Forschung, Wissenschaft

Mechanisms of Nucleophilic Aromatic and Hetero-aromatic Substitution. Recent Developments*

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Abstract

There are now at least five well defined mechanisms of nucleophilic aromatic and heteroaromatic substitution. Three of them, the S_NAr, the benzyne and the S_N1 mechanism, have been known for a long time, whereas the $S_{RN}1$ and the S_N (ANRORC) mechanisms are relatively recent discoveries. The former is a radical chain mechanism which has a wide applicability in synthesis while the latter has only been found in heterocyclic systems and involves a nucleophilic addition followed by ring opening and ring closure processes. An S_NAr mechanism, initiated by the transfer of an electron from the nucleophile to the substrate, has also been proposed, but evidence for it has not yet been conclusive. In recent years considerable progress has also been made in understanding the more subtle aspects of the older mechanisms. For example, base catalysis in S_NAr reactions with amine nucleophiles has been shown to be a consequence of rate limiting proton transfer despite the fact that proton transfer is diffusion controlled. Benzyne has been isolated and many theoretical calculations on its structure have been performed. The S_N1 mechanism has been shown to involve reversible loss of nitrogen from arenediazonium ions, a fact of considerable import because it is the first example of a reaction of an organic species with nitrogen.

Introduction

The field of nucleophilic aromatic and heteroaromatic substitution has developed quite extensively over the last decade. Several new mechanisms have been discovered. They include the $S_{RN}1$ radical chain mechanism and the S_N(ANRORC) mechanism which involves ring opening and ring closure steps. An S_NAr mechanism initiated by an electron transfer from the nucleophile to the aromatic substrate has also been proposed. Considerable progress has been made in our understanding of the older mechanisms such as the S_NAr or σ-complex mechanism, the benzyne mechanism and the aromatic S_N1 mechanism.

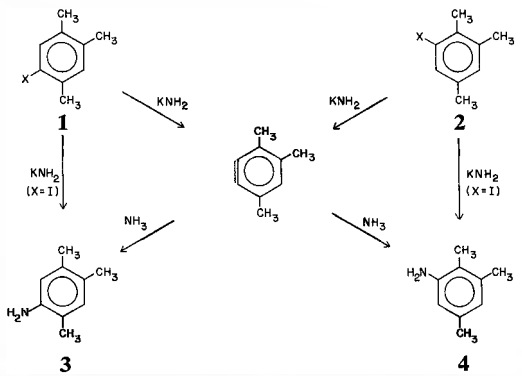
In this paper, which does not attempt to be a comprehensive review, I will first discuss the three new mechanisms with an emphasis on the $S_{RN}1$ mechanism and its scope since it is the one with the widest synthetic applications. In the discussion of the older mechanisms selected areas of current or recent interest will be emphasized. In the benzyne mechanism, this will be questions of structure of arynes and hetarynes and attempts at isolation or direct detection of arynes. With the S_NAr mechanism the focus will be on our changing views on the mechanism of base catalysis of aminolysis reactions which will be put into the context of changing notions about acid-base catalysis in general. In the case of the S_N1 mechanism the whole story will have to be told since the confusion in this area has only come to a rest very recently.

Photochemical nucleophilic aromatic substitutions need to be mentioned but they will not be treated in this paper [1].

$S_{RN}1$ Mechanism

This mechanism which has been reviewed recently [2] was discovered almost by accident by *Bunnett* and *Kim* [3] in 1970. They were investigating the reactions of 5-halo and 6-halopseudocumenes **1** and **2**, respectively, with KNH_2 in liquid ammonia, anticipating reaction by the benzyne mechanism (Scheme 1). Based on this mechanism they expected to obtain the same product ratio **4** : **3** regardless of the halogen X, or of whether they started with **1** or **2**. This expectation was borne out for the chloro and bromo pseudocumenes where the product ratio was **4** : **3** = 1.46. With the iodo substrates the product ratio was dependent on the initial position of the halogen: **1**(I) gave **4** : **3** = 0.63, **2**(I) gave **4** : **3** = 5.9. These results indicated an additional, non-rearranging pathway.

