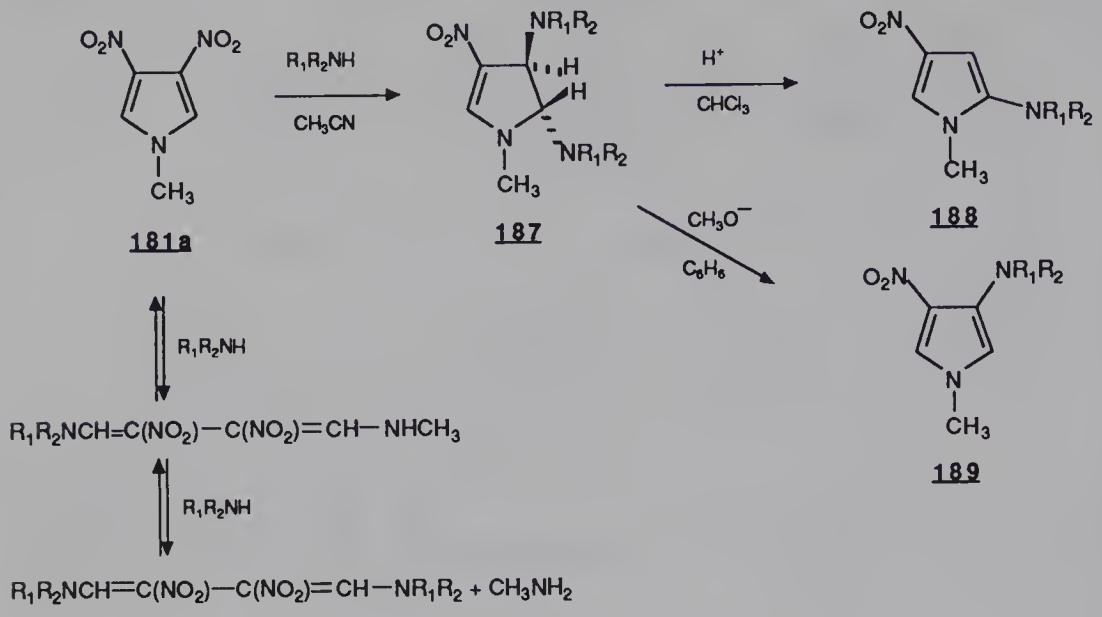
Like their thiophene counterparts, 3,4-dinitropyrroles undergo formal nucleophilic substitution of hydrogen via cine-substitution processes. There are, however, major differences in the reaction patterns. Thus, 1-methyl- and 1-*t*-butyl-3,4-dinitropyrroles (**181a** and **181b**) react with methoxide ion in methanol to give first the isolable *trans*-4,5-dimethoxy-3-nitro-1-alkyl-2-pyrrolines **182**.[149,150] However, the exact sequence leading to **182** has not been established. The pyrrolines **182** can eliminate a methanol molecule in different



Scheme 5.23.

ways, which are shown in Scheme 5.23.[150] In acidic medium in methanol, the elimination occurs via an E_1 pathway, where the initial protonation of the pyrroline is followed by departure of a molecule of methanol and finally by loss of H^+. Pyrrolenium cations such as **183** and **184** are known to be intermediates of some stability. The elimination is regiospecific in the case of **181a**, where only **185a**, the product of cine substitution, is obtained. It is highly regiospecific in the case of **181b**, where a small amount of **186b**, the product of formal S_NAr substitution, is formed in addition to **185b**.[150] The pyrrolines **182** can also lose a molecule of methanol in basic media.[150] In these instances, a regiospecific elimination leading to **186** is observed in both cases. Since the vicinity of the NO_2 group of **182** is expected to increase the acidity of the β-hydrogen atom, an E_1cB mechanism has been suggested for the reactions.[150]

Treatment of **181a** with piperidine and morpholine in acetonitrile at room temperature yields the isolable *trans*-4,5-dipiperidino- and dimorpholinopyrrolines **187**.[151] These behave like their methoxy analogues **182** and undergo regiospecific elimination of an amine molecule to give the cine substitution products **188** in acidic media, and the products of formal direct denitration **189** in basic media (Scheme 5.24).[151,152] The formation of the pyrrolines **187** is not so straightforward, however, since it competes with the reversible ring-opening reaction shown in Scheme 5.24 under certain experimental conditions.



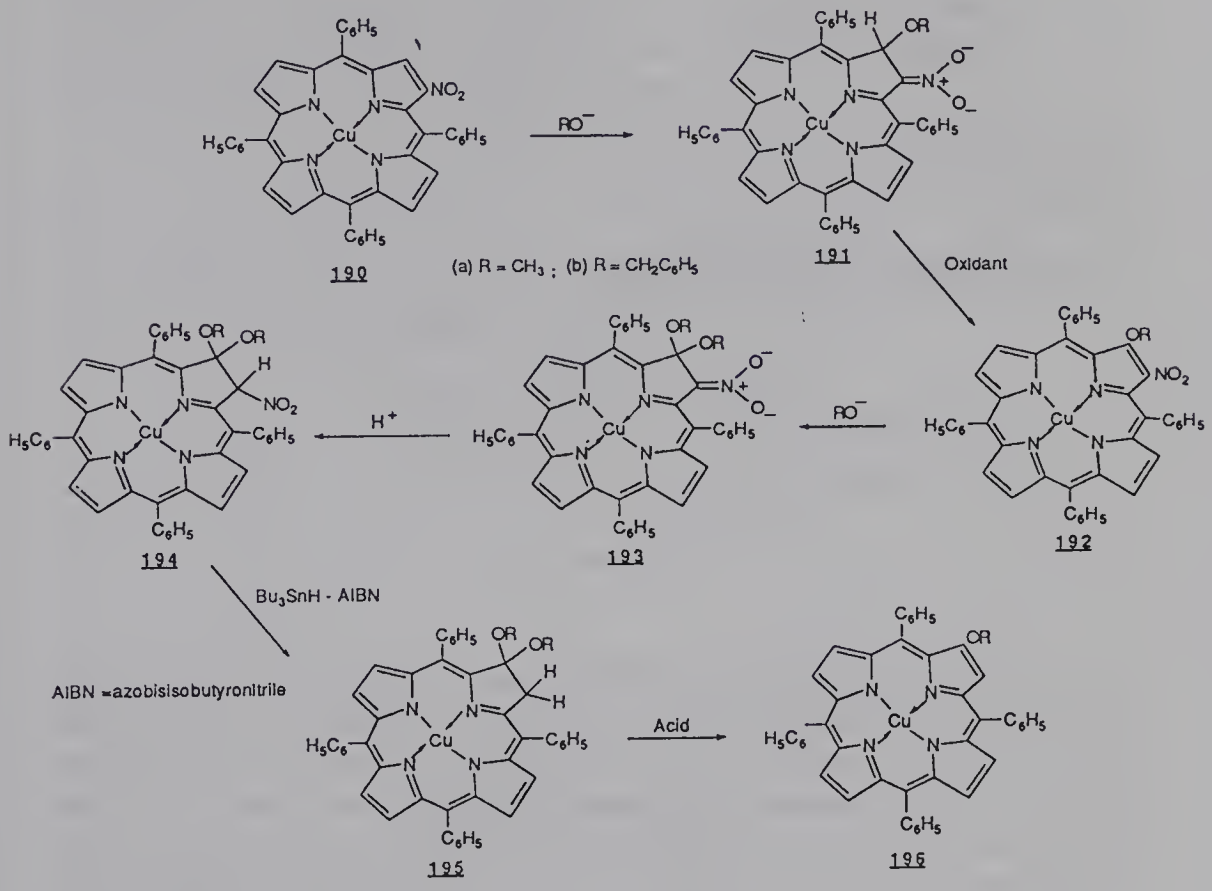
Scheme 5.24.

Ring-opening and ring-closure reactions also occur when 1-alkyl-3,4-dinitropyrroles are treated with primary amines, but, in these instances, the overall reaction sequence leads to products of formal direct substitution of an NO_2 group (i.e., **189**).[152]

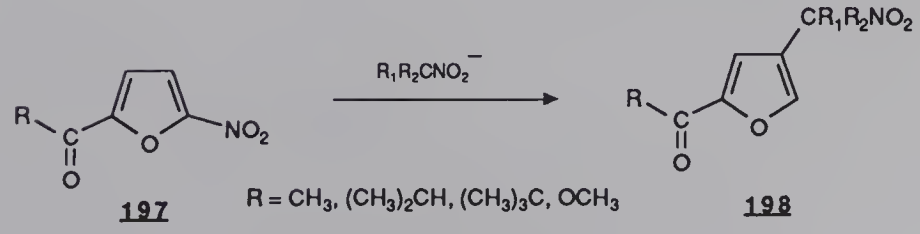
Scheme 5.25 depicts a novel reaction sequence, which accomplishes a cine substitution on a pyrrole ring of a nitroporphyrin and provides an efficient entry to the 2-oxyporphyrin systems. Treatment of (2-nitro-5,10,15,20-tetraphenyl-porphyrinato)copperII (**190**) with sodium methoxide or sodium benzylate in DMF yields initially the Meisenheimer complexes **191**, which are readily oxidized with loss of a hydrogen atom into the 2-alkoxy-3-nitroporphyrins **192**. Further attack by RO^- yields the *gem*-dialkoxy adducts **193**, which undergo C-protonation to give **194**, a reaction that is possible because it does not disrupt the aromaticity in the macrocycle.[153] Reductive denitration of **194** followed by elimination of methanol from **195** affords the alkoxyporphyrins **196**, which are the products of the cine substitution of **190** by CH_3O^- or $C_6H_5CH_2O^-$.

Upon treatment of the 5-acyl or 5-alkoxycarbonyl-2-nitrofurans **197** with salts of secondary nitroalkanes such as 2-nitropropane and nitrocyclopentane, the cine-substitution products **198** are formed in yields of up to 90%. This process, which is the only known example of a cine substitution in the furan series, is unusual in that it does not involve an *o*-dinitro derivative. It is also very specific for carbanions of nitroalkanes (eq. 5-60).[154]

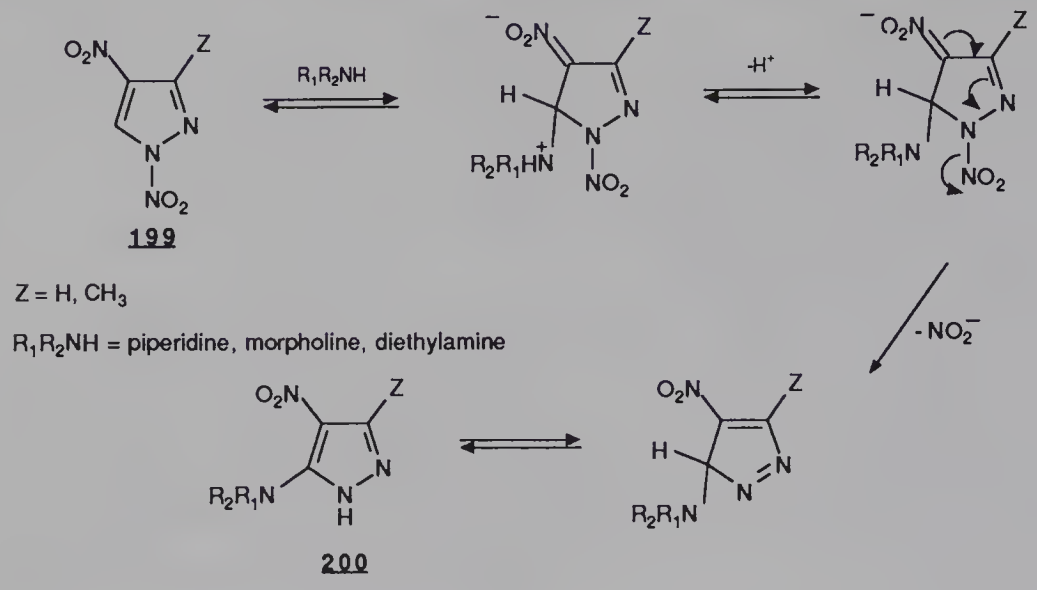
1,4-Dinitropyrazoles (**199**) undergo cine substitutions with secondary



Scheme 5.25.



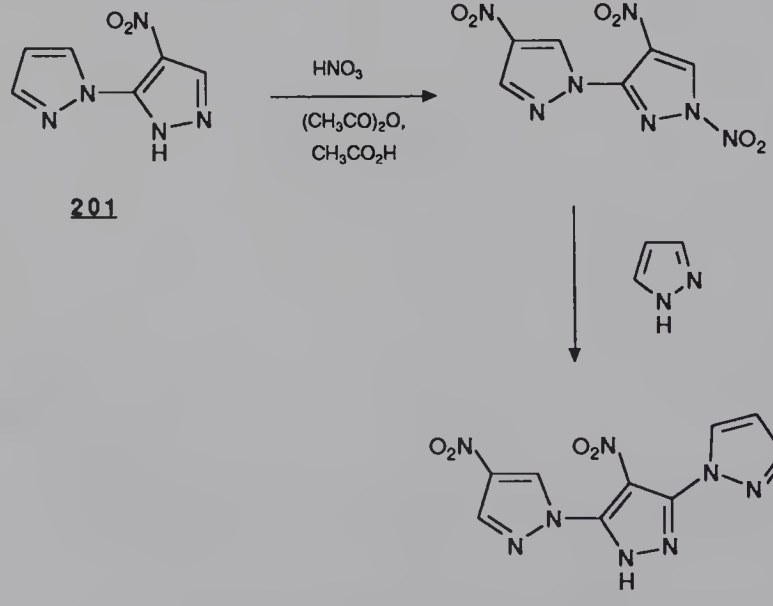
(5-60)



199 200

Scheme 5.26.

amines to give 3(5)-dialkylamino-4-nitropyrazoles (**200**).[155,156] A reasonable mechanism for the reactions is shown in Scheme 5.26. Secondary amines that react in this way include not only classical amines (e.g., morpholine, piperidine, or diethylamine) but also a number of relatively basic pyrazoles. In this case, the cine substitution provides a convenient synthesis of C—N coupled bipyrazoles such as **201**.[157] The tripyrazolyl derivative **202** has also been obtained by nitration of **201** followed by a second cine substitution with

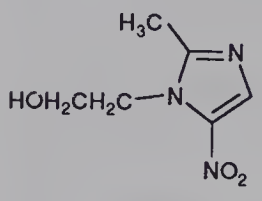


201 202

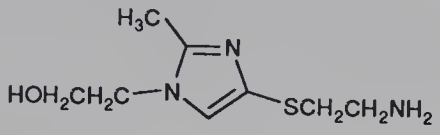
(5-61)

pyrazole (eq. 5-61).[157] Other nucleophiles (e.g., $C_2H_5O^-$, $C_2H_5S^-$, and CN^- ions) also react with 1,4-dinitropyrazoles according to Scheme 5.26. The reaction with CN^- is of special interest, since it has been applied as the key step in a novel and elegant synthesis of formycin.[158]

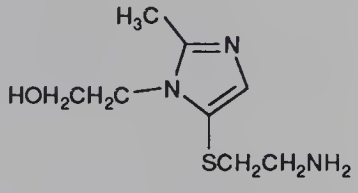
Another simple azole ring that has some tendency to nucleophilic cine substitution is the imidazole ring. The nitroimidazole **203** (metronidazole) reacts in aqueous solution with 2-aminoethanethiol to give 4-[(2-aminoethyl)thio]-2-methylimidazole-1-ethanol (**204**).[159] Depending on the experimental conditions, some of the isomeric thioimidazole **205** is also produced, via a normal S_NAr pathway.[159]



203



204



205

References

1. Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273
2. Buncel, E.; Crampton, M. R.; Strauss, M. J.; Terrier, F. in *"Electron-Deficient Aromatic- and Heteroaromatic-Base Interactions"*; Elsevier: Amsterdam, 1984, p. 433.
3. Miller, J. In *"Aromatic Nucleophilic Substitution"*. Elsevier: London, 1968, p. 372.
4. Chupakhin, O. N.; Postovskii, I. Ya. *Usp. Khim.* **1976**, *45*, 908.
5. Makosza, M. In *"Current Trends in Organic Synthesis"*, Nozaki, H., ed. Pergamon Press, New York, 1983, p. 401.
6. Makosza, M.; Winiarski, J. *Acc. Chem. Res.* **1987**, *20*, 282.
7. Guanti, G.; Thea, S.; Dell'Erba, C. *Tetrahedron Lett.* **1976**, 461.
8. Guanti, G.; Petrillo, G.; Thea, S. *Tetrahedron*, **1982**, *38*, 505.
9. Terrier, F. *Chem. Rev.* **1982**, *82*, 77.
10. Zimmermann, W. Z. *Physiol. Chem.* **1935**, *233*, 257.
11. King, T. J.; Newall, C. E. *J. Chem. Soc.* **1962**, 367.
12. Foster, R.; Mackie, R. K. *Tetrahedron*, **1962**, *18*, 1131.

13. Gitis, S. S.; Kaminskii, A. Ya. *Usp. Khim.* **1978**, *47*, 1970.
14. Strauss, M. J. *Chem. Rev.* **1970**, *70*, 667.
15. (a) Sosonkin, I. M.; Kalb, G. L. *Zh. Org. Khim.* **1974**, *10*, 1333; (b) Sosonkin, I. M. ; Strogov, G. N.; Kaminskii, A. Ya.; Troshin, G. E.; Lakomov, F. L. *ibid.* **1979**, *15*, 1895.
16. (a) Hamana, M.; Iwasaki, G.; Saeki, S. *Heterocycles*, **1982**, *17*, 177; (b) Iwasaki, G.; Hamana, M.; Saeki, S. *ibid.* **1982**, *19*, 162.
17. Iwasaki, G.; Wada, K.; Saeki, S.; Hamana, M. *Heterocycles*, **1984**, *22*, 1811.
18. Richter, H. J.; Rustad, N. E. *J. Org. Chem.* **1964**, *29*, 3381.
19. Pietra, S.; Casiraghi, G. (a) *Gazz. Chim. Ital.* **1966**, *96*, 1630; (b) *ibid.* **1967**, *97*, 1817; (c) *ibid.* **1967**, *97*, 1826.
20. (a) Danikiewicz, W.; Makosza, M. *Tetrahedron Lett.* **1985**, *26*, 3599. (b) Makosza, M.; Jagusztyn-Grochowska, M.; Ludwikov, M. *Tetrahedron*, **1974**, *30*, 3723.
21. Renfrow, R. A.; Strauss, M. J.; Terrier, F. *J. Org. Chem.* **1980**, *45*, 471.
22. Kimura, M.; Kawata, M.; Nakadate, N.; Obi, N.; Kawazoe, A. *Chem. Pharm. Bull.* **1968**, *16*, 634.
23. Kaminskii, A. Ya.; Gitis, S. S. *Zh. Obshch. Khim.* **1964**, *34*, 3743.
24. Kimura, M.; Obi, N.; Kawazoi, M. *Chem. Pharm. Bull.* **1972**, *20*, 452.
25. Taylor, R. P. *J. Org. Chem.* 1970, 35, 3578
26. Wennerström, O. (a) *Acta Chem. Scand.* **1971**, *25*, 789; (b) *ibid.* **1971**, *25*, 2341.
27. Bjorklund, C.; Nilsson, M.; Wennerström, O. *Acta Chem. Scand.* **1970**, *24*, 3599.
28. Möberg, C.; Wennerström, O. (a) *Acta Chem. Scand.* **1971**, *25*, 2871; (b) *ibid.* **1971**, *25*, 2355.
29. Hallé, J. C.; Pouet, M. J.; Simonnin, M. P.; Terrier, F. *Tetrahedron Lett.* **1985**, *26*, 1307.
30. Pinson, J.; Armand, J.; Boulares, L.; Hallé, J. C.; Terrier, F. Unpublished results.
31. Stahly, G. B. *J. Org. Chem.* **1985**, *50*, 3091.
32. Buncel, E.; Murarka, S. K.; Norris, A. R. *Can. J. Chem.* **1984**, *62*, 534.
33. Shein, S. M.; Byval'kevich, O. G.; Khmelinskaya, A. D. *Zh. Org. Khim.* **1976**, *12*, 134.
34. Buncel, E.; Renfrow, R. A.; Strauss, M. J. *J. Org. Chem.* **1987**, *52*, 488.
35. Guthrie, R. D.; Nutter, D. E. *J. Am. Chem. Soc.* **1982**, *104*, 7478.
36. Buncel, E.; Norris, A. R.; Proudlock, W. *Can. J. Chem.* **1968**, *46*, 2759.

37. Vickery, B. *Chem. Ind.* **1967**, *36*, 1523.
38. Lobry de Bruyn, M. C. A. (a) *Recl. Trav. Chim. Pays-Bas*, **1883**, *2*, 105; (b) *ibid.* **1904**, *23*, 47.
39. Blanksma, J. J. *Recl. Trav. Chim. Pays-Bas*, **1902**, *21*, 424.
40. Momose, T.; Okhura, Y.; Shiota, J. *Chem. Pharm. Bull.* **1968**, *16*, 2370.
41. Okhura, Y.; Murakami, J.; Shiota, J.; Momose, T. *Chem. Pharm. Bull.* **1970**, *18*, 2164.
42. Huisgen, R. *Ann. Chem.* **1948**, *559*, 101.
43. (a) Okamoto, T.; Takahashi, H. *Chem. Pharm. Bull.* **1968**, *16*, 1700; (b) Okamoto, T.; Takahashi, H.; Takayama, H.; Kitagawa, T.; Ikeda, M. *ibid.* **1969**, *17*, 140; (c) Takahashi, H. ; Otomasu, H. *ibid.* **1970**, *18*, 22.
44. (a) Tomioka, Y.; Mochiike, A.; Himeno, J.; Yamazaki, M. *Chem. Pharm. Bull.* **1981**, *29*, 1286 ; (b) Tomioka, Y.; Miyake, J.; Yamazaki, M. *ibid.* **1982**, *30*, 851.
45. Tomioka, Y.; Ohkubo, K.; Yamazaki, M. *Chem. Pharm. Bull.* **1985**, *33*, 1360.
46. Landolt, R. G.; Snyder, H. R. *J. Org. Chem.* **1968**, *33*, 403.
47. Chapas, R. B.; Knudsen, R. D.; Nystrom, R. F.; Snyder, H. R. *J. Org. Chem.* **1975**, *40*, 3746.
48. Gorvin, J. H. *J. Chem. Soc., Chem. Commun.* **1971**, 1120.
49. (a) Wohl, A. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 3486. (b) Wohl, A.; Aue, W. *ibid.* **1901**, *34*, 2442.
50. Bernasconi, C. F. *Pure Appl. Chem.* **1982**, *54*, 2335.
51. Jones, J. R. "*The Ionization of Carbon Acids*". Academic Press: London and New York, 1973.
52. Zoltewicz, J. A.; Helmick, L. S.; Oestreich, T. M.; King, R. W.; Kandetzki, P. E. *J. Org. Chem.* **1973**, *38*, 1947.
53. Illuminati, G.; Stegel, F. *Adv. Heterocycl. Chem.* **1983**, *34*, 306.
54. Tondys, H.; Van der Plas, H. C. *J. Heterocycl. Chem.* **1986**, *23*, 621.
55. Tondys, H.; Van der Plas, H. C.; Wozniak, M. *J. Heterocycl. Chem.* **1985**, *22*, 353.
56. Pozharskii, A. F.; Simonov, A. M.; Doron'kin, V. N. *Usp. Khim.* **1978**, *47*, 1933.
57. Bradley, W.; Robinson, R. *J. Chem. Soc.* **1932**, 1254.
58. Levitt, L. S.; Levitt, B. W. *Chem. Ind.* **1975**, 520.
59. Gandhi, S. S.; Gibson, M. S.; Kaldas, M. L.; Vines, S.M. *J. Org. Chem.* **1979**, *44*, 4705.
60. De Montmollin, G.; De Montmollin, M. *Helv. Chim. Acta* **1923**, *9*, 94.

61. Huisgen, R.; Rist, H. *Ann. Chem.* **1955**, *594*, 159.
62. Bergstrom, F. W.; Granara, I. M.; Erickson, V. *J. Org. Chem.* **1942**, *7*, 98.
63. Konieczny, M. T.; Ledochowski, A.; Sowinski, P. *Pol. J. Chem.* **1979**, *53*, 1541.
64. Konieczny, M. T.; Ledochowski, A. *Pol. J. Chem.* **1980**, *54*, 2233.
65. Wohl, A. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 4135.
66. (a) Onysko, P. P.; Gololobov, Yu. G. *Zh. Obshch. Khim.* **1979**, *49*, 39; (b) Onysko, P. P.; Kashukhin, L. F.; Gololobov, Yu. G. *ibid.* **1978**, *48*, 342.
67. Reznick, A.; Strauss, M.J. *Tetrahedron Lett.* **1970**, 4439.
68. Kalinkin, M. J.; Parnes, Z. N.; Puzanova, V. E.; Khmelinskaya, A. D.; Shein, S. M.; Kursanov, D. N. *Zh. Org. Khim.* **1973**, *9*, 2354.
69. Kimura, M. J. *Pharm. Soc. Japan* **1953**, *73*, 1219.
70. (a) Nilsson, M.; Ullenius, C.; Wennerström, O. *Tetrahedron Lett.* **1971**, 2713; (b) Buncel, E.; Murarka, S. K.; Onyido, I. *Gazz. Chim. Ital.* **1988**, *118*, 25.
71. Bard, R. R.; Strauss, M. J. *J. Org. Chem.* **1977**, *42*, 435.
72. (a) Wozniak, M.; Van der Plas, H. C.; Tormula, M.; Van Veldhuizen, A. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 511. (b) Wozniak, M.; Van der Plas, H. C.; Van Veldhuizen, B. *J. Heterocycl. Chem.* **1983**, *20*, 9.
73. Van der Plas, H. C.; Charuskin, V. N.; Van Veldhuizen, B. *J. Org. Chem.* **1983**, *48*, 1354.
74. Nazel, A.; Van der Plas, H. C.; Van Veldhuizen, B. *Recl. Trav. Chim. Pays-Bas*, **1975**, *94*, 95.
75. Counotte-Potman, A. D.; Van der Plas, H. C.; Van Veldhuizen, B. *J. Org. Chem.* **1981**, *46*, 2138, 3805.
76. Oostveen, E. A.; Van der Plas, H. C.; Jougejan, H. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 114.
77. (a) Rajanbabu, T. V.; Fukunaga, T. *J. Org. Chem.* **1984**, *49*, 4571; (b) Rajanbabu, T. V.; Reddy, G. S.; Fukunaga, T. *J. Am. Chem. Soc.* **1985**, *107*, 5473.
78. Rajanbabu, T. V.; Chenard, B. L.; Petti, M. A. *J. Org. Chem.* **1986**, *51*, 1704.
79. Bartoli, G.; Rosini, G. *Synthesis* **1976**, 270.
80. Bartoli, G. *Acc. Chem. Res.* **1984**, *17*, 109.
81. Bartoli, G.; Bosco, M.; Baccolini, G. *J. Org. Chem.* **1980**, *45*, 522.
82. Kienzle, F. *Helv. Chim. Acta* **1978**, *61*, 449.

83. Armilleta, N.; Bartoli, G.; Bosco, M.; Dalpozzo, R. *Synthesis*, **1982**, 836.
84. Bartoli, G.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* **1985**, *26*, 115.
85. Ballini, R.; Bartoli, G.; Bosco, M.; Dalpozzo, R.; Marcantoni, E. *Tetrahedron*, **1988**, *44*, 6435.
86. Bartoli, G.; Bosco, M.; Foresti, E.; Pradella, G. *J. Org. Chem.* **1981**, *46*, 3109.
87. Bartoli, G.; Bosco, M. *Synthesis*, **1980**, 616.
88. Baccolini, G.; Bartoli, G.; Bosco, M.; Dalpozzo, R. *J. Chem. Soc., Perkin Trans. 2*, **1984**, 363.
89. Bartoli, G.; Bosco, M.; Dalpozo, R.; Ciminale, F. *J. Am. Chem. Soc.* **1982**, *47*, 5227.
90. Bartoli, G.; Dalpozzo, R.; Grossi, L.; Todesco, P. E. *Tetrahedron*, **1986**, *42*, 2563.
91. Bartoli, G.; Dalpozzo, R.; Grossi, L. *J. Chem. Soc., Perkin Trans. 2*, **1989**, 573.
92. Meisenheimer, J.; Patzig, E. *Chem. Ber.* **1906**, *39*, 2533.
93. Gitis, S. S.; Glaz, A. I.; Grigores, V. V.; Kaminskii, A. Ya.; Martymenko, A. S.; Sankov, P. I. *Zh. Org. Khim.* **1967**, *3*, 1617.
94. Hasegawa, M.; Okamoto, T. *Yakugaku Zasshi*, **1973**, *93*, 1019, 1024.
95. Golinski, J.; Makosza, M. *Tetrahedron Lett.* **1978**, 3495.
96. Makosza, M.; Glinka, T. *J. Org. Chem.* **1983**, *48*, 3860.
97. Makosza, M.; Golinski, J.; Baran, J. *J. Org. Chem.* **1984**, *49*, 1488.
98. Makosza, M.; Glinka, T.; Kinowski, A. *Tetrahedron*, **1984**, *40*, 1863.
99. Makosza, M.; Ludwiczak, S. *J. Org. Chem.* **1984**, *49*, 4562.
100. (a) Makosza, M.; Danikiewicz, W.; Wojciechowski, K. *Justus Liebigs Ann.* Chem. **1987**, 711; (b) Makosza, M.; Chylinska, B.; Mudryk, B. *Ibid.* **1984**, 8; (c) Makosza, M.; Kinowski, A.; Danikiewicz, W.; Mudryk, B. *ibid.* **1986**, 69.
101. Makosza, M.; Golinski, J.; Rykowski, A. *Tetrahedron Lett.* **1983**, *23*, 3277.
102. (a) Makosza, M.; Slomka, E. *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1984**, *32*, 69; (b) Bernard, M. K.; Szoja, C.; Wrzeciono, U. *Justus Liebigs Ann. Chem.* **1990**, 755.
103. Makosza, M.; Ludwickzak, S. *Synthesis*, **1986**, 50.
104. (a) Makosza, M.; Golinski, J.; Pankowski, J. *Synthesis*, **1983**, 40; (b) Makosza, M.; Golinski, J. *ibid.*, **1983**, 1023.
105. Traynelis, V. J.; McSweeney, J. V. *J. Org. Chem.* **1966**, *31*, 243.
106. Metzger, H.; Konig, H.; Seelert, K. *Tetrahedron Lett.* **1964**, *867*,

107. Russell, G. A.; Weiner, S. A. *J. Org. Chem.* **1966**, *31*, 248.
108. Makosza, M.; Winiarski, J. (a) *J. Org. Chem.* **1980**, *45*, 1534; (b) *ibid.* **1984**, *49*, 1494.
109. Stahly, G. P.; Stahly, B. C.; Lilje, K. C. *J. Org. Chem.* **1984**, *49*, 578.
110. Stahly, G. P.; Stahly, B. C.; Maloney, J. R. *J. Org. Chem.* **1988**, *53*, 690.
111. Tanaka, A.; Usui, T. *J. Heterocycl. Chem.* **1979**, *16*, 1.
112. Makosza, M.; Winiarski, J. *J. Org. Chem.* **1984**, *49*, 5272.
113. Makosza, M.; Golinski, *J. Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 451.
114. Makosza, M.; Owczarczyk, Z. *J. Org. Chem.* **1989**, *54*, 5094.
115. Makosza, M.; Wojciechowski, K. *Tetrahedron Lett.* **1984**, *25*, 4791.
116. Wojciechowski, K.; Makosza, M. *Tetrahedron Lett.* **1984**, *25*, 4793.
117. (a) Katritzky, A. R.; Laurenzo, K. S. *J. Org. Chem.* **1986**, *51*, 5039; (b) Katritzky, A. R.; Laurenzo, K. S. *ibid.* **1988**, *53*, 3978; (c) Makosza, M.; Sienkiewicz, K. *Ibid.* **1990**, *55*, 4979.
118. Loudon, J. D.; Smith, D. M. *J. Chem. Soc.* **1964**, 2806.
119. Kliegl, A.; Holle, W. *Chem. Ber.* **1926**, *59*, 901.
120. Norris, R. K.; Smyth-King, R. J. *Aust. J. Chem.* **1979**, *32*, 1949.
121. IUPAC Glossary of Terms Used in Physical Organic Chemistry, *Pure Appl. Chem.* **1983**, *55*, 1281.
122. Von Richter, V. (a) *Chem. Ber.* **1871**, *4*, 21, 459, 553; (b) *ibid.* **1874**, *7*, 1145; (c) *ibid.* **1875**, *8*, 1418.
123. (a) Bunnett, J. F.; Cormack, J. F.; Mc Kay, F. C. *J. Org. Chem.* **1950**, *15*, 481; (b) Bunnett, J. F.; Rauhut, M. M.; Knutson, D.; Bussell, G. E. *J. Am. Chem. Soc.* **1954**, *76*, 5755; (c) Bunnett, J. F.; Rauhut, M. M. *J. Org. Chem.* **1956**, *21*, 939, 944.
124. Rosenblum, M. *J. Am. Chem. Soc.* **1960**, *82*, 3796.
125. Samuel, D. *J. Chem. Soc.* **1960**, 1318.
126. Cullen, E.; L'Ecuyer, P. *Can. J. Chem.* **1961**, *39*, 862, and references therein.
127. Ibne-Rasa, K. M.; Koubek, E. *J. Org. Chem.* **1963**, *28*, 3240.
128. March, J. in "*Advanced Organic Chemistry*". McGraw Hill, New York, 1977, p. 612.
129. Rogers, G. T.; Ulbricht, J. L. V. *Tetrahedron Lett.* **1968**, 1029.
130. (a) Tomitori, E.; Okamoto, T.; Ido, T. *Yakugaku Zasshi* **1983**, 103, 601; (b) Tomitori , E. ; Okamoto, T. *ibid.* **1984**, *104*, 1122.
131. (a) Morrison, D. C. *J. Org. Chem.* **1962**, *27*, 296; (b) Morrison, D. C. U.S. Pat. 3,294,838 (1966); *Chem. Abstr.* **1967**, *66*, 55277p; (c) U. S. Pat. 3,177,241 (1965); *Chem. Abstr.* **1965**, *62*, 1614c.

132. Nasielski-Hinkens, R.; Pauwels, D.; Nasielski, J. *Tetrahedron Lett.* **1978**, 2125.

133. Guanti, G. ; Thea, S. ; Novi, M. ; Dell'Erba, C. *Tetrahedron Lett.* **1977**, 1429.

134. Novi, M.; Guanti, G.; Thea, S.; Sancassan, F.; Calabro, D. *Tetrahedron*, **1979**, *35*, 1783.

135. Novi, M.; Dell'Erba, C.; Sancassan, F. *J. Chem. Soc., Perkin Trans. 1*, **1983**, 1145.

136. Novi, M.; Guanti, G.; Dell'Erba, C.; Calabro, D.; Petrillo, G. *Tetrahedron*, **1980**, *36*, 1879.

137. Self, D. P.; West, D. E.; Stillings, M. R. *J. Chem. Soc., Chem. Commun.* **1980**, 281.

138. Bunnett, J. F.; Sekiguchi, S.; Smith, L. A. *J. Am. Chem. Soc.* **1981**, *103*, 4865.

139. Barnett, K. G.; Dickens, J. P.; West, D. E. *J. Chem. Soc., Chem. Commun.* **1976**, 849.

140. Markwell, R. E. *J. Chem. Soc., Chem. Commun.* **1979**, 428.

141. Dell'erba, C.; Spinelli, D.; Leandri, G. *Gazz. Chim. Ital.* **1969**, *99*, 535.

142. Novi, M.; Guanti, G.; Sancassan, F.; Dell'Erba, C. *J. Chem. Soc., Perkin Trans. 1*, **1978**, 1140.

143. Novi, M.; Guanti, G.; Dell'Erba, C.; Spinelli, D. *J. Chem. Soc., Perkin Trans. 1*, **1976**, 2264.

144. Dell'Erba, C.; Spinelli, D.; Leandri, G. *J. Chem. Soc., Chem. Commun.* **1969**, 549.

145. Magnoli, A.; Dell'Erba, C.; Guanti, G.; Novi, M. *J. Chem. Soc., Perkin Trans. 2*, **1980**, 1764.

146. Magnoli, A.; Novi, M.; Guanti, G.; Dell'Erba, C. *Cryst. Struct. Commun.* **1978**, 7, 703.

147. Novi, M.; Sancassan, F.; Guanti, G.; Dell'Erba, C. *J. Chem. Soc., Chem. Commun.* **1976**, 303.

148. Petrillo, G.; Novi, M.; Garbarino, G.; Dell'erba, C.; Magnoli, A. *J. Chem. Soc., Perkin Trans. 2*, **1985**, 1291.

149. Mencarelli, P.; Stegel, F. *J. Chem. Soc., Chem. Commun.* **1978**, 564.

150. Bonaccina, L.; Mencarelli, P.; Stegel, F. *J. Org. Chem.* **1979**, *44*, 4420.

151. Mencarelli, P.; Stegel, F. *J. Chem. Soc., Chem. Commun.* **1980**, *123*,

152. Devincenzis, G.; Mencarelli, P.; Stegel, F. *J. Org. Chem.* **1983**, *48*, 162.

153. Catalano, M. M.; Crossley, M. J.; King, L. G. *J. Chem. Soc., Chem. Commun.* **1984**, 1537.

154. Barnes, B. J.; Newcombe, P. J.; Norris, R. K.; Wilson, K. *J. Chem. Soc., Chem. Commun.* **1985**, 1408.

155. Habraken, V. L.; Poels, E. K. *J. Org. Chem.* **1977**, *42*, 2893.

156. Cohen-Fernandes, P.; Erkelens, C.; Van Eendenburg, C. G. M.; Verhoeven, J. J.; Habraken, C. L. *J. Org. Chem.* **1979**, *44*, 4156.

157. Berbee, R. P. M.; Habraken, C. L. *J. Heterocycl. Chem.* **1981**, *18*, 559.

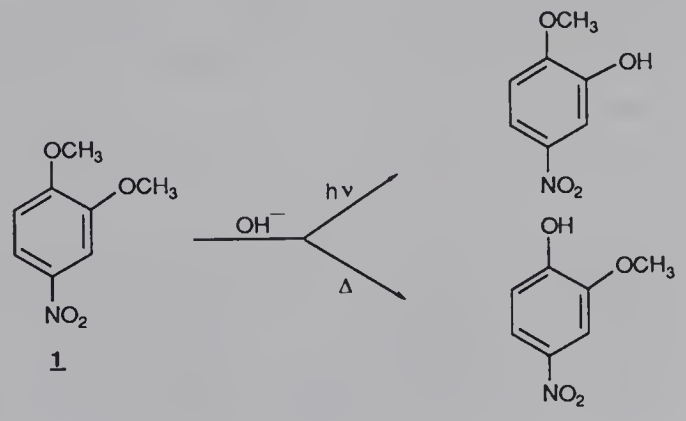
158. Buchanan, J. G. ; Stobie, A.; Wightman, R. H. *Can. J. Chem.* **1980**, *58*, 2624.

159. Goldman, P.; Wuest, J. W. *J. Am. Chem. Soc.* **1981**, *103*, 6224.

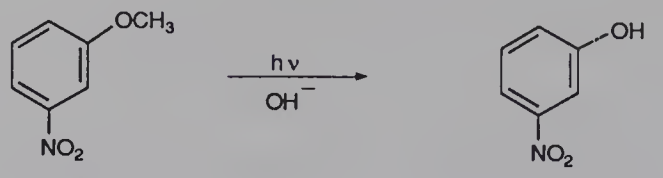
CHAPTER 6. Nucleophilic Aromatic Photosubstitutions

6.1 Introduction and General Features

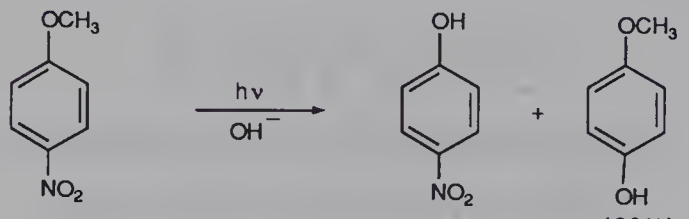
Heterolytic nucleophilic aromatic photosubstitutions were first reported in 1956 when Havinga *et al.* found that light irradiation of aqueous alkaline solutions of nitrophenyl phosphates and sulfates promotes the conversion of these derivatives into the corresponding nitrophenols.[1–5] Subsequent exploratory work revealed that nitrophenyl ethers are similarly susceptible to photosubstitution.[3–15] A remarkable feature, however, was the observation that the NO_2 group exerted a meta-directing effect in the reactions studied, thus contrasting with the specific ortho/para-directing influence of this group in general—also referred to as thermal S_NAr reactions.[3–5] This behavior is shown in eq. 6-1, which compares the thermal and photohydrolysis of 1,2-dimethoxy-



(6-1)



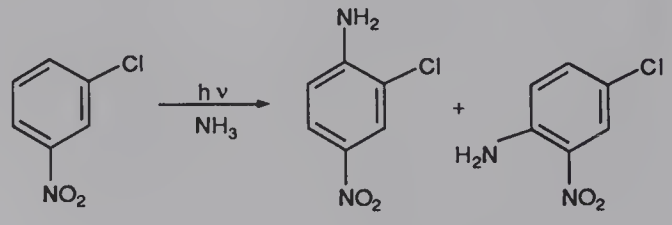
3-NA (6-2)



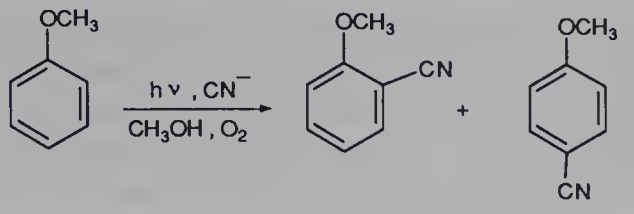
4-NA (20%) (80%) (6-3)

4-nitrobenzene (1) (4-nitroveratrole).[3–5,16] Another illustrative reaction is the photohydrolysis of 3-nitroanisole (3-NA), which essentially does not undergo thermal hydrolysis.[7,8] This reaction proceeds cleanly and with a good quantum yield ($\phi = 0.22$) to give 3-nitrophenol (eq. 6-2). In contrast with that of 3-NA, the methoxy groups of 4-nitro- and 2-nitroanisoles (4-NA and 2-NA) are less readily photohydrolyzed (e.g., $\phi = 0.085$ for 4-NA).[4,11,13] In addition, the reactions give a substantial amount of para- and ortho-methoxyphenols; that is, ipso substitution of the NO_2 group occurs, as shown in eq. 6-3 for the hydrolysis of 4-NA.

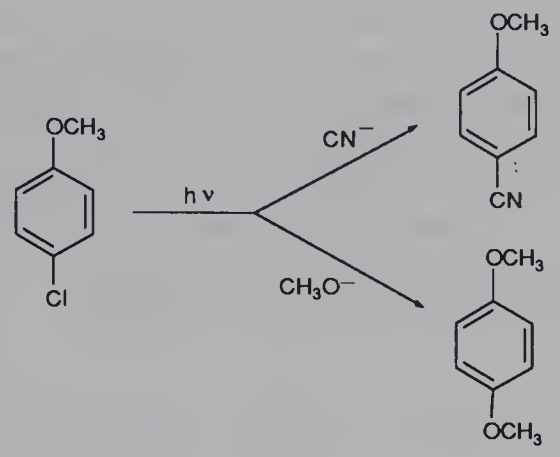
Thorough and systematic investigations of nucleophilic aromatic photosubstitutions have followed the discovery of the unorthodox role of the NO_2 group in the reactions above.[3–5,17] These studies have confirmed that meta activation by electron-withdrawing groups, especially an NO_2 group, is a major feature determining the efficiency and the regioselectivity of many reactions, but they have also revealed the existence of other reactivity patterns. Thus, an increasing number of photosubstitutions have been found in which an electron-withdrawing group exerts the same activating and ortho and/or para-directing effect as it usually does in thermal substitutions.[3–5,17] A typical example is the photoamination of 3-chloronitrobenzene, which does not afford 3-nitroaniline but a mixture of 2-chloro-4-nitro- and 4-chloro-2-nitroanilines (eq. 6-4).[4,5,9] Interestingly, these anilines are formally the products of nucleophilic aromatic substitutions of a hydrogen atom. On the other hand, results have been obtained that showed that a number of aromatic substrates activated by electron-donat-



(6-4)



(6-5)



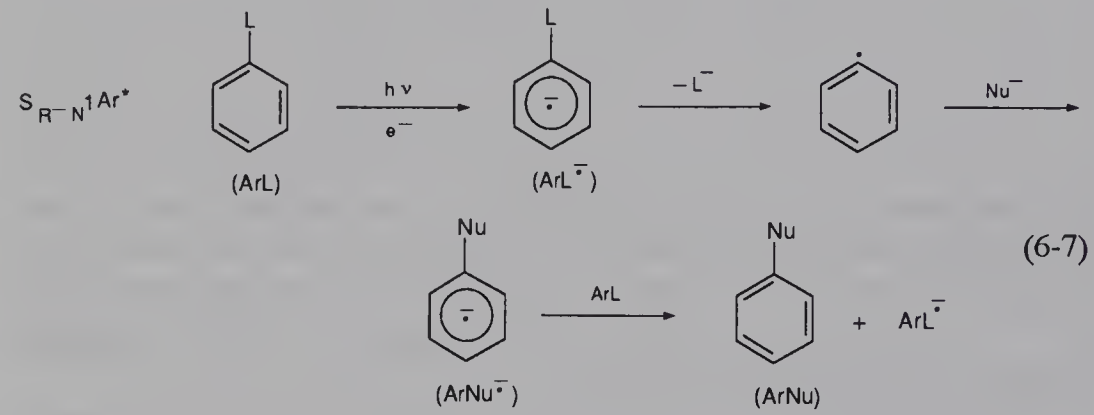
(6-6)

ing substituents (e.g., OH, OCH_3, NR_2) can undergo clean and efficient nucleophilic photosubstitutions.[3–5,17] The reactions of anisole and 4-haloanisoles with CN^- or CH_3O^- illustrate this behavior (eqs. 6-5 and 6-6).[4,5,17–19] The methoxy group behaves as a strong activating and ortho/para-directing substituent in these systems.