Scheme 1:



* Based on a lecture given at the 7th International Colour Symposium, September 24–27, 1979, at Interlaken, organized by the Association of Swiss Chemists.

The fact that in the presence of radical trapping agents the product ratio for the iodo pseudocumenes shifted towards that of the benzyne mechanism whereas in the presence of potassium metal which generates solvated electrons there were only unrearranged products, was taken as evidence for a radical mechanism which was represented by Scheme 2. Steps 1 and 5 are initiation and termination steps, respectively, whereas steps 2–4 are propagation steps with Y^- being the nucleophile.

Scheme 2:

$$\text{electron donor} + ArX \rightarrow [ArX]^{\cdot -} \quad (1)$$

$$[ArX]^{\cdot -} \rightarrow Ar^{\cdot} + X^- \quad (2)$$

$$Ar^{\cdot} + Y^- \rightarrow [ArY]^{\cdot -} \quad (3)$$

$$[ArY]^{\cdot -} + ArX \rightarrow ArY + [ArX]^{\cdot -} \quad (4)$$

$$\text{termination steps} \quad (5)$$

There are three types of reactive intermediates: a radical $Ar^{\cdot}$ and two radical anions, $[ArX]^{\cdot -}$ and $[ArY]^{\cdot -}$. That the overall result is a nucleophilic substitution can be appreciated if eqs 2–4 are added together, eq. 6.

$$ArX + Y^- \rightarrow ArY + X^- \qquad (2+3+4) = (6)$$

This mechanism which was originally proposed by *Kornblum* et al. [3a] and by *Russell* et al. [3b] for certain reactions at aliphatic centers was named $S_{RN}1$ because steps 2 and 3 resemble those of an S_N1 reaction; the "R" stands for "radical".

The $S_{RN}1$ mechanism has a wide scope and allows facile substitution in cases where neither the S_NAr or the benzyne mechanism would provide an easy route to products. In particular, there is no need for activation of the aromatic substrate by strong electron withdrawing groups. For example, simple phenyl halides as well as alkyl, alkoxy, phenyl, carboxylate ($-COO^-$) and benzoyl substituted phenyl halides undergo substitution easily [4, 5]; however, dimethylamino, ionized hydroxy ($-O^-$) and nitro groups impede the reaction [4, 5].

Another remarkable feature is the insensitivity to steric hindrance which is in marked constrast to aliphatic S_N2 [6] as well as to S_NAr substitutions [7]. For example, mesityl bromide or iodide react in good yield with picolyl anions [8] and even the reaction of 1-iodo-2,4,6-triisopropylbenzene with acetone enolate gives significant amounts of substitution product [2]. This insensitivity to steric effects is easily rationalized by the $S_{RN}1$ mechanism since no step involves the formation of a crowded transition state.

The initiation of the reaction can be achieved in various ways. In some cases there is spontaneous initiation in the dark, as in the reaction of amide ion with 5- or 6-iodopseudocumenes [3] or the reaction of pinacolone enolate ion with iodobenzene in Me_2SO [9]. The mechanism of this autoinitiation has not been established; the possibility of a thermally activated electron transfer according to

$$Y^- + ArX \rightarrow Y^{\cdot} + [ArX]^{\cdot -} \quad (7)$$

has been suggested [9].

Alkali metals in liquid ammonia which produce solvated electrons is a very effective way of initiation [3, 10–14]. Photostimulation has also been a very successful method both with aromatic [15] and heteroaromatic systems [16]. The mechanism of photoinitiation is not known but an attractive possibility is that absorption of a photon by a charge transfer complex between nucleophile and substrate induces an electron transfer [17], as for example in eq. 8.

$$PhI \cdot (EtO)_2PO^- \xrightarrow{h\nu} [PhI]^{\cdot -} + (EtO)_2PO^{\cdot} \quad (8)$$

Recently, electrochemically initiated $S_{RN}1$ reactions have been reported [18].