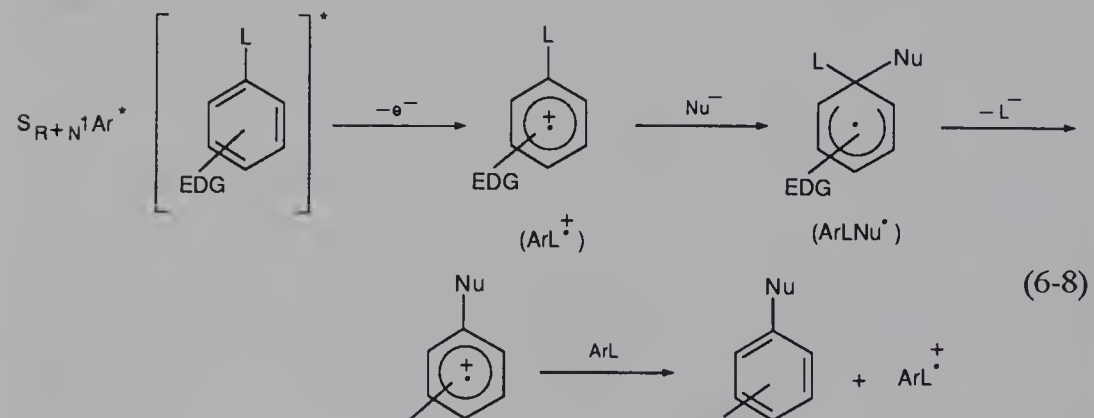
When it became clear in the early 1970s that nucleophilic aromatic photosubstitutions include a variety of phenomena, special attention was directed to the understanding of the substitution patterns. These efforts have led to the recognition that the reactions may proceed by one of the five mechanisms exemplified in eqs. 6-7 to 6-11.[3–5,17,20] The first two mechanisms described in eqs. 6-7 and 6-8(*) are most commonly known as the $S_{RN}1Ar^*$ and $S_{RN}1Ar^*$ mechanisms, respectively.[3,17,20–22] They are not encountered with aromatics activated by strong electron-withdrawing groups like NO_2 groups, however, and therefore they are not discussed in this chapter. Information on these mechanisms is available in a selection of reviews and books.[3,17,21,22]

(*) The chain reaction of eq. 6-8 represents the accepted $S_{RN}1Ar^*$ mechanism when L is a good leaving group (Cl, F, OCH_3). When L is a bad leaving group like hydrogen, the formation of the radical cation of the product ($ArNu^{\bullet+}$) from the neutral radical σ-complex ($ArLNu^{\bullet}$) is not a reasonable step.[17,22] In this case, the formation of the substitution product from $ArLNu^{\bullet}$ is likely to occur in a single step with elimination of $H^{\bullet}$ or in two consecutive steps as an electron and a proton.[17])

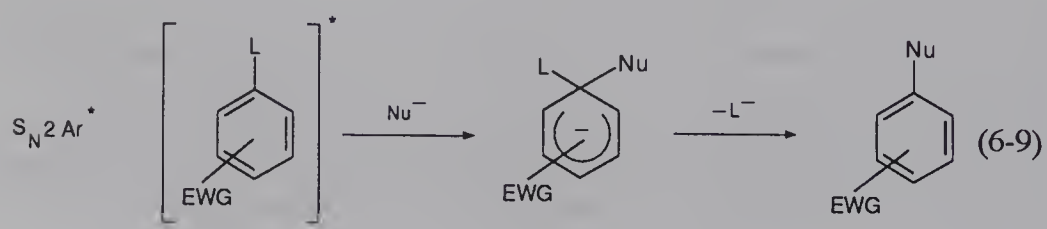
Regarding the other three mechanisms, they all deal with the behavior of nitroaromatics, but it is noteworthy that only in the past few years have they been firmly established.[17,20,23–29] Accordingly, in this chapter, we first draw our attention to the mechanistic aspects of the reactions shown in eqs. 6-9 to 6-11, which describe substitutions now referred to as the S_RN2Ar^*,[17] $S_RN(ET)Ar^*$,[30] and S_RN1Ar^*[17] substitutions. For simplicity, this is accomplished by using some illustrative systems. Then, the relationship between the operative mechanisms and the regioselectivity observed in the photosubstitutions is discussed on the basis of recent theoretical models.[17,20,29] Finally, a few selected reactions are reviewed to emphasize the influence of the structure of the aromatics (simple or fused-ring systems, leaving group, etc.) and the attacking nucleophile on the course of the processes.



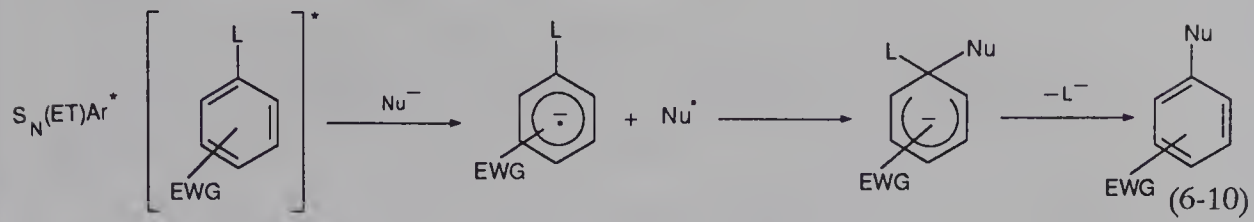
(6-7)



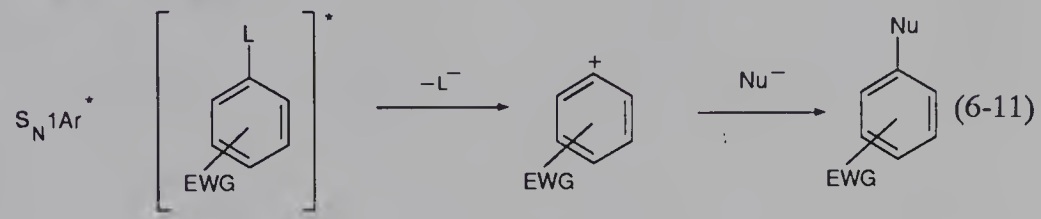
(6-8)



(6-9)



(6-10)



(6-11)

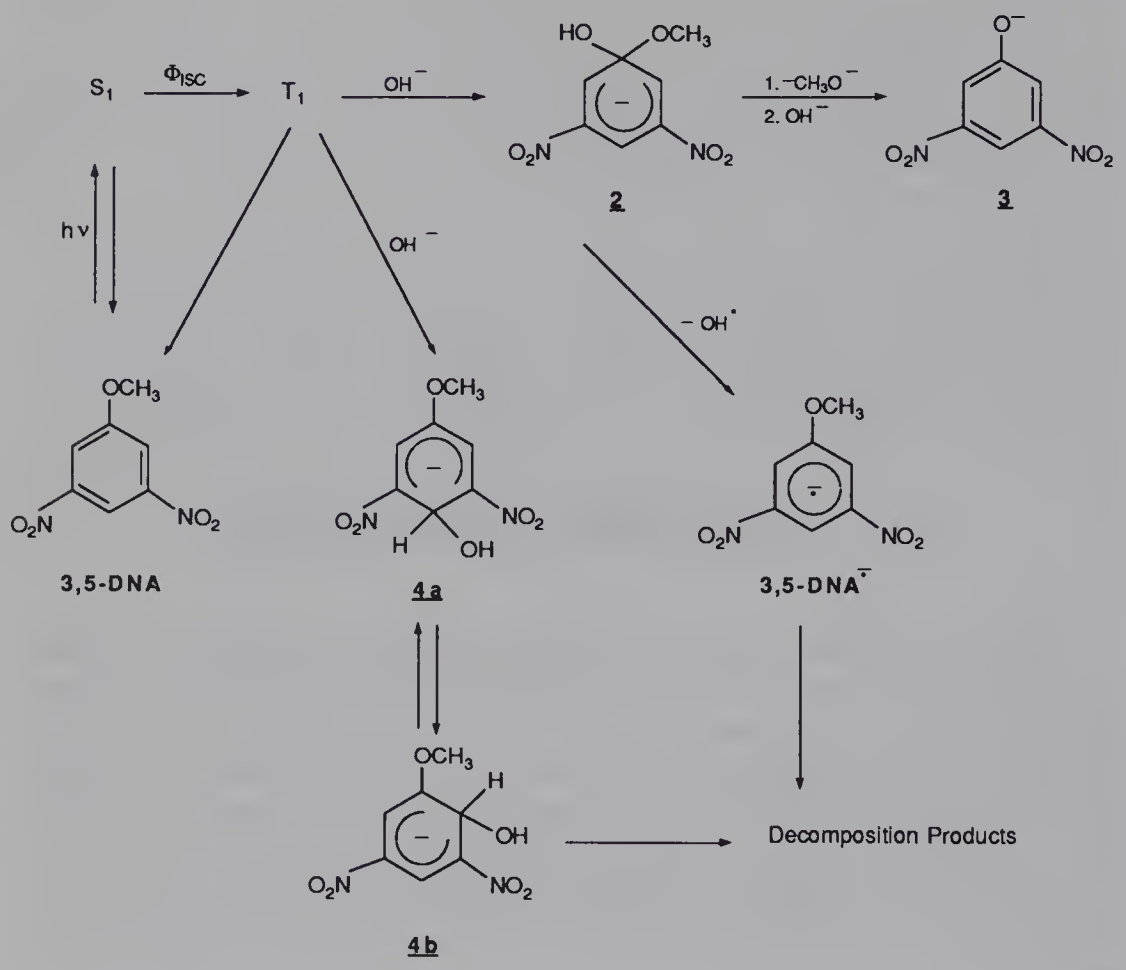
6.2 Reaction Mechanisms

In all nucleophilic aromatic photosubstitutions, the primary step is the excitation of the aromatic molecule, usually in the lowest π-π* singlet or triplet state.[3,5,20] With nitroaromatics, triplet reactions are most commonly encountered, but a few systems in which the reactive excited species is a singlet have been identified.[3,8,31] So far, no clear relationship between the multiplicity of the excited state and the manner in which it reacts with a nucleophile has been established, and the finding that triplet reactions are the most numerous would simply reflect longer lifetimes of triplet than of singlet excited states.[17,31]

6.2.1 The S_N2Ar^* Mechanism

By far the most important mechanism for activated nucleophilic aromatic photosubstitutions is the S_N2Ar^* mechanism of eq. 6-9.[3,5,17,20] As will be pointed out later, this pathway is typical for photosubstitutions involving meta activation by an NO_2 group. It involves addition of the nucleophile to the photostimulated molecule to give a σ-complex that can either revert to the starting materials or decompose to products. Depending on whether the reacting excited state is a triplet or a singlet, this mechanism is denoted by $S_N2^{(3)}Ar^*$ or $S_N2^{(1)}Ar^*$.[17]

Formation of an intermediate σ-complex along the photosubstitution pathway was first suggested in a study of the alkaline photohydrolysis of 3,5-dinitroanisole (3,5-DNA) in a 1:1 water/acetonitrile mixture. The overall



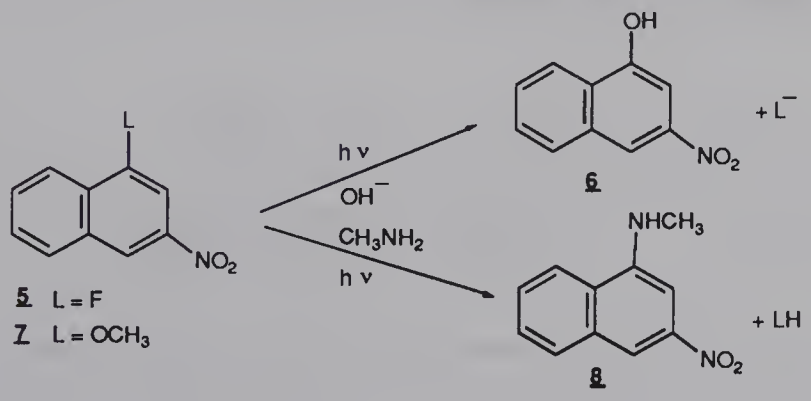
Scheme 6.1.

reaction pathway is shown in Scheme 6.1.[3,5,32] Preliminary sensitization and quenching experiments have revealed that the reaction proceeds via a triplet excited state T_1 with a lifetime of about 20 ns.[32] Subsequently, irradiation experiments have been carried out using a microsecond nitrogen discharge flash as well as a nanosecond laser flash. These studies have shown that the formation of the substitution product (i.e., 3,5-dinitrophenoxide, **3**), is achieved within 10^{-6} s but follows that of two very short-lived species. The first one (λ_{max} = 475 nm) was safely identified as the triplet T_1 on the basis of its lifetime ($t_{1/2} \sim 20$ ns) and the observation that it forms also upon illumination of 3,5-DNA in the absence of base. In contrast, the second species (λ_{max} = 412 nm) forms exclusively in the presence of OH^-, and it has been proposed that it is the σ-complex **2**.[3,5,32] Note that the rapid decomposition of **2** ($t_{1/2} \sim 400$ ns) did not result only in the formation of **3**. Some amount of a relatively

long-lived, purple species (λ_{max} = 550–570 nm) was also formed, apparently in a competitive process. At the time of the experiments, this species, which undergoes slow decomposition to products, was identified as the radical anion of 3,5-DNA.

More elaborate studies of the reaction of 3,5-DNA with OH^- have been made recently.[33,34] These studies have confirmed the view that OH^- addition to the methoxy-bearing carbon C-1 of 3,5-DNA is the rate-limiting step of the photosubstitution, but they have also revealed that the adduct **2** decomposes too rapidly to **3** to be the second transient species identified in the above-mentioned nanosecond laser flash experiments. In fact, this species is more probably the σ-adduct **4a** arising from competitive OH^- addition to the unsubstituted C-4 position of excited 3,5-DNA. Subsequent isomerization of **4a** would occur to give the more stable C-2 adduct **4b** as the species early identified as the radical anion 3,5-DNA$^{\bullet-}$. The reasons for, and the mechanism of, the facile isomerization of C-4 to C-2 complexes in the reactions of 1-Z-3,5-dinitrobenzenes with various nucleophiles were discussed in Chapter 2.

Kinetic studies of a number of systems undergoing clean photosubstitutions are consistent with the reaction pathway proposed for S_N2Ar^* reactions. Representative examples are the photoactivated substitutions of 1-fluoro- and 1-methoxy-3-nitronaphthalenes **5** and **7** with OH^- and methylamine, which proceed with very good quantum yields in 1:1 water/acetonitrile (v/v), to give the naphthol or the *N*-methylamino derivatives **6** and **8** as shown in eq. 6-12.[31]



(6-12)

$$\underline{5} + OH^- \qquad \phi^{-1} = 2.4 + \frac{0.057}{[OH^-]} + \frac{130[TMDD]}{[OH^-]} \qquad (6\text{-}13)$$

$$\underline{5} + CH_3NH_2 \qquad \phi^{-1} = 3.6 + \frac{0.046}{[CH_3NH_2]} \qquad (6\text{-}14)$$

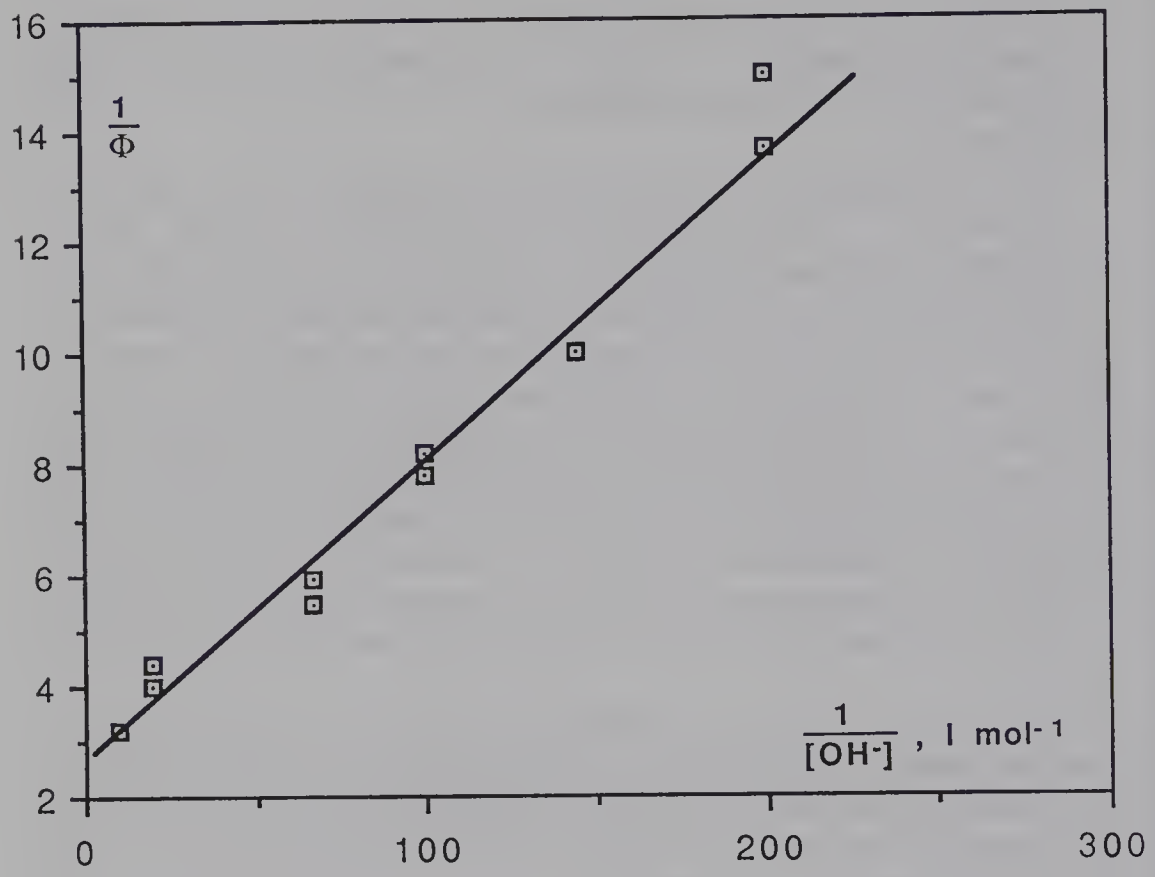


Figure 6.1. Effect of the reciprocal concentration of OH^- on the reciprocal quantum yield for the photohydrolysis of 1-fluoro-3-nitronaphthalene (**5**) in 1:1 (v/v) water/acetonitrile. (Reproduced with permission from ref. 31.)

$$\mathbf{7} + OH^- \qquad \phi^{-1} = 10.0 + \frac{1.84}{[OH^-]} + \frac{70[TMDD]}{[OH^-]} \qquad (6\text{-}15)$$

$$\mathbf{7} + CH_3NH_2 \qquad \phi^{-1} = 10.0 + \frac{1.62}{[CH_3NH_2]} + \frac{40[TMDD]}{[CH_3NH_2]} \qquad (6\text{-}16)$$

As in the case of 3,5-DNA reacting with OH^-, these reactions occur via triplet states.[31] Rate experiments showed that the quantum yields ϕ of the substitutions increase with increasing concentration of OH^- or CH_3NH_2 but decrease with increasing concentration of a typical triplet quencher like 3,3,4,4-tetramethyldiazetine dioxide (TMDD). Plots of $1/\phi$ versus $1/[OH^-]$ or $1/[CH_3NH_2]$ at low to moderate nucleophile concentrations, and of $1/\phi$ versus [TMDD] at constant nucleophile concentrations are linear (Figs. 6.1 and 6.2). Based on the rate data, the reciprocal quantum yields measured for the various reactions (eq. 6-12) are given by eqs. 6-13 to 6-16.[3]

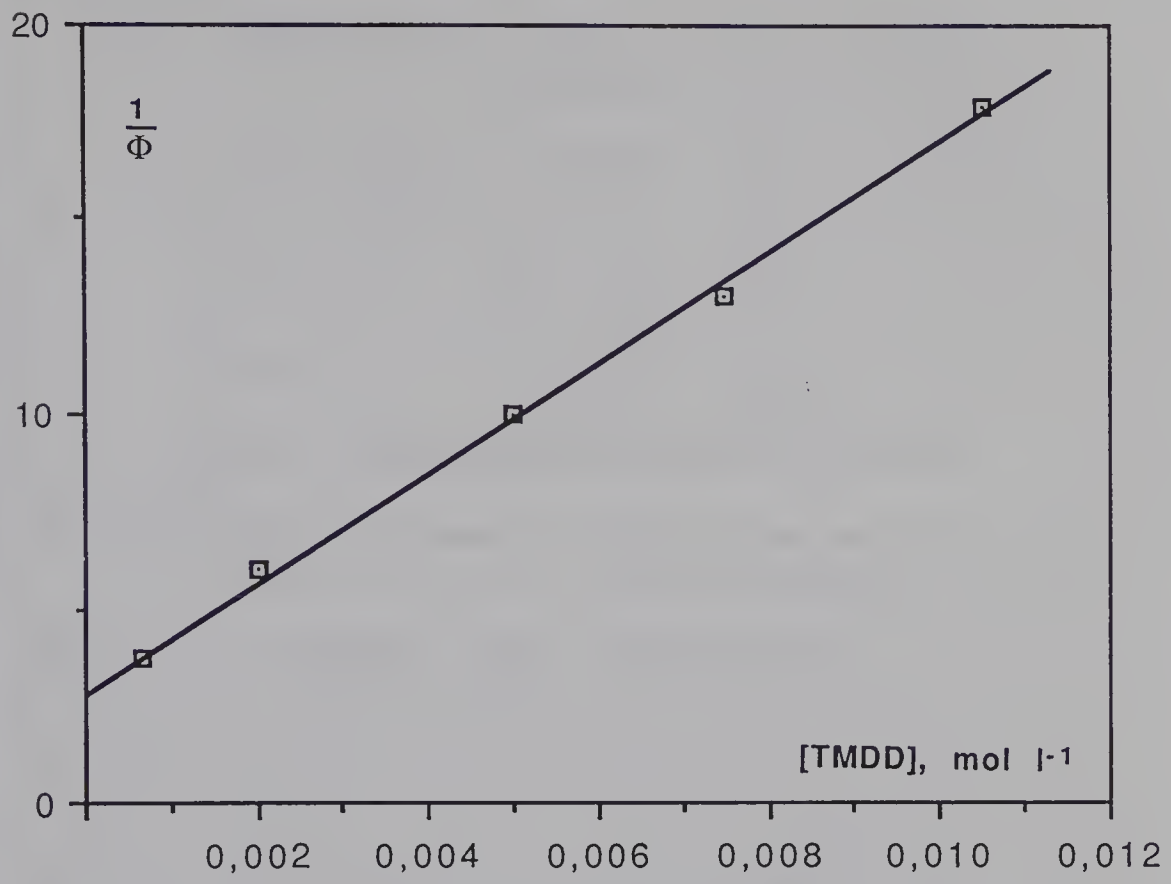
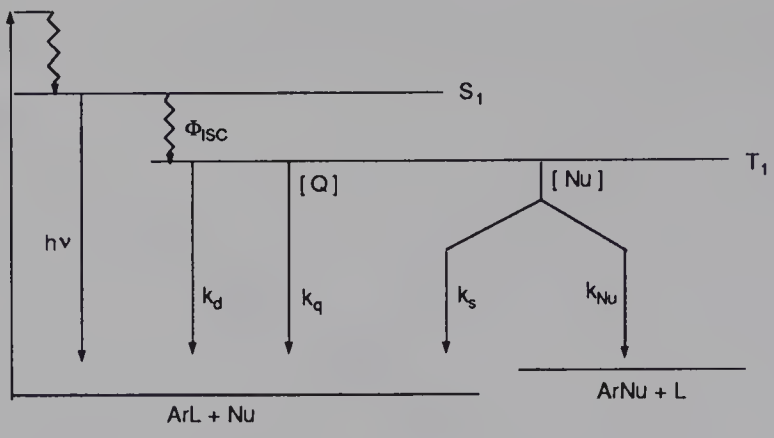


Figure 6.2. Effect of the concentration of 3,3,4,4-tetramethyldiazetine dioxide (TMDD) on the reciprocal quantum yield for the photohydrolysis of 1-fluoro-3-nitronaphthalene (**5**) in 1:1 (v/v) water/acetonitrile containing 0.1 mol l-1 NaOH. (Reproduced with permission from ref. 31.)

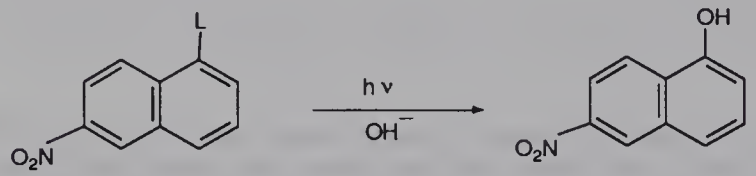
In the presence of a quencher, clean $S_N2^{(3)}Ar^*$ substitutions are expected to involve the various elementary steps depicted in Scheme 6.2.[3,17,31] Based on this scheme, the general expression 6-17 for the reciprocal yield ϕ^{-1} of such substitutions is derived. In eq. 6-17, ϕ_{ISC} represents the intersystem crossing efficiency of the substrate (ArL), whereas the rate constants k_d, k_q, k_s, and k_{Nu} are associated with the various reaction pathways of the triplet state: deactivation to the ground state in a radiative or nonradiative process (k_d), quenching by an added substance Q like TMDD (k_q) or the nucleophile (k_s), and reaction with the nucleophile (k_{Nu}) to form the substitution product (Ar—Nu). Clearly, eqs. 6-13 to 6-16 fit eq. 6-17 very well, supporting the idea that the photosubstitutions of eq. 6-12 are $S_N2^{(3)}Ar^*$ processes. Other representative reactions for which rate data agree well with eq. 6-17 are the photoamination



Scheme 6.2. Schematic representation of a $S_N2^{(3)}Ar^*$ reaction.

of 3-NA,[5] the photocyanation of 2-nitrothiophene,[5,35] and the photohydrolysis of 1-fluoro-6-nitronaphthalene (**9**)[31] (eq. 6-18) and of 3,5-DNA.[32]

$$\phi^{-1} = \phi_{ISC}^{-1}\left[\frac{k_s + k_{Nu}}{k_{Nu}} + \frac{k_d}{k_{Nu}[Nu]} + \frac{k_q[Q]}{k_{Nu}[Nu]}\right] \qquad (6\text{-}17)$$



(6-18)

9 L = F
10 L = OCH_3

Using the most reasonable ϕ_{ISC} values obtained for the naphthalene substrates **5**, **7**, **9**, and assuming that quenching by TMDD is diffusion controlled ($k_q \sim 10^{10}$ l mol^{-1} s^{-1}), the rate constants k_{Nu}, k_s, and k_d of Scheme 6.2 were estimated for reactions 6-12 and 6-18.[31] The results are summarized in Table 6.1. They point to remarkably high rate constants k_{Nu} for the reaction between the triplet excited molecules and the nucleophiles: $k_{Nu} \sim 10^8 - 10^9$ l mol^{-1} s^{-1}. Most importantly, Table 6.1 reveals that it is the compounds with the lowest k_{Nu} values (i.e., the two fluoro derivatives **5** and **9**) that undergo photosubstitution with the highest quantum yields. The reason is that the triplet lifetime is about 10^2 times greater for **5** and **9** ($\tau \sim 2 \times 10^{-7}$ s) than for the methoxy derivative **7**. Thus, it is clear that the lifetime of the excited species plays a predominant role, together with the intersystem crossing efficiency ϕ_{ISC} and the rates of reaction k_{Nu} and k_s, in determining the quantum yield of a nucleophilic photosubstitution.[31] A consequence of this finding is the greater feasibility of the $S_N2^{(3)}Ar^*$ than of the $S_N2^{(1)}Ar^*$ reactions. However, it is of

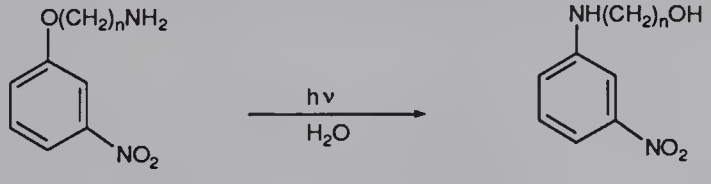
Table 6.1.Rate Constants for the $S_N2(3)Ar^*$ Reactions of Equations 6-12 and 6-18[a]

Aromatic	Nucleophile	ϕISC	k_{Nu} ($l\ mol^{-1}\ s^{-1}$)	k_s ($l\ mol^{-1}\ s^{-1}$)	$\tau = k_d^{-1}$ (s)
5	OH^-	0.8	9.6×10^7	8.8×10^7	2.3×10^{-7}
	CH_3NH_2	0.8	1.2×10^8	2.3×10^8	2.3×10^{-7}
7	OH^-	0.2	7.1×10^8	7.1×10^8	3.8×10^{-9}
	CH_3NH_2	0.2	1.2×10^9	1.2×10^9	2.5×10^{-9}
9	OH^-	0.8	1.0×10^8	1.5×10^8	2.5×10^{-7}

[a]Data from ref. 31.

interest to mention that the photosubstitution of 1-methoxy-6-nitronaphthalene (**10**) with OH^- (eq. 6-18) has been shown to be a singlet reaction.[31]

Compelling kinetic evidence that S_N2Ar^* reactions proceed through intermediate σ-complexes has been obtained by Wubbels and Celander in a very elegant study of the photoinduced Smiles rearrangement of 2-(3-nitrophenoxy)ethylamine (**11a**) into *N*-β-hydroxyethyl-3-nitroaniline (**12a**) (eq. 6-19)—a reaction that is quantitative in aqueous solution and involves a triplet excited state.[23a] These authors found that the quantum yield ϕ for reaction 6-19 is increased when increasing amounts of OH^- are added to the solutions. This behavior is illustrated in Fig. 6.3, which shows that a plot of $1/\phi$ versus $1/[OH^-]$ is linear at high base concentrations. Working at constant pH, but in the presence of various general bases, also enhances ϕ (Table 6.2), indicating that the photoreaction is subject to general base catalysis.



11 (a) n = 2 ; (b) n = 3 ; (c) n = 4 **12** (6-19)

All the observations above are consistent with the mechanisms shown in Scheme 6.3, which are reminiscent of the mechanisms proposed for thermal Smiles rearrangements of similar derivatives (see Chapter 4).[36–40] Intramolecular nucleophilic attack of the amino group takes place in the excited molecule to give the zwitterionic spiro complex ZH, which subsequently decomposes to **12a** via the indicated uncatalyzed and base-catalyzed path-

Table 6.2. Dependence of the Quantum Yield ϕ for Reaction 6-19 (n = 2) on Bases[a]

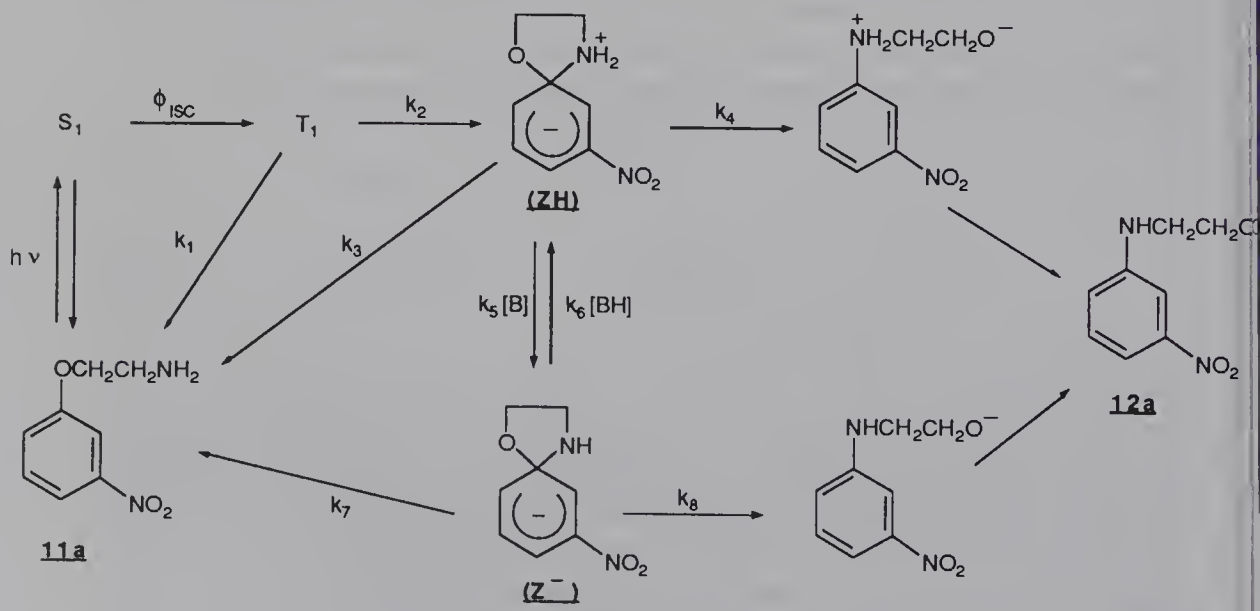
Base B	pK_a^{BH}	[B] (mol/l)	ϕ
None			0.088
CH_3COONa	4.76	0.100	0.103
$NaHCO_3/Na_2CO_3$	6.37 10.25	0.100[b]	0.200
Na_2HPO_4	7.21	0.100	0.206
Morpholine[c]	8.33	0.100	0.152
$HOCH_2CH_2NH_2$[c]	9.50	0.077	0.168

[a]Data from ref. 23a. All reactions conducted at pH 10.04 ± 0.02.

[b]Total carbonate concentration.

[c]Morpholine and ethanolamine may quench the excited state.

ways.[23a,b] Based on Scheme 6.3, the general expression for ϕ in hydroxide solutions was derived by assuming a steady state for each intermediate. Under the conditions of general base catalysis (i.e., $k_6 << k_7 + k_8$), ϕ is given by eq. 6-20, where $f = k_8/k_7 + k_8$ and k_5[B] represents the summation $\Sigma_i k_5^{B_i}[B_i]$ of the individual contributions of the various general bases B_i to the catalysis. On the other hand, the various rate constants are defined as shown in Scheme 6.3 and ϕ_{ISC} is the intersystem crossing quantum yield of **11a**.



Scheme 6.3.

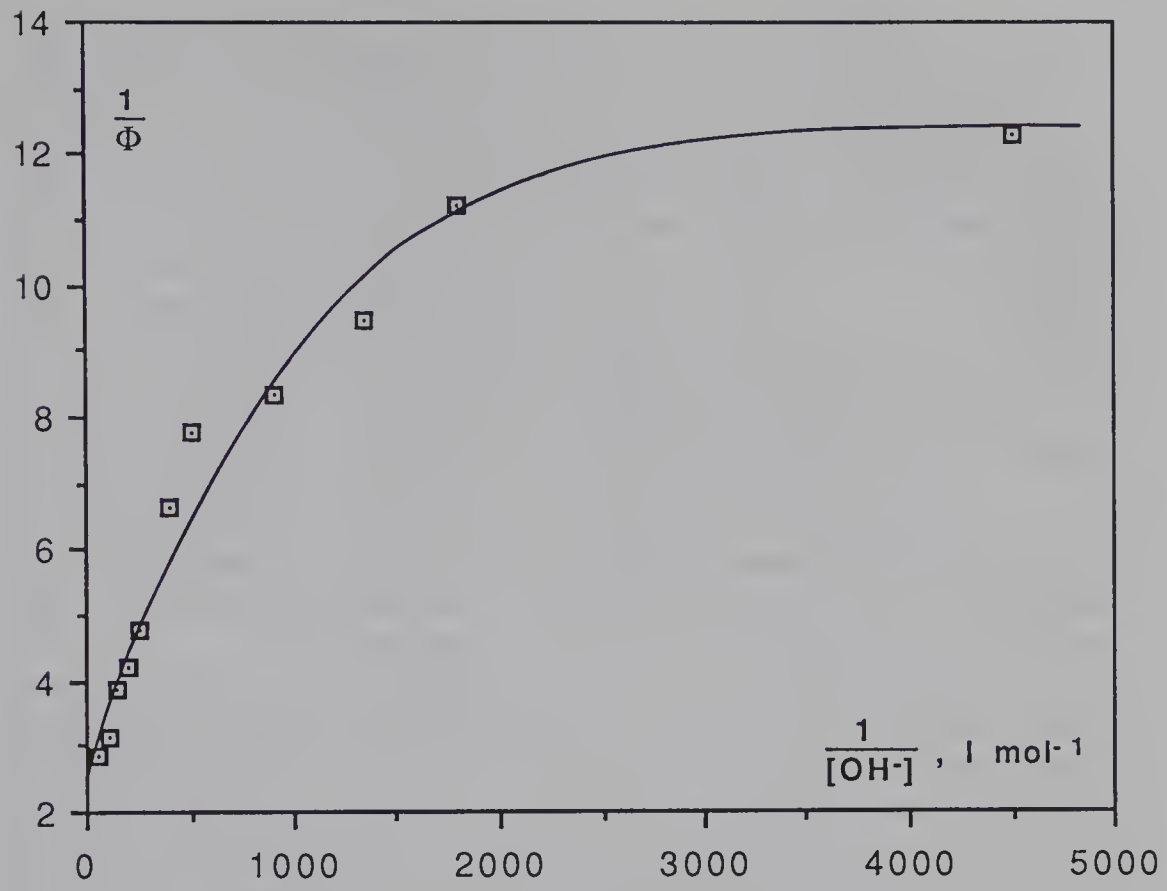


Figure 6.3. Effect of the reciprocal concentration of OH^- on the reciprocal quantum yield for the photo-Smiles rearrangement of 2-(3-nitrophenoxy) ethylamine (**11a**) in aqueous solution. (Reproduced with permission from ref. 23a.)

$$\phi = \phi_{ISC} \frac{k_2}{k_1 + k_2} \frac{k_4 + fk_5[B]}{k_3 + k_4 + k_5[B]} \tag{6-20}$$

$$\frac{1}{\phi} = \frac{1}{\phi_{ISC}}\left(1 + \frac{k_1}{k_2}\right) \frac{k_3 + k_4 + k_5[B]}{k_4 + fk_5[B]} \tag{6-21}$$

$$\frac{1}{\phi} = \frac{1}{\phi_{ISC}}\left(1 + \frac{k_1}{k_2}\right)\left(1 + \frac{k_3}{k_4}\right) \tag{6-22}$$

$$\frac{1}{\phi} = \frac{1}{\phi_{ISC}}\left(1 + \frac{k_1}{k_2}\right)\left(\frac{1}{f} + \frac{k_3 + k_4}{fk_5[B]}\right) \tag{6-23}$$

Inversion of eq. 6-20 yields eq. 6-21, for which two limiting situations may be envisioned: (1) at sufficiently low base concentrations, k_5[B] becomes small relative to k_4, in which case eq. 6-21 reduces to eq. 6-22; and (2) at high base concentrations, k_5[B] becomes large relative to k_4, in which case eq. 6-21 simplifies to eq. 6-23. Obviously, the behavior expected for eqs. 6-22 and 6-23 is reflected in Fig. 6-3,

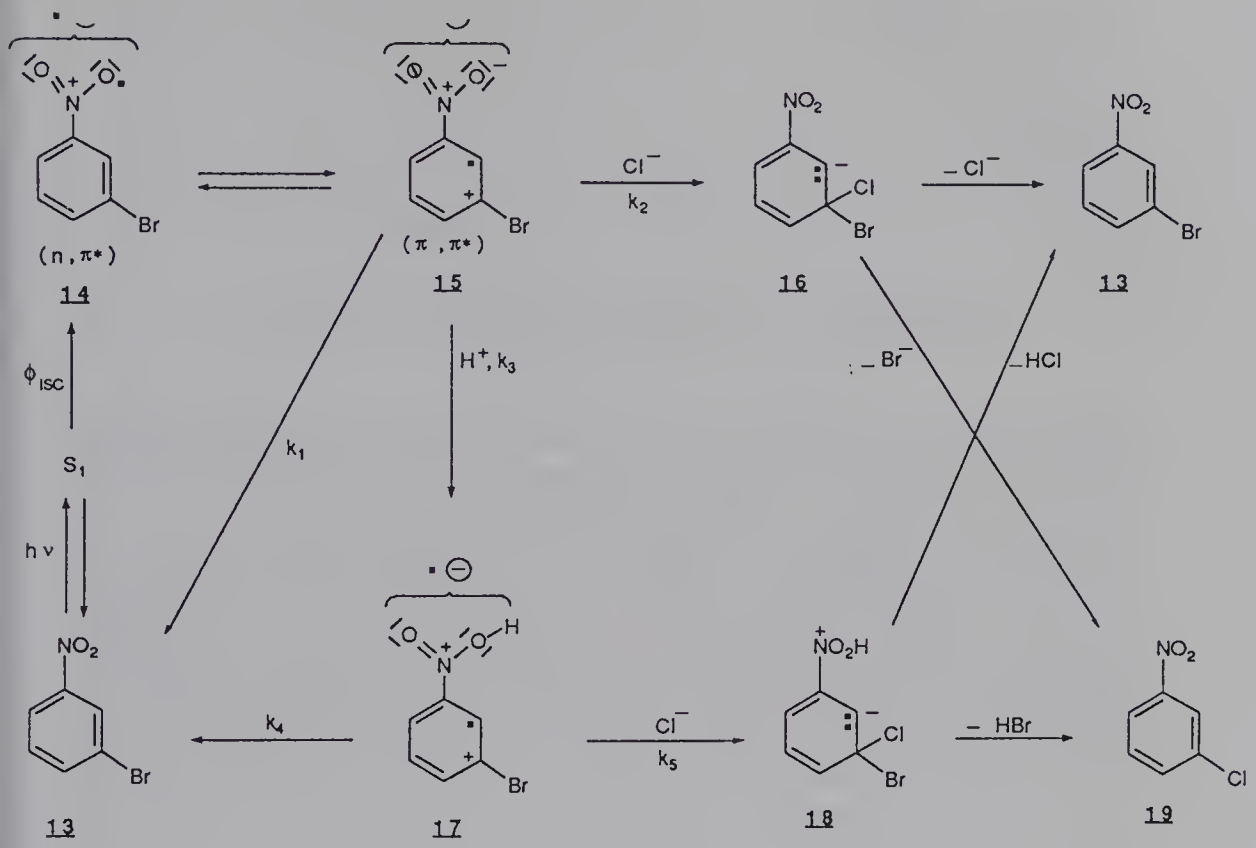
by the lack of dependence of ϕ on OH^- at low concentrations and also by the observed linear dependence of $1/\phi$ on $1/[OH^-]$ at high hydroxide concentrations.

Assuming that k_5 for hydroxide ion is diffusion controlled ($k_5^{OH} = 2 \times 10^{10}$ l mol^{-1} s^{-1}) and that the partitioning factor f is unity (the leaving group abilities of RO^- and $R\text{-}NH^-$ moieties are known to be very different in σ-complex chemistry),[36,37,39,40] the rate constants k_4 and k_3 have been calculated: $k_4 = 1.8 \times 10^7$ s^{-1}; $k_3 = 7.1 \times 10^7$ s^{-1}.[23a] Such high values account well for the nonobservance of base catalysis at low base concentrations, where both k_4 and k_3 are much greater than the k_5[B] term. On the other hand, the rate constant k_5 could be calculated for HPO_4^{2-} and CH_3COO^- as the general bases: $k_5^{HPO_4^{2-}} = 4.6 \times 10^8$ l mol^{-1} s^{-1}; $k_5^{CH_3COO^-} = 2 \times 10^7$ l mol^{-1} s^{-1}. These values show a rapid falloff of k_5 with decreasing base strength, indicating that the plateau in Fig. 6-3 cannot be associated with catalysis by water acting as a general base. The uncatalyzed reaction is therefore the reflection of the unimolecular ring opening of the zwitterionic adduct ZH.[23a]

It is worth noting that complexation of **11a** by α-cyclodextrin has been found to inhibit by 40 and 15%, respectively, the efficiency of the base-catalyzed and uncatalyzed rearrangements of Scheme 6.3.[23c] Analysis of the kinetic data reveals that the complexation has two major effects: (1) it reduces the rate of formation (k_2) of the zwitterion (ZH), presumably for steric reasons, and (2) it stabilizes this intermediate with respect to C—N bond breaking, thus lowering k_3 and favoring its partitioning toward product (k_4). In the base-catalyzed process where ZH goes essentially to its anionic counterpart Z^-, the second factor cannot compensate for the decrease in k_2, accounting for the observation of a greater inhibition than in the uncatalyzed process.[23c]

Nanosecond flash photolysis studies of the rearrangements of **11a** and its analogues **11b** and **11c** with $n = 3$ and 4 have allowed the spectroscopic identification of the zwitterionic as well as the anionic σ-complexes involved in Scheme 6.3.[24] They have also shown that no exciplex intermediates form prior to the σ-adducts.[24]

3-Nitrobromobenzene (**13**) is converted into 3-nitrochlorobenzene (**19**) upon UV irradiation in a 4:1 H_2O/CH_3CN medium that contains chloride ion.[25] A kinetic study of this photosubstitution showed that a plot of $1/\phi$ versus $1/[Cl^-]$ is linear and that addition of hydronium ion concentrations greater than about 0.1 M catalyzes the reaction. A feature of interest is that the value of ϕ at infinite H^+ concentration is greater by a factor of 2 than the plateau quantum yield for the uncatalyzed reaction. These observations have been explained in terms of the sophisticated S_N2Ar^* mechanism shown in Scheme 6.4. The formation of the σ-complex **16** would arise from chloride ion addition to the higher energy triplet of π,π* configuration **15** rather than to the lower energy triplet of *n*,π*

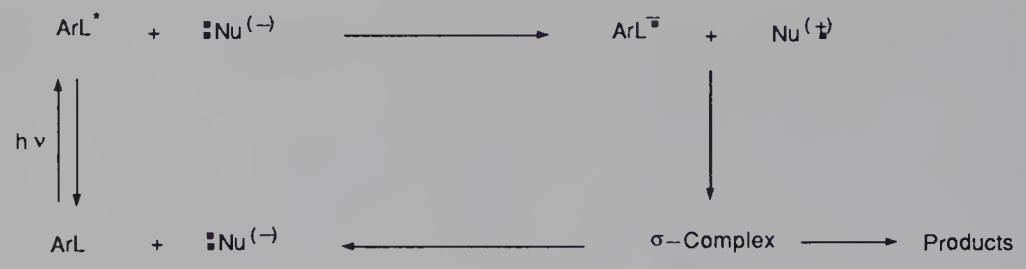


Scheme 6.4.

configuration **14**. On the other hand, the acid catalysis observed when $[H^+]$ exceeds 0.1 M would be a manifestation of the protonation of the π,π* state, giving **17**, which will readily add chloride ion to yield the protonated σ-complex **18**.