Various nucleofugic groups are suitable for substitution. For example, in the reaction of monosubstituted benzenes with acetone enolate ion, fair to excellent yields of substitution products were found with X = I, Br, Cl, F, SPh, $\overset{+}{N}Me_3$ and $OPO(OEt)_2$ [11]. The fact that the diethylphosphate group is easily replaceable allows the straightforward conversion of a phenol into a primary aromatic amine by the following sequence [10].

$$ArOH \xrightarrow[NaOH]{(EtO)_2POCl} ArOPO(OEt)_2 \xrightarrow[KNH_2]{K} ArNH_2 \quad (9)$$

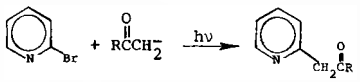
Such a conversion of phenols would be very difficult to achieve by standard methods.

The list of nucleophiles which have been successfully used in $S_{RN}1$ reactions include the amide ion (NH_2^-) [3, 10], arenethiolate [19–21] and alkanethiolate ions [14, 22], the benzeneselenolate ion ($PhSe^-$) [23], carbanions of the ketone enolate (4, 9, 11, 12, 14–16, 24–26] and ester enolate type [2, 27], α-cyanoalkyl anions [9, 13, 14], picolyl anions [8], anions derived from fluorene [12], 1,3-pentadiene [12], and phosphanions such as $(EtO)_2PO^-$ [28], $(EtO)_2PS^-$, Ph_2PO^-, $PhP(OC_4H_9)O^-$, $(Me_2N)_2PO^-$ and Ph_2P^- [2]. Among nucleophiles which do *not* promote the $S_{RN}1$ reaction we find alkoxide ions, phenoxide ions, benzenesulfinate ion and anions derived from malonic ester and from nitromethane [16, 29].

$S_{RN}1$ reactions are by no means restricted to benzene derivatives; they have been shown to occur in naphthalene [4, 5, 14, 19, 28], phenanthrene [4], and anthracene [4] derivatives as well as in heteroaromatic systems [16, 20, 24–26, 30, 31]. For example *Hay* and *Wolfe* [16] report the reaction 10

(10)

or *Komin* and *Wolfe* [26] the reaction 11



(11)

In fact, halopyridines and haloquinolines react more readily than the halobenzenes. Other heteroaromatic systems which react according to the $S_{RN}1$ mechanism include halothiophenes [31] and pyrimidine derivatives [30].

It should be mentioned that there is a large number of experimental observations pertaining to side products, inhibition, reactivity patterns, etc. which can all be accounted for by the $S_{RN}1$ mechanism or some extension thereof, and which therefore constitute further evidence for the correctness of the mechanism. They have been excellently reviewed by Bunnett [2] and a full discussion would be beyond the scope of this paper. I shall only mention two very recent studies which yielded some information about the rates of some of the steps in Scheme 1.

$$PhX + (EtO)_2PO^- \xrightarrow{h\nu} \underset{\mathbf{4a}}{PhPO(OEt)_2} \qquad (12)$$

$$PhX + Me_3CC(=O)CH_2^- \xrightarrow{h\nu} \underset{\mathbf{4b}}{PhCH_2C(=O)CMe_3} \qquad (13)$$

In the first, reactions 12 and 13 were conducted in competition with each other, with X = I, Br, Cl, F, SPh, and N^+Me_3 [32]. The product ratio **4a** : **4b** was 1.36 ± 0.08 for all six substrates. This result further supports the $S_{RN}1$ mechanism and is inconsistent with a possible alternative $S_{RN}2$ mechanism for which the propagation cycle would be as in eq. 14 and 15. In this latter mechanism the nucleophile reacts with $[ArX]^{\cdot-}$ and the relative nucleophilic reactivities should depend on X while in the $S_{RN}1$ mechanism it is $Ar^{\cdot}$ which reacts with the nucleophile and thus no dependence on X is expected.

$$[ArX]^{\cdot-} + Y^- \rightarrow [ArY]^{\cdot-} + X^- \qquad (14)$$

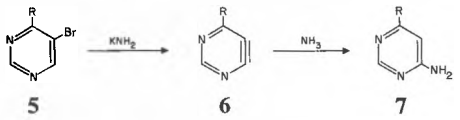
$$[ArY]^{\cdot-} + ArX \rightarrow ArY + [ArX]^{\cdot-} \qquad (15) = (4)$$

The authors [32] also present arguments to show that the rate of reaction of the phenyl radical with the two nucleophiles may be close to the encounter-controlled limit.