6.2.2 The S_N(ET)Ar* Mechanism

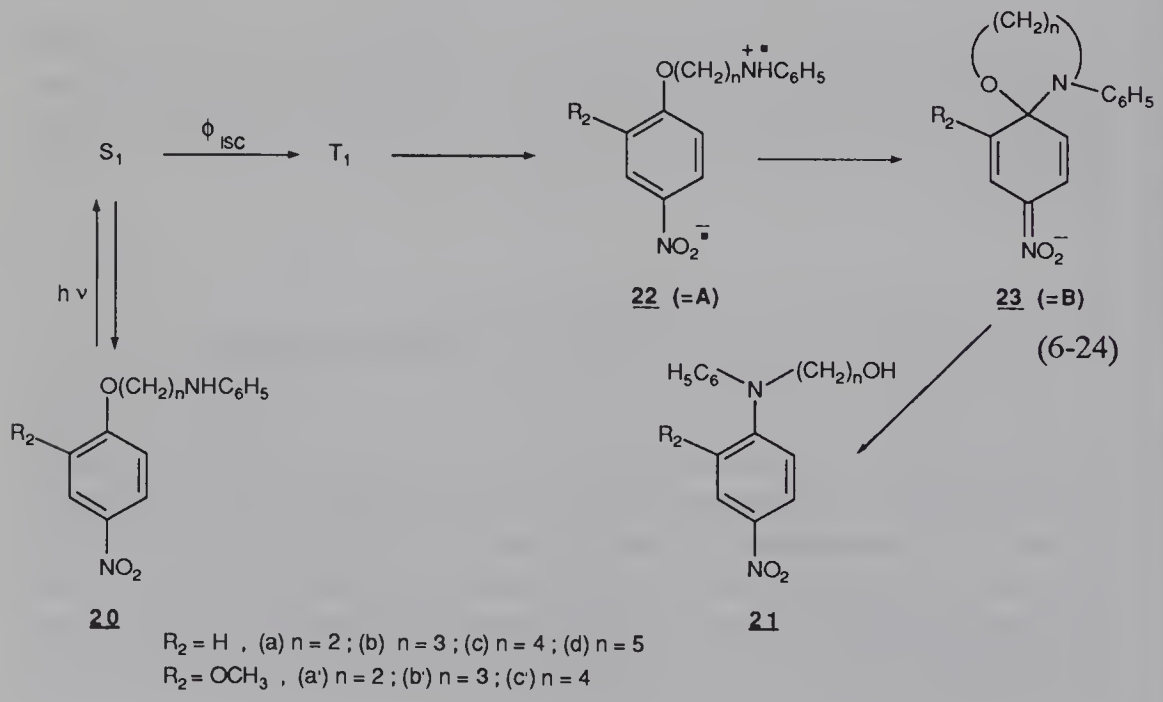
The S_N(ET)Ar* mechanism of eq. 6-10 was suggested in 1969 by Havinga and coworkers and firmly recognized in 1980 by Mutai and coworkers in photosubstitutions exhibiting ortho/para activation by an NO_2 group.[26–30] As indicated in a simplified manner in Scheme 6.5, the primary event in these reactions is an electron transfer from the nucleophile to the photoexcited nitroaromatic molecule with formation of a radical anion and, depending on



Scheme 6.5. The Reaction Pathway of a *S*N(ET)Ar* Reaction.

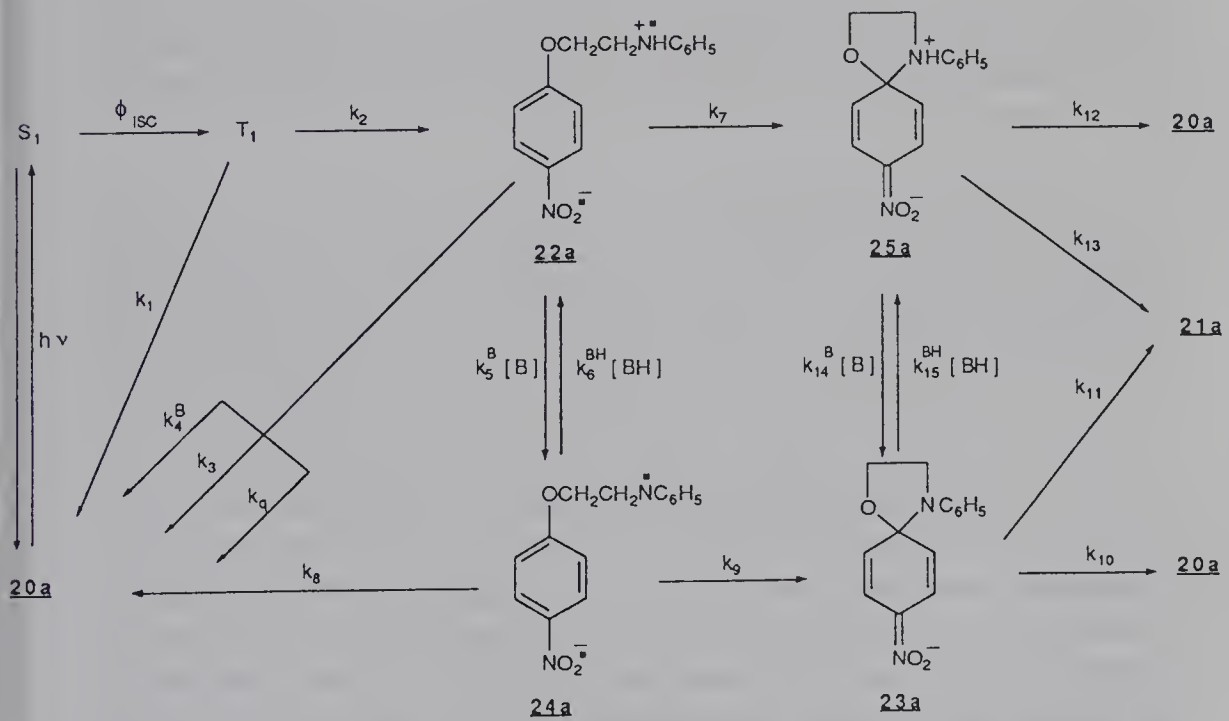
the nature of the nucleophile, a cationic or a neutral radical. Subsequently, radical coupling occurs, to give a σ-complex that can either revert to starting materials or decompose to yield the photosubstitution products.

The first spectroscopic evidence for the formation of the radical and σ-complex intermediates of Scheme 6.5 has been obtained in a nanosecond flash photolysis study of the Smiles rearrangements of eq. 6-24.[27,28] Irradiation of solutions of *N*-[2-(4-nitrophenoxy)ethyl]aniline (**20a**) in acetonitrile results in a clean conversion to *N*-phenyl-*N*-(β-hydroxyethyl)-4-nitroaniline (**21a**); but the formation of **21a** is preceded by two short-lived intermediates A and B.[27,28] The first intermediate A forms within the excitation pulse time (10 ns) and has a lifetime of about 60–100 ns. The possibility that this species was the reacting triplet T_1 was rejected because its absorption spectrum (λ_{max} = 450 nm) does not at all resemble those recorded for triplets of nitroanisoles and



anilines.[27,28] In contrast, the spectrum of A is a nice reflection of the superposition of the absorption spectra recorded for the radical anion of *p*-nitrophenol and the radical cation of N-methylaniline.[27] Based on this observation, and on the finding that A does not form when the NH group of **20a** is protonated, Mutai *et al.* have concluded that both the nitrophenyl ether and aniline moieties of **20a** are involved in the formation of A and that this species is the ion pair **22a** (eq. 6-24).[27] The fact that A could be detected in other polar solvents like ethanol and THF but not in nonpolar solvents like benzene and cyclohexane is consistent with the highly polar character of **22a**.[27] Structure **22a** is also supported by the observation that the rearrangement is subject to magnetic field effects.[41–43] The second species B has a lifetime of a few milliseconds and a visible spectrum strongly suggesting that it is the Meisenheimer complex **23a**.[27] Similar results were obtained in studies of the photocyclization of the long chain homologues of **20a** with $n \leq 5$ (i.e., **20b** – **20d**), as well as of the related methoxy derivatives **20a'** – **20c'**.[27,28,30,44]

Like their ground-state counterparts, the photo-Smiles rearrangements of eq. 6-24 are subject to general base catalysis.[45] A detailed kinetic analysis of this behavior has been made in acetonitrile, using a number of amines as base



Scheme 6.6.

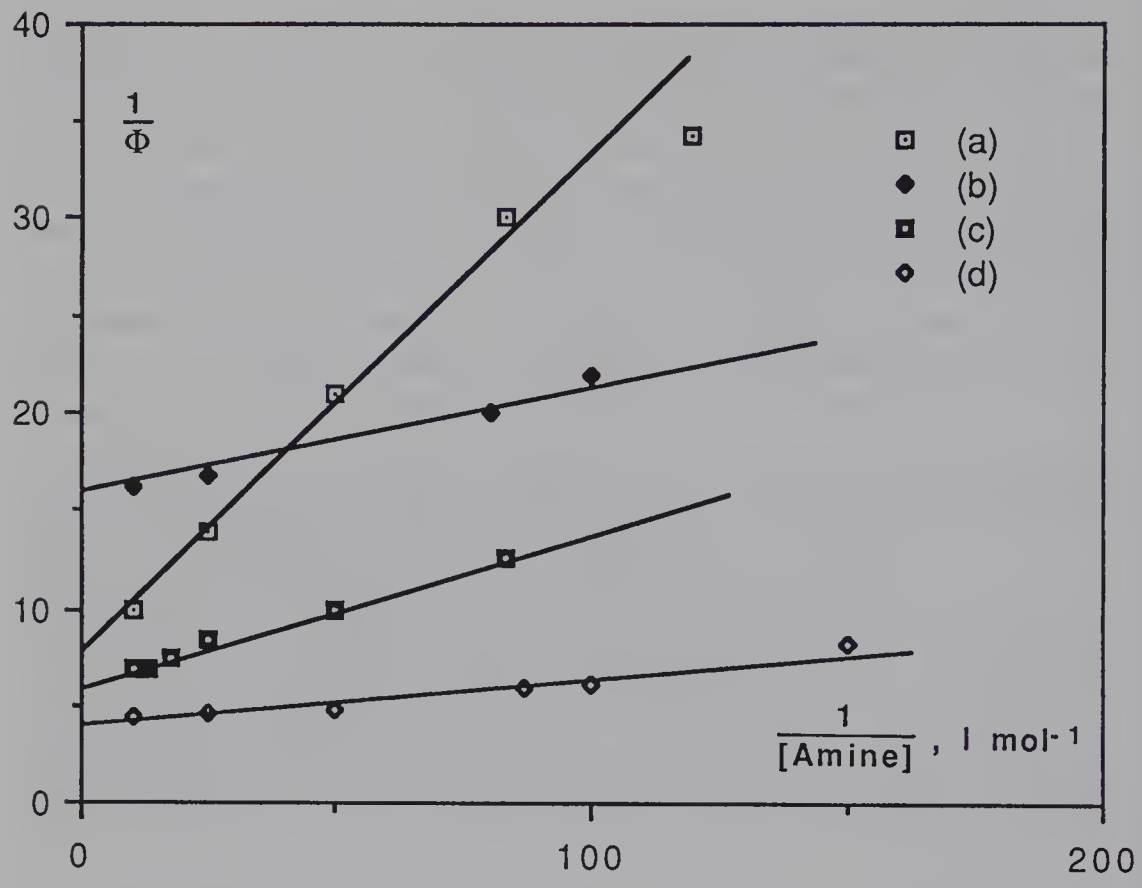
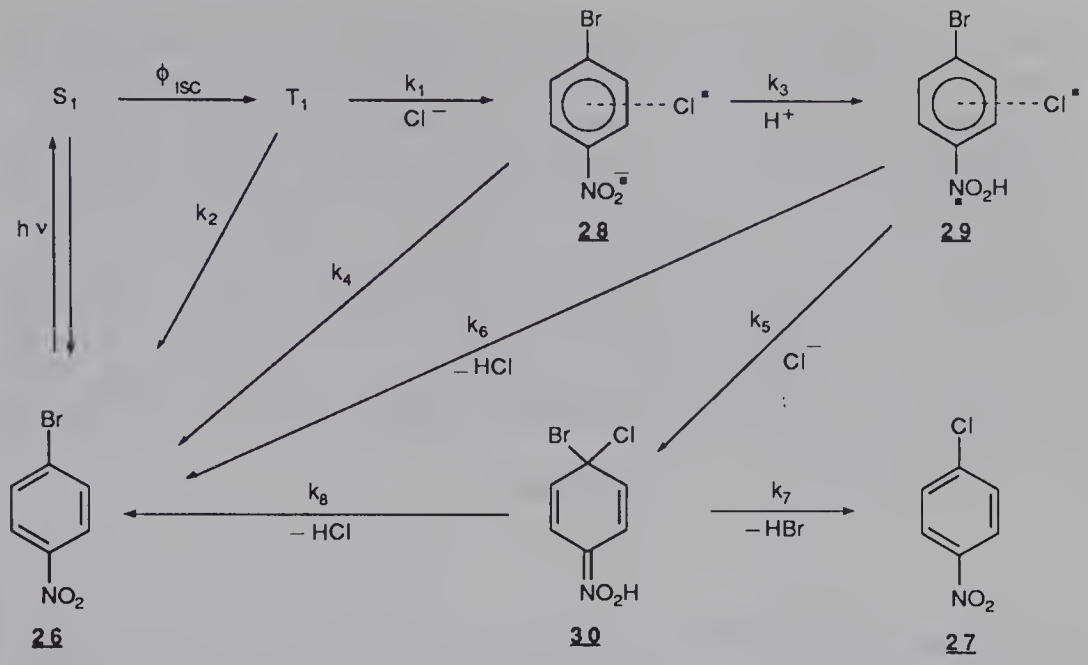


Figure 6.4. Effect of the reciprocal concentration of amine on the reciprocal quantum yield for the photo-Smiles rearrangement of N-[2-(4nitrophenoxy) ethyl]aniline (**20a**) in acetonitrile: (a) triethylamine, (b) DABCO, (c) morpholine, and (d) ethanolamine. (Reproduced with permission from ref. 45.)

catalysts. Figure 6.4 shows the variation in quantum yield of the rearrangement of **20a** for various concentrations of triethylamine, DABCO, morpholine, and ethanolamine. As can be seen, the data for each amine make a straight line in a double-reciprocal plot; but the most noteworthy feature is the finding that the various plots have different intercepts. If each amine were acting solely as a base catalyst, these intercepts, which correspond to the limiting quantum yield obtained at infinite base concentration, should be identical. That they are not implies that the amines quench as well as catalyze the reaction, and the linear double-reciprocal plots of Fig. 6-4 can result only if the quenching and the catalysis involve the same intermediate in the mechanism. On this ground, Wubbels *et al.* proposed the mechanism of Scheme 6.6 and concluded that the proton-donating and quenchable intermediate is the zwitterionic diradical **22a**. Deprotonation of **22a** would give the anionic diradical **24a**, whose cyclization affords the observed σ-complex **23a**. Since the uncatalyzed rearrangement of



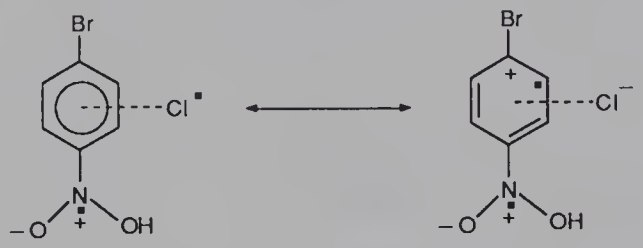
Scheme 6.7.

20a to **21a** proves to be very inefficient, it follows that the zwitterionic σ-complex **25a** (ZH), if present in equilibrium with **23a**, is not an intermediate leading to the photoproduct **21a** (via k_{13}). Therefore, the situation is very different from that which prevails in the ground-state rearrangements.[36–40]

The cyclization of **20a** into **21a** has also been studied in the presence of α-cyclodextrin (α-CD), a complexant of the nitrophenyl ether moiety.[46] The complexation reduces the efficiency of the rearrangement because it enhances the decay of the intermediate radical ion pair **22a**—for example, by reverse electron transfer. In contrast, the kinetic results show that the complexation has no effect on the efficiency of reaching **22a**. This suggests that the electron transfer takes place through σ-bonds rather than through close approach of the π-electron clouds of the two phenyl rings.[45]

The reaction of 4-nitrobromobenzene (**26**) with Cl^- to give 4-nitrochlorobenzene (**27**) is an example of an intermolecular reaction occurring via the S_N(ET)Ar* mechanism of Scheme 6.5.[47] A kinetic study in 4:1 (v/v) H_2O/CH_3CN and 4:1 (v/v) H_2O/CH_3COOH has shown that the dependence of the quantum yield for the formation of **27** on the Cl^- concentration is quadratic at constant H^+ concentration.[47] This suggests that there are two kinetically important steps in the reaction sequence that involve Cl^- ion. Strong catalysis of the photosubstitution by acid was also observed, a linear plot of $1/\phi$ versus $1/[H^+]$ being obtained at constant $[Cl^-]$.[47] These results fit the simplified

Scheme 6.7, where the primary step is electron transfer from Cl^- to the reacting triplet, which is presumably in the n,π^* state.[47] The resulting exciplex **28** has a high tendency to revert to the starting bromo derivative **26** ($k_4 \sim 10^9\ s^{-1}$), so that conversion of **26** into **27** in the absence of acid is very inefficient. In contrast, the decay process becomes less effective in the presence of H^+ ions because protonation of the NO_2 group of **28** occurs rapidly ($k_3 \sim 10^{10}$ l mol^{-1} s^{-1}) to give the "electrophilic" complex **29**. Conversion of **29** to the adduct **30** then follows in a chloride ion catalyzed process. Elimination of HBr from **30** gives the chloro derivative **27**. Wubbels *et al.* have rationalized the electrophilic character of the intermediate complex **29** by the resonance structures **29a** ↔ **29b**.[25]

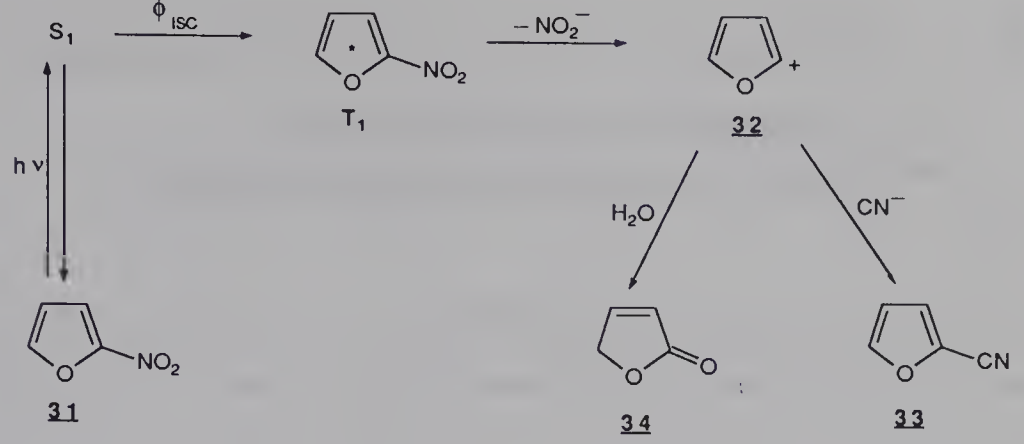


29a **29b**

In view of its novelty, the S_N(ET)Ar* mechanism is currently the subject of many investigations.[26–30,41–51] In particular, attempts are being made to detect radical intermediates by ESR spectroscopy.[29] This approach has proved to be successful in the case of the photoamination of 4-nitrochlorobenzene (**27**).[29] Upon irradiation of a solution of **27** in liquid ammonia, a paramagnetic species is formed which gives an ESR spectrum identical to that of the 4-nitrochlorobenzene radical anion.[29] However, this characterization does not provide, in itself, definitive evidence that the observed radical anion is the intermediate postulated in the S_N(ET)Ar* mechanism.

6.2.3 The S_N1Ar* Mechanism

The S_N1Ar* mechanism has been proposed to account for some photosubstitutions that exhibit an unexpected unimolecular behavior.[3–5] These include the photohydrolysis of 3-nitrophenyl sulfate and 5-chloro-3-nitrophenyl phosphate. Both proceed efficiently with a pH-independent quantum yield, in marked contrast to the results observed in the S_N2 Ar*-type



Scheme 6.8.

photohydrolysis of 3-nitrophenyl phosphate.[2–5,52] Similarly, changes in the hydroxide ion concentration have no effect on the hydrolysis of most halopyridines.[4,5]

It is a study of the photocyanation of 2-nitrofuran (**31**) that has shed light on these reactions.[35] While the quantum yield in the formation of 2-cyanofuran (**33**) normally increases with increasing CN^- concentration to reach a maximum value of $\phi = 0.51$ at $[CN^-] = 1$ mol/l, the quantum yield of disappearance of the parent **31** is constant and is equal to 0.51, even in the absence of CN^- ion. This observation shows that **31** reacts efficiently with both H_2O and CN^-; this was confirmed by the presence of γ-butenolide **34**—the stable tautomer of 2-hydroxyfuran—among the photosubstitution products.[35] It has been suggested that one deals with a system in which the quantum-yield-determining step is the primary photodissociation of **31** into the aromatic cation **32** and nitrite ion (Scheme 6.8). Both subsequent reactions of **32** with water and CN^- are fast; but the rate of reaction with CN^- increases when the CN^- concentration is increased, accounting for the preferred formation of **33** at high CN^- concentrations.

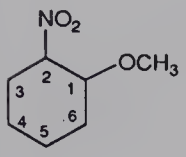
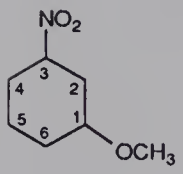
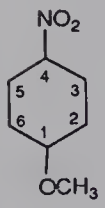
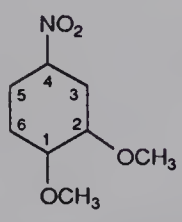
It may well be that the mechanism of Scheme 6.8 is operative in various photohydrolyses reported to occur with pH-independent quantum yields. A possible alternative, however, is that the excited state is very reactive and undergoes direct ipso substitution of the NO_2 group, even with such a weak nucleophile as water. In this instance, the observed quantum yield would represent the efficiency of formation of the reacting triplet.[3,5] A drawback of this hypothesis is that the ϕ values for product formation are generally lower than the ϕ_{ISC} values estimated for intersystem crossing.[5]

6.3 Chemical Theory, Mechanisms, and Regiochemistry of the Photosubstitutions

Attempts to understand the regioselectivity of nucleophilic aromatic photosubstitutions in terms of chemical theory have been made.[3–5,17,29] In a first approach, possible correlations between the ring position of nucleophilic attack and the charge distribution in the excited aromatic molecule were considered.[20] As representative examples, calculations carried out for the three isomeric nitroanisoles and 1,2-dimethoxy-4-nitrobenzene (**1**) are shown in Table 6-3. The results reveal that the highest positive charge is located at the methoxy-bearing carbon C-1 in each of the three nitroanisoles and at the methoxy-bearing carbon C-2 in **1**.[20] Interestingly, these ethers undergo many excited-state nucleophilic displacements at these carbons. Thus, the photohydrolysis and the photocyanation of 3-NA yield exclusively 3-nitrophenol and 3-nitrobenzonitrile, respectively.[7,8,12] Similarly, the photohydrolysis of **1** occurs only at C-2 to give 2-methoxy-5-nitrophenol.[16,20] On the other hand, 2-NA and 4-NA are photosubstituted by OH^-, though less readily, with formation of 2-nitro- and 4-nitrophenols.[11,13,20,53] In these cases, the reactions also afford 2-methoxy- and 4-methoxyphenols, but this result can be understood if one realizes that the carbon atoms bearing the NO_2 group have a substantial positive charge.

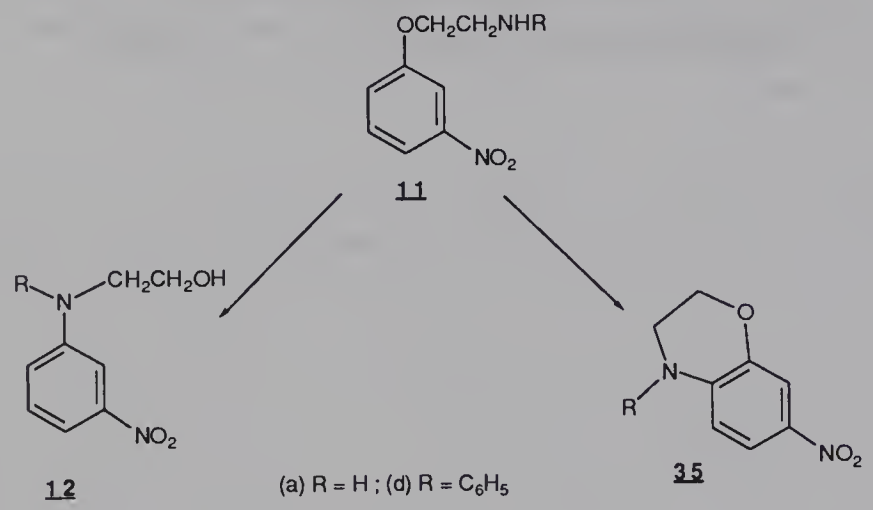
The examples above suggest at first that the regiochemistry of the photosubstitutions is simply related to the electron deficiency of the ring carbons of the excited state. The situation is not so straightforward, however, since there are many results that do not fit such a relationship. In particular, it is difficult to understand why photosubstitution of the NO_2 group is observed for 4-NA and 2-NA but not at all for 3-NA and **1**, for all carbon atoms bearing an NO_2 group are notably positive. More important, the behavior of nitrophenyl analogues of these ethers is found to disagree sharply with the predictions of regiochemistry based on calculated charge distributions. Thus, while the photolysis of 2-(3-nitrophenoxy)ethylamine (**11a**) results in the quantitative formation of the expected Smiles rearrangement product **12a** (see Section 6.2.1), that of the *N*-phenyl analogue **11d** yields the benzoxazine **35d** rather than **12d** (eq. 6-25).[48] A similar contrasting behavior is observed in the photolysis of the two 4-nitrophenoxyethylamino derivatives **20a** and **20e**. Here, it is the *N*-phenyl derivative **20a** that reacts normally to give the Smiles rearrangement product **21a**, while the hydrogen derivative **20e** affords the

Table 6.3. Charges at Ring Carbon of Nitroanisoles and 1,2-Dimethoxy-4-nitrobenzene in the Lowest Triplet State[a]

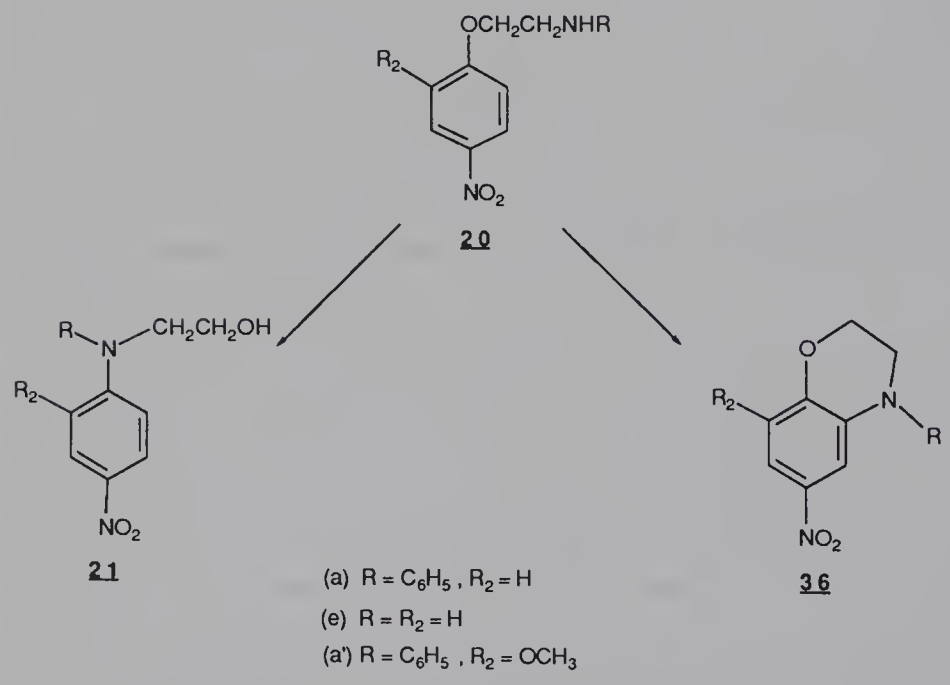
Compound		C-1	C-2	C-3	C-4	C-5	C-6
	2-NA	+0.146	+0.046	–0.006	0.000	+0.010	–0.035
	3-NA	+0.185	–0.070	+0.105	–0.043	+0.037	–0.062
	4-NA	+0.160	–0.026	–0.005	+0.068	–0.005	–0.034
	1	+0.110	+0.145	–0.055	+0.088	–0.028	–0.016

[a]Calculations by the PPP-SCF-CI method; data from ref. 20.

benzoxazine **36e** rather than the Smiles product **21e** (eq. 6-26).[27,28,54] Clearly, the charge distributions in the excited state do not allow accurate predictions of the regioselectivity of all photosubstitutions.



(6-25)



(6-26)

6.3.1 The Frontier Molecular Orbital Theory

A more sophisticated approach has been developed, which is based on the frontier molecular orbital theory.[55–57] Epiotis has suggested that the preferred regioselectivity of nucleophilic aromatic photosubstitutions is the one that simultaneously maximizes the $HOMO^{Nu}$–$HOMO^{Ar}$ matrix element and min-

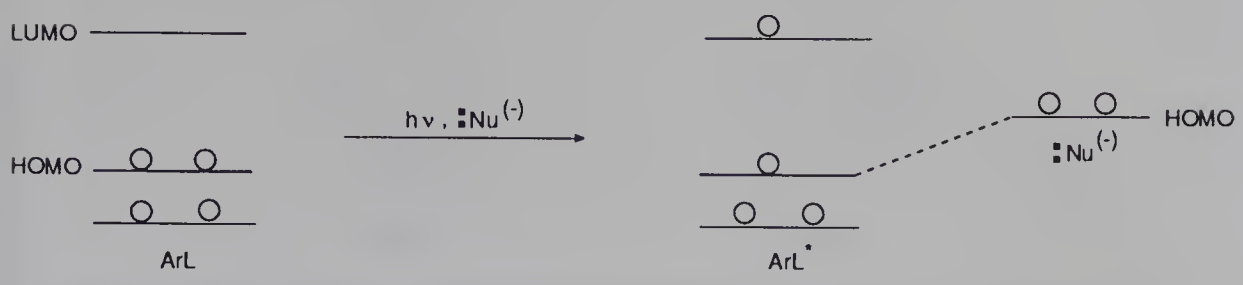


Figure 6.5. The possible course of an S_N2Ar^* reaction. (Reproduced with permission from ref. 29.)

imizes the $HOMO^{Nu}$–$LUMO^{Ar}$ matrix element, where the Nu denotes the nucleophile and Ar the aromatic.[56,57] (In other words, the nucleophile will attack at the ring position that has the highest HOMO electron density and the lowest LUMO electron density.) On this ground, calculations of the electron densities in the HOMO and LUMO of the ring carbon atoms of ethers like 3-NA, 4-NA, and **1** have been made. The results showed that the photobehavior of these derivatives agrees well with prediction.[20] However, the different regioselectivities observed in eqs. 6-25 and 6-26 remained unanswered.[29,49]

Mutai and coworkers have recently shown that frontier molecular orbital theory can adequately describe a large variety of photosubstitutions, provided the theoretical analysis refers to both the S_N2Ar^* and $S_N(ET)Ar^*$ mechanisms as possible reaction pathways.[29,49,50] In fact, these authors have demonstrated that there is a close relationship between the regiochemistry and the mechanism of a photosubstitution. The following two rules have been proposed.[29,49]

1. Nucleophilic photosubstitutions that involve formation of an intermediate σ-complex through direct interaction between the excited nitroaromatic substrate and the nucleophile (i.e., the S_N2Ar^* reactions) are $HOMO^{Ar}$ controlled, as illustrated in Fig. 6.5.

This rule proposes a diagnostic that refers only to the electron densities in the $HOMO^{Ar}$. It is therefore a simplification of Epiotis' conclusions that in such photosubstitutions the nucleophile will attack preferentially the ring position having simultaneously the highest HOMO electron density and the lowest LUMO electron density.[56,57]

2. Nucleophilic photosubstitutions that occur via initial electron transfer from the nucleophile to the excited nitroaromatic substrate followed by cou-

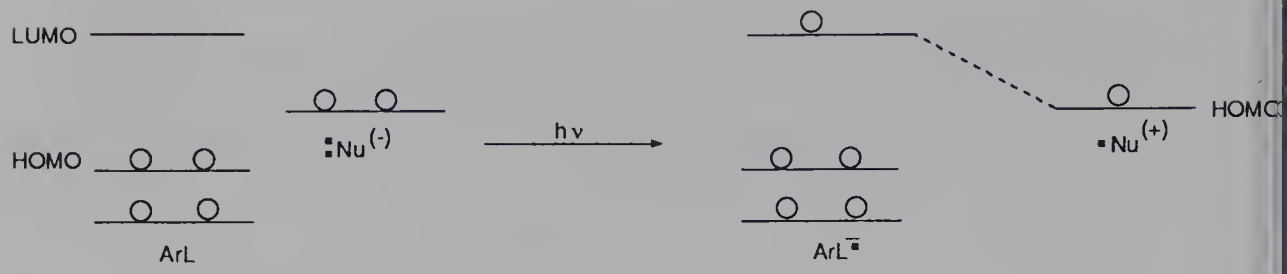


Figure 6.6. The possible course of an S_N(Et)Ar* reaction. (Reproduced with permission from ref. 29.)

pling of the resulting radicals to give a σ-complex [i.e., the S_N(ET)Ar*] reactions are $LUMO^{Ar}$ controlled.

As shown in Fig. 6.6, the electron transfer promotes the interaction between the singly occupied MO of the nitroaromatic and the singly occupied HOMO of the nucleophile. Since the singly occupied orbital of the aromatic compound corresponds to the LUMO of the ground state, the orientation may be considered to be LUMO controlled.[29,49]

Although they do not take direct account of such important factors as the nature of the leaving group and the nucleophile (see Section 6.4), these two rules allow a good understanding of the regioselectivity of most photosubstitutions.[29] The following examples are illustrative.

6.3.1.1 3-Nitroalkoxybenzenes

The frontier electron density (FED) maps of Fig. 6.7 suggest that 3-nitroalkoxybenzenes should undergo preferentially HOMO-controlled photosubstitutions at C-4, C-2, and C-1.[29] In fact, the results show that substitution at C-1 is very much favored because the alkoxy group is a much better leaving group than hydrogen.[29] Thus, 3-nitroanisole is essentially photosubstituted at C-1 with OH^-,[6,7] CN^-,[12] ammonia,[9] and methylamine.[6] However, in the case of the photoamination in liquid ammonia, some substitution at C-4, and also at C-2, has been detected.[9] The intramolecular rearrangement of the ethylamine derivative **11a** to the Smiles product **12a** (eq. 6-25 and Scheme 6.3)[23] is also in agreement with Fig. 6.7. It should be recalled that direct evidence for formation of an intermediate σ-complex, and therefore for an S_N2Ar^* mechanism, has been obtained in this instance.[24]

In contrast to its hydrogen analogue, the *N*-phenyl derivative **11d** rearranges via an S_N(ET)Ar* mechanism to give **35d** (eq. 6-25).[48] This benzoxazine

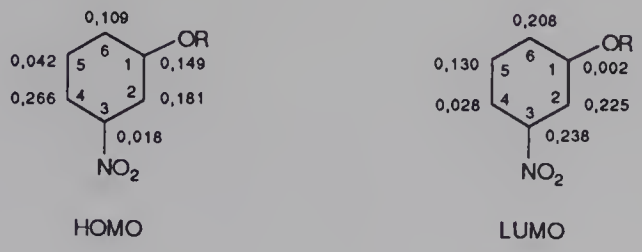


Figure 6.7. FED maps of the HOMO and LUMO of 3-nitroalkoxybenzenes. (Reproduced with permission from ref. 29.)

results from intramolecular nucleophilic attack of the amino group at the unsubstituted carbon C-6, which has a high LUMO electron density. Although Fig. 6.7 suggests that attack at C-2 would also be a reasonable process, the reaction at C-6 is obviously favored for steric reasons.[29]

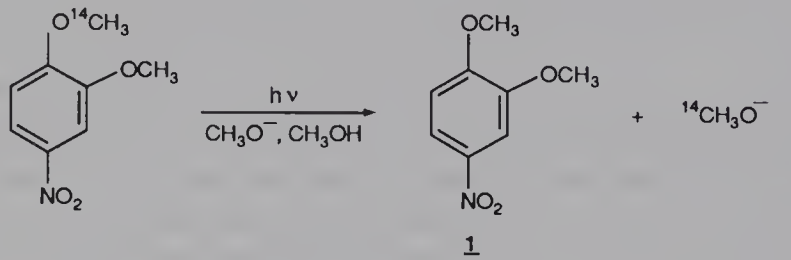
That the S_N2Ar^* substitutions of 3-NA and **11a** show meta-nitro regioselectivity while the $S_N(ET)Ar^*$ substitution of **11d** shows para-nitro regioselectivity is thus consistent with Fig. 6-7. The contrasting behavior of **11a** and **11d** is interesting, however, since it emphasizes the importance of the nucleophile in determining the reaction mechanism. In this regard, one can reasonably expect that only those nucleophiles which have relatively low ionization potential should be involved in $S_N(ET)Ar^*$ pathways. The gas phase ionization potentials of methylamine and *N*-methylaniline, which can be used as a measure of the ease of ionization of the amino moieties of **11a** and **11d**, are 9.45 and 7.65 eV, respectively.[54,58] Thus, a photoinduced electron transfer is more favorable in the case of **11d** than of **11a**, in accord with the observed mechanisms and regioselectivities in the rearrangements of these compounds.

6.3.1.2 1,2-Dialkoxy-4-Nitrobenzenes and Related Derivatives

The FED maps of 1,2-dialkoxy-4-nitrobenzenes (Fig. 6-8) reveal that the highest electron density in the HOMO is located at C-2, a position that also bears a good leaving group.[29] On this ground, it is satisfactory that these derivatives show meta-nitro regioselectivity in S_N2Ar^* photosubstitutions. For example, 1,2-dimethoxy-4-nitrobenzene (**1**) reacts with OH^-, ammonia, and CN^- to give 2-methoxy-5-nitrophenol, 2-methoxy-5-nitroaniline, and 2-methoxy-5-nitrobenzonitrile, respectively.[3–5,20,59] However, photosubstitutions of the S_N2Ar^* type are not unreasonable at C-1 because this other

Figure 6.8. FED maps of the HOMO and LUMO of 1,2-dialkoxy-4-nitrobenzenes. (Reproduced with permission from ref. 29.)

methoxy-bearing carbon also has a high FED. Indeed, the photochemical methoxide exchange of eq. 6-27 occurs, but the quantum yield of the reaction is much lower than that found for the analogous process at C-2.[20]

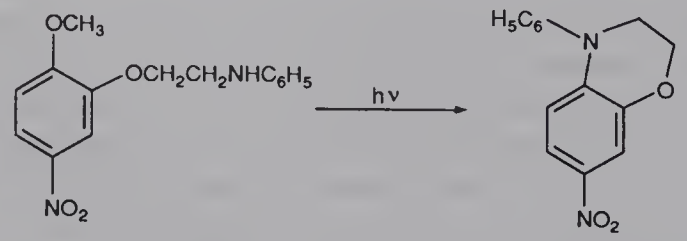


(6-27)

1

In the LUMO, the FED of C-1 is much greater than that of C-2, so that S_N(ET)Ar* reactions are expected to occur with para-nitro regioselectivity. The finding that the amino ether **20a'** rearranges into nitroaniline **21a'** (eq. 6-26) agrees with this prediction.[26–28,44] The same is true for the rearrangement of the ethers **37** into **38** (eq. 6-28).[48] In these cases, attack at C-3, which has the highest FED, is precluded for structural reasons.

Isomers of 1,2-dialkoxy-4-nitrobenzenes also react in agreement with Mutai's rules.



(6-28)

37 **38**

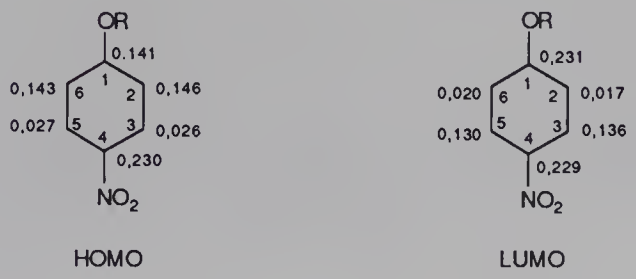


Figure 6.9. FED maps of the HOMO and LUMO of 4-nitroalkoxybenzenes. (Reproduced with permission from ref. 29.)

6.3.1.3 4-Nitroalkoxybenzenes

As can be seen in Fig. 6-9, the highest FEDs in the HOMO of 4-nitroalkoxybenzenes are located at carbons C-4, C-1, and C-2/C-6.[29] In agreement with this situation, photosubstitutions believed to be of the S_N2Ar^* type occur at these positions. As illustrated by eq. 6-3, the photohydrolysis of 4-nitroanisole results in the formation of both *p*-nitro- and *p*-methoxyphenols; that is, competitive attack occurs at C-1 and C-4.[4,11,13] On the other hand, photodisplacements of methoxide ion from 4-NA by methyl-, dimethyl-, or ethylamine to give 4-nitroanilines are clean and efficient reactions in aqueous solutions.[15,60] Finally, hydrogen displacement at C-2 has been observed in the reaction of 4-NA with cyanide ion, affording 2-cyano-4-nitroanisole, as well as in the intramolecular rearrangement of the ethylamine derivative **20e** to the benzoxazine **36e** (eq. 6-26).[54]

Significantly, carbons C-1 and C-4 also have high FEDs in the LUMO.[29] One can therefore expect S_N(ET)Ar* reactions to show the same regioselectivity as the S_N2Ar^* reactions. The observation that N-2-(4-nitrophenoxy)ethylaniline (**20a**) reacts normally at C-1 to give the Smiles rearrangement product **21a** (eq. 6-26) via initial electron transfer from the aniline moiety to the nitroaromatic ring is in accord with this prediction.[27,28] Intramolecular substitution at the nitro-bearing carbon C-4 is sterically precluded in this system.

6.3.1.4 Chloronitrobenzenes

The three isomeric chloronitrobenzenes undergo photoamination at the position para to the nitro group.[4,9,29] As can be seen in Fig. 6-10, the FED at this position is so low in the HOMO of the ortho and meta derivatives that

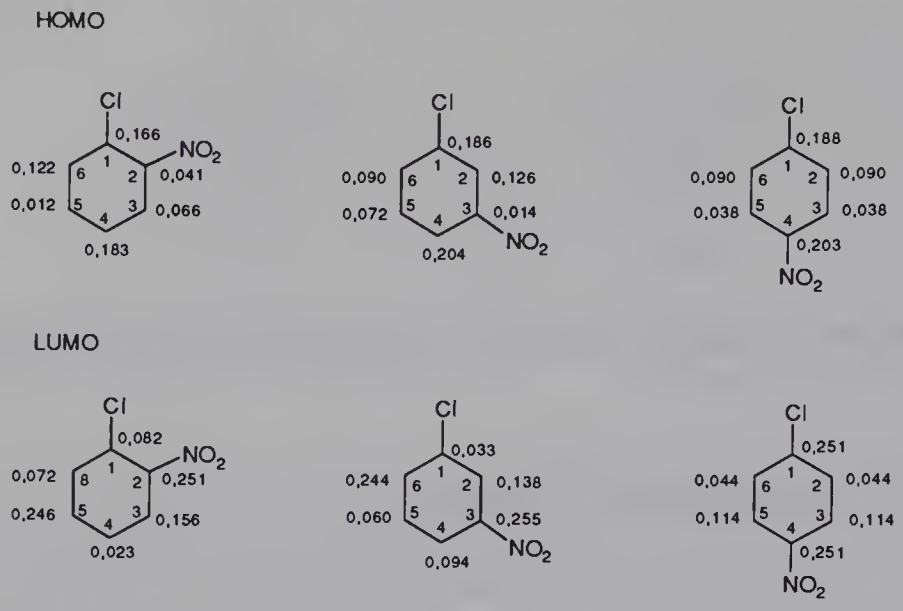


Figure 6.10. FED maps of the HOMO and LUMO of chloronitrobenzenes. (Reproduced with permission from ref. 29.)

there is little doubt that the reactions of these two compounds with NH_3 are LUMO controlled and are of the S_N(ET)Ar* type. The situation is less clear-cut for 4-nitrochlorobenzene (**27**), since the carbon bearing the chlorine atom has a high FED in both MOs. However, the observation that the photoamination at C-1 is accompanied by some substitution at C-3 (a position that has a notable FED in the LUMO but not in the HOMO) suggests that the reactions are also LUMO controlled and proceed via the S_N(ET)Ar* mechanism.[29] This has been confirmed by the identification of the radical anion of **27** in liquid ammonia.[29]

The FED maps of Fig. 6.10 can also be used as a reactivity index for bromonitrobenzenes. It was mentioned in Section 6.2.1 that there is convincing evidence for a S_N2Ar* pathway in the photoconversion of 3-nitrobromobenzene (**13**) into 3-nitrochlorobenzene (**19**).[25] Clearly, the meta-nitro regioselectivity of this reaction agrees with the presence of a high FED at C-1 in the HOMO of the starting aromatic.[29] Similarly, it has been demonstrated that the reaction of 4-nitrobromobenzene with Cl^- to give 4-nitrochlorobenzene involves initially a photoinduced electron transfer.[47] This LUMO-controlled reaction is consistent with Fig. 6.10.

From the examples above, it is clear that the photosubstitutions of many nitrobenzene derivatives show a regioselectivity that agrees satisfactorily with Mutai's rules. A similar agreement has been found for reactions involving a number of naphthalene derivatives.[50] This general consistency suggests that

Mutai's rules constitute a very useful guide to both the regiochemistry and the mechanisms of nucleophilic aromatic photosubstitutions. They do not lead, however, to unambiguous predictions when the highest FEDs are located at the same ring positions in the HOMO and LUMO—a situation that is illustrated by the results for *p*-alkoxy and *p*-chloronitrobenzenes.

6.3.2 The "Energy Gap" Model

A rationalization of the preferred meta-nitro regioselectivity of S_N2Ar^* photosubstitutions based on the size of the energy gap between the excited- and ground-state potential energy surfaces has recently been proposed by Van Riel, Lodder, and Havinga.[20a] This idea is illustrated in Fig. 6.11.

Interaction of the nucleophile with the excited nitroaromatic molecule ArL* leads to the formation of an encounter complex or an exciplex (point C') which can either decompose into its components or be converted to the σ-complex C on the ground-state surface. The reaction may then proceed to yield the substitution product, or it may revert to the starting material. Since

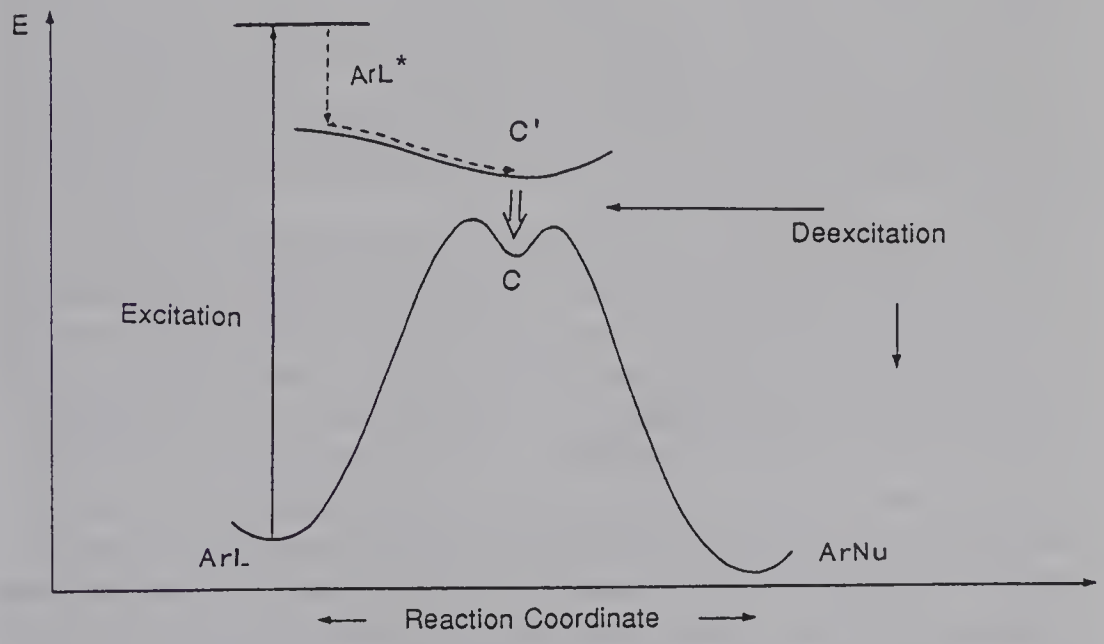


Figure 6.11. The possible course of an S_N2Ar^* reaction in the "energy gap" model. (Reproduced with permission from ref. 20a.)

Table 6.4. Differences in the Energies of Formation of Ground-State meta-, ortho-, and para-Nitro-Substituted σ-Complexes ($\Delta\Delta E$) and Differences in the Energies of the Lowest Triplet States of These Adducts (ΔE^*)[a]

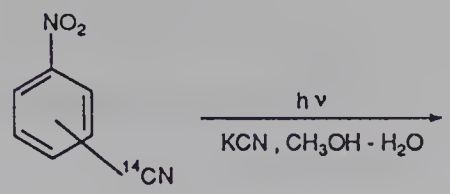
Reaction	$\Delta\Delta E$ (kJ. mol^{-1})	ΔE^* (kJ. mol^{-1})
Methoxy exchange of 3-NA and 4-NA	64.16	–59.23
Hydrolysis of 3-NA and 4-NA	67.30	
Methoxy exchange of 4-nitroveratrole (1)[b]	69.26	–59.02
Hydrolysis of 4-nitroveratrole (1)[b]	70.90	
Cyano exchange of 3- and 4-nitrobenzonitriles	86.73	–90.37
Cyano exchange of 2- and 4-nitrobenzonitriles	63.37	–26.42

[a]Data from refs. 17 and 20.

[b]*m*- Versus *p*-methoxy groups.

the transition probability of C′ to C is related to the energy gap between the two surfaces, the formation of the intermediate σ-complex will be the more favored when the ground-state surface is of high energy and the excited state surface is of low energy.[17,20] In this regard, it is well known that σ-adducts with meta-NO_2 groups are of much higher energy than those which have ortho- or para-NO_2 stabilizing groups (see Chapter 2).[36,38] Accordingly, S_N2Ar^* photosubstitutions not only should occur preferentially but also should proceed more efficiently at positions that are meta rather than para or ortho to an NO_2 group.

For a more detailed analysis of this model, the energies of the starting materials and σ-complexes involved in some typical S_N2Ar^* photosubstitutions, namely the photohydrolysis and the photochemical methoxide exchange of 3-NA, 4-NA, and 4-nitroveratrole (1): eqs. 6-1 to 6-3 and 6-7), and the photochemical cyanide exchange of ^{14}C-labeled *o*-, *m*-, and *p*-nitrobenzonitriles (eq. 6-29), have been calculated by the CNDO/2 method.[17,20] From these calculations, the $\Delta\Delta E$ values, representing the differences in the energies of formation of the various meta-, para-, and ortho-NO_2-substituted, ground-state σ-complexes, which are formed in the reactions, have been obtained (Table 6.4).[17,20] The results show that the σ-complexes resulting from nucleophilic attack meta to the NO_2 group lie 63–75 kJ/mol higher in energy than those from para or ortho attack. On the other hand, the energies of the



(6-29)

lowest triplet states of the σ-complexes have been calculated and used to derive approximate values of the differences ΔE^* in the energy levels of the excited-state surfaces for meta and para or meta and ortho substitution. Table 6.4 reveals that the lowest triplet states of *m*-nitro-substituted adducts are of much lower energy than those of ortho and para analogues. Thus, the observed trends in the $\Delta\Delta E$ and ΔE^* values lead to the conclusion that the energy gap between the excited-state and ground-state surfaces of S_N2Ar^* substitutions will be considerably smaller for reactions occurring in positions meta rather than ortho or para to an NO_2 group. On this basis, one can readily understand why meta-nitro substitutions are favored and occur with high selectivity.[17,20]

The "energy gap" model also accounts for the general observation that the NO_2 group is more activating than any other electron-withdrawing group in S_N2Ar^* reactions. Introduction of an NO_2 group in a benzene or an anisole molecule results in an appreciable decrease in the energy of the lowest triplet state: $ET_{benzene}$ = 355 kJ/mol; $ET_{anisole}$ = 335 kJ/mol; $ET_{nitrobenzene}$ = 251 kJ/mol; $ET_{4\text{-}NA}$ = 251 kJ/mol; $ET_{3\text{-}NA} \sim$ 251 kJ/mol.[17,20] This means that the energy of the excited-state surface is also substantially lowered and therefore that the energy gap between this surface and the ground-state surface is decreased, accounting for the activation of the reactions by the NO_2 group. In contrast, other electron-withdrawing groups like the CN and aza groups, which have about the same effect as the NO_2 group in the ground state, do not decrease the energy of the triplet state to a notable extent ($ET_{3\text{-}cyanoanisole}$ = 301 kJ/mol $ET_{4\text{-}cyanoanisole}$ = 314 kJ/mol; $ET_{naphthalene}$ = 255 kJ/mol; $ET_{quinoline}$ = 255 kJ/mol), so that the energy gap is not reduced.[17,20] As a result, 3-cyano- and 4-cyanoanisoles and methoxy-quinolines show low reactivity as well as low selectivity in photosubstitution reactions.

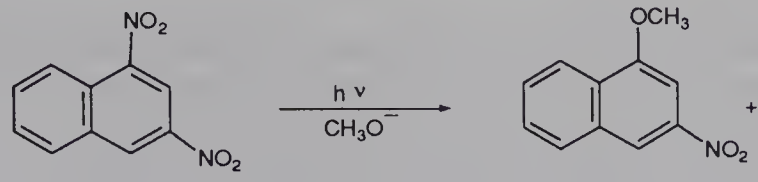
In conclusion, there is no doubt that the "energy gap" model provides the most rigorous understanding of the S_N2Ar^* photosubstitutions. Mutai's rules are of more practical use, however, since they deal with both S_N2Ar^* and $S_N(ET)Ar^*$ reactions, and in many cases allow a rapid prediction of the reaction pattern and the regioselectivity that can be expected for a given photosubstitution.

6.4 Effect of Variation in the Structure of the Nitroaromatic and the Nucleophile

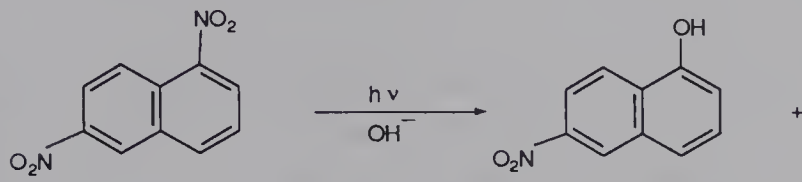
At this stage of our discussion, it is to be recalled that nucleophilic aromatic photosubstitutions can proceed through the reaction pathways considered above, provided the aromatic substrates are sufficiently activated by electron-withdrawing substituents.[3,5,17,20] This implies that the presence of the NO_2 group is in itself a primary factor determining the behavior of a nitroaromatic in a photosubstitution process. However, other structural features in the aromatic residue, as well as the nature of the nucleophile, have a noticeable effect. The aim of the following discussion is to pay more specific attention to these influences, which have been mentioned only occasionally in the preceding sections.

6.4.1 Variation in the Aromatic

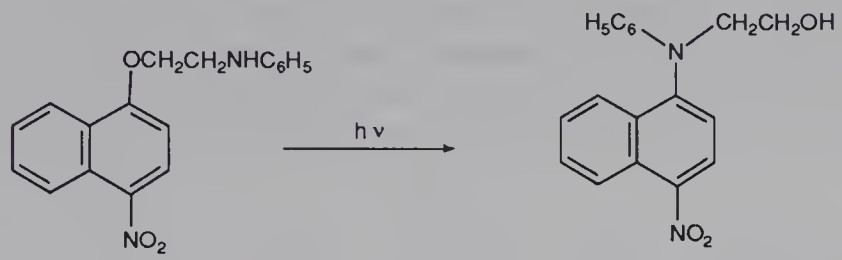
Nucleophilic photosubstitutions of polycyclic nitroaromatic compounds often proceed more readily than those of benzene derivatives.[3,5] Reactions that are good models for clean and efficient meta-nitro-activated S_N2Ar^* substitutions are those of 1-fluoro- and 1-methoxy-3-nitronaphthalenes (5 and 7) with OH^- and methylamine to give the corresponding hydroxy or *N*-methylamino derivatives.[31] These were discussed in depth in Section 6.2.1 (see eq. 6-12). Also noteworthy is the behavior of 1,3- and 1,6-dinitronaphthalenes, which is depicted in eqs. 6-30 and 6-31, respectively.[4,5,61] The occurrence of the photosubstitutions of these derivatives at the 1-position illustrates that, other things being equal, naphthalenes are preferentially substituted in the α-position.[3–5] Other polycyclic aromatics like azulenes and phenanthrenes show this α-reactivity pattern, which is not typical of nitro compounds. This pattern is encountered in photosubstitutions of fused-ring systems not bearing electron-withdrawing groups.[3–5] This behavior is also reminiscent of the situation observed in thermal reactions. Although there are not many known reactions of this type in the naphthalene series, available results show that nitronaphthalenes behave as their nitrobenzene analogues in $S_N(ET)Ar^*$ reactions.[50] A representative example is given in eq. 6-32.



(6-30)

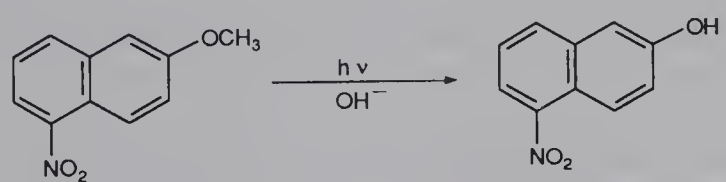


(6-31)



(6-32)

There is accumulated evidence that the meta-directing influence of an NO_2 group is about the same regardless of whether this group is directly attached to the ring undergoing substitution.[3,5] The situation is best illustrated by the results obtained in the kinetic study of the photohydrolysis of 1-fluoro-3-nitro- and 1-fluoro-6-nitronaphthalenes (**5** and **9**), in 1:1 H_2O/CH_3CN (eqs. 6-12 and 6-18).[31] As can be seen in Table 6.1, the rate constant k_{Nu} for reaction between the triplet excited state and OH^- is essentially the same in these two $S_N2^{(3)}Ar^*$ reactions: $k_{Nu} = 9.6 \times 10^7$ l mol^{-1} s^{-1} for **5** and $k_{Nu} = 1 \times 10^8$ l mol^{-1} s^{-1} for **9**. This strong activation by an NO_2 group far removed from the reaction center is not observed in normal S_NAr substitutions. It accounts for the ease of S_N2Ar^* photosubstitutions of many nitronaphthalenes,[5] as further exemplified by eqs. 6-31 and 6-33.[61]

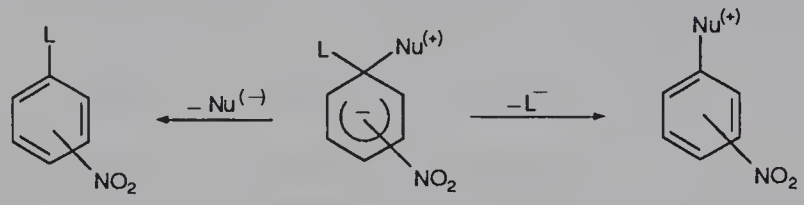


(6-33)

The atom or substituent (L) that finally departs in a photosubstitution may have a marked influence on the reactivity of the excited nitroaromatic molecule. Again referring to eq. 6-12 and Table 6.1, it can be seen that two structurally similar derivatives like 1-fluoro- and 1-methoxy-3-nitronaphthalenes (**5** and **7**), which are both susceptible to ready $S_N2^{(3)}Ar^*$ substitutions, exhibit a different behavior in the initial stage of the reactions.[31] Thus, the

triplet excited state of **7** reacts about 8 times more rapidly than that of **5** with OH^-: $k_{Nu}{}^5 = 9.6 \times 10^7$ l mol^{-1} s^{-1} and $k_{Nu}{}^7 = 7.1 \times 10^8$ l mol^{-1} s^{-1}.[31] Nevertheless, it is the fluoro derivative **5** that is photosubstituted with the highest quantum yield, at least in part because the lifetime of the triplet of **5** ($\tau = 2.3 \times 10^{-7}$ s^{-1}) is much greater than that of the triplet of **7** ($\tau = 3.8 \times 10^{-9}$ s^{-1}).[31]

Another factor of prime importance regarding the influence of the departing group is, however, the fact that the S_N2Ar^* and $S_N(ET)Ar^*$ pathways involve the formation of an asymmetrical intermediate σ-complex. Accordingly, the feasibility of the overall substitutions should depend on the tendency of this metastable intermediate to decompose thermally with return to the starting materials or to form the products. This is visualized in eq. 6-34, which shows that the situation is the same as that encountered in classical S_NAr



(6-34)

reactions (see Chapter 2). On this basis, good leaving groups in S_NAr reactions may be expected to be also good leaving groups in S_N2Ar^* and $S_N(ET)Ar^*$ reactions. The experimental observations support this idea.[3,5] Halogen atoms (F, Cl, Br), alkoxy groups (OCH_3), and the NO_2 group are generally very good departing groups in nucleophilic aromatic photosubstitutions.[3–5] Other substituents susceptible to facile departure are the phosphate and sulfate groups, as well as the CN group.[3–5] Not unexpectedly, a hydrogen atom is not commonly ejected. Like the analogous thermal processes (see Chapter 5), hydrogen photosubstitutions require the presence of an oxidant, (e.g., atmospheric oxygen), and they occur especially well when the attacking nucleophile is CN^- or NH_3.[3–5] For instance, the photoreaction of 4-nitroanisole with cyanide ion gives 2-cyano-4-nitroanisole in high yield when it is carried out in protic solvents like 10% CH_3CN/90% water (v/v) or 4% *t*-BuOH/96% water (v/v).[12]

Competitive photosubstitutions have been observed in many systems,[3–5] in agreement with Mutai's predictions that a given excited nitroaromatic molecule is susceptible to nucleophilic attack at all ring carbon atoms having a high electron density.[29] In these instances, the importance of the various pathways should largely reflect the differences in the electron densities at the possible sites of nucleophilic attack as well as the differences in the leaving group abilities of the substituents attached to these positions. The contrasting results obtained in the photohydrolysis of 3-NA and 4-NA provide a good

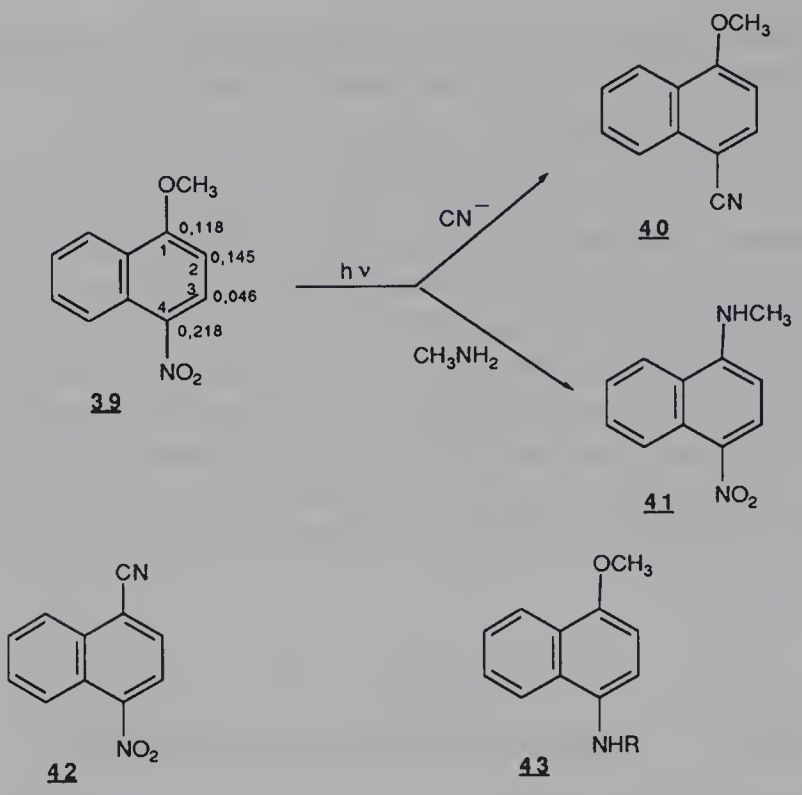
illustration of this situation. The FED maps in Figs. 6.7 and 6.9 show the following HOMO electron density sequences for these derivatives:

3-NA: C-4 > C-2 > C-1 4-NA: C-4 > C-1 ≈ C-2/C-6

This suggests that they may undergo S_N2Ar^* photosubstitutions at three different positions. However, 3-NA reacts exclusively at the methoxy-bearing carbon C-1 to give 3-nitrophenol because of the much higher leaving group ability of the OCH_3 group compared to a hydrogen atom.[7,8] On the other hand, 4-NA reacts at both C-1 and C-4 to give a mixture of 4-nitro and 4-methoxyphenols in a 1:4 ratio,[4,11,13] in accord with the facts that both OCH_3 and NO_2 are good leaving groups and that the nitro-bearing carbon C-4 has a higher electron density than the methoxy-bearing carbon C-1. Steric factors can also play a role in determining the relative importance of possible competitive pathways.[17,26,27]

6.4.2 Variation in the Nucleophile

Rates of nucleophile addition to excited nitroaromatic molecules are considerably higher (see Table 6.1) than those found in ground-state chemistry. Nevertheless, common nucleophiles show a reactivity order that is about the same in photoactivated and normal S_NAr substitutions.[3,5] This observation again suggests that the decomposition of the σ-complex plays an important role in determining the ease of S_N2Ar^* and $S_N(ET)Ar^*$ photosubstitutions. Equation 6-34 shows clearly that the nature of the nucleophile interplays with that of the leaving group in this process, which in most cases will be controlled by the relative stabilities of the incoming and outgoing groups (see Chapter 2). In some instances, however, the stability of the resulting substitution product is apparently the important factor determining the course of the photosubstitution. For example, eq. 6-35 shows that 1-methoxy-4-nitronaphthalene (**39**) is photosubstituted at the methoxy-bearing carbon C-1 by methylamine but at the nitro-bearing carbon C-4 by CN^-.[5,62] Since both C-1 and C-4 bear a significant electron density in the HOMO of **39**, these two S_N2Ar^*-type reactions are not unexpected.[50] According to Havinga *et al.*, the observed selectivity would be related to the degree of resonance stabilization of the resulting compounds.[3,5] Thus, addition of CN^- at C-4 of **39** will be favored because 4-cyano-1-methoxynaphthalene (**40**) is a compound in which the electron-withdrawing cyano group and the electron-donating methoxy group are suitably located for efficient resonance stabilization.[3,5] In contrast, attack



(6-35)

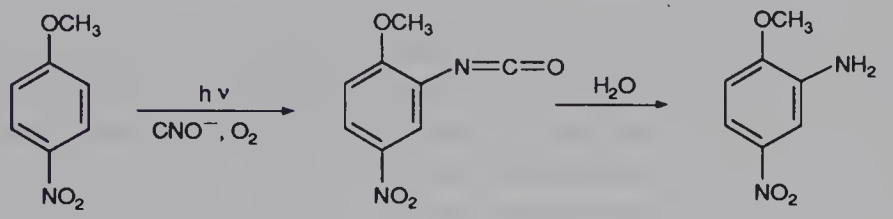
(a) R = CH_3 ; (b) R = n-C_3H_7 ; (c) R = i-C_4H_9

at C-1 would afford 1-cyano-4-nitronaphthalene (**42**), in which there is conflicting interaction between the two electron-withdrawing NO_2 and CN groups. Similarly, the reaction of methylamine will be preferred at C-1 and not at C-4 because resonance stabilization is possible in 1-methylamino-4-nitronaphthalene (**41**) but not in 1-methoxy-4-methylaminonaphthalene (**43a**). This effect has been referred to as a "merging resonance" effect by Havinga.[3,5] A recent report by Bunce *et al.* that the reaction of **39** with methylamine as well as other primary amines like *n*-propylamine and isobutylamine occurs in fact at the nitro-bearing carbon to give **43a–c** under various experimental conditions, suggests that this effect is not always a primary factor determining the course of a S_N2Ar^* substitution.[63]

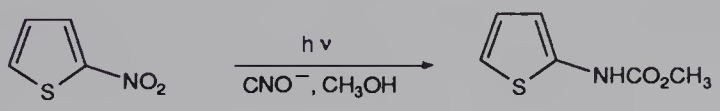
With respect to the "merging resonance effect," it is worth noting that similar influences have been encountered in normal S_NAr reactions. A typical illustration is the reaction of cyanide ion with 2,4-dinitrochlorobenzene, which yields 3-cyano-2,4-dinitrochlorobenzene (i.e., a product of hydrogen displacement) rather than 2,4-dinitrobenzonitrile, the product of chlorine displacement.[64,65] The von Richter conversion of para-bromonitrobenzene to meta-bromobenzoic acid, and related reactions, are other examples of this effect (see Chapter 5).

As evidenced by the great number of clean photohydrolysis and

photomethoxylations quoted in available reviews,[3–5] hard nucleophiles like OH^- and CH_3O^- anions are very efficient reagents in S_N2Ar^* processes. The cyanide ion is also a valuable nucleophile in many substitutions of this type.[3–5] Depending on the electrophilic aromatic partner, chloride anion may be involved in S_N2Ar^* or $S_N(ET)Ar^*$ processes.[25] Other anionic reagents that have been used are hydride and cyanate anions.[3–5,14,66] The latter is a promising reagent for synthetic purposes, leading to amines in water (eq. 6-36) and carbamates in alcohols (eq. 6-37).[4,14,35]

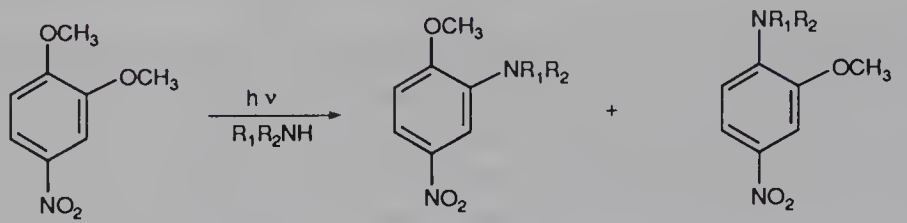


(6-36)



(6-37)

Ammonia and amines are efficient neutral nucleophiles in many photosubstitutions.[3–5] Due to a relatively low ionization potential, aromatic amines are especially susceptible to photoinduced electron transfers and are therefore involved in $S_N(ET)Ar^*$reactions.[26–29,41,48,49] This behavior was extensively discussed in Section 6.2.2. The situation is less clear-cut with aliphatic and alicyclic amines, since the reaction pattern is apparently dependent on the size of the amino moiety.[53,60,63,67–70] Thus, methylamine reacts, as does NH_3, with 4-nitroveratrole (**1**) to give the 2-methoxy-5-nitroanilines **44a** and **44b** (eq. 6-38).[4,60,68] The meta-nitro regioselectivity of these reactions indicates that they proceed via an S_N2Ar^* mechanism. As discussed in Section 6.2.1, intramolecular cyclizations of 2-(nitrophenoxy)ethylamines also occur via this reaction pathway.[23,47] In contrast, the reactions of **1** with dimethylamine and morpholine afford only the 2-methoxy-4-nitroanilines **45c** and **45d**,[60] suggesting that an $S_N(ET)Ar^*$ mechanism is operative in these cases. Interestingly, the reaction of **1** with butylamine shows an intermediate behavior and leads to a mixture of the isomeric amines **44e** and **45e**.[60] The finding that the ionization potential decreases with increasing size of the amine supports the mechanistic change.[63,71,72] Other examples of changes in regioselectivity upon changes in the nucleophile have been recently reported.[73–75]

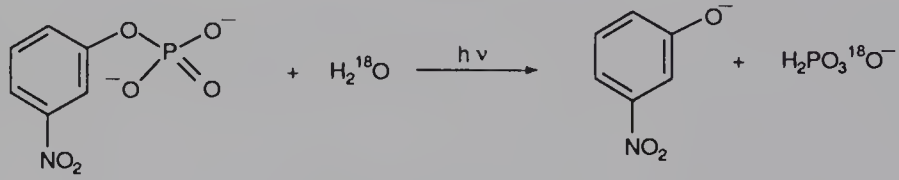


(6-38)

1 44 45

(a) $R_1 = R_2 = H$; (b) $R_1 = H$, $R_2 = CH_3$; (c) $R_1 = R_2 = CH_3$; (d) R_1 -------$R_2 = C_4H_8NO$; (e) $R_1 = H$, $R_2 = n\text{-}C_4H_9$

Water and methanol are weak neutral nucleophiles that react generally through specific mechanisms.[3,5] Thus, the photohydrolysis of compounds like 2-nitrofuran, 3-nitrophenyl sulfate, and 5-chloro-3-nitrophenyl phosphate proceed with a pH-independent quantum yield that has been accounted for in terms of the S_N1Ar^* mechanism (see Section 6.2.3).[2–5,35,52] On the other hand, irradiation of neutral aqueous solutions of 3-nitrophenyl phosphate results in the formation of 3-nitrophenol; however, experiments with [^{18}O] H_2O show that the photohydrolysis occurs with breaking of the O—P bond rather than of the C—O bond; that is, the reaction is not a true aromatic photosubstitution (eq. 6-39).[2,4,52] The methanolysis of 3-nitrophenyl phosphates also involves breaking of the O—P bond.[4,6]



(6-39)

References

1. Havinga, E.; de Jongh, R. O.; Dorst, W. *Recl. Trav. Chim. Pays-Bas*, **1956**, *75*, 378.
2. De Jongh, R. O.; Havinga, E. *Recl. Trav. Chim. Pays-Bas*, **1968**, *87*, 1318.
3. Havinga, E.; Cornelisse, J. *Pure Appl. Chem.* **1976**, *47*, 1.
4. Cornelisse, J.; Havinga, E. *Chem. Rev.* **1975**, *75*, 353.
5. Cornelisse, J.; de Gunst, G. P.; Havinga, E. *Adv. Phys. Org. Chem.* **1975**, *11*, 225.
6. Havinga, E.; de Jongh, R. O. *Bull. Soc. Chim. Belg.* **1962**, *71*, 803.
7. De Jongh, R. O.; Havinga, E. *Recl. Trav. Chim. Pays-Bas*, **1966**, *85*, 275.

8. Den Heijer, J.; Spee, T.; de Gunst, G. P.; Cornelisse, J. *Tetrahedron Lett.* **1973**, 1261.
9. Van Vliet, A.; Kronenberg, M. E.; Cornelisse, J.; Havinga, E., *Tetrahedron*, **1970**, *26*, 1061.
10. Letsinger, R. L.; Steller, K. E. *Tetrahedron Lett.* **1969**, 1401.
11. Letsinger, R. L.; Ramsay, O. B.; McCain, J. H. *J. Am. Chem. Soc.* **1965**, *87*, 2945.
12. Letsinger, R. L; McCain, J. H. *J. Am. Chem. Soc.* **1966**, *88*, 2884; *ibid.*, **1969**, *91*, 6425.
13. De Vries, S.; Havinga, E., *Recl. Trav. Chim. Pays-Bas*, **1965**, *84*, 601.
14. Hartsuiker, J.; de Vries, S.; Cornelisse, J.; Havinga, E., *Recl. Trav. Chim. Pays-Bas*, **1971**, *90*, 611.
15. Kronenberg, M. E.; Van der Heyden, A.; Havinga, E. *Recl. Trav. Chim. Pays-Bas,* **1966**, *85*, 56.
16. Stratenus, J. L., Ph. D. thesis, University of Leiden, 1966.
17. Cornelisse, J.L.; Lodder, G.; Havinga, E., *Rev. Chem. Intermed.*, **1979**, *2*, 231.
18. Nilsson, S. *Acta Chem. Scand.* **1973**, *27*, 329.
19. Den Heijer, J.; Shadid, O. B.; Cornelisse, J.; Havinga, E. *Tetrahedron*, **1977**, *33*, 779.
20. (a) Van Riel, H. C. H. A.; Lodder, G.; Havinga, E. *J. Am. Chem. Soc.* **1981**, *103*, 7257. (b) Lodder, G. In "*The Chemistry of Functional Groups*", Supplement D, Patai, S.; Rappoport, Z., eds. Wiley: New York, 1983, p. 1605.
21. Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413.
22. (a) Rossi, R. A.; de Rossi, R.H. "*Aromatic Substitution by the $S_{RN}1$ Mechanism*", ACS Monograph 178. American Chemical Society: Washington, DC, 1983. (b) Julliard, M.; Chanon, M. *Chem. Rev.* **1983**, *83*, 425.
23. (a) Wubbels, G. G.; Celander, D. W. *J. Am. Chem. Soc.* **1981**, *103*, 7669; (b) Wubbels, G.G.; Celander, D. W. *ibid.* **1982**, *104*, 2677. (c) Wubbels, G. G.; Cotter, W. D. *Tetrahedron Lett.* **1989**, *30*, 6477.
24. Wubbels, G. G.; Van Zeyl, P. H. M.; Varma, C. A. G. O. *Abstracts of 185th National Meeting of the American Chemical Society*, Seattle, March 1983; ORGN 50.
25. Wubbels, G. G.; Susens, D. P.; Coughlin, E. B. *J. Am. Chem. Soc.* **1988**, *110*, 2538.
26. Van Vliet, A.; Cornelisse, J.; Havinga, E. *Recl. Trav. Chim. Pays-Bas*, **1969**, *88*, 1339.

27. Yokohama, K.; Nakagaki, R.; Nakamura, J.; Mutai, K.; Nagakura, S. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2472.

28. (a) Mutai, K.; Kobayashi, K. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 462; (b) Mutai, K.; Yokohama, K.; Kauno, S.; Kobayashi, K. *ibid.* **1982**, *55*, 1112.

29. Mutai, K.; Nakagaki, R.; Tukada, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2066.

30. Nakagaki, R.; Hiramatsu, M.; Mutai, K., Nagakura, S. *Chem. Phys. Lett.* **1985**, *121*, 262.

31. Lammers, J. G.; Tamminga, J. J.; Cornelisse, J.; Havinga, E. *Isr. J. Chem.* **1977**, *16*, 304.

32. De Gunst, G. P.; Havinga, E. *Tetrahedron*, **1973**, *29*, 2167.

33. Varma, C. A. G. O.; Plantenga, F. L.; van den Ende, C. A. M.; van Zeyl, P. H. M.; Tamminga, J. J.; Cornelisse, J. *J. Chem. Phys.* **1977**, *22*, 475.

34. (a) Varma, C. A. G. O.; Tamminga, J. J.; Cornelisse, J. *J. Chem. Soc., Faraday Trans.* **1982**, *78*, 265; (b) Van Zeijl, P. H. M.; Van Eijk, L. M. J.; Varma, C. A. G. O. *J. Photochem.* **1985**, *29*, 415.

35. Groen, M. B.; Havinga, E. *Mol. Photochem.* **1974**, *6*, 9.

36. Buncel, E.; Crampton, M. R.; Strauss, M. J.; Terrier, F. "*Electron-Deficient Aromatic– and Heteroaromatic–Base Interactions*". Elsevier: Amsterdam, 1984, p. 233.

37. Bernasconi, C. F. ; Gehriger, C. L.; de Rossi, R. H. *J. Am. Chem. Soc.* **1976**, *98*, 8451.

38. Terrier, F. *Chem. Rev.* **1982**, *82*, 77.

39. Bernasconi, C. F. *Acc. Chem. Res.* **1978**, *10*, 147.

40. Knipe, A. C.; Lound-Keast, J.; Sridhar, N. *J. Chem. Soc., Perkin Trans. 2*, **1984**, 1885.

41. (a) Nakagaki, R.; Hiramatsu, M.; Mutai, M.; Tanimoto, Y.; Nagakura, S. *Chem. Phys. Lett.* **1987**, *134*, 171; (b) Hiramatsu, M.; Nakagaki, R.; Tanimoto, Y.; Mutai, M.; Tukada, H.; Nagakura, S. *ibid.* **1987**, *142*, 413; (c) Nakagaki, R.; Mutai, K.; Nagakura, S. *ibid.* **1989**, *154*, 581.

42. Nakagaki, R.; Mutai, K.; Hiramatsu, M.; Tukada, H.; Nagakura, S. *Can. J. Chem.* **1988**, *66*, 1989.

43. Mutai, M.; Nakagaki, R.; Tukada, H. *Chem. Lett.* **1987**, 2261.

44. Yokohama, K.; Nakamura, J.; Mutai, K.; Nagakura, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 317.

45. Wubbels, G. G.; Sevetson, B. R.; Sanders, H. *J. Am. Chem. Soc.* **1989**, *111*, 1018.

46. Wubbels, G. G.; Sevetson, B. R.; Kaganove, S. N. *Tetrahedron Lett.* **1986**, *27*, 3103.

47. Wubbels, G. G.; Snyder, E. J.; Coughlin, E. B. *J. Am. Chem. Soc.* **1988**, *110*, 2543.
48. Mutai, K.; Kobayashi, K.; Yokohama, K. *Tetrahedron* **1984**, *40*, 1755.
49. Mutai, K.; Nakagaki, R. *Chem. Lett.* **1984**, 1537.
50. Mutai, K.; Nakagaki, R. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3663.
51. Mutai, K.; Kanno, S.; Kobayashi, K. *Tetrahedron Lett.* **1978**, 1273.
52. De Jongh, R. O.; Havinga, E. *Recl. Trav. Chim. Pays-Bas*, **1968**, *87*, 1327.
53. Bunce, N. J.; Laboute Stephenson, K. *Can. J. Chem.* **1989**, *67*, 220.
54. Wubbels, G. G.; Halverson, A. M.; Oxman, J. D.; de Bruyn, V. H. *J. Org. Chem.* **1985**, *50*, 4499.
55. Fleming, I. "*Frontier Orbitals and Organic Chemical Reactions*". Wiley: New York, 1976, p. 223.
56. Epiotis, N. D. "*Theory of Organic Reactions*". Springer-Verlag, New York, 1978, p. 171.
57. Epiotis, N. D.; Shaik, S. *J. Am. Chem. Soc.* **1978**, *100*, 29.
58. Maier, J. P.; Turner, D. W. *J. Chem. Soc., Faraday Trans. 2,* **1973**, *69*, 521.
59. Lok, C. M.; Havinga, E. *Proc. K. Ned. Akad. Wet. B,* **1974**, *77*, 15.
60. Cervello, J.; Figueredo, M.; Marquet, J.; Moreno-Manas, M.; Bertran, J.; Lluch, J. M. *Tetrahedron Lett.* **1984**, *25*, 4147.
61. Beijersbergen van Henegonwen, G. M. J.; Havinga, E. *Recl. Trav. Chim. Pays-Bas,* **1970**, *89*, 907.
62. Letsinger, R. L.; Hautala, R. R. *Tetrahedron Lett.* **1969**, 4205.
63. Bunce, N. J.; Cater, S. R.; Scaiano, J. C.; Johnston, L. J. *J. Org. Chem.* **1987**, *52*, 4214.
64. Blanksma, J. J. *Recl. Trav. Chim. Pays-Bas*, **1902**, *21*, 424.
65. Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273.
66. Petersen, W. C.; Letsinger, R. L. *Tetrahedron Lett.* **1971**, 2197.
67. Kronenberg, M. E.; Van der Heyden, A.; Havinga, E. *Recl. Trav. Chim. Pays-Bas*, **1967**, *86*, 254.
68. Castello, A.; Marquet, J.; Moreno-Manas, M.; Sirera, X., *Tetrahedron Lett.* **1985**, *26*, 2489.
69. Cantos, A.; Marquet, J.; Moreno-Manas, M. *Tetrahedron Lett.* **1987**, *28*, 4191.
70. Marquet, J.; Moreno-Manas, M.; Vallribera, A.; Virgili, A.; Bertran, J.; Gonzalez-Lafont, A.; Lluch, J. M. *Tetrahedron* **1987**, *43*, 351.

71. Aue, D. H.; Webb, H. M.; Bowers, M. T. *J. Am. Chem. Soc.* **1976**, *98*, 311, 318.
72. Taft, R. W.; Levitt, L. S. *J. Org. Chem.* **1977**, *42*, 916, and references therein.
73. Cantos, A.; Marquet, J.; Moreno-Manas, M.; Castello, A. *Tetrahedron*, **1988**, *44*, 2607.
74. Cantos, A.; Marquet, J.; Moreno-Manas, M.; Castello, A. *Tetrahedron Lett.* **1989**, *30*, 2423.
75. Van Eijk, A. M. J.; Huizer, A. H.; Varma, C. A. G. O.; Marquet, J. *J. Am. Chem. Soc.* **1989**, *111*, 88.

CHAPTER 7.
Radical Nucleophilic Aromatic Substitutions

7.1 Introduction

There is a growing awareness that single electron transfer may be the initial step in a wide range of chemical reactions.[1–7] The ability of nitroaromatic compounds to undergo one-electron reduction in the presence of a variety of electron donors was established by Russell and subsequently by many other workers.[8–15] At present, it is well recognized that radical anions are the primary intermediates in nucleophilic substitutions occurring *at the sp^3 carbon* of *p*-nitrobenzyl halides and related derivatives. Details on these substitutions, which are typical for the radical chain $S_{RN}1$ mechanism, are available in many standard references.[16–18] $S_{RN}1$ substitutions at an aromatic sp^2 carbon are generally inhibited by nitro substitution in the ring.[7] Radical anions are also accepted as being intermediates in reduction processes of nitroaromatics.[19–21]

The possible intermediacy of radical anions in nucleophilic aromatic substitutions of nitroaromatics is a question that we have only partially addressed in the preceding chapters. Recent evidence obtained by Mutai that electron transfer from a nucleophile to a photoexcited nitroarene molecule is the primary event in some photosubstitutions—the S_N(ET)Ar* substitutions—was discussed in Chapter 6.[22] Contrasting with this situation, some nucleophilic aromatic substitutions of hydrogen are believed to involve electron transfer, with concomitant radical anion formation only in the late stages of the processes (see Chapter 5). A prototype example is the reaction of potassium *tert*-butoxide with nitrobenzene to give ortho- and para-*tert*-butoxynitrobenzenes in THF.[15] We proceed now with a detailed consideration of the evidence that electron transfer may well be the promoting step in

activated nucleophilic aromatic displacements, which formally appear to follow normal $S_{RN}Ar$ mechanisms.[9,12,23,24] This discussion includes examination of a very recent proposal by Bunton that some of these substitutions may proceed via charge–transfer complexes with significant anion radical character at the nitroarene moiety rather than via free radical anions.[25–28]

Homolytic nucleophilic aromatic substitutions of nitroaromatics with alkyl radicals are also considered in this chapter.[29]

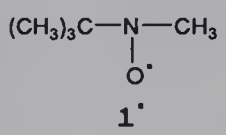
7.2 Substitutions via Nitroarene Radical Anions

7.2.1 Radical Anion Formation in "$S_{RN}Ar$" Systems

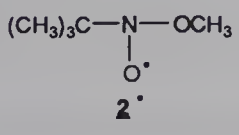
As discussed in Chapter 1, reactions of nitroaromatics like *p*- halonitrobenzenes, 1-halo-2,4-dinitrobenzenes, picryl chloride, and *p*- or *o*-dinitrobenzenes with nucleophiles like OH^-, CH_3O^-, or amines are common prototype systems for $S_{RN}Ar$ reactions.[30] However, ESR investigations have revealed that such systems may involve radical anion formation from the nitroarene reactants under some experimental conditions.[5,6,9,12,23,24]

In an attempt to establish whether the detected radical anions can result from *direct electron transfer* from the nucleophiles to the parent nitroaromatics (Ar-L), ESR experiments have been carried out in the presence of nitroxides like *tert*-nitrosobutane (*t*-C_4H_9NO).[31] These nitroxides were used to trap the short-lived free radicals that were expected from the oxidation of the nucleophilic species. Thus, ESR spectra of the stable radical $\underline{1}^{\bullet}$ and the radical anions $\underline{4}^{\bullet-}$ and $\underline{5}^{\bullet-}$ of *p*-chloronitrobenzene (**4**) and *p*-dinitrobenzene (*p*-DNB) (**5**), respectively, have been obtained in the reactions of these nitroaromatics with potassium hydroxide in a 80:20 (v/v) DMSO/H_2O mixture in the presence of *t*-C_4H_9NO, while $\underline{2}^{\bullet}$ was observed in a 10:1 (v/v) CH_3OH/DMSO mixture. The formation of $\underline{1}^{\bullet}$ and $\underline{2}^{\bullet}$ was accommodated by the reaction sequence shown in eqs. 7-1 to 7-4. The fact that the rate of reaction of the hydroxyl radical with DMSO (eq. 7-2; $Nu^{\bullet} = OH^{\bullet}$) occurs at an essentially diffusion-controlled rate

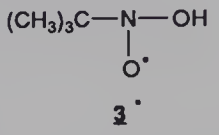
would prevent the formation of the hydroxyl analogue **3**$^{\bullet}$ of **2**$^{\bullet}$ according to eq. 7-5.[32]



1$^{\bullet}$

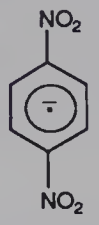


2$^{\bullet}$

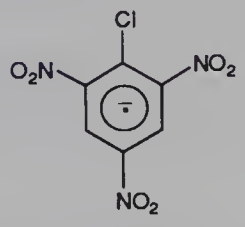


3$^{\bullet}$

4$^{\bullet-}$



5$^{\bullet-}$



6a$^{\bullet-}$

$$Ar\text{–}L + Nu^{-} \rightarrow ArL^{\bullet-} + Nu^{\bullet} \qquad (7\text{-}1)$$

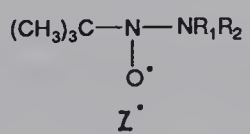
$$Nu^{\bullet} + CH_3SOCH_3 \rightarrow CH_3SONu + CH_3^{\bullet} \qquad (7\text{-}2)$$

$$CH_3^{\bullet} + t\text{–}C_4H_9NO \rightarrow \underline{1}^{\bullet} \qquad (7\text{-}3)$$

$$CH_3O^{\bullet} + t\text{–}C_4H_9NO \rightarrow \underline{2}^{\bullet} \qquad (7\text{-}4)$$

$$OH^{\bullet} + t\text{–}C_4H_9NO \rightarrow \underline{3}^{\bullet} \qquad (7\text{-}5)$$

In a similar way, electron transfer between *p*-DNB (**5**) or picryl chloride (**6a**) and primary or secondary amines like cyclohexylamine, piperidine, or diethylamine would occur in DMSO, DMF, or benzene.[31] In these cases, formation of the radical anions **5**$^{\bullet-}$ and **6a**$^{\bullet-}$ implies the concomitant formation of the radical cations $R_1R_2NH^{\bullet+}$ (eq. 7-6). These were not observed by ESR spectroscopy, however, since they undergo further electron transfer reactions, which, in the presence of *t*-C_4H_9NO, yielded the stable nitroxide radicals **7**$^{\bullet}$, according to eqs. 7-7 and 7-8. As indicated by eq. 7-2 with $Nu^{\bullet} = C_5H_{10}N^{\bullet}$ and

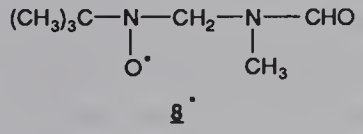


7$^{\bullet}$

$R_1 = R_2 = C_2H_5$

$R_1 = H,\ R_2 = C_6H_{11}$

$R_1 \cdots R_2$ = piperidino



8$^{\bullet}$

eq. 7-3 or by eq. 7-9a and 7-9b, the radicals **1**$^{\bullet}$ and **8**$^{\bullet}$ were also observed in the piperidine systems in DMSO and DMF, respectively.[31]

$$Ar\text{–}L + R_1R_2NH \rightarrow ArL^{\bullet -} + R_1R_2NH^{\bullet +} \quad (7\text{-}6)$$

$$R_1R_2NH^{\bullet +} + R_1R_2NH \rightarrow R_1R_2N^{\bullet} + R_1R_2NH_2^{+} \quad (7\text{-}7)$$

$$R_1R_2N^{\bullet} + t\text{-}C_4H_9NO \rightarrow \mathbf{7}^{\bullet} \quad (7\text{-}8)$$

$$C_5H_{10}N^{\bullet} + CH_3N(CH_3)CHO \rightarrow C_5H_{10}NH + {}^{\bullet}CH_2N(CH_3)CHO \quad (7\text{-}9a)$$

$$t\text{-}C_4H_9NO + {}^{\bullet}CH_2N(CH_3)CHO \rightarrow \mathbf{8}^{\bullet} \quad (7\text{-}9b)$$

The formulation of eqs. 7-1 and 7-6 assumes that the radical anions $ArL^{\bullet -}$ detected in the above-mentioned experiments form as a result of a primary electron transfer from the base to the parent nitroarenes.[31] According to Nagakura and Tanaka, electron transfer in nitroaromatic–base interactions would occur from the highest occupied molecular orbital (HOMO) of the base to the lowest unoccupied molecular orbital (LUMO) of the nitroarene.[4] Based on estimated energy differences between the two orbitals, these authors concluded that facile electron transfers can be anticipated in the gas phase for various systems (e.g., the OH^--nitrobenzene and OH^--*p*- or *o*-DNB systems), and it was presumed that this situation would extend to various experimental conditions in solutions, especially in dipolar aprotic solvents.[4,12,27] These solvents combine a poor ability to solvate small anions (OH^-, RO^-, etc.) with a strong tendency to stabilize large and polarizable anionic species like the resulting nitroarene radical anions.[33,34] In contrast, the ease of electron transfer and the stability of radical anions should be less favorable in protic solvents because of the high solvation energies of anionic nucleophiles as well as because of the reduced stabilization of large anions with a delocalized negative charge.[33,34] In qualitative agreement with these ideas, formation of nitroarene radical anions has been most readily detected in DMSO, DMF, and 1,2-dimethoxyethane (DME), or in aqueous or alcoholic solutions of these dipolar aprotic solvents.[8–15]

Eberson reexamined the feasibility of direct electron transfers between anionic nucleophiles and nitroaromatics on the basis of the Marcus theory and formulated the following conclusions:

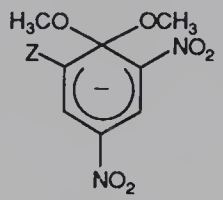
1. Equation 7-1 is a reasonable electron transfer pathway if Nu^- is a carbanionic donor. Even though positive standard redox potentials (E°) are found for strongly resonance-stabilized species, most car-

banions are characterized by negative $E°$ values and are therefore readily oxidizable anions.