In the second study a number of electrochemically initiated $S_{RN}1$ reactions in liquid ammonia were investigated by cyclic voltammetry [33]. The rate constant for iodide departure from 2-iodoquinoline radical anion (step 2 in Scheme 2) was estimated to be 3×10^6 sec^{-1} whereas the rate constants for the reaction of the quinolyl radical with several nucleophiles span a range from 6×10^6 ($4\text{-Cl-}C_4H_6S^-$) to 4.5×10^7 M^{-1} sec^{-1} ($C_6H_5COCH_2^-$).

S_N(ANRORC) Mechanism

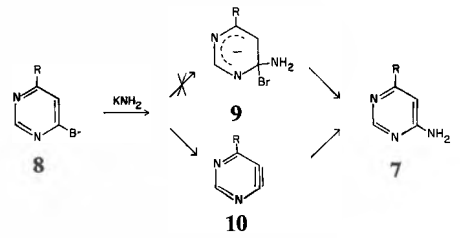
Another new mechanism, discovered by van der Plas in the early 1970s and recently reviewed by the same author [34] is the so-called S_N(ANRORC) mechanism. Its discovery, like that of the $S_{RN}1$ mechanism, occurred during an investigation of substitution reactions which were presumed to proceed by the benzyne mechanism. One of the reactions studied was that of 5-bromo-4-R-pyrimidine **5** (R = t-C_4H_9, C_6H_5, CH_3, OCH_3, OH, NH_2) with KNH_2 in liquid ammonia which gave exclusively the cine product 6-amino-4-R-pyrimidine **7** and no 5-amino-4-R-pyrimidine [35,36].



(16)

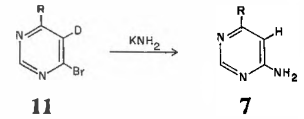
The obvious explanation for the product obtained was to assume a pyrimidyne intermediate **6**.

Another reaction was that of 6-bromo-4-R-pyrimidine **8** (R = t-C_4H_9 or C_6H_5) with KNH_2 which also yielded **7** as the sole product [37]. In this case the result is



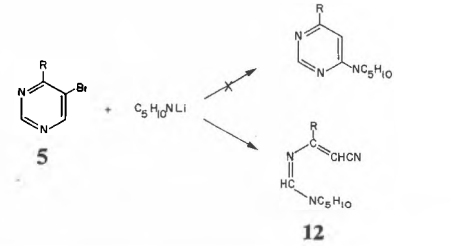
(17)

consistent either with an S_NAr pathway via **9** or the hetaryne pathway via **10**. The S_NAr pathway could however be excluded by showing that 5-deuteriopyrimidine **11**, after reaction with KNH_2, has lost the deuterium in the product, whereas **7** and **11** do not exchange deuterium under the reaction conditions.



(18)

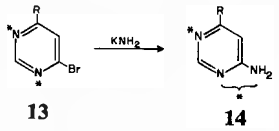
Doubts about the hetaryne interpretation arose however when the reaction of **5** (R = t-C_4H_9 od C_6H_5) with lithium piperidide in piperidine/ether was investigated [38]. No 6-piperidino-4-R-pyrimidine was found; instead 2-aza-4-cyano-1-piperidine-1,3-butadiene **12** was isolated. This suggested that lithium piperidide attacks the 2-position of the pyrimidine ring



(19)

which is followed by ring opening and loss of bromide ion.

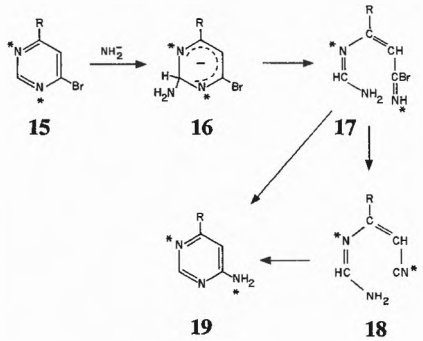
Suspecting that the reaction with KNH_2 may also occur by nucleophilic attack on the 2-position followed by ring opening and subsequent ring closure, van der Plas [39, 40] reacted ^{15}N-labeled 6-bromo-4-phenyl-pyrimidine **13** (label scrambled over the two nitrogens) with KNH_2. They found that no ^{15}N had been lost in the product but that 83% of the label at the 1-position in **13** had moved to the exocyclic nitrogen in **14**. This shows that at least 83% of the reaction did not occur by the hetaryne mechanism.



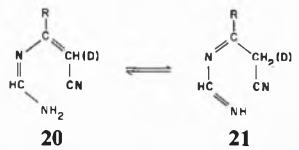
(20)

The results are consistent with the mechanism shown in Scheme 3. Conversion of **17** to the product may occur either directly of after loss of HBr via **18**; **18** is the analogue to **12** which was isolated in the piperidide reaction. Since the mechanism involves *A*ddition of a *N*ucleophile, followed by *R*ing *O*pening and *R*ing *C*losure, it was called S_N(ANRORC).

Scheme 3:



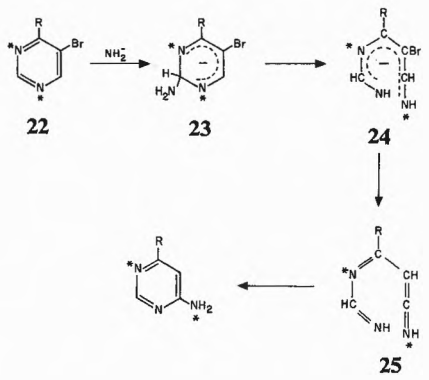
The S_N(ANRORC) mechanism can account for other observations mentioned earlier. For example, the loss of deuterium in reaction 18 can be explained by a tautomeric equilibrium between **20** and **21** [34]. The reactions of 5-bromo-4-R-pyrimines **5** which lead exclusively to the cine substitution products **7** are also



(21)

consistent with an S_N(ANRORC) mechanism as shown by ^{15}N labeling experiments, Scheme 4 [41]. Note that this mechanism is somewhat different from that of Scheme 3 in as much as it leads to cine substitution, while the one of Scheme 3 leads to substitution at the same carbon.

Scheme 4:

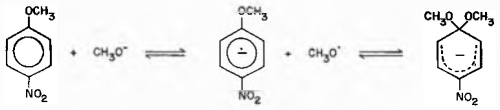


Van der Plas has suggested that one may distinguish the two mechanisms by the superscripts n (for "normal") and cine, e.g., S_N(ANRORC)^{cine} [34].

The S_N(ANRORC) mechanism has been most thoroughly investigated for the reactions of pyrimidine derivatives but it has also been encountered with other azines. Some noteworthy examples are the reactions of KNH_2 with chloropyrazine to form aminopyrazine [42], with phenyl-1,3,5-triazine to form aminophenyl-1,3,5-triazine [43], of 2-chloropurine to form 2-aminopurine [34], and many others [34].

Electron Transfer S_NAr Mechanism

There have been a number of claims that radical anions are precursors in the substitution reactions of certain nitro aromatic compounds [44–52]. In 1969 *Shein* [45] proposed a mechanism in which σ-complex formation proceeds through prior radical anion formation as shown for the case of p-nitroanisole and NaOMe (eq. 22).



(22)

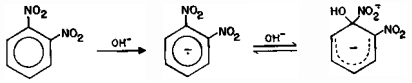
Interestingly, nitro aromatic compounds are among the substrates which do *not* undergo substitution by the $S_{RN}1$ radical chain mechanism discussed above.