2. Equation 7-1 does not appear to be a realistic pathway if Nu^- is an oxyanionic donor like OH^- or RO^- ions. Such species have highly positive $E°$ values, even in dipolar aprotic solvents.[35]

Thus, the formation of the radical anions $ArL^{\bullet-}$ detected in the aforementioned OH^-- or CH_3O^--*p*-DNB or *p*-chloronitrobenzene systems will not be feasible at all via eq. 7-1. Other mechanisms have therefore been considered to account for the formation of the corresponding $ArL^{\bullet-}$ species.

Electrochemical measurements have shown that not only the dinitro adduct **9a** but also the trinitro adduct **9b** are more efficient donors than alkoxide ions

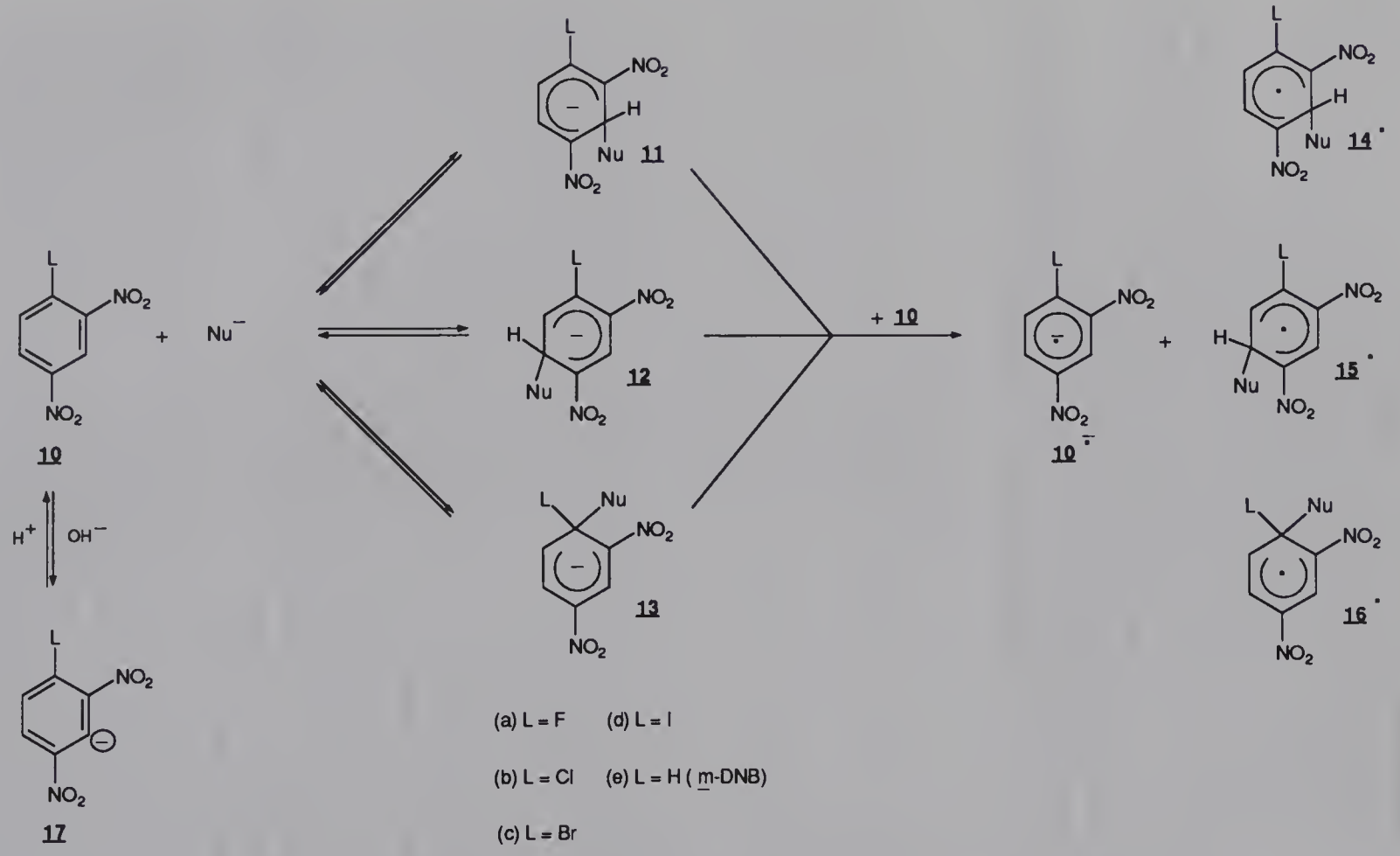


9a Z = H

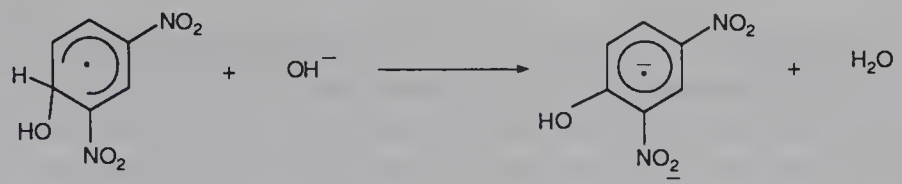
9b Z = NO_2

in DMSO.[19] On this ground, it has been suggested that radical anion formation would preferably occur via electron transfer from a donor σ-adduct rather than from the nucleophile, at least if the precursor aromatic is sufficiently activated to form a σ-complex to some extent under the experimental conditions used. Recalling that covalent nucleophilic addition occurs in general at a much faster rate at an unsubstituted than at a substituted carbon, the situation for substituted 1-L-2,4-dinitrobenzenes **10** (L = F, Cl, Br, I) can be envisioned as shown in Scheme 7.1, where all three adducts **11**, **12**, and **13** can act as electron donors toward the parent nitroaromatics. Of course, the adduct **13** may be the precursor of a normal S_NAr pathway if the rate of departure of the leaving group L is greater than or of the same order of magnitude as that of electron transfer to form the radical anion $\mathbf{10}^{\bullet-}$.

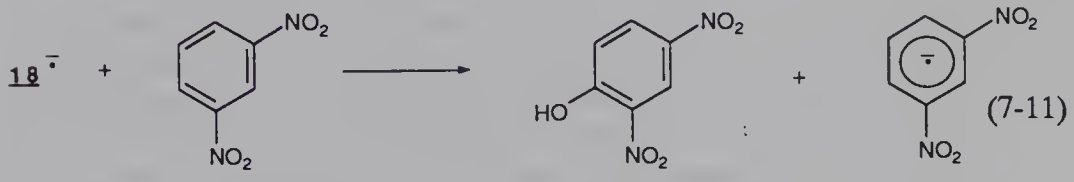
The occurrence of the electron exchanges shown in Scheme 7.1 is consistent with the observation that some nitroaromatics—for example, *m*-dinitrobenzene (*m*-DNB = **10e**)—undergo, at least to some extent, nucleophilic aromatic substitution of hydrogen in the presence of OH^-, yielding the corresponding phenol (e.g., 2,4-dinitrophenol: **18**). The mechanism presented in eqs. 7-10 and 7-11 has been suggested to account for the formation of **18** from **10e** via $\mathbf{15e}^{\bullet}$ (= $\mathbf{16e}^{\bullet}$, Nu = OH).[8b]


L
NO2
+ Nu−
10
H+
OH−
17
H
Nu
11
12
13
+ 10
10 ·−
14 ·
15 ·
16 ·
(a) L = F
(b) L = Cl
(c) L = Br
(d) L = I
(e) L = H (m-DNB)

Scheme 7.1.

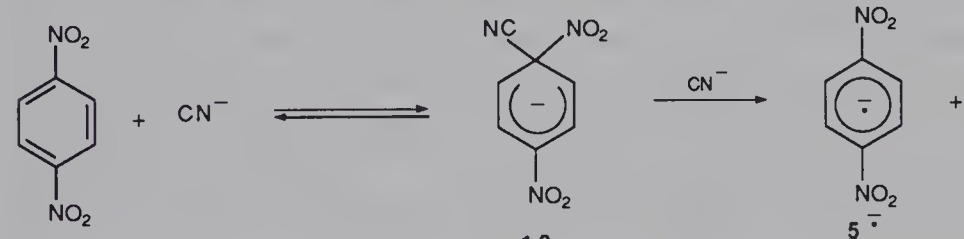


15• 18•⁻ (7-10)



10 (m-DNB) 18 10•⁻ (7-11)

A very recent study, which supports the occurrence of facile electron transfers from donor σ-adducts, is a kinetic analysis of the formation of the radical anion $5^{\bullet-}$ in the reaction of *p*-DNB with cyanide ion in DMF.[36] The results fit well the idea that in this instance $5^{\bullet-}$ is formed according to eq. 7-12 in which the formation of the intermediate σ-complex **19** is rate limiting.[36]



5 (p-DNB) 19 5•⁻ (7-12)

Nitroarenes can equally undergo some aromatic proton abstraction, yielding nitroaryl anions (e.g., 17) in basic solutions (Scheme 7.1).[33,34] Considering the ease of electron transfer between carbanions and nitroaromatics,[8b,15,35,37] the possibility that these anions act as electron donors in forming the nitroarene radical anions has also been advanced.[21]

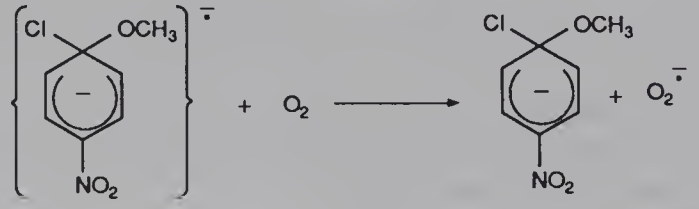
7.2.2 Radical Chain Substitutions

The idea that radical anion formation can be the promoting step in an activated S_NAr nucleophilic aromatic substitution pathway has been derived from various kinetic studies by ESR or electron absorption spectroscopy of the appearance and/or disappearance of the radical anions, parent substrates, and final products under various experimental conditions.[5,6,9,12,23,24,38] Pioneering studies in this area were reported by Shein *et al*, who investigated, in particular, the reactions of *p*-chloronitrobenzene (4) and 1-chloro-2,4-

dinitrobenzene (**10b**) with methoxide ion, affording *p*-nitroanisole (*p*-NA = **22a**) and 2,4-dinitroanisole (2,4-DNA), respectively, in CH_3OH/DMSO mixtures, and the reaction of **4** with hydroxide ion to give *p*-nitrophenoxide ion in H_2O/DMSO mixtures.[5,23,24] Although their kinetic analysis was only semiquantitative, these authors reported the following key observations:

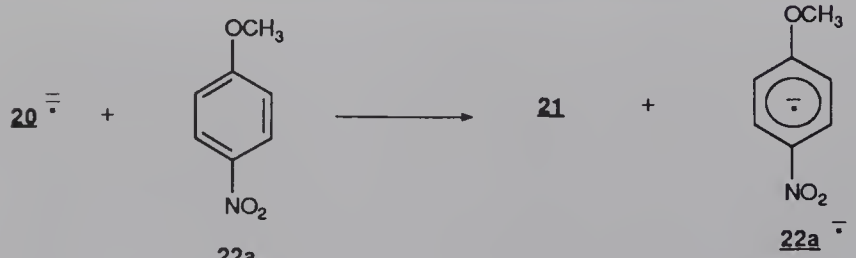
1. The rates of substitution are increased in the presence of oxygen, upon irradiation of the solutions with a mercury lamp and, in the case of the *p*-chloronitrobenzene–methoxide system, upon initial addition of **22a** (*p*-NA)—the resulting substitution product.[5,9,23,24]
2. The rates of substitution are markedly decreased in the presence of inhibitors like tetracyanoethylene or tetracyanoquinodimethane.[5,9,24]

Based on these findings as well as on other features discovered in related processes (e.g., the accelerating effect of peroxides)[38c] the radical chain mechanism of Scheme 7.2, which postulates the formation of a radical dianion intermediate like $\mathbf{20}^{2\cdot-}$, by methoxide ion addition to the radical anion precursor $\mathbf{4}^{\cdot-}$, has been suggested for the reactions in CH_3OH/DMSO mixtures. The intermediacy of $\mathbf{20}^{2\cdot-}$ was supported by the ESR identification of such a radical dianionic species in the reaction of 2,4,6-trinitroanisole (TNA) with methoxide ion.[24b] The role of oxygen and of the parent anisole in promoting the chain was tentatively accommodated by eqs. 7-13 to 7-16.[5,23,24a] Note that the feasibility of some of the steps formulated by Shein—for example, the direct electron transfers from CH_3O^- or $O_2^{\cdot-}$ to **4**—is now questioned.[35,39]



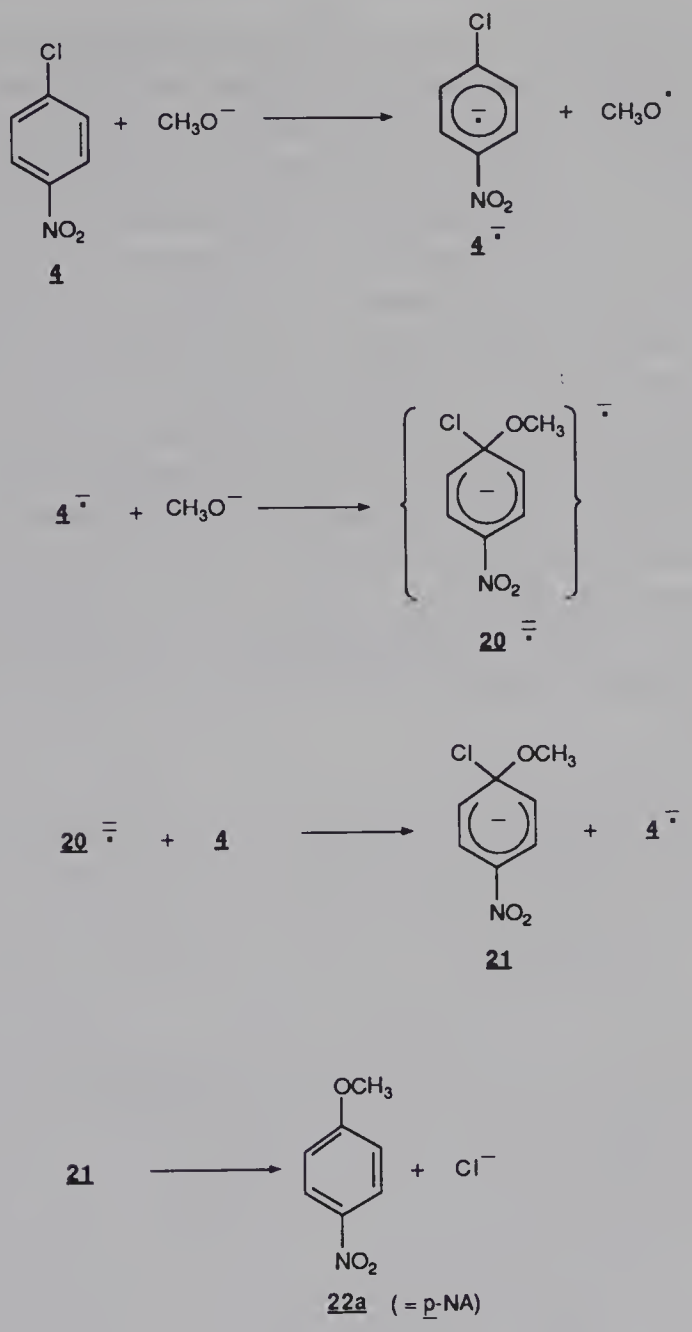
20$^{\cdot-}$ **21** (7-13)

(7-14)



22a **22a**$^{\cdot-}$ (7-15)

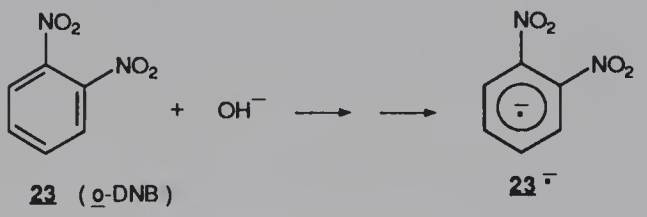
(7-16)



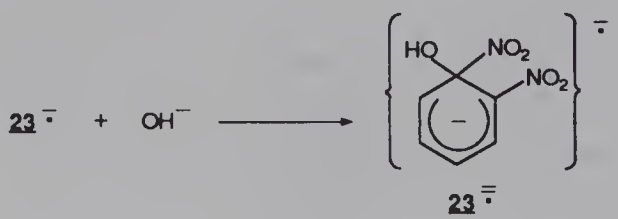
Scheme 7.2.

Other early claims for the role of radical anions in overall S_NAr displacements have come from a kinetic study by Abe and Ikegami of the substitutions of *o*-DNB (23) and *p*-DNB (5) with OH^- ion to give *o*- and *p*-nitrophenols (24 and 25) in 96% DMSO/4% H_2O.[12] In these systems the radical anions $5^{\bullet-}$ and $23^{\bullet-}$ are formed initially to a considerable extent (eq. 7-17), and the time

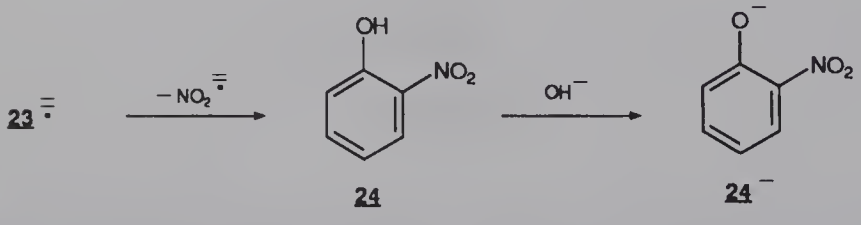
dependence of their concentrations was found to be the same as that indicated by changes in the visible spectrum or by ESR spectroscopy. Interestingly, the decay of $5^{\bullet-}$ and $23^{\bullet-}$ was extremely slow in experiments conducted with [OH^-] < 3[DNB] but fast in experiments with [OH^-] >> 3[DNB], exhibiting here a first-order kinetic behavior at a given OH^- concentration. These observations indicated that the decomposition of $5^{\bullet-}$ or $23^{\bullet-}$ consumes hydroxide ion, thus excluding a unimolecular mechanism of the $S_{RN}1$ type and suggesting the formation of a radical dianion, as shown in eq. 7-18 for the *o*-DNB system. For the conversion of $\underline{23}^{2\bullet-}$ or its *p*-DNB analogue $\underline{5}^{2\bullet-}$ to the corresponding nitrophenols **24** and **25**, the two possible mechanisms shown in eqs. 7-19 and 7-20 were proposed. Both fitted well the time dependence of the visible absorption, recorded at various wavelengths at which the radical anions $23^{\bullet-}$ or $5^{\bullet-}$ and the resulting phenoxide ions absorb. As can be seen, eq. 7-19 requires the elimination of the radical dianion $NO_2^{2\bullet-}$, while eq. 7-20 assumes loss of nitrite ion from the radical dianion, followed by electron transfer from the resulting nitrophenol radical anion to the corresponding unreacted *o*-dinitrobenzene.[12]



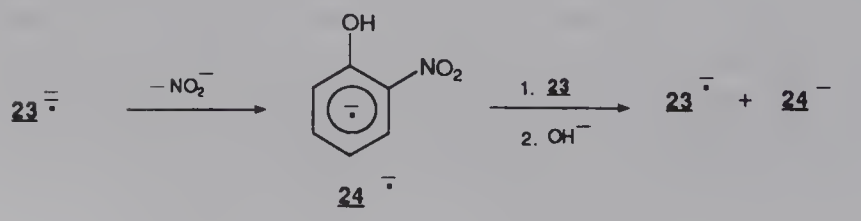
23 (o-DNB) $\underline{23}^{\bullet-}$ (7-17)



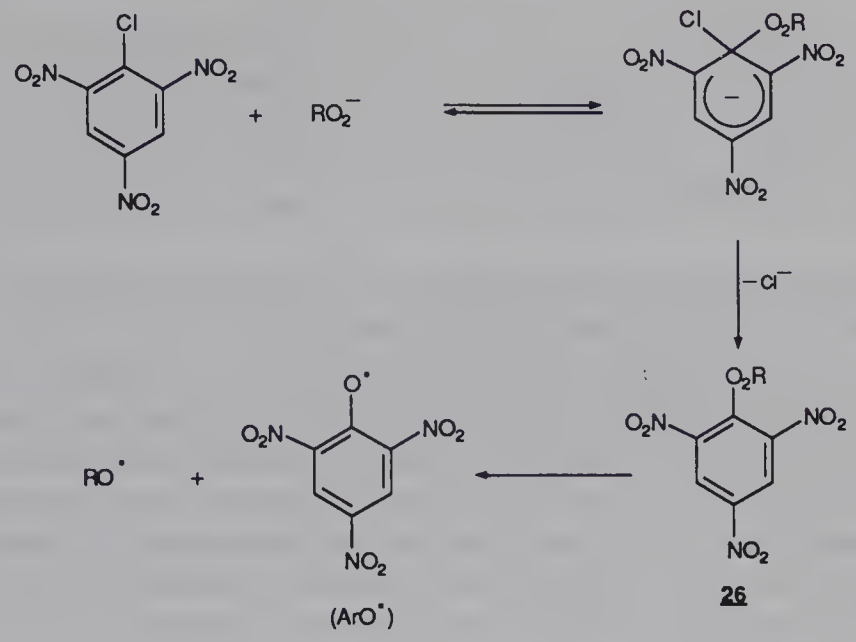
$\underline{23}^{2\bullet-}$ (7-18)



24 $\underline{24}^{-}$ (7-19)

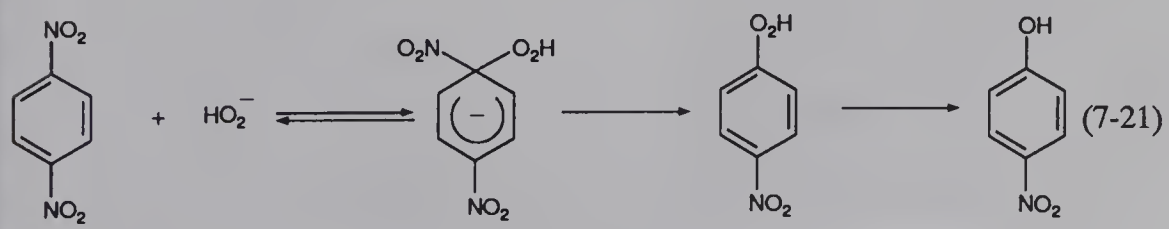


$\underline{24}^{\bullet-}$ (7-20)



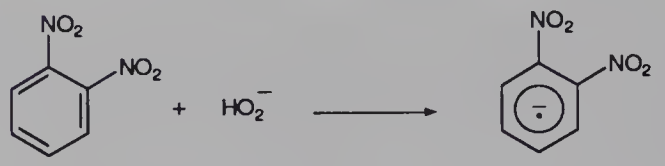
Scheme 7.3.

Kropf and coworkers have suggested that the catalytic effect of hydroperoxide ions on the conversion of picryl chloride (**6a**) or 2,4,6-trinitroanisole to picric acid in various solvents (DMSO, DME, toluene, or methanol) originates mainly from the stronger nucleophilic character of ROO^- compared to RO^- ions (Scheme 7.3).[40] The reaction would first produce the S_NAr product, that is, the alkylarylperoxide **26**, which would undergo spontaneous decomposition to the alkyloxy (RO•) and aryloxy (ArO•) radicals. It is these radicals that would enter a radical chain process leading to picric acid. Heller and Weiler have succeeded in firmly identifying by NMR techniques *p*-nitrophenylhydroperoxide (**27**), which is a reasonably stable intermediate in the reaction of *p*-DNB with basic hydrogen peroxide to give *p*-nitrophenol (**25**) in aqueous dioxane (eq. 7-21).[41] In this case, however, the exact mechanism of the conversion of **27** to **25** has not been established. Similarly, the intermediacy of *o*-nitrophenylhydroperoxide is now proposed to account for the accelerating effect of H_2O_2 on the conversion of *o*-DNB to *o*-nitrophenol (**24**) in basic solution.[42] The idea that the reaction might proceed according to eqs. 7-18 to 7-20 with a much faster formation of the *o*-DNB radical anion $\mathbf{23}^{\bullet}$ via



(7-21)

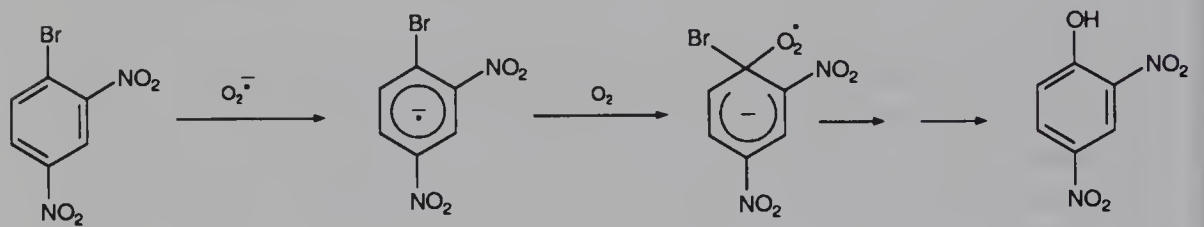
5 (p-DNB) **27** **25**



23 (o-DNB) **23**$^{\bullet-}$ (7-22)

eq. 7-22 ($E°HO_2^{\bullet}/HO_2^-$ = 0.8 V)[43] than via the unlikely step of eq. 7-17 ($E°_{HO^{\bullet}/HO^-}$ = 1.9 V)[43] has now been rejected.[41,42]

1-Halo-2-nitro- or 1-halo-4-nitrobenzenes, 1-halo-2,4-dinitrobenzenes, as well as *o*-DNB and *p*-DNB, are converted to the corresponding nitrophenols upon reaction with superoxide ion $O_2^{\bullet-}$ in DMSO, DMF, and benzene, and in the gas phase.[44–46] In the case of 1-bromo-2,4-dinitrobenzene (**10c**), experiments carried out with ^{18}O-labeled KO_2 in benzene solutions saturated with $^{32}O_2$ have given only a small amount of ^{18}O-labeled 2,4-dinitrophenol.[44] Thus, it was concluded that the phenolic oxygen is incorporated for the most part after equilibration with molecular oxygen dissolved in the solution, and the mechanism of eq. 7-23 was suggested.[44] This involves initial electron transfer



10c **10c**$^{\bullet-}$ **28**$^{\bullet-}$ **18** (7-23)

between $O_2^{\bullet-}$ and **10c** to yield the radical anion **10c**$^{\bullet-}$, which is subsequently scavenged by molecular oxygen to form the intermediate radical anionic σ-adduct **28**$^{\bullet-}$. The manner in which **28**$^{\bullet-}$ is converted to the resulting phenol **18** was not described.[44] Kinetic studies of the reactions of monohalonitrobenzenes with electrogenerated superoxide ion in DMSO and DMF have instead led to

$$ArL + O_2^{\bullet-} \rightarrow ArLO_2^{\bullet-}$$

$$ArLO_2^{\bullet-} \rightarrow ArO_2^{\bullet} + L^-$$

$$ArO_2^{\bullet} + O_2^{\bullet-} \rightarrow ArO_2^- + O_2$$

$$ArO_2^- \rightarrow ArO^- + \tfrac{1}{2}O_2$$

Scheme 7.4.

$$ArL + O_2^{\bullet-} \rightarrow ArLO_2^{\bullet-}$$

$$ArLO_2^{\bullet-} \rightarrow ArO_2^{\bullet} + L^-$$

$$ArO_2^{\bullet} \rightarrow ArO^{\bullet} + \tfrac{1}{2}O_2$$

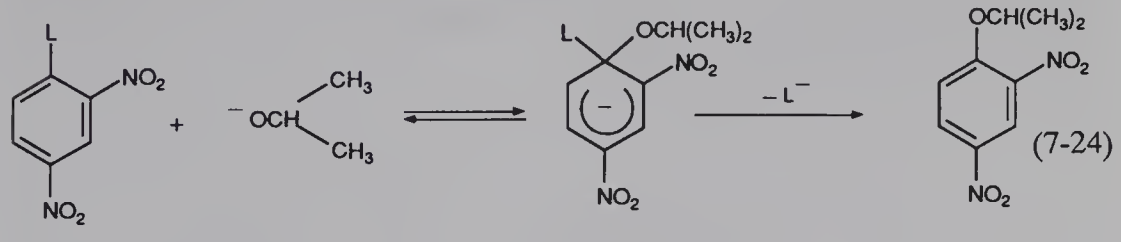
$$ArO^{\bullet} + O_2^{\bullet-} \rightarrow ArO^- + O_2$$

Scheme 7.5.

the conclusion that the substitutions proceed via rapid initial nucleophilic attack of $O_2^{\bullet-}$ to form a σ-adduct intermediate of type **28**$^{\bullet-}$.[47,48] The two reaction sequences of Schemes 7.4 and 7.5, where $ArLO_2^{\bullet-}$ represents this intermediate σ-adduct, can account for the results obtained in DMSO.[48] Both involve the consumption of 2 molecules of $O_2^{\bullet-}$ to convert the halide (ArL) into the phenol (ArO^-).

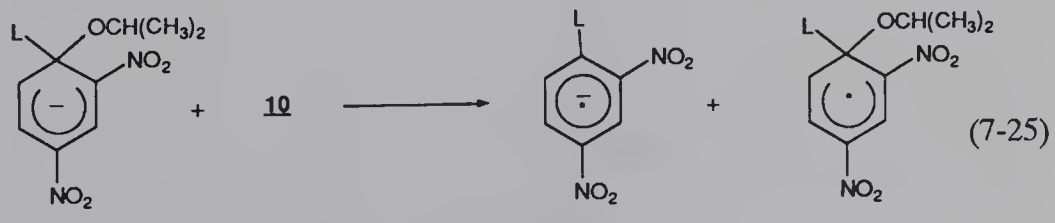
The reactions of 1-chloro- and 1-iodo-2,4-dinitrobenzenes (**10b**) and (**10d**) with potassium 2-propoxide in a 1:1 (v/v) 2-propanol/benzene mixture have been shown to proceed normally by the S_NAr mechanism, yielding the expected 1-(2-propoxy)-2,4-dinitrobenzene (**30**) (eq. 7-24).[20] However, substantial amounts of 2,4-dinitrophenol (**18**) were obtained at the expense of **30** upon addition of crown ethers (e.g., dicyclohexyl-18-crown-6) to the solutions.[20] A significant feature was the identification of the radical anion **10b**$^{\bullet-}$ under these experimental conditions. Scheme 7.6, which consists of eqs. 7-25 to 7-28, was formulated to account for the formation of **18**. The formation of **10b**$^{\bullet-}$ or of its iodo analogue **10d**$^{\bullet-}$ is assumed to occur by electron transfer from the Meisenheimer complex **29** to the parent halo derivatives (eq. 7-25). Such a transfer would be less favorable in the absence of a crown ether, due to stabilization of **29** by ion pairing with a potassium counterion.[20] Once **10b**$^{\bullet-}$ or **10d**$^{\bullet-}$ had formed, it would react according to eqs. 7-26 to 7-28, affording **18**. The identification of some propene among the reaction products was consistent with the anticipated consumption of the isopropyl radical in further radical processes.[20]

Scheme 7.6 is interesting in that eqs. 7-26 and 7-27 are identical with the two first steps of the propagation cycle of the radical chain $S_{RN}1$ mechanism proposed by Bunnett to account for nucleophilic aromatic substitution in aryl halides (Ar-L), which do not contain strongly electron-withdrawing groups



(7-24)

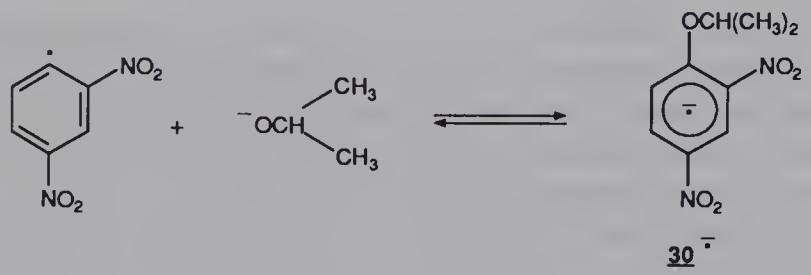
10 (b) L = Cl; (d) L = I **29** **30**



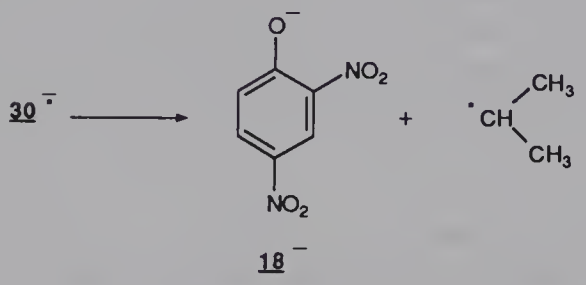
(7-25)

29 **10**$^{\bullet-}$

(7-26)



(7-27)



(7-28)

Scheme 7.6.

(Scheme 7.7). Generally, nitroaryl halides do not avail themselves of the $S_{RN}1$ pathway.[7,49] The ketoalkyl deiodination of *o*-iodonitrobenzene depicted in eq. 7-29 remains the only documented exception.[49] Also, the reaction of 1-chloro-2,4-dinitrobenzene with the anion of 2-nitropropane shown in eq. 7-30, might occur in part by the $S_{RN}1$ mechanism.[50]

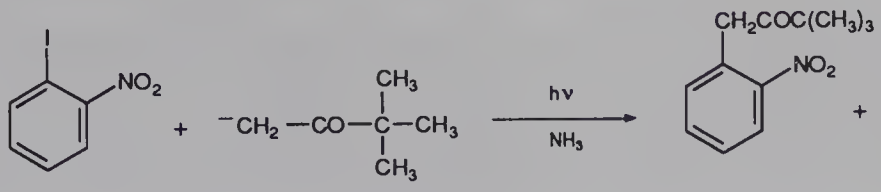
$$Ar\text{–}L \xrightarrow{e^-} ArL^{\cdot -}$$

$$Ar\text{–}L^{\cdot -} \rightarrow Ar^{\cdot} + L^-$$

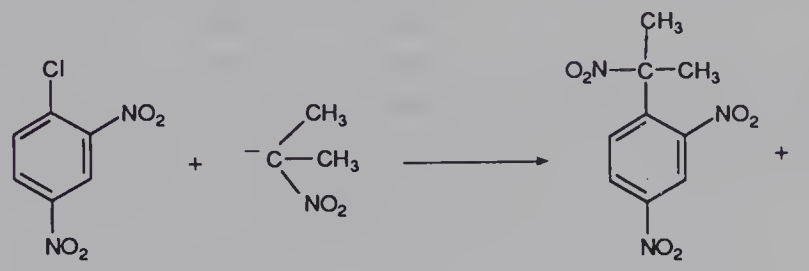
$$Ar^{\cdot} + Nu^- \rightarrow Ar\text{–}Nu^{\cdot -}$$

$$Ar\text{–}L + Ar\text{–}Nu^{\cdot -} \rightarrow Ar\text{–}L^{\cdot -} + Ar\text{–}Nu$$

Scheme 7.7.



(7-29)



(7-30)

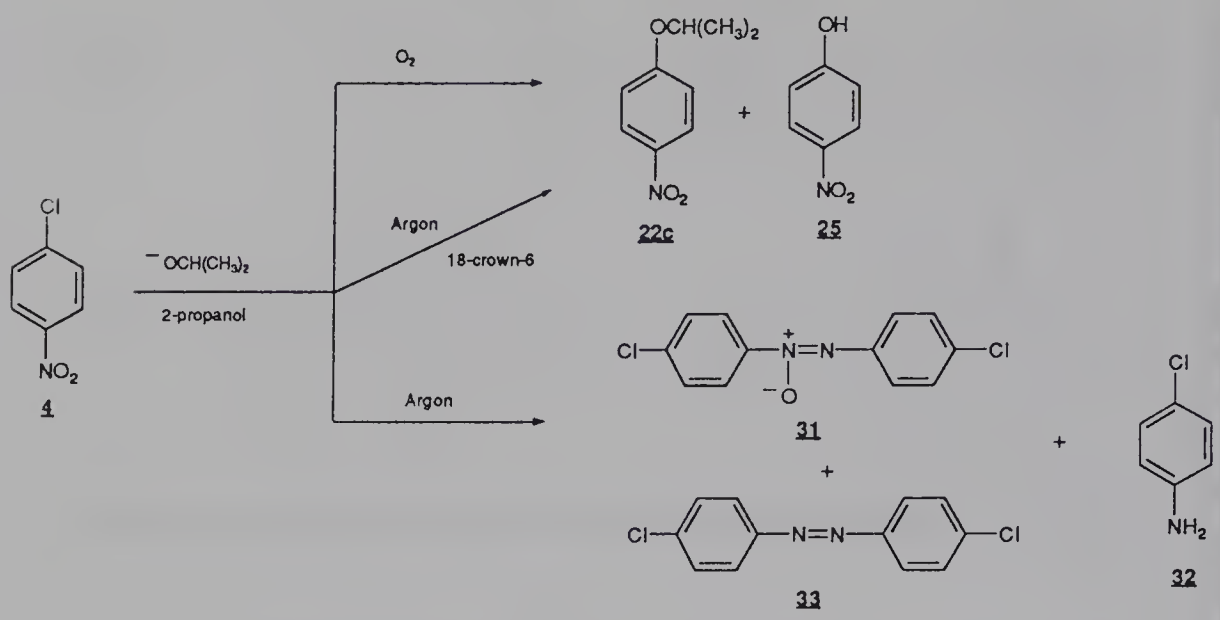
10b

7.2.3 Substitution Versus Reduction Processes

In many instances, nitroarene radical anions are apparently formed, but they are unable to enter nucleophilic aromatic substitution pathways because they react more rapidly in competing processes. This is especially characteristic of moderately activated substrates, as exemplified by the results obtained in various studies of the reactions of *p*-chloronitrobenzene (**4**) with alkoxide ions in the parent alcohol.[19–21,50–56]

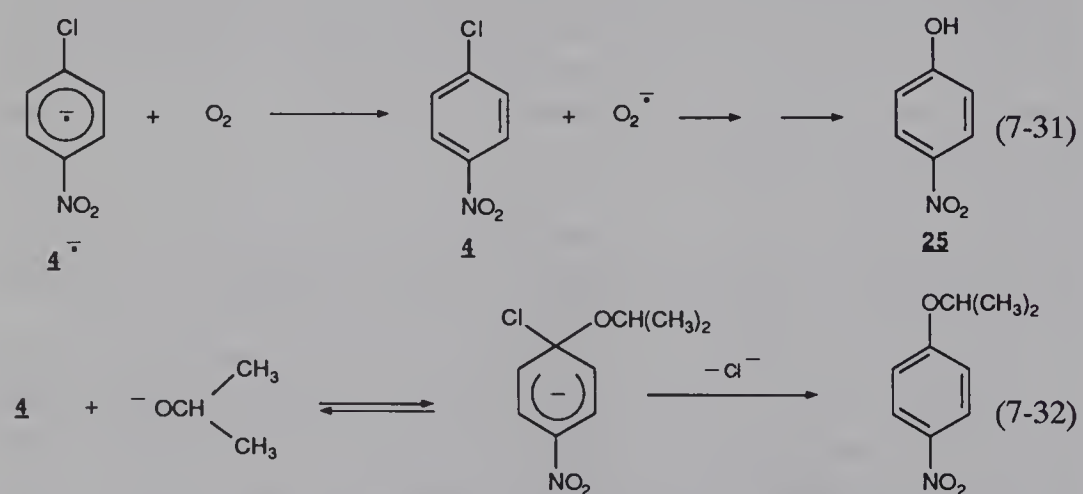
Upon treatment of **4** with methoxide and ethoxide ions in air in methanol and ethanol, respectively, substantial amounts of the corresponding ethers, *p*-nitroanisole (**22a**), and *p*-nitrophenetole (**22b**) are obtained, apparently as the result of clean S_NAr substitutions. In contrast, a similar treatment with 2-propoxide ions in 2-propanol affords the expected 2-propoxy ether **22c** in a rather poor yield, together with a small amount of *p*-nitrophenol (**25**). With the same system in an inert atmosphere (argon), the products obtained are reduction products, namely 4,4′-dichloroazoxybenzene (**31**), 4-chloroaniline (**32**), and to a smaller extent 4,4′-dichloroazobenzene (**33**).[21,51–56] On the other hand, **4** reacts similarly with 2-propoxide ions in air and in argon when crown ethers like 18-crown-6 are added to the solutions. In these instances, alkoxydechlorination occurs to give the ether **22c** in 95% yield. The results for the 2-propoxide/2-propanol system are summarized in Scheme 7.8. Reduction products are also obtained using the *tert*-butoxide/*tert*-butanol system.[21]

Scorrano and coworkers have recently discussed the mechanistic aspects of Scheme 7.8.[21,51,54,56] The major feature of the aerobic interactions in 2-propanol would be that some of the *p*-chloronitrobenzene radical anion ($4^{\bullet-}$) is formed, presumably via a complex mechanism involving dianion intermediates.[57] However, $4^{\bullet-}$ would have no chance to promote a radical substitu-



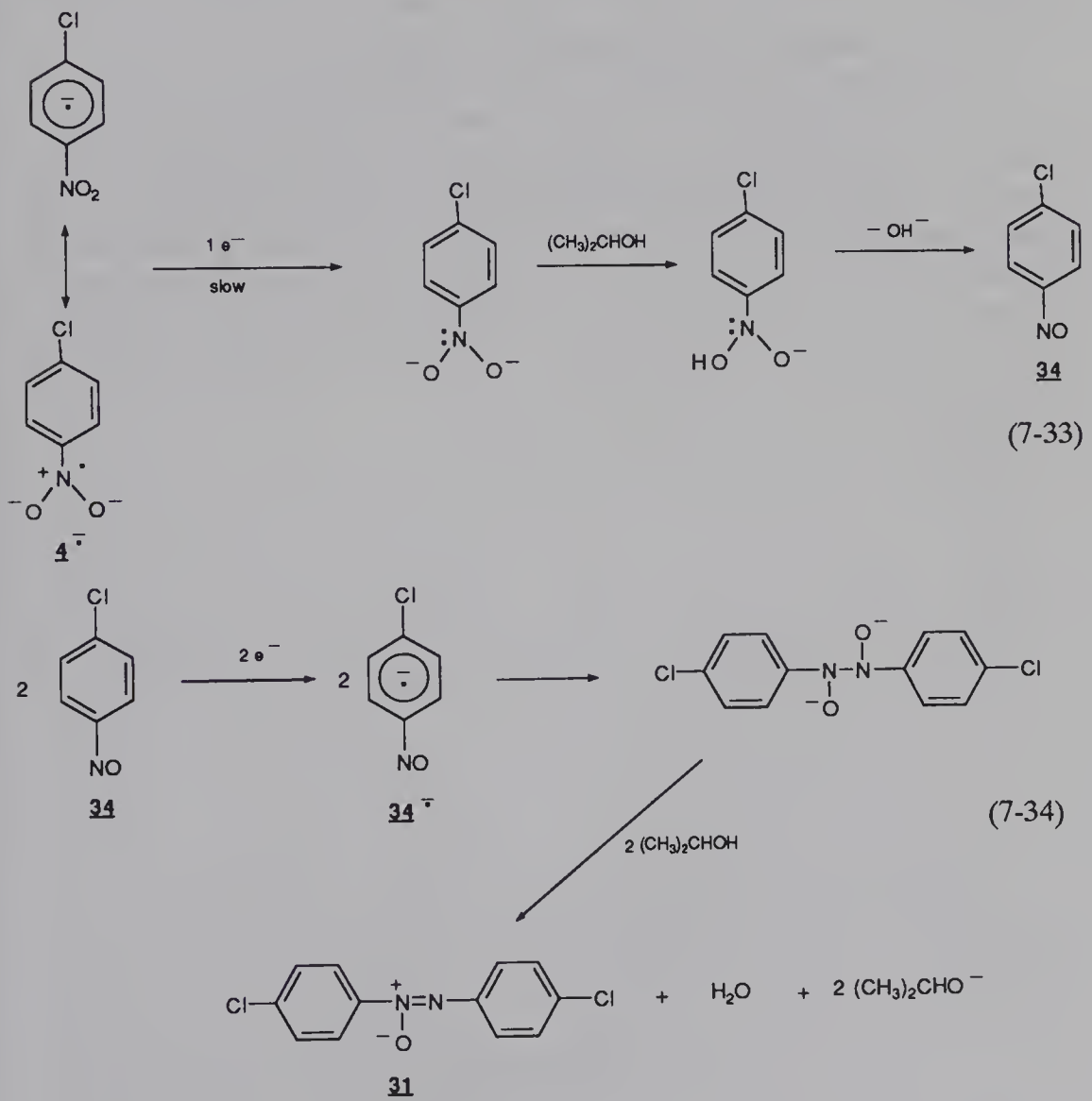
Scheme 7.8.

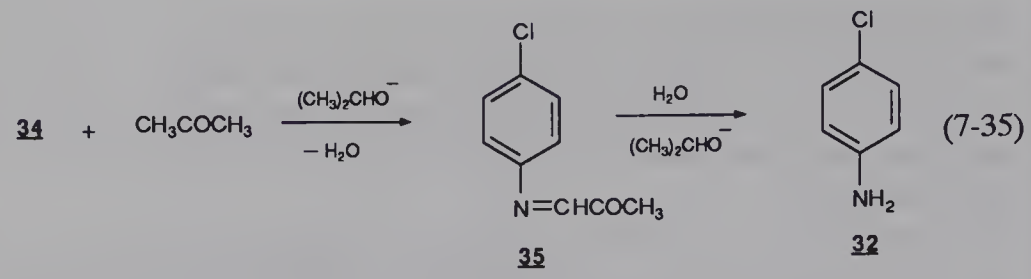
tion process leading to the ether **22c** because it is very rapidly quenched by the oxygen present in the solution.[51,54] In the latter case, the destruction of $\underline{4}^{\bullet-}$ is accompanied by the recovery of the parent substrate **4** and formation of superoxide ion, which would react with **4** to yield *p*-nitrophenol (**25**) (eq. 7-31), probably via a multistep sequence of the type described in Schemes 7.4 and 7.5. Concomitantly, formation of the ether **22c** occurs to some extent by a normal $S_{RN}Ar$ pathway (eq. 7-32). Confirmation that **22c** forms via this classical mechanism is provided by the results of the experiments carried out in air in



the presence of crown ethers to prevent ion pairing of potassium 2-propoxide.[21,52,53,56] Because free 2-propoxide ions exhibit a greater S_NAr reactivity than the corresponding ion pairs, better yields of **22c** are then obtained. Also, the kinetics of the reactions exhibited the familiar features of S_NAr pathways.

In the absence of efficient quenching by oxygen, reduction of the NO_2 group of **4** takes place via the intermediate radical anion **4**$^{\bullet-}$. Equations 7-33 and 7-34 describe the formation of the azoxy derivative **31** via dimerization of the initially formed *p*-chloronitrosobenzene (**34**). Further reduction of **31** affords the corresponding azobenzene **33**.[51,54,56] Interestingly, the reduction of **4** to **34** is accompanied by oxidation of 2-propanol to acetone and the formation of water.[51,54] Under basic conditions, condensation of acetone with

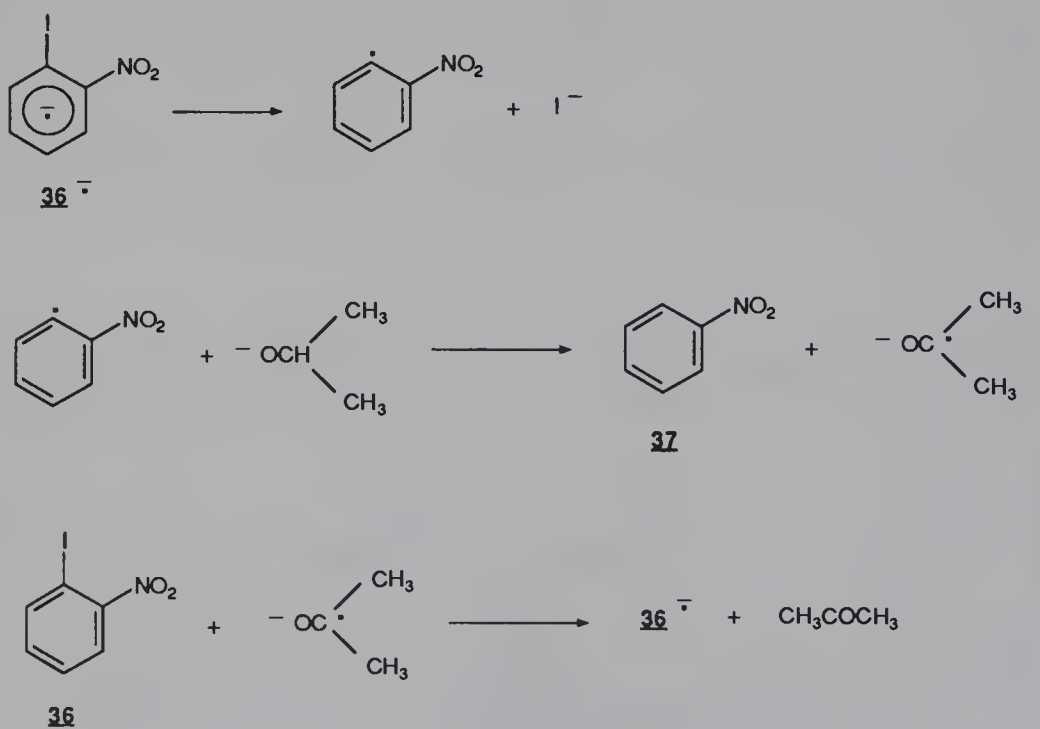




(7-35)

the nitroso derivative can occur to give the imino compound **35**, which is subsequently hydrolyzed to yield **32** (eq. 7-35).[51,54] Detailed studies of this reduction process have allowed the devising of suitable experimental conditions for the synthesis of anilines or azoxybenzenes from mononitrobenzenes in basic alcoholic media.[54,55] In the presence of 18-crown-6 ether in an inert atmosphere, the rate of reduction is reduced while the rate of the $S_{RN}Ar$ substitution is markedly increased.[56] This accounts for the essentially complete formation of **22c** under these experimental conditions.

Examination of the behavior of other mononitrohalobenzenes under the same experimental conditions as those used for **4** has allowed the characterization of another radical pathway that leads to hydrodehalogenation of the starting nitroarene.[56] Nitrobenzene (**37**) is thus formed in quantitative yield upon treatment of 2-iodonitrobenzene (**36**) with potassium 2-propoxide in 2-propanol. Scheme 7.9 describes the mechanism proposed for the reaction,

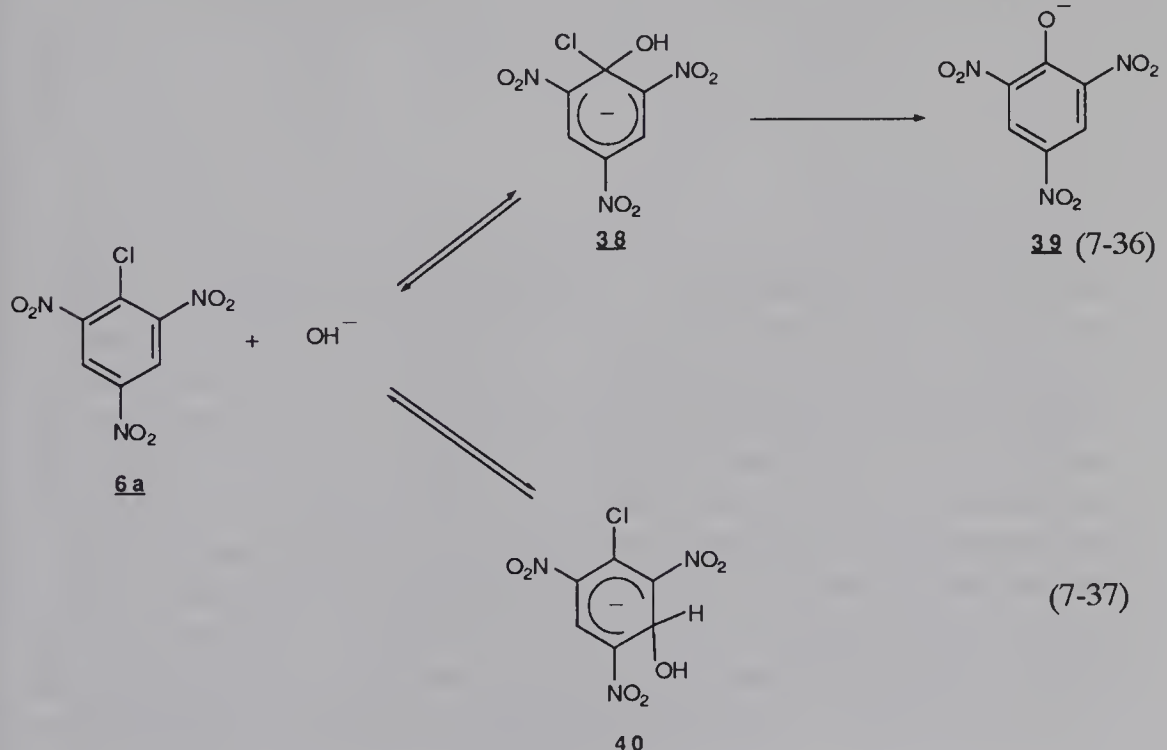


Scheme 7.9.

which proceeds especially well in anaerobic conditions and in the presence of crown ethers.[56] A crucial step in this scheme is the fragmentation of the C—I bond of the initially formed radical anion **36**$^{\bullet-}$. While the normal effect of a nitro group is to reduce the rate of fragmentation of haloarene radical anions,[58] there is electrochemical evidence that cleavage of the C—I bond in **36**$^{\bullet-}$ occurs at an appreciable rate in DMF.[59] Steric effects have been invoked to account for this reactivity, which is also reflected in the ability of **36** to undergo an $S_{RN}1$ substitution with the enolate of pinacolone (eq. 7-29).[49] Some other reactions believed to involve C–halogen bond cleavage in a radical anion intermediate have been reported (e.g., eq. 7-26).[20]

7.3 Substitutions via Charge–Transfer Complexes of Anionic Radical Character

As discussed in Chapter 1, the generally accepted mechanism for the substitution of picryl chloride (**6a**) with hydroxide ion in aqueous solution involves rate-limiting formation of the intermediate σ-complex **38**, which

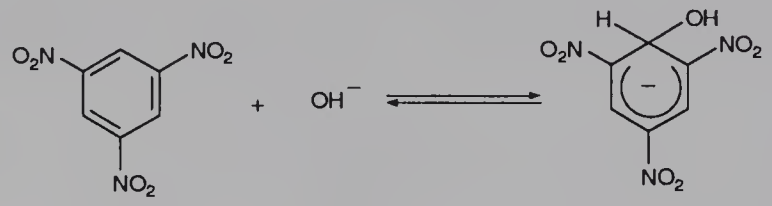


(7-36)

(7-37)

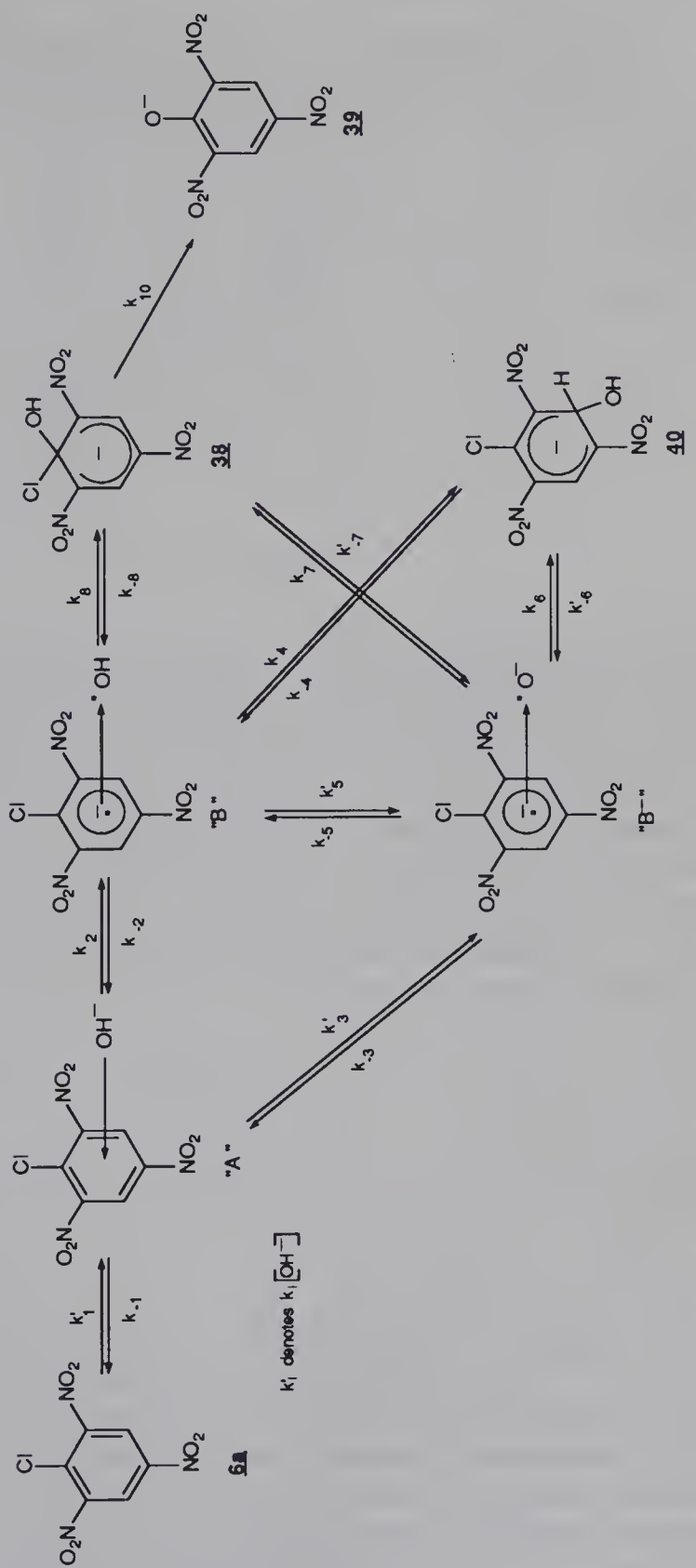
rapidly decomposes to picrate ion (**39**) (eq. 7-36). Formation in a side equilibrium of the 1,3-complex **40**, which is an inactive species with respect to the substitution pathway of **6a**, occurs prior to that of **38** at high hydroxide ion concentrations (eq. 7-37).

Very recently, Bunton *et al.* have reinvestigated the kinetics of the reaction of **6a** with OH^- in water and in 50:50 (v/v) H_2O/DMSO.[25,27] In most of the experiments that they have carried out over a large range of OH^- concentrations (0.001–2.5 mol/l in water), these authors have detected the formation of two new short-lived intermediates between substrate and substitution product. When observed, the first intermediate, A (λ_{max} = 500 nm), was formed too rapidly to be followed in a stopped-flow spectrometer. In contrast, the disappearance of A could be studied and the rate measured for this process was the same as that measured with the appearance of the second identified intermediate, B (λ_{max} = 260 nm). Decomposition of B followed in parallel to the appearance of a mixture of picrate ion (**39**) and the 1,3-complex **40**. Slow conversion of this latter adduct to **39** eventually occurs. Interestingly, two intermediates of type A and B were also identified prior to the formation of the stable σ-adduct **41** in the reaction of 1,3,5-trinitrobenzene (TNB) with OH^- under the same experimental conditions as those used for the picryl chloride systems (eq. 7-38).[25,27]

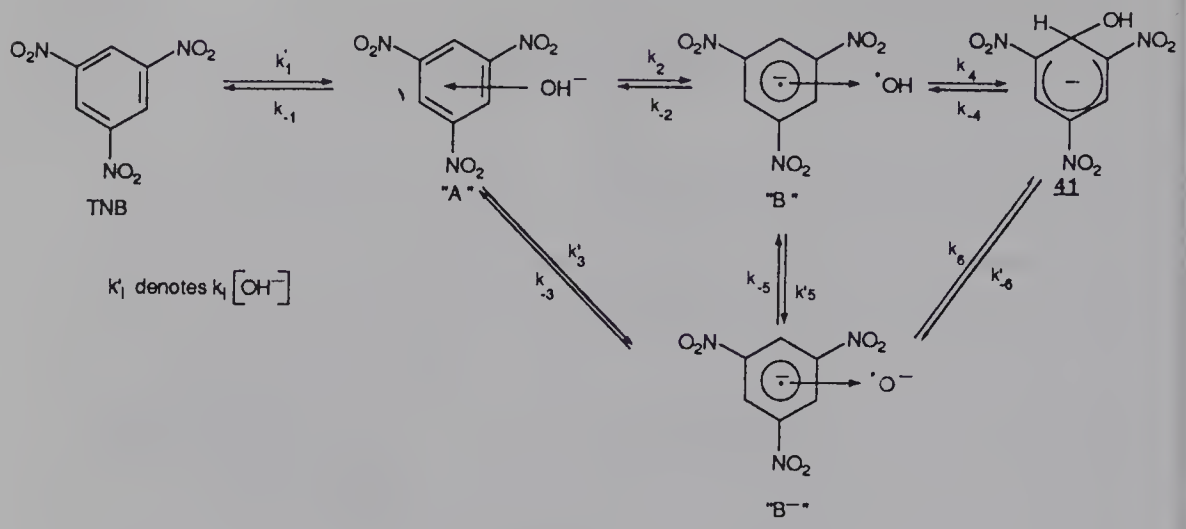


TNB **41** (7-38)

Schemes 7.10 and 7.11 have been proposed to account for the various observations in the substitution of **6a** and in the OH^- addition to TNB, respectively. As can be seen, Bunton *et al.* suggest that the first intermediate A is a substrate-OH^- π-complex. The second intermediate B is formulated as a charge–transfer (CT) complex formed by a single electron transfer from the nucleophile to the substrate. Since the $OH^{\bullet}$ radical has a pK_a of 11.8–11.9 in aqueous solution, deprotonation of B to the conjugate base B^- needs to be taken into account under the experimental conditions chosen.[60,61] Interaction of the two partners in B and B^- leads to bond formation and rearrangement to either the 1,1-complex **38** or the 1,3-complex **40** in Scheme 7.10, and to the stable TNB complex **41** in Scheme 7.11. The "$S_{RN}Ar$" product (i.e., the picrate ion **39** would then form by two different routes as shown in Scheme 7.10; (1) by direct

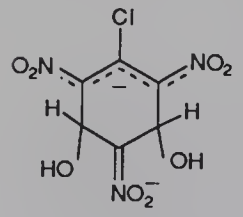


Scheme 7.10.



Scheme 7.11.

elimination of chloride ion from the 1,1-complex **38** (however, this process occurs so rapidly that **38** cannot be observed) or (2) by return of the 1,3-complex **40** to B and B^- and by partitioning of these CT complexes into the isomeric 1,1-complex **38**. Note that, for simplicity, Scheme 7.10 does not include consideration of the ionization of the hydroxy group of the adduct **40**, which is known to occur in concentrated aqueous hydroxide solutions.[62,65] The same remark holds for the adduct **41** in Scheme 7.11.[33,63,64]. Also, the possible formation of the dihydroxy and trihydroxy adducts **42**, **43**, and **44** in the more basic solutions has been omitted.[66,67]



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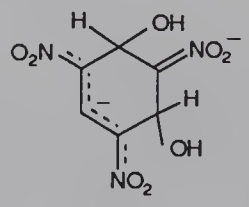

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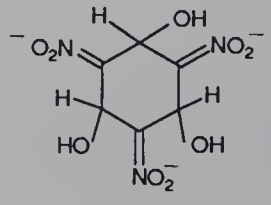


44

Using experimental rate data, the various rate and equilibrium constants for most individual reactions in Schemes 7.10 and 7.11 were calculated by applying relaxation theory.[27,68] The results are summarized in Tables 7.1 and 7.2. Use of these rate and equilibrium parameters to calculate the second-order rate constant for overall substitution of **6a** ($k_{calc} = K_1K_2k_8 = 0.53$ l mol^{-1} s^{-1}) or the overall equilibrium constant for OH^- addition to TNB ($K_{calc} = K_1K_2K_4 = 2.47$ l/mol) gives results in agreement with values directly measured in dilute

Table 7.1. Equilibrium Constants for Individual Steps in the Reactions of OH- with Picryl Chloride (6a) and TNB According to Schemes 7.10 and 7.11[a]

Compound	Solvent[b]	K_1 ($l\ mol^{-1}$)	K_2	K_3 ($l\ mol^{-1}$)	K_4	K_5 ($l\ mol^{-1}$)	K_6 ($l\ mol^{-1}$)
TNB	H_2O	0.16	0.578	2.61	26.7	4.52	5.94
	H_2O/DMSO	1.47	2.71	13.9	257	4.40	50.1
6a	H_2O	0.143	0.86	1.67	2.28	0.51	1.17
	H_2O/DMSO	1.65	0.807	1.89	319	10.8	136

[a] t = 25°C; data from ref. 27.

[b] 50:50 (v/v) H_2O/DMSO.

aqueous hydroxide solutions, where intermediates A and B do not form (k_{obs}6a = 0.46 or 0.506 l mol^{-1} s^{-1}; K_{obs} TNB = 2.6, 2.7, or 3.73 l/mol).[27a,33,67,69,70] The calculated equilibrium constant for formation of the 1,3-complex 40 of picryl chloride in water is also consistent with a reported value (K_{calc} = 0.28; K_{obs} = 0.43 l/mol).[27a,62,65]

The formulation of the first intermediates, A, as π-complexes is based on the known tendency of excellent electron acceptors like TNB to form stable π-complexes with various donors, especially in nonpolar solvents.[71–78] While the possibility that σ-complex forming reactions involve formation of a π-complex in a preliminary step has been considered by various authors (see Chapter 1), this has recently been reinforced by MNDO calculations on the interaction of various nucleophiles (e.g., CH_3O^-, CH_3S^-) with *p*-chloronitrobenzene.[79] These calculations suggest a substitution pathway involving initial formation of a charge–dipole complex of some stability, which would have the nucleophile centered at a van der Waals distance over the nitroaromatic ring. It is this complex, which is characterized by a slight shifting of charge distribution in the arene, without any acceptance of charge from the nucleophile, that Bunton *et al.* considered to be a good model for the intermediates A.[28] In aqueous media, these π-complexes should contain solvated OH^-, separated by water molecules from the aromatic system.

The proposal that the intermediates B are CT complexes, rather than free radical anions, was based in part on the observation that nitroarene radical anions are not generally observed by ESR spectroscopy in polar hydroxylic solvents.[8,27] Interestingly, such radical anions absorb strongly in the visible region,[8,12,33b] while the intermediates B absorb only in the UV region.

Table 7.2. Rate Constants for Individual Steps in the Reactions of OH^- with Picryl Chloride (6a) and TNB According to Schemes 7.10 and 7.11[a]

Compound	Solvent[b]	k_2 (s^{-1})	k_{-2} (s^{-1})	k_3 ($l\,mol^{-1}s^{-1}$)	k_{-3} (s^{-1})	k_4 (s^{-1})	k_{-4} (s^{-1})	k_6 (s^{-1})	k_{-6} ($l\,mol^{-1}s^{-1}$)	k_7 (s^{-1})	k_8 (s^{-1})
TNB	H_2O	618	1069	939	359	245	9.16	164	27.6		
	H_2O/DMSO	1270	468	1780	128	139	0.54	173	3.45		
6a	H_2O	904	1040	1190	707	89.9	39.4	44.9	38.4		4.31
	H_2O/DMSO	260	322	320	169	206	0.65	210	1.54	97	6.76

[a] t=25°C; data from ref. 27.

[b] 50:50 (v/v) H_2O/DMSO.

Steenken has suggested the occurrence of CT interactions between nitrobenzenes and neutral α-hydroxy- and α-alkoxyalkyl radicals in aqueous solution.[80]

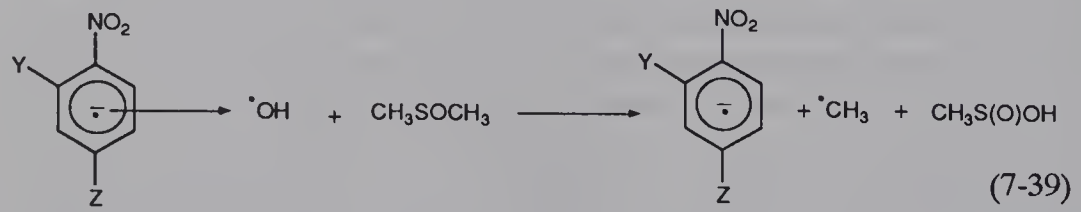
Theoretical calculations support structures like B. AM1 calculations, using the AMPAC program of Dewar, indicate that approach of OH^- to the center of TNB corresponds essentially to a complete one-electron transfer to the aromatic system and a gain of about 146 kJ/mol at about 2.2 Å.[28,81] Such a gain in the reaction enthalpy is larger than the solvation enthalpy of OH^- (~ 89 kJ/mol in H_2O), which must be overcome in aqueous solution.[27a,28] In a more general way, the calculations predict that *all nitroarenes with more than one nitro group can react with* OH^-, as well as with similar ions like CH_3O^-, *to form CT complexes* of type B which exhibit considerable anionic radical character at the nitroarene moiety.[28] As a matter of fact, Bunton *et al.* have also characterized CT complexes (as well as π-complexes) in the reactions of various 1-substituted-2,4-dinitronaphthalenes with OH^- in 50:50 (v/v) H_2O/DMSO.[27b] In contrast, the formation of such species from mononitroarenes would be unlikely in polar solvents, even though AM1 and MNDO calculations do not rule out this possibility in the gas phase.[28,79] In view of the picture formulated for the π-complexes in aqueous media, the energy barrier for going from species A to the CT complexes B would primarily be desolvation of OH^-, which would become free to approach the aromatic system closely.[28] In this regard, it is interesting that fairly similar equilibrium constants K_2 have been derived for conversion of the π-complexes into the CT complexes in the picryl and 2,4-dinitronaphthyl systems studied.[27]

In Schemes 7.10 and 7.11, the CT complexes B and B^- are the key intermediates that rearrange to the unreactive complexes **40** or **41**, or to the reactive 1,1-complex **38**, which can directly eliminate the leaving group and give the substitution product. AM1 calculations suggest that the collapse of the CT intermediates is largely dependent on the charge density in the aromatic moiety, bond formation occurring faster at the carbon atom with the lowest electron density.[28] This will account for the preferential rearrangement of B and B^- into the 1,3-complex **40** in Scheme 7.10. However, the relative thermodynamic stabilities of isomeric 1,1- and 1,3-complexes remain governed by factors discussed in detail in Chapter 2.[33] So, because of a lower thermodynamic stability, the 1,3-complex **40** rearranges with formation of the more stable 1,1-isomer **38** and then the substitution product **39**.

The formation of the CT complexes between radicals in the foregoing interactions is in accord with accumulated evidence that many interactions between nucleophiles and electrophiles occur via single-electron transfer rather than two-electron transfers.[1,2,33b,82–85] According to Pross, the dif-

ference between processes in which a single-electron transfer can or cannot be observed is due mainly to the localization of the first transferred electron and to steric interactions.[84] If the transferred electron is localized in the vicinity of the original nucleophile and if there is no important steric interference to formation of the new bond, the CT complex will have a very short life and may not be observable. In the case of acceptors like trinitrobenzenes, the possibility for a high delocalization of the unpaired electron is coupled with steric interactions involving ortho–nitro groups that hinder the formation of the Meisenheimer adducts.[27] These two factors would contribute to increasing the life of the CT complexes B, enabling one to follow their formation and their disappearance.[27]

In keeping with the idea that one-electron transfer is an essential step in activated nucleophilic aromatic substitution, there is a close relationship between Bunton's proposal of the intermediacy of the CT complexes B in aqueous solution and the evidence for free nitroarene radical anions in dipolar aprotic media of low water content. Let us assume that in schemes of the types illustrated previously (Schemes 7.10 or 7.11), the lifetime of the CT complexes becomes relatively long. Then they may, over time, dissociate to give free radical anions that can generate radical chain substitutions or overall reductions.[27] These free radicals could also become observable by ESR spectroscopy, or they could be trapped by scavengers like oxygen or nitroxides.[27,28] This situation can be expected to prevail in dipolar aprotic solvents, and probably also in many aprotic apolar solvents. Interestingly, Abe and Ikegami have suggested that the radical anions **5**$^{\cdot-}$ and **23**$^{\cdot-}$, which form readily upon treatment of *p*-DNB and *o*-DNB, respectively, with OH^- in 96% DMSO/4% H_2O, would arise from the dissociation of the CT complexes **45** and **46** according to the reaction shown in eq. (7-39).[12] In contrast, this dissociation



(7-39)

45 Y = H, Z = NO_2 — **5**$^{\cdot-}$

46 Y = NO_2, Z = H — **23**$^{\cdot-}$

would be very unfavorable in polar protic solvents that encompass the CT complexes in a solvent cage.[27] This would be especially so in solvents of high water content, because the ordered water structure should help to keep the

partners together and assist the rearrangement to the σ-complexes. Note that the intermediacy of CT complexes of type B in such media provides a good understanding of the anomalies observed in hydrogen exchange of many nitroarenes in D_2O or DMSO-d_6-D_2O solutions.[26] Similarly, line broadening of the NMR proton signals of unreacted substrate (a common observation in DMSO-d_6/D_2O solutions) is understandable in terms of an exchange between a CT complex and the parent nitroarene.[26] The occurrence of one-electron transfer in forming an intermediate CT complex might also explain why nucleophilic additions to nitrohaloarenes do not follow the reactivity–selectivity principle.[86]

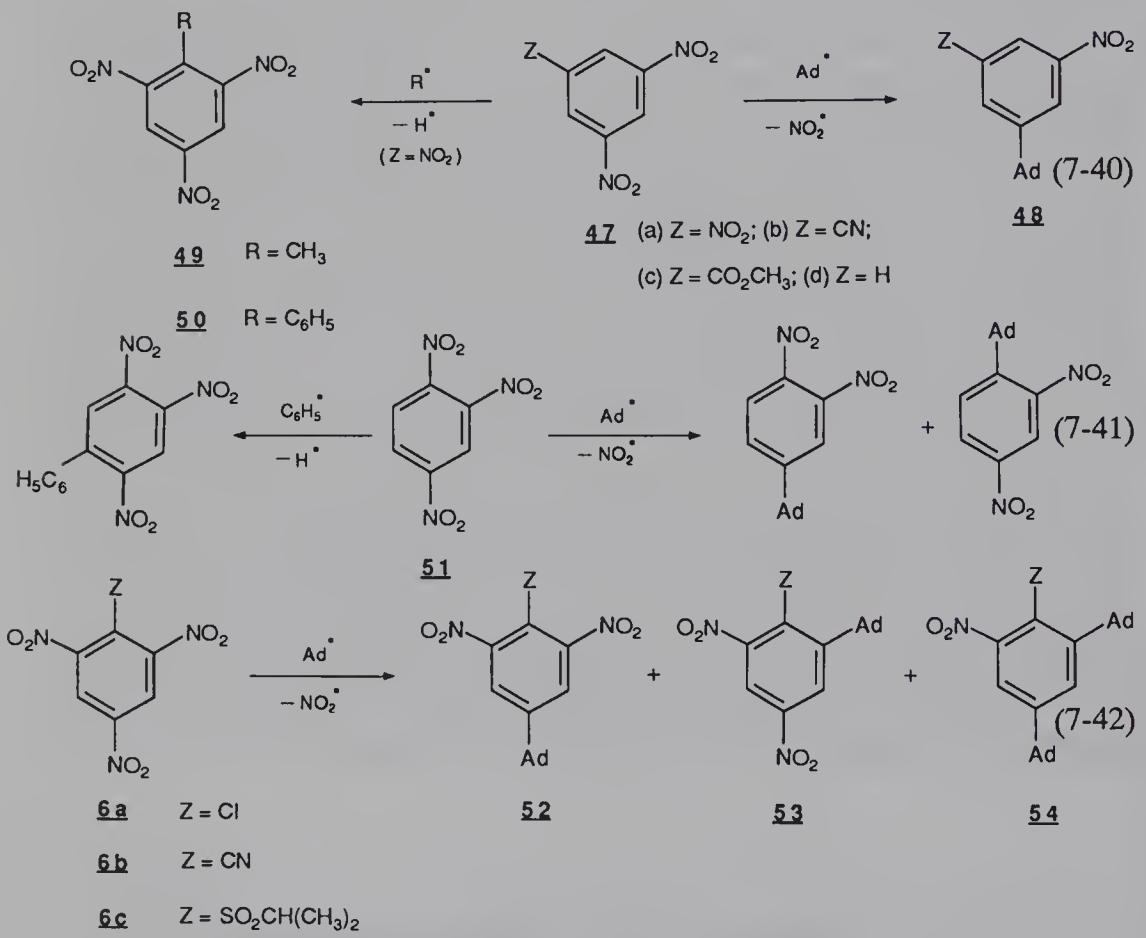
The discovery of the intermediacy of π- and CT complexes in the reactions depicted in Schemes 7.10 and 7.11 has considerable mechanistic implications. In fact, it leads to a reconsideration of the generally accepted two-step sequence of the S_NAr mechanism, at least for nucleophilic substitutions of strongly activated nitroarenes like dinitro- and trinitrobenzenes or dinitronaphthalenes, or of such heterocyclic compounds as nitropyridines and nitropyrimidines.[25–28] However, it seems that the time has not come to draw definitive conclusions, since Crampton *et al.*[65] were not able to detect the proposed intermediates in a recent reexamination of the behavior of TNB and 1-L-2,4,6-trinitrobenzenes (L = F, Cl, Br, I) in aqueous solution under experimental conditions similar to those used by Bunton *et al.*

Also, there is a conflicting conclusion regarding the possible role of the CT complexes as deduced from AM1 and MNDO calculations.[28,79] While the former are in accord with the idea that the CT complexes can be true intermediates in the addition or substitution processes, MNDO calculations predict that these complexes would form only in a side equilibrium pathway. Only the formation of the Π-complexes could precede that of the σ-complex intermediate along the minimum energy pathway of the substitution.[79]

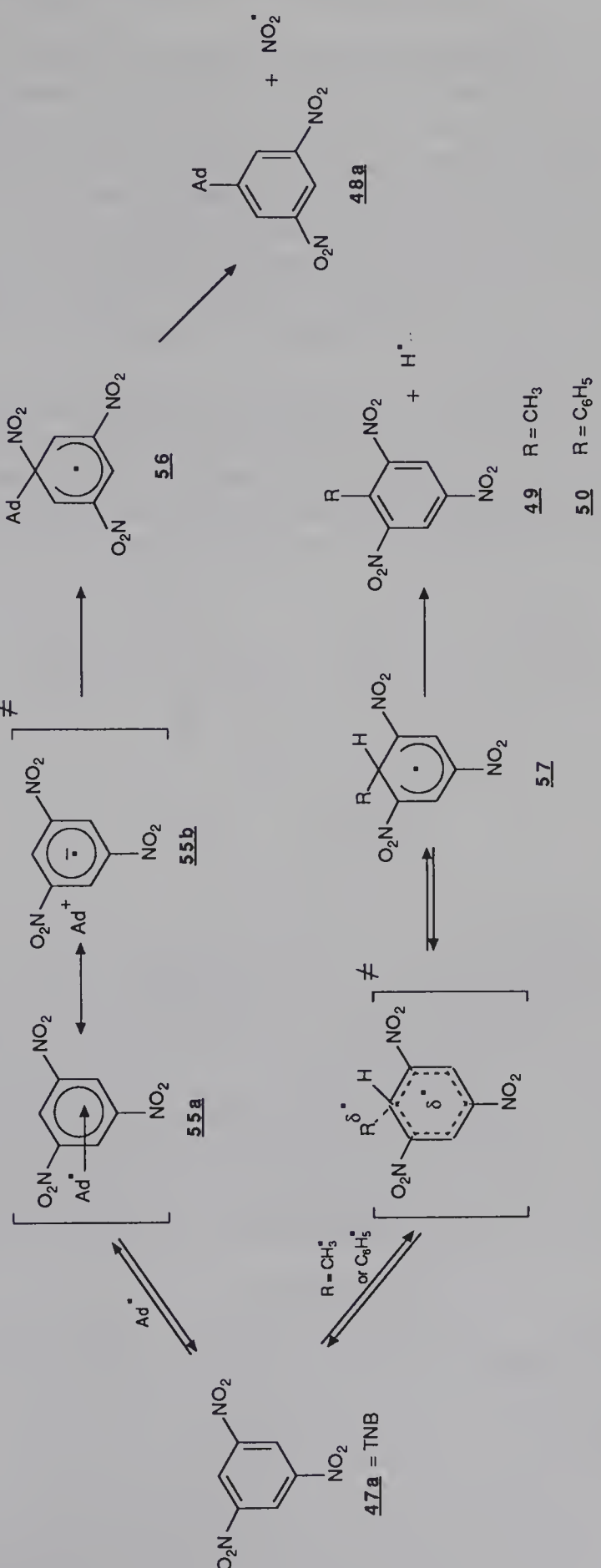
7.4 Homolytic Substitutions

Tiecco and coworkers have discovered that suitably activated nitroaromatics and nitroheteroaromatics can react with carbon radicals to afford either products derived from displacement of a nitro group or products derived from attack at a hydrogen-bearing carbon.[29,87–89] The substitutions of TNB and the related 1-Z-3,5-dinitrobenzenes **47** depicted in eq. 7-40 are illustrative of this behavior. While the adamantyl radical **Ad**$^{\bullet}$ gives selectively

the adamantyl-denitration or "ipso-substitution" products **48**, the methyl and phenyl radicals react with TNB to give rise exclusively to the products of hydrogen substitution, that is, 2,4,6-trinitrotoluene (**49**) and 2,4,6-trinitrobiphenyl (**50**).[29,88] Similar contrasting behavior was observed in the reactions of 1-Z-substituted-2,4-dinitrobenzenes like 1,2,4-trinitrobenzene (**51**) (eq. 7.41). With 1-Z-substituted-2,4,6-trinitrobenzenes (**6a**, **6b**, **6c**), ipso substitution of the para-nitro group to give **52** [Z = Cl, CN, $SO_2CH(CH_3)_2$], of the ortho-nitro group to give **53** (Z = Cl, CN), and of these two nitro groups to give **54** (Z = CN) was observed (eq. 7-42).[29,88]



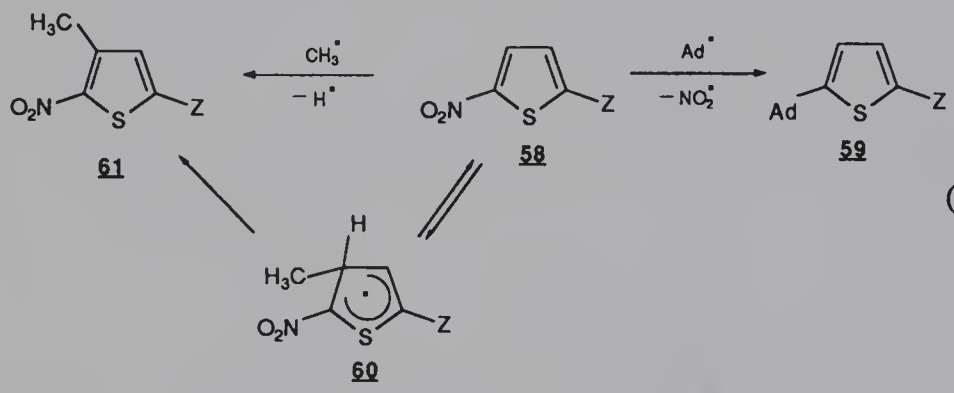
Considering that these homolytic substitutions proceed through the addition–elimination sequences shown for the TNB systems in Scheme 7.12, the differences in the reactivity of $Ad^\bullet$ and methyl or phenyl radicals would reflect the differences in the polar character of these species.[29,88] Bridgehead alkyl radicals like the adamantyl radical are strongly nucleophilic, implying that polar effects may contribute greatly to the stabilization of the transition state leading to the intermediate σ-complex **56**.[29,90–92] Tiecco, who has viewed this transition state as having the character of a charge–transfer complex with a



Scheme 7.12.

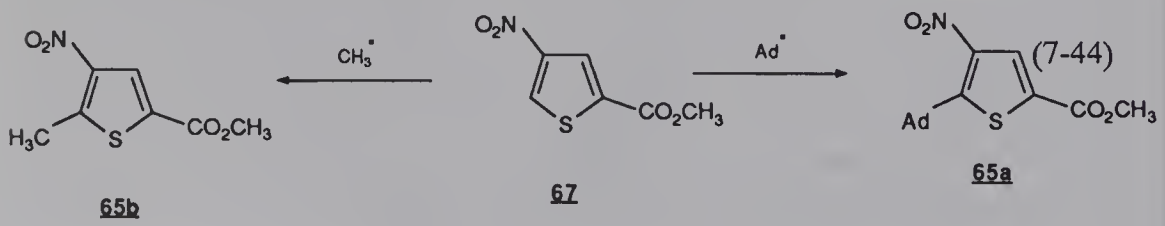
considerable contribution from the polar structure **55a** ↔ **55b**, has suggested that this CT interaction results in a more favorable charge density for addition of Ad$^{\bullet}$ at the carbon bearing the nitro groups than at the unsubstituted ring carbons.[29,88] In contrast to Ad$^{\bullet}$, the methyl and phenyl radicals are essentially apolar species, so that the preferred positions for addition of the $CH_3^{\bullet}$ and $C_6H_5^{\bullet}$ radicals will be those corresponding to the formation of stable cyclohexadienyl intermediates. In this respect, attack of these radicals at a hydrogen-bearing carbon of TNB is to be expected, since it gives rise to a σ-complex (**57**) whose unpaired electron can be efficiently delocalized through the ortho- and para-nitro groups.[29,88]

Results obtained with various nitrothiophenes have been explained along similar lines.[89] With substituted 2-Z-5-nitrothiophenes (**58**), the Ad$^{\bullet}$ radical affords exclusively the products of substitution of the 5-nitro group (i.e., **59**), while the methyl radical adds selectively at the unsubstituted 4-position to give **61** (eq. 7-43).[84] The latter reactions would proceed via the σ-complex **60**,



(7-43)

whose stabilization benefits from the particular ability of an ortho-nitro group to delocalize an odd electron.[93,94] Interestingly, the $CH_3^{\bullet}$ radical behaves like the Ad$^{\bullet}$ radical in displacing the 5-nitro group of methyl 4,5-dinitrothiophene-2-carboxylate (**62**) to give **65b**. In this instance, the 5-position of **62** is the preferred site of addition, both in terms of charge density caused by the CT interaction **63** and in terms of possible stabilization of the σ-complex-like transition state **66** (Scheme 7.13).[89] Similarly, these two factors favor addition of Ad$^{\bullet}$ and $CH_3^{\bullet}$ at the same unsubstituted carbon of methyl 4-nitrothiophene-2-carboxylate (**67**) to give **65a** and **65b**, respectively (eq. 7-44).[89]



(7-44)

Scheme 7.13.

References

1. (a) Eberson, L.; Radner, F. *Acc. Chem. Res.* **1987**, *20*, 53. (b) Eberson, L. *Adv. Phys. Org. Chem.* **1982**, *18*, 79.
2. Pross, A. *Acc. Chem. Res.* **1985**, *18*, 212.
3. Bordwell, F. G.; Clemens, A. H.; Smith, P. E.; Begemann, J. *J. Org. Chem.* **1985**, *50*, 1151.
4. (a) Nagakura, S.; Tanaka, J. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 734; (b) Nagakura, S. *Tetrahedron*, **1963**, *19*, Suppl. 2, 361.
5. Blyumenfeld, L. A.; Bryukhovetskaya, L. V.; Fomin, G. V.; Shein, S. M. *Russ. J. Phys. Chem.* **1970**, *44*, 518.
6. Todres, Z. V. *Usp. Khim.* **1978**, *47*, 260.
7. Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413.
8. (a) Russell, G. A.; Janzen, E. G. *J. Am. Chem. Soc.* **1962**, *84*, 4153; (b) Russell, G. A.; Janzen, E. G.; Strom, E. T. *ibid.* **1964**, *86*, 1807.
9. Shein, S. A.; Bryukhovetskaya, L. V.; Pishchugin, F. V.; Starichenko, V. F.; Panfilov, V. N.; Voevodskii, V. V. *Zh. Strukt. Khim.* **1970**, *11*, 243.
10. Savin, V. I. *Zh. Org. Khim.* **1978**, *14*, 2090.
11. Relles, H. M.; Johnson, D. S.; Manello, J. S. *J. Am. Chem. Soc.* **1977**, *99*, 6677.
12. Abe, T.; Ikegami, Y. (a) *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3227; (b) *ibid.* **1978**, *51*, 196.
13. Symons, M. C. R.; Bowman, W. R. (a) *J. Chem. Soc., Perkin Trans. 2*, **1988**, 533; (b) *ibid.* **1987**, 1133.
14. Fendler, E. J.; Fendler, J. H.; Arthur, N. L.; Griffin, C. E. *J. Org. Chem.* **1972**, *37*, 812.
15. Guthrie, R. D.; Nutter, D. E. *J. Am. Chem. Soc.* **1982**, *104*, 7478.
16. (a) Kornblum, N. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 734. (b) Kornblum, N. In "*The Chemistry of Functional Groups*", Patai, S.; Rappoport, Z., eds. Wiley: New York, 1982, Supplement F, Chapter 10.
17. Norris, R. K. In "*The Chemistry of Functional Groups*", Patai, S.; Rappoport, Z., eds. Wiley: New York, 1983, Supplement D, Chapter 16.
18. Beletskaya, I. P.; Drozd, V. N. *Usp. Khim.* **1979**, *48*, 793.
19. Mariani, C.; Modena, G.; Pizzo, G. P.; Scorrano, G.; Kistenbrügger, L. *J. Chem. Soc., Perkin Trans. 2*, **1979**, 1187.
20. Maggini, M.; Paradisi, C.; Scorrano, G.; Daniele, S.; Magno, F. *J. Chem. Soc., Perkin Trans. 2*, **1986**, 267.