The presence of radicals which have been detected by ESR spectroscopy in many of the investigated systems is beyond doubt. What has been more difficult to prove is that the radicals are on the reaction coordinate of the substitution reaction rather than the products of side reactions. Two recent papers by *Abe* [51, 52] present evidence that the radical anions formed by the interaction of hydroxyde ion with o- and p-dinitrobenzene in aqueous Me_2SO may in fact be intermediates in the substitution reactions, which lead to o- and p-nitrophenol, respectively.

These workers report that the decay of the dinitrobenzene radical anion has the same rate as the appearance of the product and that no other radical beside the dinitrobenzene radical anion could be detected. This latter point indicates that the hydroxyl

radical which is a by-product of radical anion formation is rapidly converted into some other species; it implies that the identity of the rates of radical anion decay and nitrophenol formation is *not* a consequence of the radical anion just being formed in a side equilibrium.

Since the decay of the radical anion is base catalyzed, *Abe* [51, 52] proposed the following mechanism for the initial phase of the reaction.



(23)

26 **27** **28**

Product formation is visualized as occurring either as in eq. 19 or eq. 20. The authors have no experimental evidence which would allow a distinction between the two possibilities.

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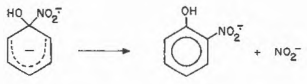
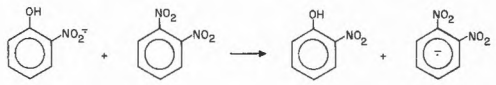


(25a)

28 **29**

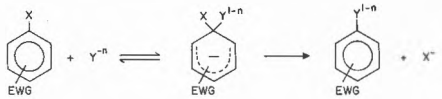


(25b)

26 **29** **27**

S_NAr Mechanism

This is the oldest mechanism and the one which prevails in aromatic and heteroaromatic systems activated by strong electron withdrawing groups. The basic features of this mechanism are summarized by eq. 26; they have been understood for a long time and reviewed frequently [7, 53–55].



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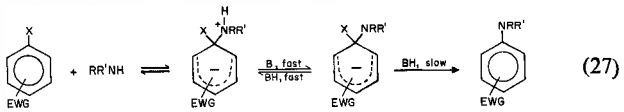
A great deal of research over the last 10–15 years has been focussed on the σ-complex or Jackson-Meisenheimer complex **30** [56, 57] which is formed in the first step of all S_NAr reactions. In weakly activated systems the σ-complex can usually not be detected directly but its presence has been demonstrated kinetically in a number of cases [55, 58]. With several strongly activating substituents σ-complexes can be detected by spectroscopic methods and in certain cases even isolated [56, 57]. NMR spectroscopy has played a central role in the structural characterization of σ-complexes [56, 57] and flow NMR techniques have recently extended the scope of this method to short-lived complexes [59, 60].

Another important development has been the increasing availability of fast reaction techniques to several laboratories, in particular the stopped-flow and temperature-jump techniques, which have allowed the kinetic characterization of σ-complex formation and decay; this area has been reviewed recently [61].

Our own work in this field has led to some important changes in our understanding of S_NAr reactions with amine nucleophiles. General base catalysis is often observed in reactions of secondary amines with activated aromatic substrates when the leaving group is a relatively sluggish one [55, 58]. Until recently the virtually universally accepted [55] mechanism for this catalysis has been the one shown in eq. 27, first proposed by *Bunnett* [62, 63]. It consists of a rapid equilibrium deprotonation of the zwitterionic σ-complex, **31**, followed by rate limiting general acid catalyzed leaving group departure from the anionic σ-complex, **32**; it is generally known as the SB-GA (*S*pecific *B*ase *G*eneral *A*cid) mechanism.



(27)

31 **32** **33**

It is a mechanism which satisfies the chemist's intuition because proton transfer involving normal acids and bases are known to be very rapid [64] and acid catalyzed leaving group departure assigns a logical function to the catalyst. In Me_2SO solution there is in fact direct evidence for this mechanism in the reaction of n-butylamine and t-butylamine with 1-ethoxy-2,4-dinitronaphthalene [59, 65]. In protic solvents the situation is quite different though, and several pieces of evidence indicate beyond any reasonable doubt that deprotonation of the zwitterion **31** is the rate limiting step.