21. Paradisi, C.; Scorrano, G. In "*Nucleophilicity*", Harris, J. M.; McManus, S. A., eds., ACS Advances in Chemistry Series. American Chemical Society: Washington, DC, 1987, p. 339.
22. Mutai, K.; Nakagaki, R.; Tukada, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2066.
23. Shein, S. M.; Bryukhovetskaya, L. V.; Khmelinskaya, A. D..; Starichenko, V. F.; Ivanova, T. M. *Reakt. Sposobnost Org. Soedin.* **1969**, *6*, 1087.
24. (a) Shein, S. M.; Bryukhovetskaya, L. V.; Ivanova, T. M. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1973**, 1594; (b) Bryukhovetskaya, L. V.; Mironova, L. V.; Shein, S. M. *ibid.* **1973**, 1601.
25. Bacaloglu, R.; Bunton, C. A.; Cerichelli, G. *J. Am. Chem. Soc.* **1987**, *109*, 621.
26. Bacaloglu, R.; Bunton, C. A.; Cerichelli, G.; Ortega, F. *J. Am. Chem. Soc.* **1988**, *110*, 3495.
27. (a) Bacaloglu, R.; Bunton, C. A.; Ortega, F. *J. Am. Chem. Soc.* **1988**, *110*, 3503; (b) *ibid.*, **1988**, *110*, 3512.
28. Bacaloglu, R.; Bunton, C. A.; Ortega, F. *J. Am. Chem. Soc.* **1989**, *111*, 1041.
29. Tiecco, M. *Pure Appl. Chem.* **1981**, *53*, 239.
30. Miller, J. "*Aromatic Nucleophilic Substitution*", Elsevier: Amsterdam, 1968.
31. Bilkis, I. I.; Shein, S. M. *Tetrahedron*, **1975**, *31*, 969.
32. Gilbert, B. C.; Norman, R. O. C.; Sealy, R. C. *J. Chem. Soc., Perkin Trans. 2*, **1975**, 303.
33. (a) Terrier, F. *Chem. Rev.* **1982**, *82*, 77; (b) Buncel, E.; Crampton, M. R.; Strauss, M. J.; Terrier, F. In "*Electron-Deficient Aromatic–Base Interactions*", Elsevier: Amsterdam, 1984.
34. Buncel, E.; Wilson, H. *Adv. Phys. Org. Chem.* **1977**, *14*, 133.
35. Eberson, L. *Acta Chem. Scand.* **1984**, *B38*, 439.
36. Sauer, A.; Wagestian, F.; Barabasch, B. *J. Chem. Soc., Perkin Trans. 2*, **1990**, 1317.
37. Buncel, E.; Menon, B. C. *J. Am. Chem. Soc.* **1980**, *102*, 3499.
38. Ivanova, T. M.; Shein, S. M. (a) *Zh. Org. Khim.* **1979**, *15*, 348; (b) *ibid.*, **1979**, *15*, 1666; (c) *ibid.* **1980**, *16*, 1221.
39. Meot-Ner, M.; Neta, P. *J. Phys. Chem.* **1986**, *90*, 4648.
40. Kropf, H.; Ball, M.; Siegfriedt, K. H.; Wagner, S. *J. Chem. Res.* (S) **1981**, 339; (M) 4001.
41. Heller, R. A.; Weiler, R. *Can. J. Chem.* **1987**, *65*, 251.

42. Heller, R. A.; Fewster, M.; Lambert, T. *Can. J. Chem.* **1983**, *44*, 2455.
43. Berdnikov, V. M.; Bazhin, N. M. *Russ. J. Phys. Chem.* **1970**, *44*, 395.
44. Frimer, A.; Rosenthal, I. (a) *Tetrahedron Lett.* **1976**, 2809; (b) *Photochem. Photobiol.* **1978**, *28*, 711.
45. Poupko, R.; Rosenthal, I. *J. Phys. Chem.* **1973**, *77*, 1722.
46. Levonowich, P. F.; Tannenbaum, H. P.; Dougherty, R. C. *J. Chem. Soc., Chem. Commun.* **1975**, 597.
47. Sagae, H.; Fujihira, M.; Komazawa, K.; Lund, H.; Osa, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2188.
48. Gareil, M.; Pinson, J.; Saveant, J. M. *Nouv. J. Chim.* **1981**, *5*, 311.
49. Bunnett, J. F.; Mitchel, E.; Galli, C. *Tetrahedron*, **1985**, *41*, 4119.
50. Russell, G. A.; Norris, R. K.; Pauck, E. J. *J. Am. Chem. Soc.* **1971**, *93*, 5839.
51. Basani, A.; Prato, M.; Rampazzo, P.; Quintily, U.; Scorrano, G. *J. Org. Chem.* **1980**, *45*, 2263.
52. Paradisi, C.; Quintily, U.; Scorrano, G. *J. Org. Chem.* **1983**, *48*, 3022.
53. Prato, M.; Quintily, U.; Salvagno, S.; Scorrano, G. *Gazz. Chim. Ital.* **1984**, *114*, 413.
54. Prato, M.; Quintily, U.; Scorrano, G. *J. Chem. Soc., Perkin Trans. 2*, **1986**, 1419.
55. Prato, M.; Quintily, U.; Scapol, L.; Scorrano, G. *Bull. Soc. Chim. Fr.* **1987**, 99.
56. Arca, V; Paradisi, C.; Scorrano, G. *J. Org. Chem.* **1990**, *55*, 3617.
57. Prato, M.; Quintily, U.; Scorrano, G. *Gazz. Chim. Ital.* **1988**, *118*, 421.
58. Behar, D.; Neta, P. *J. Phys. Chem.* **1981**, *85*, 690.
59. Danen, W. C.; Kensler, T. T.; Lawless, J. G.; Marcus, M. P.; Hawley, M. D. *J. Phys. Chem.* **1969**, *73*, 4389.
60. Gall, L. B.; Dorfman, L. M. *J. Am. Chem. Soc.* **1969**, *91*, 2199.
61. Taniguchi, H.; Schuler, R. H. *J. Phys. Chem.* **1985**, *89*, 335.
62. Crampton, M. R.; Gibson, B. *J. Chem. Soc., Perkin Trans. 2*, **1979**, 648.
63. Terrier, F.; Millot, F.; Norris, W. P. *J. Am. Chem. Soc.* **1976**, *98*, 5883.
64. Crampton, M. R. *J. Chem. Soc., Perkin Trans. 2*, **1978**, 343.
65. Crampton, M. R.; Davis, A. B.; Greenhalgh, C.; Stevens, J. A. *J. Chem. Soc., Perkin Trans. 2*, **1989**, 675.
66. Bernasconi, C. F.; Bergstrom, R. G. *J. Am. Chem. Soc.* **1974**, *96*, 2397.
67. Gold, V. ; Rochester, C. H. *J. Chem. Soc.* **1964**, 1710, 1727.

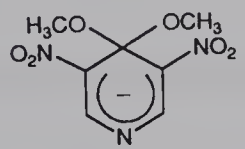
68. Bacaloglu, R.; Bunton, C. A.; Ortega, F. *Int. J. Chem. Kinet.* **1988**, *20*, 195.
69. Abe, T. *Bull. Chem. Soc. Jpn.* **1960**, *33*, 41.
70. Bernasconi, C. F. *J. Am. Chem. Soc.* **1970**, *92*, 4682.
71. Miller, R. E.; Wynne-Jones, W. K. F. *J. Chem. Soc.* **1961**, 4866.
72. Foster, R. "*Organic-Charge Transfer Complexes*". Academic Press, New York, 1969.
73. Briegleb, G. "*Electron Donor–Acceptor Complexes*". Springer-Verlag, Berlin, 1961.
74. Strauss, M. J.; Taylor, S. P. B.; Reznick, A. *J. Org. Chem.* **1972**, *37*, 3076.
75. Forlani, L.; Tortelli, V. *J. Chem. Res.* (S) **1982**, *62*, 258.
76. Forlani, L. *Gazz. Chim. Ital.* **1982**, *112*, 205.
77. Cattana, R. J.; Singh, J. O.; Anunziata, J. D.; Silber, J. J. *J. Chem. Soc., Perkin Trans. 2,* **1987**, 79.
78. Hayami, J.; Otani, S.; Yamaguchi, F.; Nishikawa, Y. *Chem. Lett.* **1987**, 739.
79. Dotterer, S. K.; Harris, R. L. *J. Org. Chem.* **1988**, *53*, 777.
80. Jagannadham, V.; Steenken, S. (a) *J. Am. Chem. Soc.* **1984**, *106*, 6542; (b) *ibid.* **1988**, *110*, 2180.
81. Dewar, M. J. S.; Zoebisch, E. G.: Healey, E. F.: Stewart, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
82. Perrin, C. L. *J. Am. Chem. Soc.* **1977**, *99*, 5516.
83. Kochi, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5235.
84. Pross, A. J. In "*Nucleophilicity*", Harris, J. M.; McManus, S. P., eds.; American Chemical Society: Washington, DC, 1987, p. 331.
85. Keumi, T.; Hamanaka, K.; Hasegawa, H.; Minamide, N.; Inone, Y.; Kitajima, H. *Chem. Lett.* **1988**, 1285.
86. (a) Ritchie, C. D. *J. Am. Chem. Soc.* **1975**, *97*, 1170. (b) Ritchie, C. D.; Sawada, M. *J. Am. Chem. Soc.* **1977**, *99*, 3754. (c) Ritchie, C. D. *Acc. Chem. Res.* **1972**, *5*, 348.
87. Testaferri, L.; Tiecco, M.; Tingoli, M. *J. Chem. Soc., Chem. Commun.* **1978**, 93.
88. Testaferri, L.; Tiecco, M.; Tingoli, M. *J. Chem. Soc., Perkin Trans. 2,* **1979**, 469.
89. Cogolli, P.; Maiolo, F.; Testaferri, L.; Tiecco, M.; Tingoli, M. *J. Chem. Soc., Perkin Trans. 2,* **1980**, 1331.
90. Minisci, F. *Top. Curr. Chem.* **1976**, *62*, 1.

91. Citterio, A.; Minisci, F.; Porta, O.; Sesana, G. *J. Am. Chem. Soc.* **1977**, *99*, 7960.
92. Clerici, A.; Minisci, F.; Porta, O. *Gazz. Chim. Ital.* **1973**, *103*, 171.
93. Rudqvist, U.; Torssell, K. *Acta Chem. Scand.* **1971**, *25*, 2183.
94. Camaggi, C. M.; De Luca, G.; Tundo, A. *J. Chem. Soc., Perkin Trans. 2*, **1972**, 412.

CHAPTER 8. S_N(ANRORC) Substitutions and Related Processes

8.1 Introduction

As a result of the inherent activation provided by their intracyclic nitrogen atom(s), aza- and polyazaaromatics have a significant electron-deficient character, which can be strongly increased upon quaternization or ring substitution by suitably located electron-withdrawing substituents.[1,2] Many azaaromatics, and more especially nitro-activated azaaromatics, have therefore a high susceptibility to reversible covalent nucleophilic addition at unsubstituted or substituted activated ring carbons.[1–15] This can give rise to thermodynamically stable σ-complexes (e.g., structures 1–3). Such adducts are readily identified by NMR spectroscopy and can sometimes be isolated as alkali salts (e.g., structure 1). This can also give rise to σ-complexes that form as transient



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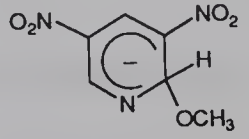

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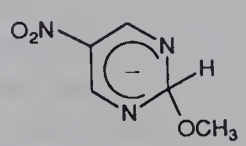

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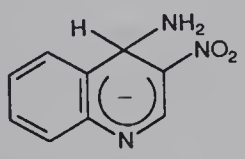


4

species (e.g., structure **4**) and are possible intermediates in different reaction pathways.[5–15]

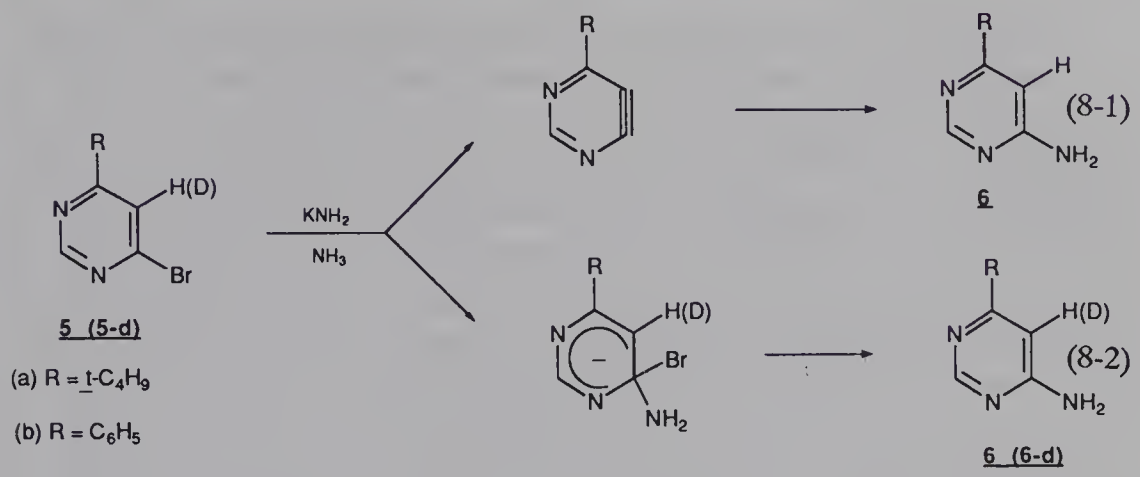
Chapter 1 has provided examples of the feasibility of classical S_NAr substitutions in activated azaaromatics when there is a potentially good leaving group at the site of nucleophilic addition. The susceptibility of some azaaromatics to undergo S_NAr^H substitutions (i.e., formal substitution of a hydrogen atom) via reaction pathways similar to those described for nitro-activated arenes, was discussed in Chapter 5. However, a peculiar feature of azaaromatic systems is that nucleophilic displacements of common leaving groups (F, Cl, Br, OCH_3, etc.), as well as of hydrogen, can occur in strongly basic media through multistep sequences involving ring opening–reclosure (RORC) of the heterocyclic system.[3,4] The primary focus of this chapter is on these reactions, commonly referred to as S_N(ANRORC) substitutions, because they are promoted by initial addition of the nucleophile (AN) at an activated unsubstituted ring carbon.[3] In accordance with the way that progress has been made in this particular field of nucleophilic aromatic substitutions, azaaromatics containing no nitro groups deserve our attention prior to nitro-activated derivatives.

Ring opening of σ-adducts also appears to be the key step for the conversion of some azaaromatic systems into other heterocyclic or carbocyclic systems.[4,13,14] Representative examples of such transformations of nitro-activated azines, especially 5-nitropyrimidine, are given in Section 8.3.

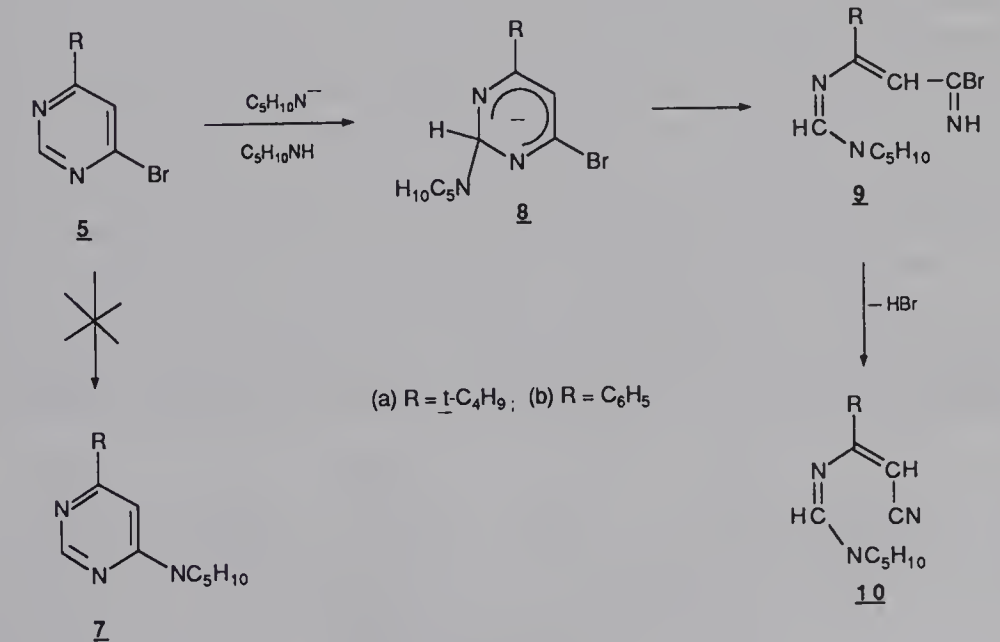
8.2 S_N(ANRORC) Substitutions

8.2.1 Azaaromatics Without Nitro Activation

Unexpected results obtained in studies of the reactions of substituted 4-R-6-bromopyrimidines **5a** (R = *t*-C_4H_9) and **5b** (R =C_6H_5) with potassium amide in ammonia, and lithium piperidide in a piperidine–ether mixture, led to the discovery of the S_N(ANRORC) substitutions by Van der Plas.[3,16,17] Treatment of **5a** and **5b** with amide ion afforded the expected 4-R-6-amino compounds **6a** and **6b**. However, carrying out the same reaction with the 5-deuteriopyrimidine **5a–d** also gave the protio-substituted product 6a.[16a] Since neither unreacted **5a–d** nor a sample of independently prepared **6a–d**



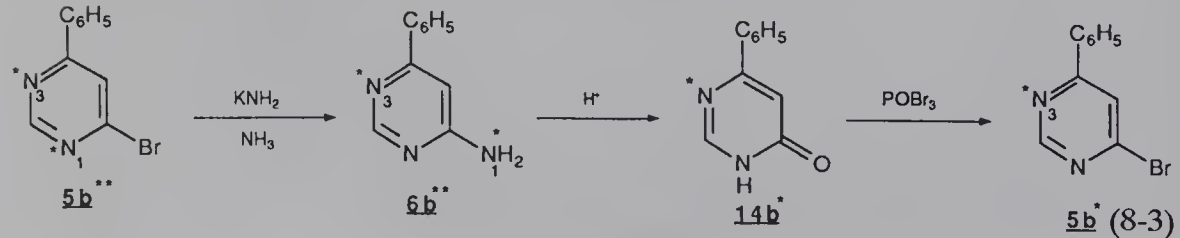
showed appreciable D/H exchange under the reaction conditions, the hetaryne mechanism of eq. 8-1 was suggested as the most reasonable mechanism for the conversion of **5** to **6**.[16a] This was really a surprising conclusion, since 6-halopyrimidines are normally involved in S_NAr reactions (eq. 8-2).[3] More surprisingly, the reaction of **5a** and **5b** with piperidide ion afforded no trace of substitution products **7a** or **7b**.[16b] Instead, the 2-aza-4-cyano-1-piperidino-1,3-butadienes **10a** and **10b** were isolated, with formation in the case of **10b** of a Z/E mixture.[16b] These compounds were assumed to form according to Scheme 8.1, where nucleophilic addition of piperidide ion at C-2 of **5a** and **5b** is followed by ring opening of the σ-adducts **8a** and **8b** and loss of hydrogen bromide from the imidoyl bromides **9a** and **9b**.[16b]



Scheme 8.1.

Although eq. 8-1 and Scheme 8.1 fitted the experimental data well, it remained difficult to understand why **5** should preferentially undergo initial deprotonation at C-5 by amide ion and nucleophilic addition at C-2 by piperidide ion. Accordingly, the question arose as to whether the conversion of **5a** and **5b** into the 6-amino compounds **6a** and **6b** could not also be promoted by initial addition of amide ion at C-2 to give the σ-complexes **11a** and **11b**. As shown in Scheme 8.2, ring opening of **11a** and **11b** would yield the imidoyl bromides **12a** and **12b**, which could possibly lose hydrogen bromide to form the 1-amino-2-aza-4-cyano-1,3-butadienes **13a** and **13b**. Then, in contrast to the situation for the piperidine systems in Scheme 8.1, both the open-chain intermediates **12** and **13** could react further, undergoing ring closure to **6a** and **6b**.[3,17] Obviously, a most remarkable feature of such a conversion of **5** to **6** would be that the nitrogen atom at position 1 (N-1) in the pyrimidine ring of the substitution products **6** is not the same as that originally present at the analogous position in the parent substrates **5**.

That Scheme 8.2 is actually operating in the conversion of **5** to **6** was convincingly demonstrated by carrying out experiments with ^{15}N-labeled substrates.[17] 6-Bromo-4-phenyl [1(3)-^{15}N]-pyrimidine (**5b****) containing 6% of ^{15}N excess equally distributed over both ring nitrogen atoms N-1 and N-3 was prepared and submitted to reaction with potassium amide in ammonia.[17] In accordance with Scheme 8.2, no change in the overall ^{15}N excess was found to occur during formation of the 6-amino product **6b**** (eq. 8-3). However, treatment of **6b**** by acid to give the 4-phenylpyrimidin-6-one **14b***, followed by reaction of this compound with phosphoryl bromide, regenerated a bromo derivative (**5b***) with a ^{15}N excess of only 3.5%. This implied that 2.5% of the ^{15}N excess was present in the exocyclic nitrogen of the parent amino compound **6b**** (eq. 8-3). Since no evidence for a base-catalyzed isomerization involving ring nitrogen–exocyclic nitrogen exchange was found after treatment of **6b** with KNH_2/NH_3, indicating that **6b** is not subject to a Dimroth rearrangement, it was concluded that the conversion of **5b**** to **6b**** must proceed for the most part (2.5/3 = 83%) with transfer of the nitrogen atom located at the 1-position of the pyrimidine ring of **5b**** to the exocyclic position in **6b****. This supports the occurrence of the overall substitution mechanism of Scheme



5b** **6b**** **14b*** **5b*** (8-3)

Scheme 8.2.

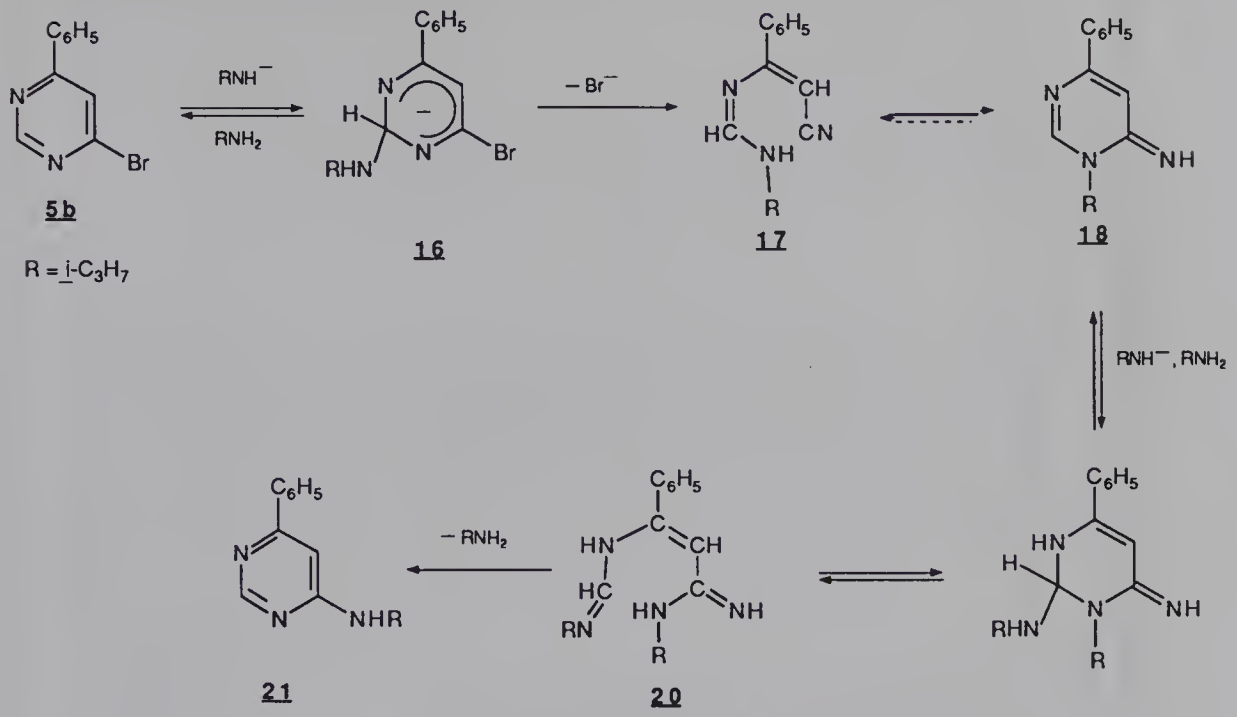
13 15 (8-4)

8.2.[3,17] An S_NAr mechanism will operate for the remaining 17% in the conversion of **5b** to **6b**.[3,17]

Other results agreed with Scheme 8.2. First, the intermediacy of the postulated open-chain product is consistent with the observation that the 6-bromo-5-deutero derivative **5b–d** undergoes loss of deuterium during its conversion to **6b**. In this case, D/H exchange at C-5 would actually occur via the tautomeric form **15** of the intermediate **13** (eq. 8-4).[3] Second, an open-chain intermediate of type **13** was unambiguously identified in the substitution of **5b** with lithium isopropylamide in isopropylamine.[18] As expected, this reaction yielded 4-phenyl-6-(isopropylamino)pyrimidine (**21**) at 20°C, but another product was isolated at –75°C which was shown to be a 10:1 mixture of **17** and its isomeric 6-imino-4-phenyl-1-isopropyl-1,6-dihydropyrimidine (**18**) on the basis of IR and ^1H NMR data. Upon standing, **17** gradually changed into **18**, which underwent a fast Dimroth rearrangement into **21** when treated with lithium isopropylamide at 20°C.[19] The characterization of the tautomeric equilibrium **17** ⇔ **18** allowed the authors to suggest the detailed mechanism of Scheme 8.3 for the conversion of **5b** into **21**.[3,18] Note that this conversion no longer occurs via an ANRORC substitution when carried out at 100°C in piperidine.[19] In this instance, because the reaction conditions are not basic enough to ensure ring opening of **16**, substitution eventually takes place via a normal S_NAr pathway.[19]

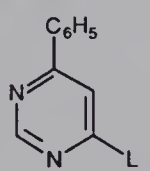
Although they afford the same substitution products as those anticipated for simple S_NAr amino-debromination processes, the substitutions of Schemes 8.2 and 8.3 are characterized by the occurrence of a novel transformation of the heterocyclic system. Since the exchange of nitrogen atoms in the pyrimidine ring upon going from **5** to **6** or **21** is accomplished in three important steps, consisting of addition of the nucleophile, ring opening of the resulting σ-complex, and ring closure of an open-chain intermediate, these substitutions were termed S_N(ANRORC) substitutions by Van der Plas.[3]

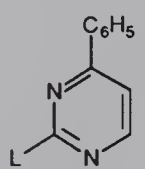
For many years, all the information obtained on the S_N(ANRORC) mechanism was derived from studies of nucleophilic substitutions of azaaromatics having no extra activation by nitro groups. Table 8.1 summarizes the results obtained for amination of a number of derivatives. As can be seen, the extent to which the S_N(ANRORC) mechanism is operating in the substitu-



Scheme 8.3.

tions strongly depends on the nature of the heterocyclic system and the nature and position of the leaving group. The latter point is well illustrated by a comparison of the behavior of 6-halo-4-phenylpyrimidines **5b–e** (entries 1–4) and 2-halo-4-phenylpyrimidines **22a–d** (entries 5–8). In the case of **5**, the fluoro and chloro compounds behave just as discussed above for the bromo analogue **5b**, undergoing mainly amino-dehalogenation via the S_N(ANRORC) mechanism.[3,17b] However, the iodo derivative **5e** appears to react preferentially via the S_N(EA) mechanism of eq. 8-1.[3,17b] In contrast, all four 2-halo-4-phenylpyrimidines **22a–d** react for the most part via the S_N(ANRORC) mechanism.[3,20] Other leaving groups like SO_2CH_3 in **22f** and SCN in **22g**,





5b L = Br
5c L = F
5d L = Cl
5e L = I

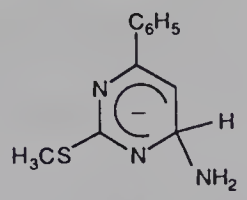
22 (a) L = F; (b) L = Cl
(c) L = Br; (d) L = I
(e) L = SCH_3; (f) L = SO_2CH_3
(g) L = SCN; (h) L = CN

Table 8.1. The Extent of the S_N(ANRORC) Mechanism in Amination of Various Azaaromatics with Potassium Amide in Ammonia.

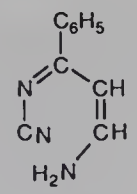
Entry	Parent compound	Product	S_NANRORC Mechanism (%)	Ref.
1	6-Fluoro-4-phenylpyrimidine	6-Amino-4-phenylpyrimidine	70	3,17b
2	6-Chloro-4-phenylpyrimidine	6-Amino-4-phenylpyrimidine	90	3,17b
3	6-Bromo-4-phenylpyrimidine	6-Amino-4-phenylpyrimidine	80	3,17b
4	6-Iodo-4-phenylpyrimidine	6-Amino-4-phenylpyrimidine	13[a]	3,17b
5	2-Fluoro-4-phenylpyrimidine	2-Amino-4-phenylpyrimidine	92	3,20
6	2-Chloro-4-phenylpyrimidine	2-Amino-4-phenylpyrimidine	100	3,20
7	2-Bromo-4-phenylpyrimidine	2-Amino-4-phenylpyrimidine	100	3,20
8	2-Iodo-4-phenylpyrimidine	2-Amino-4-phenylpyrimidine	83	3,20
9	2-Thiomethyl-4-phenylpyrimidine	2-Amino-4-phenylpyrimidine	100	3,20c
10	2-Methylsulfonyl-4-phenylpyrimidine	2-Amino-4-phenylpyrimidine	83[b]	3,20c
11	2-Sulfocyano-4-phenylpyrimidine	2-Amino-4-phenylpyrimidine	100	3,20c
12	2-Cyano-4-phenylpyrimidine	2-Amino-4-phenylpyrimidine	6[b]	3,20c
13	2-Bromopyridine	2-Aminopyridine	0[b]	3,20c
14	3-Bromoisoquinoline	3-Aminoisoquinoline	55[b]	22
15	4-Chloroquinazoline	4-Aminoquinazoline	53[b]	23
16	3-Thiomethyl-1,2,4-triazine	3-Amino-1,2,4-triazine	92	24

[a] 6-Iodo-4-phenylpyrimidine reacts preferentially via the S_N(EA) mechanism of eq. 8.1.

[b] The S_NAr mechanism is the other identified mechanism operating in these reactions.



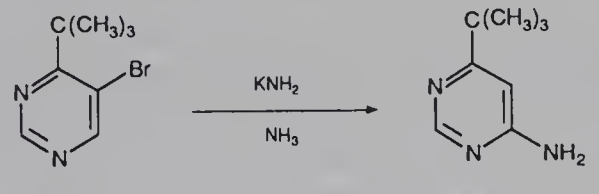
23



24

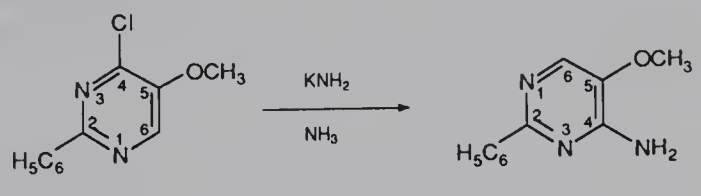
which commonly exhibit significant nucleofugalities in S_NAr substitutions, also depart in S_N(ANRORC) processes. However, the CN group in **22h** drives the substitution toward the S_NAr mechanism.[20] An interesting feature of the substitutions of **22** is that both the σ-complex **23** and the open-chain intermediate **24** have been structurally identified.[20] Regarding the nature of the heterocyclic system, it is noteworthy that no trace of an S_N(ANRORC) pathway was found in the amination of 2-bromopyridine.[21] This reaction occurs exclusively via an S_NAr process (see Chapter 1).[21]

S_N(ANRORC) processes leading to amination at a CH-bearing position with elimination of a common leaving group in an ortho or meta position have been unambiguously identified.[3] Representative examples of such formal S_NAr^H substitutions are the amination of 4-*tert*-butyl-5-bromopyrimidine (**25**), which yields the cine-substitution product **26** (eq. 8-5), and the amination of 5-methoxy-4-chloro-2-phenylpyrimidine (**27**) to give 5-methoxy-4-amino-2-phenylpyrimidine (**28**) at –33°C (eq. 8-6).[3,25–27]



(8-5)

25 26



(8-6)

27 28

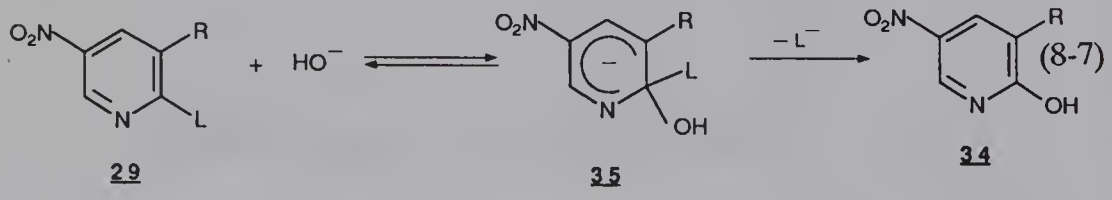
8.2.2 Nitro-Activated Azaaromatics

While halopyridines undergo nucleophilic displacement of their halogen atom via an S_NAr or an hetaryne pathway,[1,21,28–31] evidence has been provided that the S_N(ANRORC) mechanism can operate to a large extent in the substitu-

tions of halonitropyridines with strong nucleophiles like OH^- in water/DMSO mixtures rich in DMSO, or with amide ion in ammonia.[32–35] This finding is consistent with observations that electron-withdrawing groups favor the ring opening of σ-adducts.[13–15]

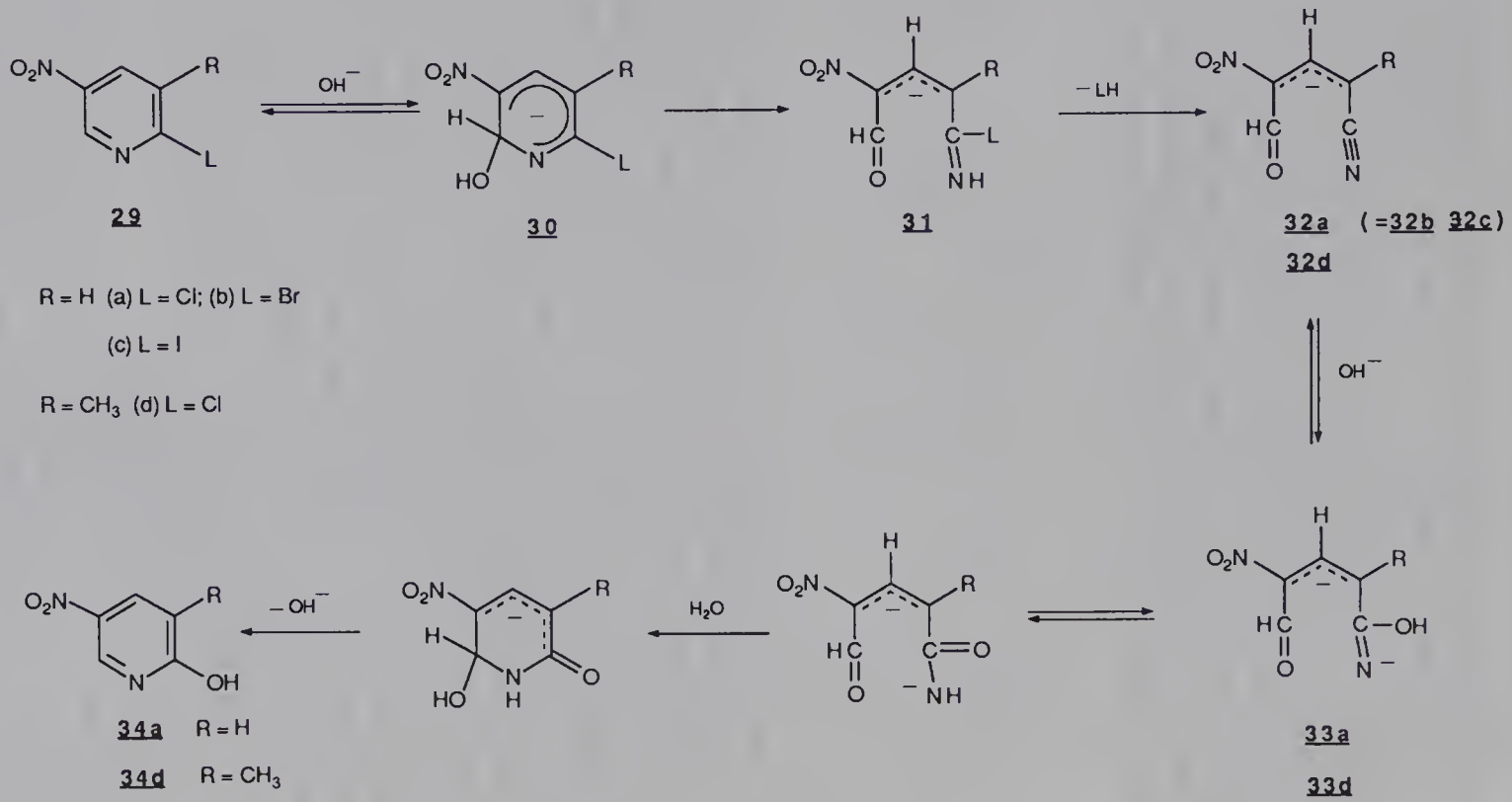
Addition of up to 2 equivalents of aqueous hydroxide to solutions of 2-chloro-, 2-bromo-, or 2-iodo-5-nitropyridines (**29a–c**) in DMSO results in the formation of a unique product which, upon further addition of base, slowly yields 2-hydroxy-5-nitropyridine (**34a**) in essentially quantitative yield.[32] Based on ^1H and ^{13}C NMR and IR data, the intermediate was identified as the formylcyanonitropropenide ion **32a**. In **32a**, the aldehyde function is associated with ^1H and ^{13}C chemical shifts at 9.7 and 182 ppm, respectively, (in 20:80 D_2O/DMSO-d_6) and an IR peak at 1640 cm^{-1}, while the nitrile function corresponds to a ^{13}C signal at 120 ppm and an IR band at 2200 cm^{-1}. On the other hand, the ^1H NMR spectra show a large coupling constant (J = 12.6 Hz) consistent with a cis arrangement of the H_3 and H_4 protons of **32a** (δH_3 and δH_4 = 6.8 and 5 ppm). Similarly, the intermediate **32d** has been identified in the substitution of 2-chloro-3-methyl-5-nitropyridine (**29d**), which affords the corresponding 2-hydroxypyridine **34d** as the final product.[32]

Identification of **32a** and **32d** has led Reinheimer *et al.* to suggest that the conversion of 2-halo-5-nitropyridines **29a–d** into the corresponding 2-hydroxy-5-nitropyridines **34a** and **34d**, occurs via the S_N(ANRORC)-type process described in Scheme 8.4 rather than by the anticipated S_NAr mechanism of eq. 8-7.[32] Possibly, the stabilization of the formylcyanonitropropenide anions **32a** and **32d** by the strongly electron-withdrawing nitro group is the driving force for ring-opening of the σ-adducts **30**. Since these complexes arise from OH^- addition at the unsubstituted C-6 carbon, their formation is normally kinetically favored over that of the C-2 isomers **35**, the required intermediates in the S_NAr pathway. It is interesting that NMR identification of adducts **30** was not feasible, suggesting that the rate of ring cleavage is faster than the rate of adduct formation.



29 **35** **34**

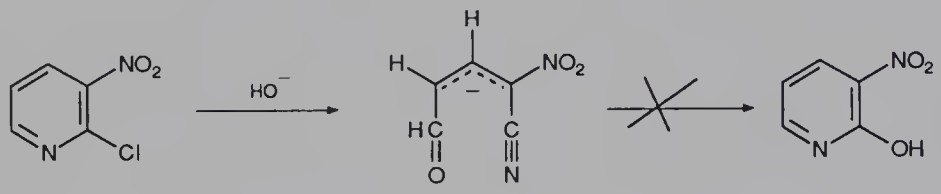
A kinetic study of the ring closure of **32a** in various H_2O/DMSO mixtures supports the mechanism of Scheme 8.4.[33] The reaction was found to be first-order in hydroxide ion and first-order in substrate, consistent with the


29
30
31
32a (=32b 32c)
32d
33a
33d
34a R = H
34d R = CH3
R = H (a) L = Cl; (b) L = Br
(c) L = I
R = CH3 (d) L = Cl
OH−
−LH
H2O
−OH−

Scheme 8.4.

rate-determining step being the addition of OH^- (a negative ion) to the cyano group of **32a** (another negative ion) to form the dianion **33a**. In accordance with this type of reaction, the ring closure was strongly accelerated upon increasing the water content and therefore the polarity of the reaction media, as well as on adding NaCl (1 equiv) to a given solvent mixture.

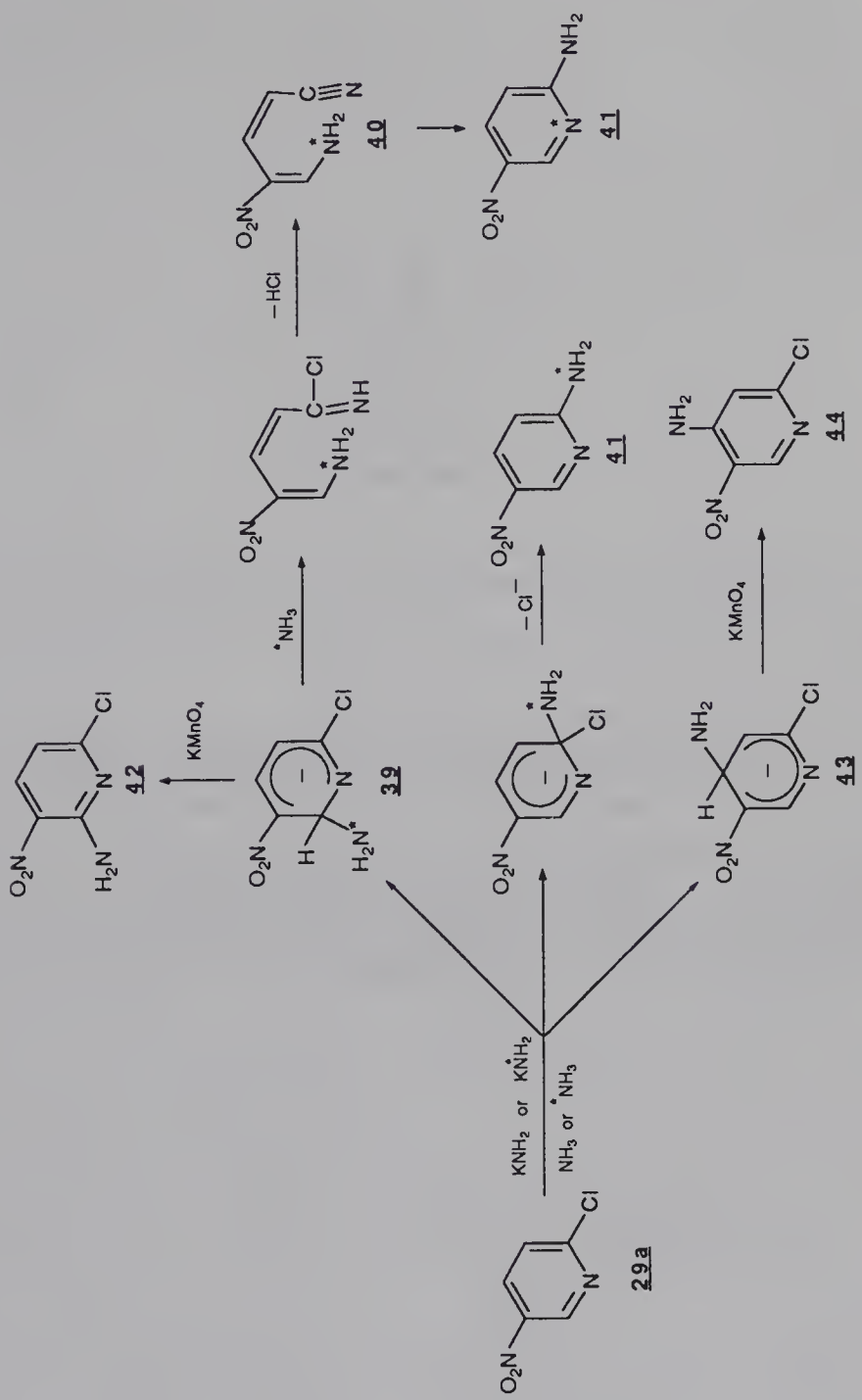
The anionic open-chain intermediate **37** was isolated and structurally identified in the reaction of 2-chloro-3-nitropyridine (**36**) with OH^-.[33] However, cyclization of **37** to 2-hydroxy-3-nitropyridine (**38**) did not occur upon further addition of base because of competing decomposition processes (eq. 8-8).