Equation 28 allows a simple discussion of the conditions under

$$\mathrm{ArX} + \mathrm{RR'NH} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{31} \underset{k_{-2p}}{\overset{k_{2p}}{\rightleftharpoons}} \mathbf{32} \xrightarrow{k_3} \mathbf{33} \qquad (28)$$

$$k_{2p} = \sum_i k_{2p}^{B_i}[B_i] + k_{2p}^{OH}[OH^-] \qquad (29)$$

$$k_{-2p} = \sum_i k_{-2p}^{BH_i}[BH_i] + k_{-2p}^{H_2O} \qquad (30)$$

$$k_3 = \sum_i k_3^{BH_i}[BH_i] + k_3^{H_2O} \qquad (31)$$

which either leaving group departure (k_3-step) or pro-

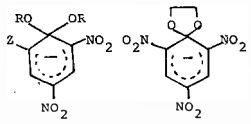
ton transfer (k_{2p}-step) is rate limiting; k_{2p} and k_{-2p} are defined by eq. 29 and 30 where k_{2p}^{Bi} and k_{2p}^{OH} refer to the deprotonation of **31** by general bases (notably RR'NH) and OH^-, respectively, while $k_{-2p}^{BH_i}$ and $k_{-2p}^{H_2O}$ refer to the protonation of **32** by general acids (notably $RR'NH_2^+$) and the solvent, respectively; k_3 is defined by eq. 31 where $k_3^{BH_i}$ refers to concerted catalysis by general acids (notably $RR'NH_2^+$) while $k_3^{H_2O}$ refers to the unassisted or solvent assisted leaving group departure.

Typically, **31** and **32** are steady state intermediates. Thus, for the SB-GA mechanism to prevail we must have $k_3 << k_{-2p}$ and $k_{-1} > (>>) k_{2p} k_3/k_{-2p}$; if only the first but not the second condition is met, the k_1 step becomes rate limiting and no base catalysis is observed. Furthermore, the k_3-step must be general acid catalyzed, i.e., $\sum k_3^{BH_i}[BH_i]$ term in eq. 31 must be large, otherwise the overall reaction becomes *specific* base catalyzed.

The conditions for rate limiting proton transfer are $k_3 >> k_{-2p}$ and $k_{-1} > (>>) k_{2p}$; again, if the latter condition is not met, no catalysis can be observed.

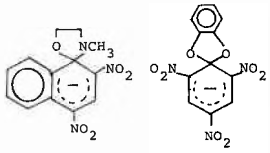
While studying the kinetic behavior of σ-complexes in protic solvents we made several observations which are inconsistent with the SB-GA mechanism but which support the notion of a rate limiting proton transfer:

1. General acid catalysis of alkoxide ion departure from complexes such as **33** [66], **34** [67], **35** [68] and **36** [69] is weak or undetectable even with acids considerably stronger than $RR'NH_2^+$, while the SB-GA mechanism calls for strong catalysis of leaving group departure by $RR'NH_2^+$.



33a Z = NO_2 **34**

33b Z = H



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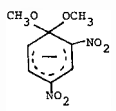
2. Suitable extrapolation of the rates of alkoxide and phenoxide ion departure from complexes such as **37** [70], **38** [71] and of spiro ring opening in **34** [67] and



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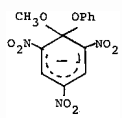
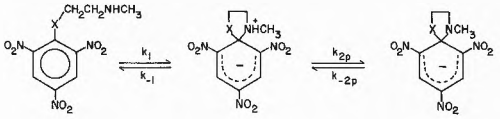


38

36 [69] have allowed us to estimate the order of magnitude of $k_3 (\approx k_3^{H_2O})$ for typical leaving groups in reaction 28 [58]. These estimates indicate that the condition $k_3 >> k_{-2p}$ usually prevails, which is inconsistent with the SB-GA mechanism but consistent with rate limiting proton transfer.