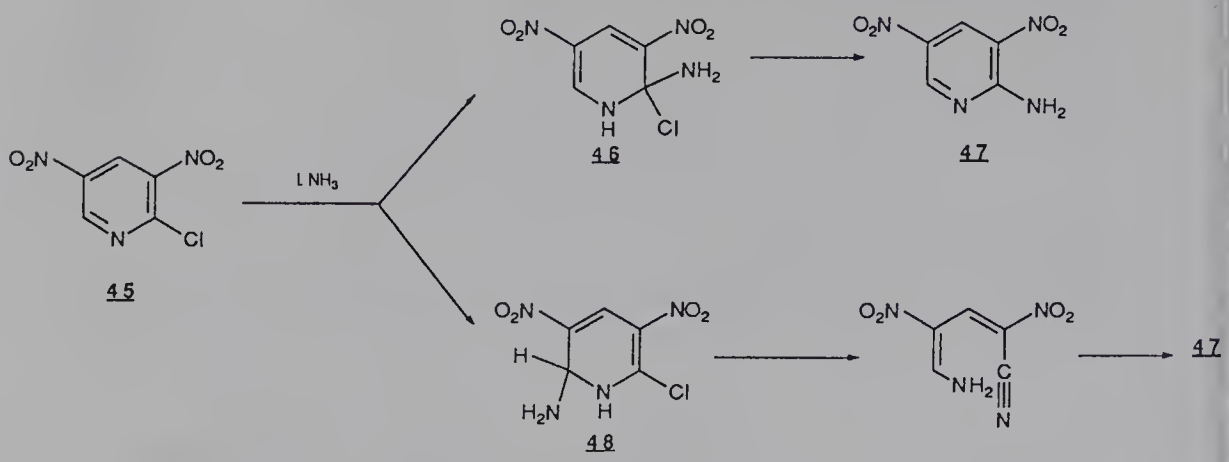
36 **37** **38** (8-8)

The reaction of **29a** with amide ion in liquid ammonia proceeds to a 25% extent via the S_NAr mechanism and to a 75% extent via the S_N(ANRORC) mechanism (Scheme 8.5).[34a] This latter pathway was elegantly demonstrated by the finding that experiments carried out with ^{15}N-labeled potassium amide/liquid ammonia yielded a sample of 2-amino-5-nitropyridine (**41**) having 75% ^{15}N incorporated into the nitrogen atom of the pyridine ring.[34a] Also, the open-chain intermediate **40**, which in this instance formed as a mixture of Z and E isomers, was successfully characterized by NMR spectroscopy at –33°C. Indirect evidence for initial formation of the C-6 adduct **39** was obtained from amination experiments carried out in the presence of a strong oxidant capable of promoting a rapid S_NArH substitution (e.g., potassium permanganate). In this case, 10% of 2-amino-6-chloro-3-nitropyridine (**42**)—a Chichibabin product—was formed.[34a] Some of 4-amino-2-chloro-5-nitropyridine (**44**), another Chichibabin product, was also obtained, indicating that competitive addition of amide ion also occurred at the unsubstituted C-4 carbon of **29a** to give the σ-adduct **43**.[34]

With potassium amide in liquid ammonia, 2-chloro-3,5-dinitropyridine (**45**) afforded tarry products rather than the expected 2-amino-3,5-dinitropyridine (**47**).[34a] Quantitative conversion of **45** into **47** occurred, however, upon simple treatment with liquid ammonia (Scheme 8.6).[34a] Although initial formation of the C-6 adduct **48** was detected by NMR techniques, this amino-dechlorination reaction was demonstrated to proceed for the most part (to a 93% extent) via the S_NAr mechanism and only to a 7% extent via the



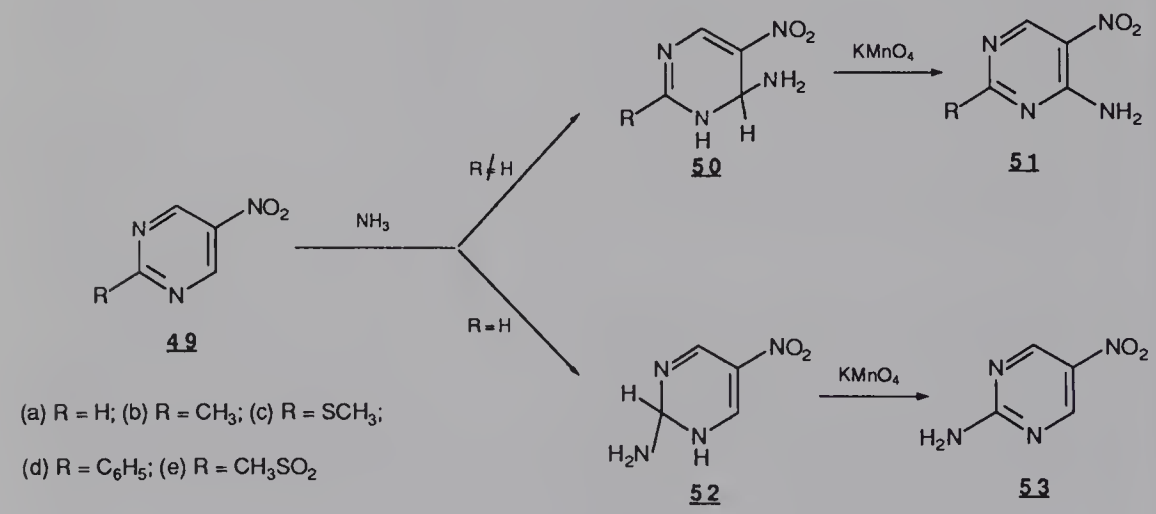
Scheme 8.5.



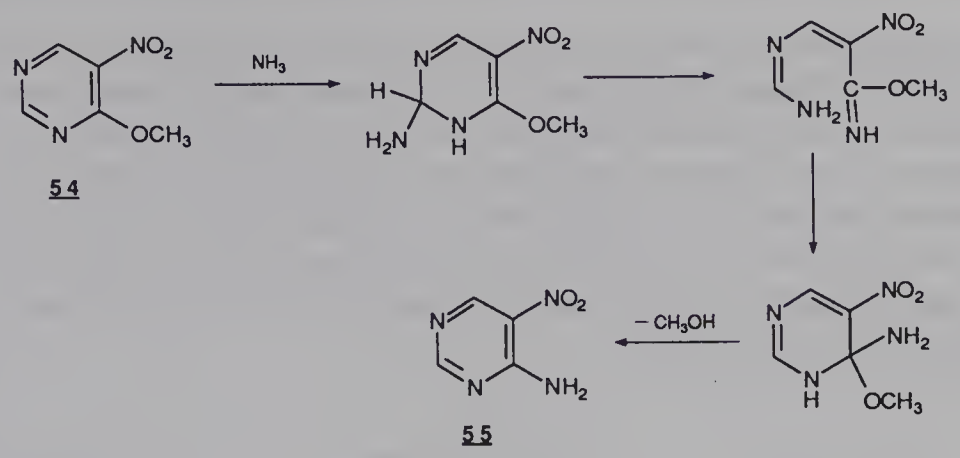
Scheme 8.6.

S_N(ANRORC) mechanism.[34] It thus appears that liquid ammonia does not provide sufficiently basic conditions to induce facile cleavage of the ring in **48**, despite its activation by two nitro groups.

Many 5-nitro-activated pyrimidines (**49**) react with ammonia similarly to **45**, undergoing nucleophilic addition at unsubstituted C-2 and/or C-4 to give the detectable σ-adducts **50** or **52**, which are not susceptible to ring opening and are readily oxidized to the corresponding amination products **51** or **53** (Scheme 8.7).[36] 4-Methoxy-5-nitropyrimidine (**54**) shows a different behavior, however, undergoing departure of the methoxy group to give 4-amino-5-nitropyrimidine (**55**) via the S_N(ANRORC) mechanism (Scheme 8.8).[36] This



Scheme 8.7.



Scheme 8.8.

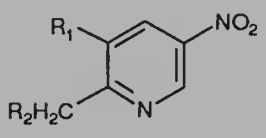
observation confirms that a pyrimidine ring, which is inherently more activated than a pyridine ring, is also more susceptible to ring opening.[3,4,13,14,37]

8.3 Ring Transformations

A number of reports have appeared pointing out that ring opening of an initially formed σ-adduct is often the important step that determines the occurrence of ring interconversions in reactions of various azaaromatics with nucleophilic reagents. In 1981 a review by Kost *et al.* summarized these reactions for pyridine derivatives activated by quaternarization and/or electron-withdrawing substituents (e.g., NO_2).[15] Similarly, reviews by Van der Plas in 1973 and 1978 described in detail the high susceptibility of pyrimidinium salts to undergo ring interconversions upon treatment with a large variety of bases.[13,14] In the past decade, much attention has been paid to the behavior of nitropyrimidines, especially 5-nitropyrimidine (**49a**). The results obtained are very appropriate for outlining the general features of such ring transformations of azaaromatics.

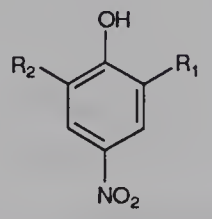
Reaction of 5-nitropyrimidine (**49a**) with ketonic reagents such as acetone, diethylketone, dibenzylketone, or acetylacetone in the presence of triethylamine or potassium ethoxide in ethanol gives either the nitropyridine derivative **56**, the nitrophenol **57**, or the 4-pyridone **58**.[38] In fact, the reaction pattern strongly depends on the nature of the nucleophile and the base used. In the presence of triethylamine, **49a** reacts with acetone and diethylketone to afford only **56a** and **56b**, respectively, although in moderate yield. Using

sodium ethoxide as the base, **49a** reacts with the same two ketones to give the nitrophenols **57a** and **57b**, respectively. Contrasting with the results above, the reactions of **49a** with acetylacetone and dibenzylketone afford the same products when conducted at room temperature in the presence of triethylamine or sodium ethoxide. The resulting products are **56d** for acetylacetone and **57c** for dibenzylketone. However, a mixture of the three products **56c**, **57c**, and **58c** was obtained on carrying out the reaction of **49a** with dibenzylketone and triethylamine at 120–130°C.[38]



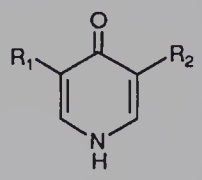
56

(a) $R_1 = R_2 = H$
(b) $R_1 = R_2 = CH_3$
(c) $R_1 = R_2 = C_6H_5$
(d) $R_1 = COCH_3$, $R_2 = H$



57

(a) $R_1 = R_2 = H$
(b) $R_1 = R_2 = CH_3$
(c) $R_1 = R_2 = C_6H_5$

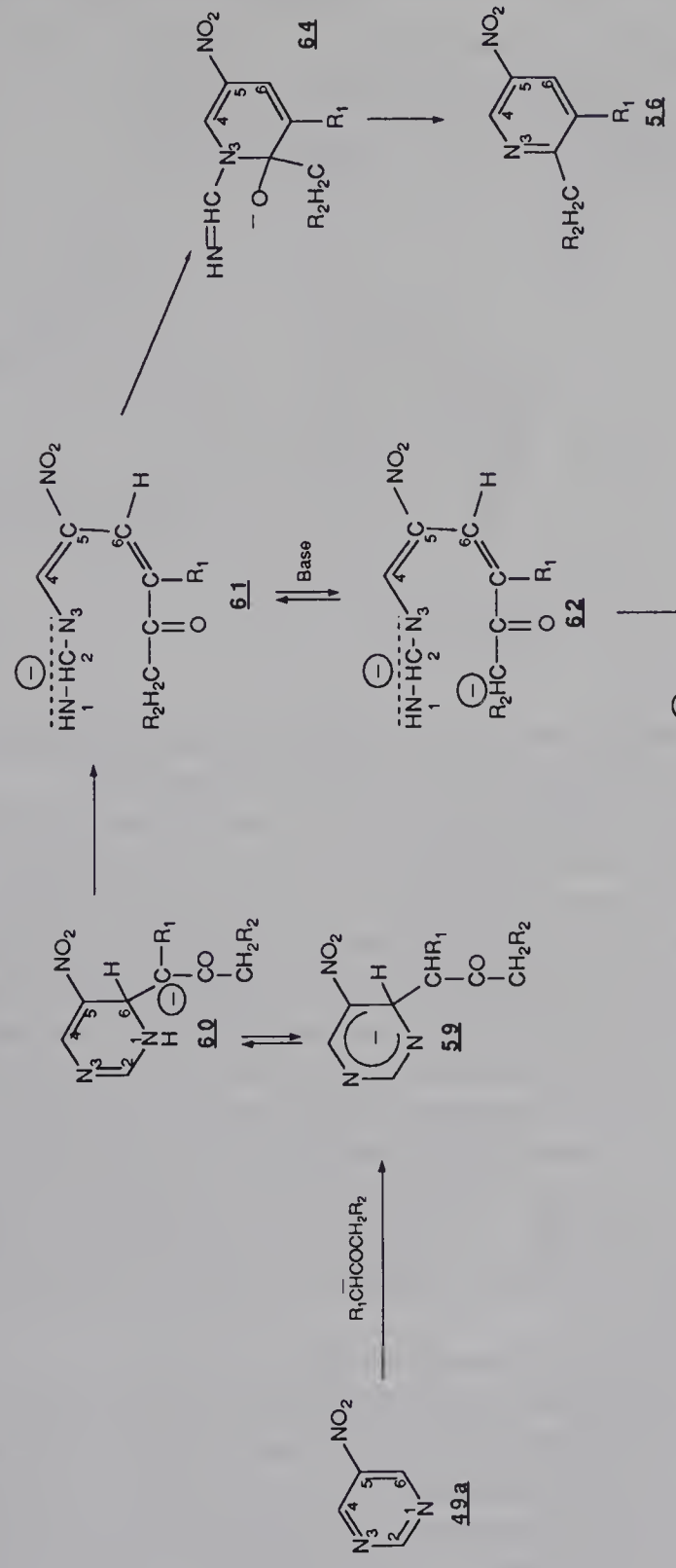


58

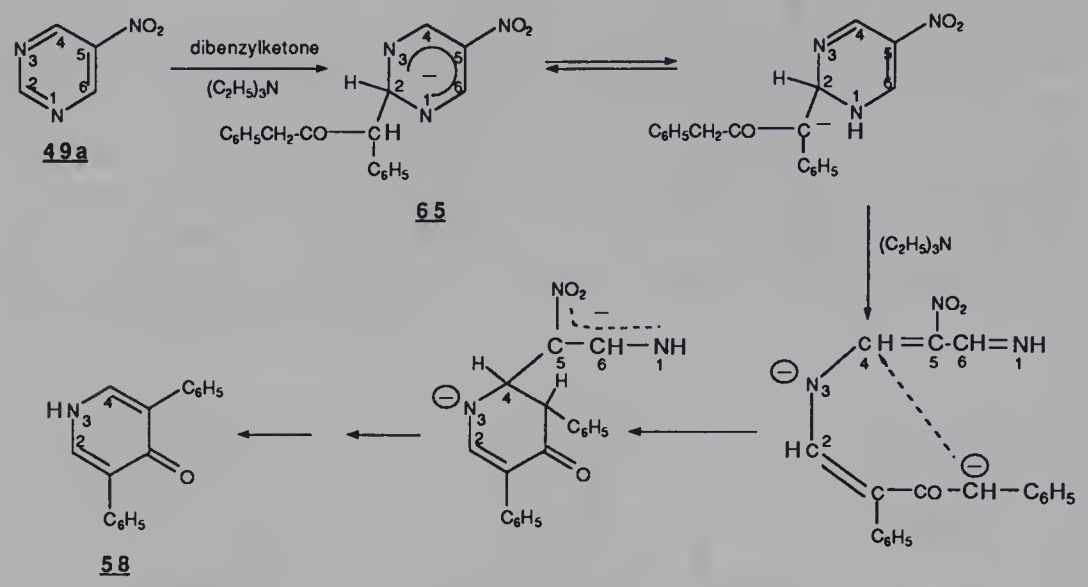
$R_1 = R_2 = C_6H_5$

The formation of the nitropyridines **56** and nitrophenols **57** has been explained in terms of Scheme 8.9. Initial formation of the ketone σ-adduct **59** would be followed by ring opening of the dihydro compound **60**, which is in prototropic equilibrium with **59**, affording **61**. Ring closure of **61** would then occur according to two main pathways. If the basicity of the medium is sufficient for deprotonation of the CH_2 group, **61** is converted to **62**, which cyclizes to **63**. After rearomatization, **63** affords the nitrophenol **57**. If deprotonation of **61** is not favored, ring closure occurs through addition of the negatively charged nitrogen atom to the carbonyl group, giving **64** which would rearomatize to **56**. A similar mechanism was suggested to explain the replacement of the N_1-C_2 fragment of a pyrimidine ring by a two-carbon fragment of a nucleophile in the conversion of pyrimidinium salts into pyridines by treatment with active methylene compounds like diethyl malonate and malononitrile.[39] The conversion of **49a** to **57** is most noteworthy. It occurs with replacement of the N_1-C_2-N_3 fragment of **49a** by a three-carbon fragment of the nucleophile, and it constitutes the first reported example of a pyrimidine–benzene ring interconversion.[40,41]

Formation of the ketonic σ-adduct **65** at C-2 would be the promoting step in the formation of the pyridone **58** through replacement of the N_1-C_6-C_5



Scheme 8.9.

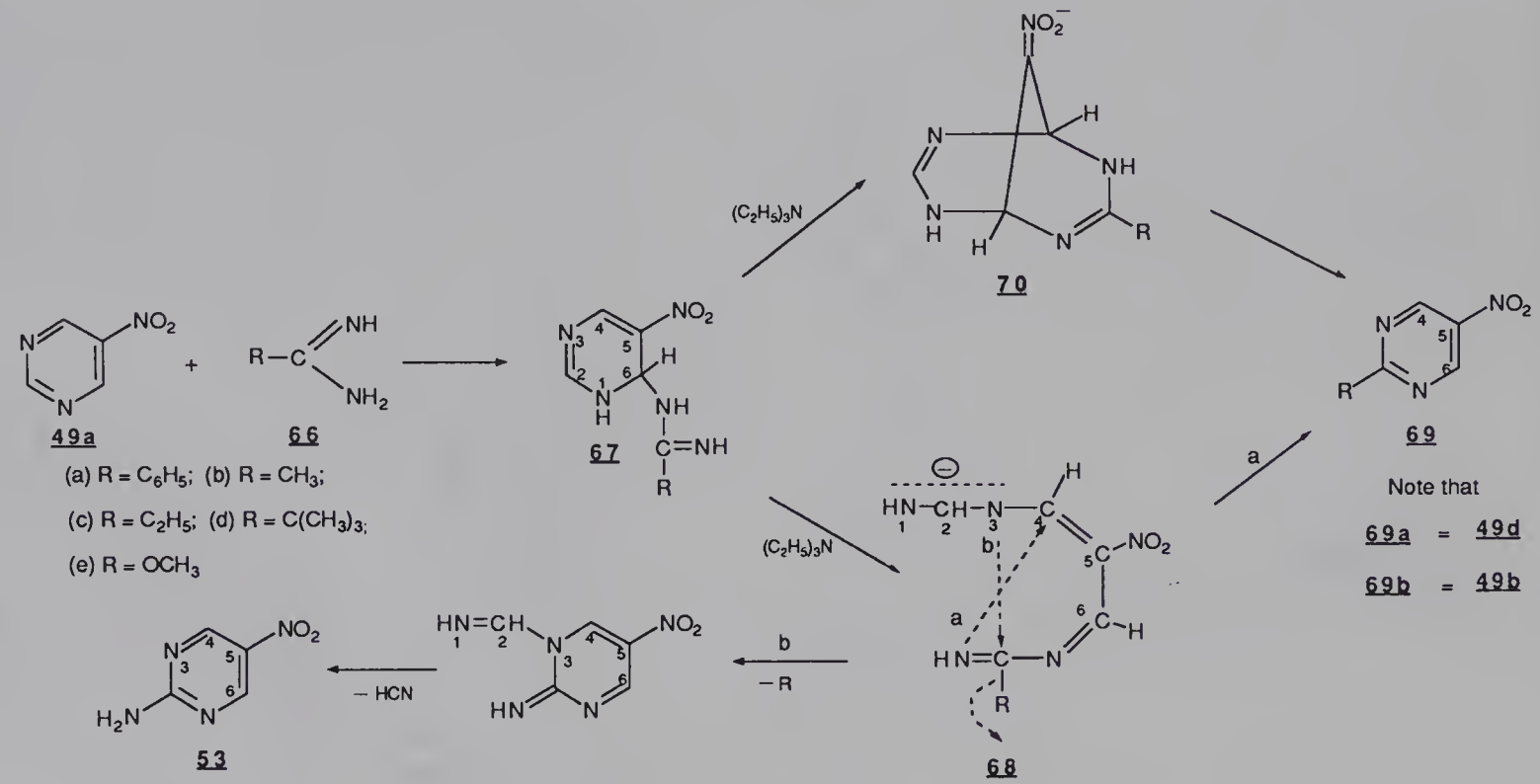


Scheme 8.10.

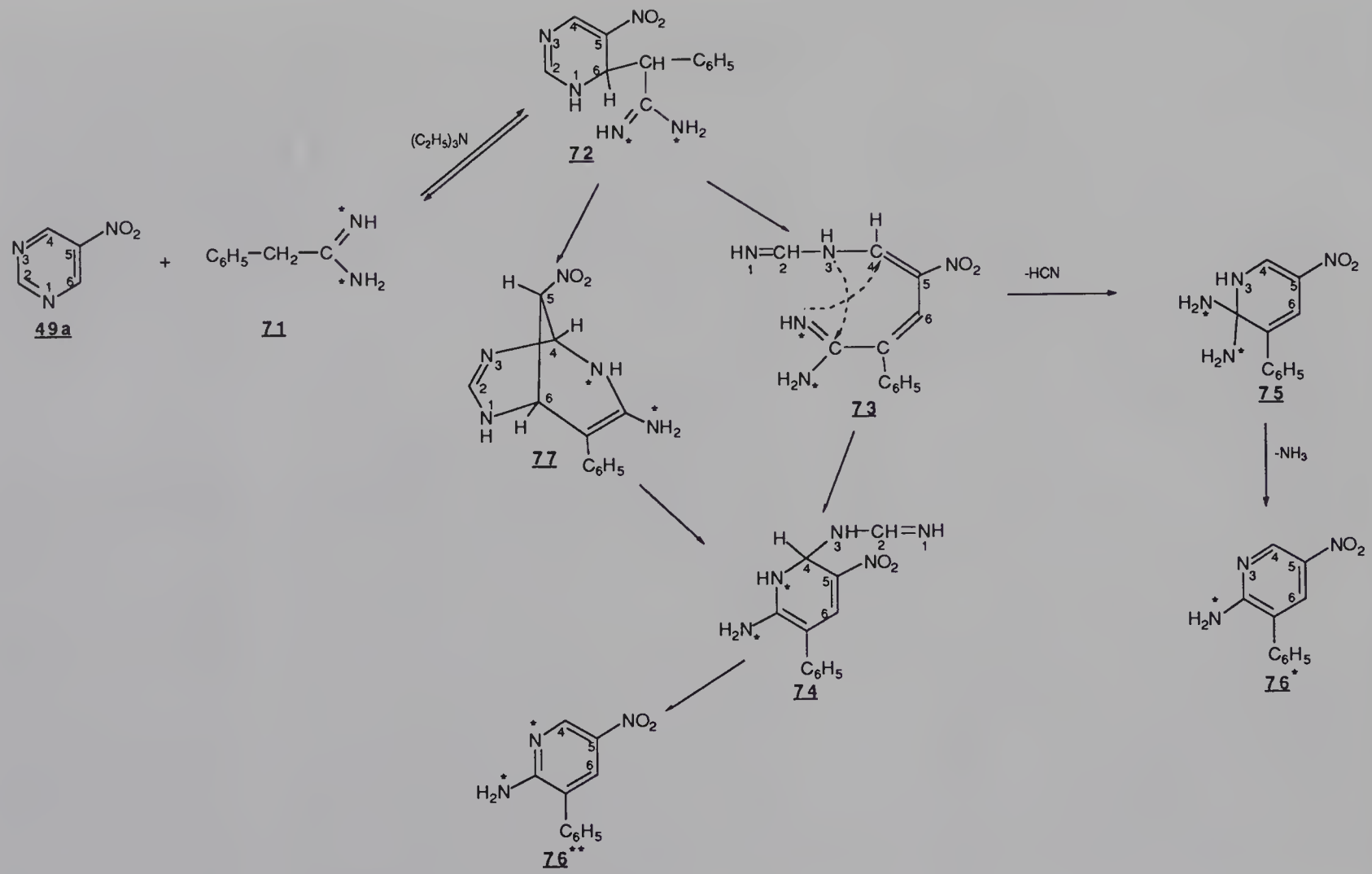
fragment of **49a** by a three-carbon fragment of the nucleophile. Scheme 8.10 outlines the most reasonable pathway for this ring transformation.[38]

Treatment of **49a** with amidines **66** gives rise to various ring transformations in which the amidine acts either as an N—C—N, a C—C—N, an N—C, or a C—C donor.[42,43] Scheme 8.11 describes the conversion of **49a** into 2-R-5-nitropyrimidines (**69**) and/or to 2-amino-5-nitropyrimidine (**53**), through replacement of the $N_1C_2N_3$ and the N_1C_2 fragments of the parent pyrimidine ring by analogous three-atom or two-atom fragments of the reacting amidine. In these instances, the initially formed dihydropyrimidine **67** is subject to ring opening with the formation of **68**. Depending on the nature of the R substituent in the parent amidine, **68** will undergo preferential cyclization via route a (benzamidine, **66a**; acetamidine, **66b**; propionamidine, **66c**; pivalamidine, **66d**) to afford **69**, or via route b (*O*-methylisourea, **66e**; cyanamide) to afford **53**.[42] Formation of **69** via the bicyclic intermediate **70** has also been suggested.

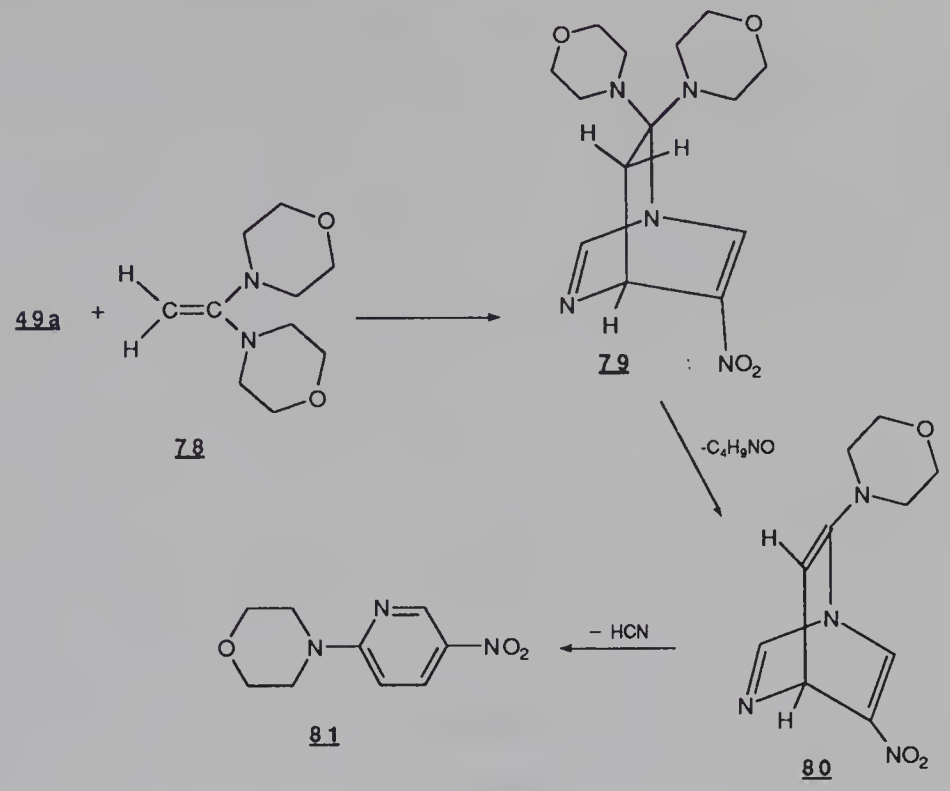
In contrast to **66a–e**, α-phenylacetamidine (**71**) acts both as a C—C—N and a C—C donor when reacting with **49a** to form the pyridine **76**. Experiments carried out with a sample of **71** with equally ^{15}N-labeled nitrogen atoms have suggested the reaction pathways shown in Scheme 8.12, which all involve initial addition of **71** as a carbon nucleophile to give the C-adduct **72**.[43] Ring opening of **72** gives **73**, which cyclizes via intramolecular nucleophilic attack of the amidine nitrogen on C-4 to form **74** or via elimination of HCN to give **75**. Rearomatization of **74** by rupture of the bond between C-4 and N-3 leads


NO2
N
N
49a
+
R–C
NH
NH2
66
(a) R = C6H5; (b) R = CH3;
(c) R = C2H5; (d) R = C(CH3)3;
(e) R = OCH3
NO2
N
NH
H
NH
C=NH
R
67
(C2H5)3N
NO2−
H
N
NH
N
H
H
N
R
70
NO2
N
R
N
69
Note that
69a = 49d
69b = 49b
a
(C2H5)3N
HN–CH–N–C
H
b
a
C–NO2
C–H
HN=C–N
R
68
b
– R
HN=CH
NO2
HN
N
– HCN
H2N
N
53

Scheme 8.11.


NO2
C6H5–CH2–C(=NH)–NH2
49a
71
(C2H5)3N
72
77
73
74
75
76*
76**
-HCN
-NH3
C6H5
NH2

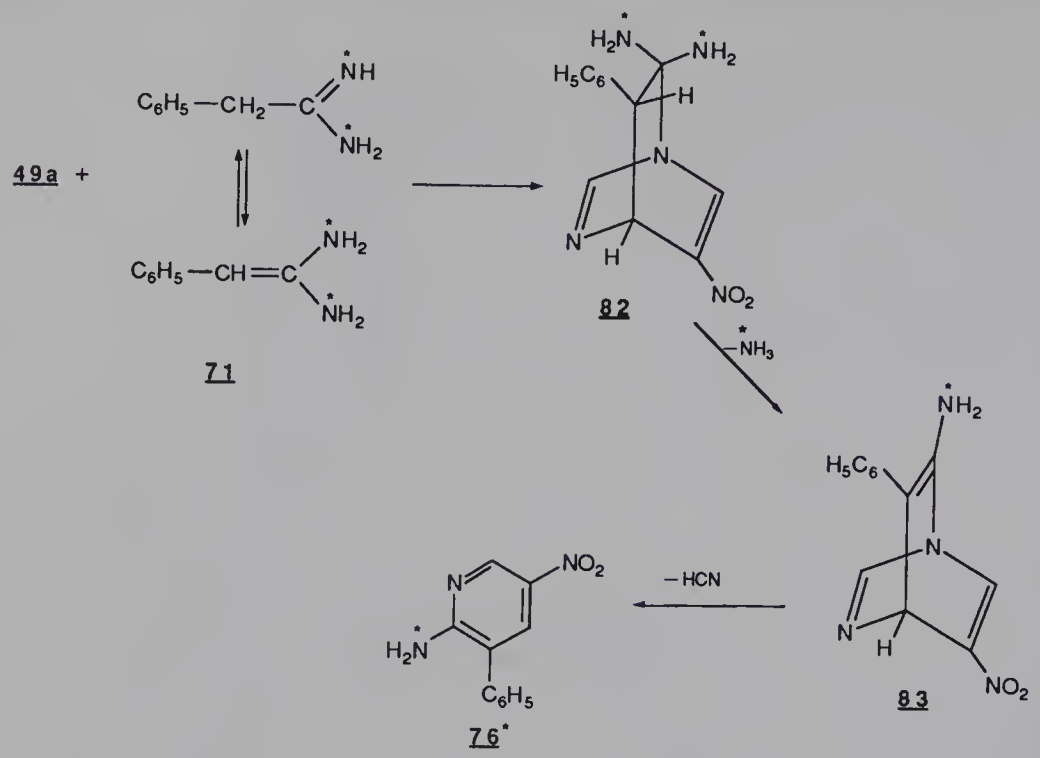
Scheme 8.12.



Scheme 8.13.

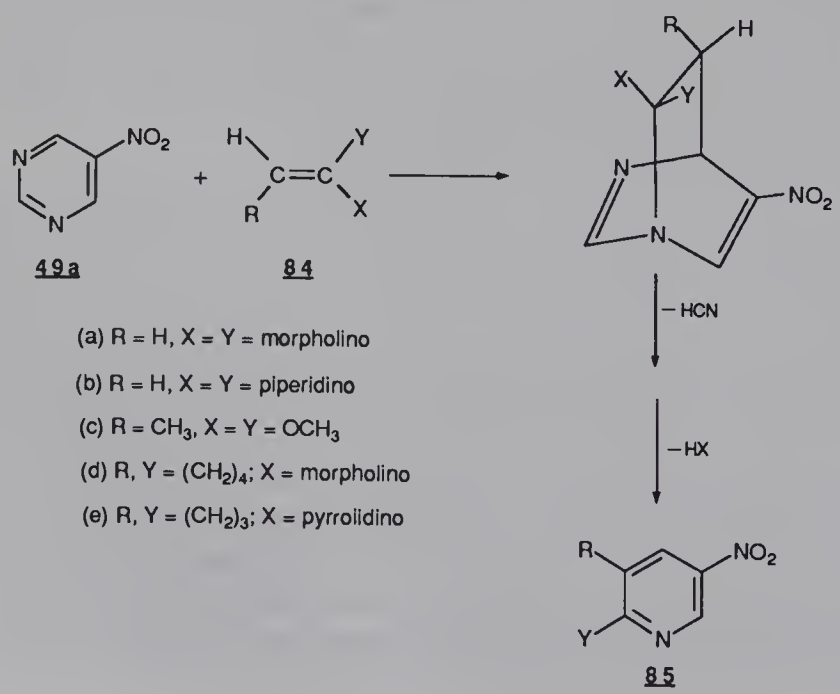
to **76****, in which both the ring and exocyclic nitrogen atoms are ^{15}N-labeled and the new N—C—C fragment derives from the parent amidine. Rearomatization of **75** occurs by loss of ammonia and affords **76*** in which only the exocyclic nitrogen atom is ^{15}N-labeled and the new C—C fragment derives from the parent amidine. Based on ^{15}N analysis, **76*** and **76**** were found to form approximately in similar amounts.

Concerning the formation of **76*** and **76****, it is interesting to note that alternative mechanistic pathways have been discussed. Thus, the formation of 76** via the bicyclic intermediate **77** cannot be excluded, since the formation of such bridged adducts from nitroarenes is well documented in the recent literature.[44–46] More significantly, results obtained with some *N,N*-disubstituted diphenylacetamidines have led to the proposal of the mechanism shown in Scheme 8.13 to explain the formation of **76***. The reaction of **49a** with *N,N'*-vinylidenedimorpholine (**78**) results in the formation of 2-morpholino-5-nitropyridine (**81**) in good yield—a reaction that can be accounted for only in terms of the intermediacy of the 1,4-cycloadducts **79** and **80**.[43] On this ground, the formation of **76*** via the intermediacy of the cycloadducts **82** and **83** is not unlikely (Scheme 8.14).The idea is supported by the finding that



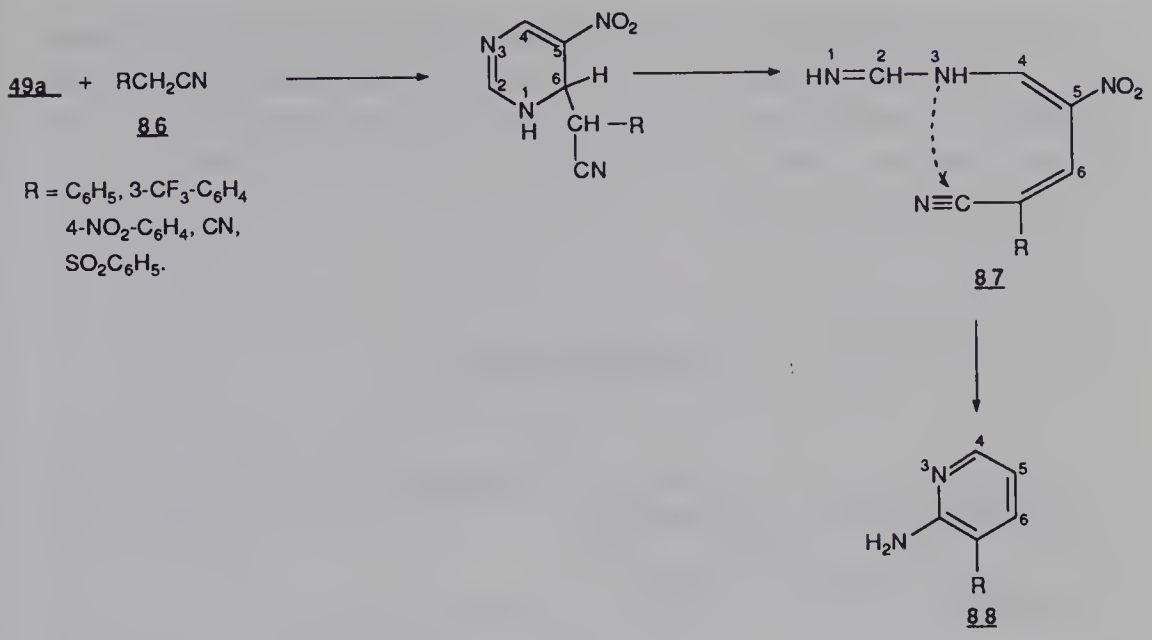
Scheme 8.14.

49a is capable of undergoing [4+2] cycloaddition reactions in which electron-rich ethylenes like the ketene-*N*,*N*-acetals **84a** and **84b**, the ketene-*O*-*O*-acetal **84c**, and the enamines **84d** and **84e** react as dienophiles and the nitro-activated pyrimidine ring as an electron-deficient diene (eq. 8-9) to form the pyridines



(a) R = H, X = Y = morpholino
(b) R = H, X = Y = piperidino
(c) R = CH_3, X = Y = OCH_3
(d) R, Y = $(CH_2)_4$; X = morpholino
(e) R, Y = $(CH_2)_3$; X = pyrrolidino

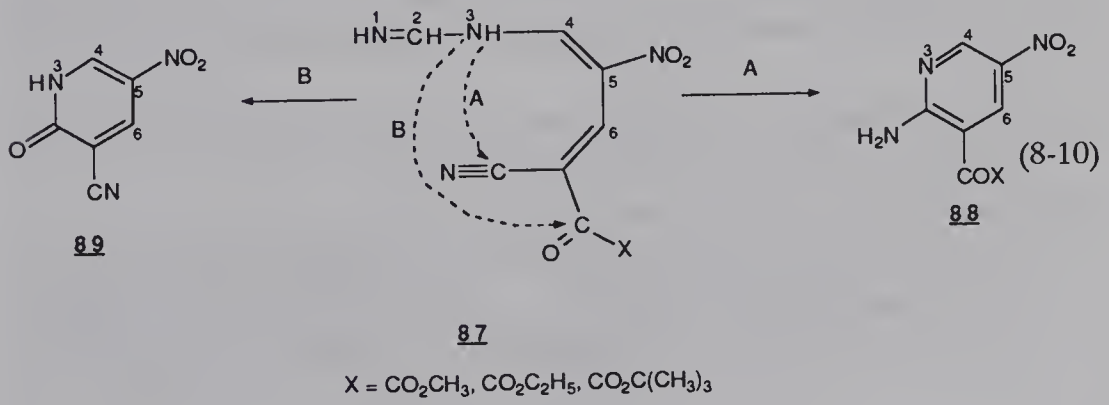
(8-9)



Scheme 8.15.

85.[47] Cycloadditions of 5-nitropyrimidines with ynamines have also been reported.[48]

Formation of pyridine derivatives via replacement of the N_1–C_2 fragment of a pyrimidine ring by a C—C portion of an attacking nucleophile occurs in the reactions of **49a** with nitriles **86** (Scheme 8.15).[49] With alkyl cyanoacetates, the resulting open-chain intermediate **87** can cyclize through intramolecular nucleophilic addition of the 3-nitrogen on either the CN or the CO group, leading to **88** or **89** (eq. 8-10). Low temperatures favor the formation of **89**, while high temperatures favor that of **88**.[49]



X = CO_2CH_3, $CO_2C_2H_5$, $CO_2C(CH_3)_3$

The transformations of 5-nitropyrimidine (**49a**) into pyridine derivatives by treatment with carbanions having a carbonyl, an amidine, or a nitrile functionality, as outlined in Schemes 8.9 to 8.15, represent valuable synthetic routes to 2-amino-, 2-oxo-, or 2-alkyl (aryl)-3-substituted pyridines.

References

1. (a) Illuminati, G. *Adv. Heterocycl. Chem.* **1964**, *3*, 285; (b) Illuminati, G.; Stegel, F. *ibid.* **1983**, *34*, 305.
2. Terrier, F. *Chem. Rev.* **1982**, *82*, 77.
3. Van der Plas, H. C. *Acc. Chem. Res.* **1978**, *11*, 462.
4. Van der Plas, H. C.; Wozniak, M.; Van den Haak, H. J. W. *Adv. Heterocycl. Chem.* **1983**, *33*, 96.
5. Biffin, M. R. C.; Miller, J.; Moritz, A. G.; Paul, D. B. *Aust. J. Chem.* **1969**, *22*, 2561; *ibid.* **1970**, *23*, 957, 963.
6. Terrier, F.; Chatrousse, A. P.; Schaal, R. *J. Org. Chem.* **1972**, *37*, 3010.
7. Bemporad, P.; Illuminati, G.; Stegel, F. *J. Am. Chem. Soc.* **1969**, *91*, 6742.
8. Schaal, R.; Terrier, F.; Halle, J. C.; Chatrousse, A. P. *Tetrahedron Lett.* **1970**, 1393.
9. Fyfe, C. A. *Tetrahedron Lett.* **1968**, 659.
10. Cherkasov, V. M.; Remmenikov, G. Ya.; Kiscsilenko, A. A.; Romanenko, K. A. *Khim. Geterosikl. Soedin.* **1980**, 239.
11. (a) Wozniak, M.; Van der Plas, H. C.; Van Veldhizen, B. *J. Heterocyclic. Chem.* **1983**, *20*, 9; (b) Tondys, H.; Van der Plas, H. C.; Wozniak, M. *ibid.* **1985**, *22*, 353.
12. (a) Zoltewicz, A.; Helnick, L. S.; O'Halloran, J. K. *J. Org. Chem.* **1976**, *41*, 1308. (b) Zoltewicz, A.; Helnick, L. S. *J. Am. Chem. Soc.* **1972**, *94*, 682.
13. Van der Plas, H. C., "*Ring Transformations of Heterocycles*", vols. 1 and 2. Academic Press: New York, 1973.
14. Van der Plas, H. C. *Heterocycles* **1978**, *9*, 33.
15. Kost, A. N.; Gromov, S. P.; Sagitullin, R. S. *Tetrahedron* **1981**, *37*, 3423.
16. (a) Van der Plas, H. C.; Smit, P.; Koudjis, A. *Tetrahedron Lett.* **1968**, 9. (b) Van der Plas, H. C.; Koudjis, A. *Recl. Trav. Chim. Pays-Bas*, **1970**, *89*, 129.

17. (a) de Valk, J.; Van der Plas, H.C. *Recl. Trav. Chim. Pays-Bas,* **1971**, *90*, 1239; (b) *ibid.* **1972**, *91*, 1414.
18. Van der Plas, H. C.; Koudjis, A. *Recl. Trav. Chim. Pays-Bas*, **1973**, *92*, 711.
19. Brown, D. J. In "*Mechanisms in Molecular Migrations*", vol. 1, Thyagarajan, B. S., ed. Wiley-Intersciences: New York, 1968, p. 209.
20. (a) Kroon, A. P.; Van der Plas, H. C. *Recl. Trav. Chim. Pays-Bas,* **1973**, *92*, 1020; (b) Kroon, A. P.; Van der Plas, H. C.; *ibid.* **1974**, *93*, 111; (c) Kroon, A. P.; Van der Plas, H. C.; Van Garderen, G., *ibid.* **1974**, *93*, 325.
21. den Hertog, H. J., Boer, H.; Streef, J. W.; Vekermans, F. C. A., Van Zoest, W. J. *Recl. Trav. Chim. Pays-Bas,* **1974**, *93*, 195.
22. Sanders, G. M.; Van Dijk, M.; den Hertog, H. J. *Recl. Trav. Chim. Pays-Bas,* **1974**, *93*, 198.
23. de Valk, J.; Van der Plas, H. C.; Jansen, F.; Koudjis, A. *Recl. Trav. Chim. Pays-Bas,* **1973**, *92*, 460.
24. Rykowski, A.; Van der Plas, H. C. *Recl. Trav. Chim. Pays-Bas,* **1974**, *94*, 204.
25. Geerts, J. P.; Rasmussen, C. A. H.; Van der Plas, H. C.; Van Veldhuizen, B. *Recl. Trav. Chim. Pays-Bas*, **1974**, *93*, 231.
26. Rasmussen, C. A. H.; Van der Plas, H. C. *Recl. Trav. Chim. Pays-Bas*, **1977**, *96*, 101.
27. Van Meeteren, H. W.; Van der Plas, H. C. (a) *Tetrahedron Lett.* **1966**, 4517; (b) *Recl. Trav. Chim. Pays-Bas,* **1971**, *90*, 105.
28. Levine, R.; Leake, W. W. *Science*, **1955**, *121*, 780.
29. Pieterse, M. J.; den Hertog, H. J. *Recl. Trav. Chim. Pays-Bas,* **1961**, *80*, 1376.
30. Kauffmann, T.; Boettcher, F. P. *Chem. Ber.* **1962**, *95*, 1528.
31. Miller, J. "*Aromatic Nucleophilic Substitution*". Elsevier: Amsterdam, 1968.
32. Reinheimer, J. D.; Mayle, L. L.; Dolnikowski, G. G. *J. Org. Chem.* **1980**, *45*, 3097.
33. Reinheimer, J. D.; Sourbatis, N.; Lavallée, R. L.; Goodwin, D.; Gould, G. *Can. J. Chem.* **1984**, *62*, 1120.
34. (a) de Bie, D. A.; Geurtsen, B.; Van der Plas, H. C. *J. Org. Chem.* **1985**, *50*, 484; (b) de Bie, D. A.; Geurtsen, B.; Berg, I. E.; Van der Plas, H. C. *ibid.* **1986**, *51*, 3209.
35. Bowden, K.; Prasannan, S.; Ranson, R. J. *J. Chem. Soc., Perkin Trans. 2*, **1987**, 181.

36. Van der Plas, H. C.; Charushin, V. N.; Van Veldhuizen, B. *J. Org. Chem.* **1983**, *48*, 1354.
37. Van der Plas, H. C.; Jongeyan, H.; Koudjis, A. *J. Heterocycl. Chem.* **1978**, *15*, 485.
38. Barczynski, P.; Van der Plas, H. C. *Recl. Trav. Chim. Pays-Bas,* **1978**, *97*, 256.
39. Oostveen, E. A.; Van der Plas, H. C. *Recl. Trav. Chim. Pays-Bas,* **1974**, *93*, 233.
40. Hirota, K.; Kitade, Y.; Senda, S. *J. Heterocycl. Chem.* **1980**, *17*, 413.
41. Fox, J. J.; Su, J. L.; Sternpel, I. M.; Watanabe, C. A. *J. Org. Chem.* **1982**, *47*, 1081.
42. Barczynski, P.; Van der Plas, H. C. *J. Org. Chem.* **1982**, *47*, 1077.
43. Charushin, V. N.; Van der Plas, H. C. *J. Org. Chem.* **1963**, *48*, 2667.
44. Bard, R. R.; Strauss, M. J. *J. Am. Chem. Soc.* **1976**, *97*, 3789.
45. Strauss, M. J.; Bard, R. R. *J. Org. Chem.* **1972**, *43*, 3600.
46. Terrier, F.; Chatrousse, A. P.; Strauss, M. J. *J. Org. Chem.* **1984**, *49*, 4172.
47. Charushin, V. N.; Van der Plas, H. C. *Tetrahedron Lett.* **1982**, *23*, 3965.
48. Marcelis, A. M. T.; Van der Plas, H. C.; Harkema, S. *J. Org. Chem.* **1985**, *50*, 270.
49. Charushin, V. N.; Van der Plas, H. C. *Recl. Trav. Chim. Pays-Bas,* **1983**, *102*, 373.

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