3. Temperature-jump studies on model reactions such



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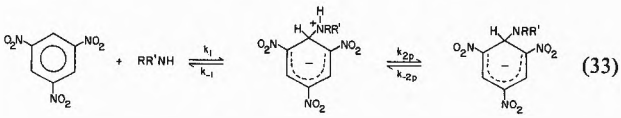


(33)

as eq. 32 (X = NCH_3 [72], X = 0 [68]), 33 [73] and similar systems [74] showed that at low base concentrations proton transfer is rate limiting in the formation of the anionic σ-complex. Interestingly, this is not because proton transfer is abnormally slow (the rates are close to the diffusion controlled limit) but because k_{-1} is high, leading to the condition $k_{-1} > (>>) k_{2p}$. Extrapolation of these results to typical S_NAr substrates suggests even higher k_{-1} values [58] making rate limiting proton transfer in «real» substitution reactions even more prevalent.

As little as 8–10 years ago the suggestion that a diffusion controlled proton transfer step can be rate limiting in reactions whose overall rates are slow and measurable by conventional techniques would have been met with a lot of scepticism. One of the first examples where a diffusion controlled proton transfer step was definitely shown to be rate limiting was in the intramolecular aminolysis of a thiol ester and the hydrolysis of a thiazoline [75]. Over the last 10 years an increasing number of reactions have been reported, mainly in the area of nucleophilic additions to carbonyl carbon, where diffusion controlled deprotonation of a zwitterionic tetrahedral intermediate (amine reactions) or protonation on the alkoxy oxygen of tetrahedral intermediates is rate limiting [76, 77]. In fact, the ever increasing number of such examples, most recently also reported in the nucleophilic addition of amines to olefins [78], indicates that rate limiting diffusion controlled proton transfer is a very common phenomenon in chemistry.

Arynes and Hetarynes

The discovery of the aryne mechanism, first firmly established by *Roberts* [79, 80] in 1953 in the classical isotope scrambling experiment shown in eq. 34, has

(34)

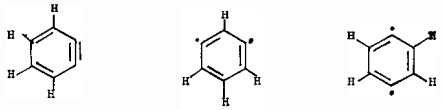
led to the development of a whole new field in organic chemistry whose scope reaches far beyond nucleophilic aromatic substitutions. This large scope is mainly due to the fact that arynes can be generated under a variety of non-basic conditions and can react with a large number of reagents which lead not only to aromatic substitution but to cyclo-additions, Diels-Alder reactions and others. The field has been reviewed frequently [81–86].

A landmark event in the investigation of a reaction mechanism involving unstable intermediates is the isolation and/or physical (spectroscopic) characterization of such intermediates. Due to the low thermodynamic as well as kinetic stability of arynes this has been quite a difficult task but in 1973 *Chapman* et al. [87] succeeded in isolating benzyne in an argon matrix at 8 °K and taking its IR spectrum.

Using a similar technique, the IR spectrum of 9,10-dehydroanthracene, which can be regarded as a model for p-benzyne, has also been obtained [88]. The results are consistent with a singlet diradical structure.

In a different approach, *Jayalekshmy* and *Mazur* [89, 90] used the "pseudodilution" technique for the generation of a benzyne with a life time of over a minute at room temperature. In this technique the benzyne precursor is attached to a polymer film which effectively prevents the very rapid dimerization of benzyne to biphenylene [91], one of the main factors responsible for the short life time of benzyne.

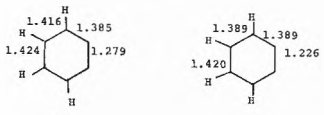
The structure of arynes and hetarynes has, not surprisingly, fascinated theoretical chemists for some time. Depending on the type and sophistication of the calculations, quite different and sometimes contradictory conclusions have been drawn. For example, calculations based on the, probably unrealistic, assumption that the geometries of o-, m- and p-benzyne are similar to



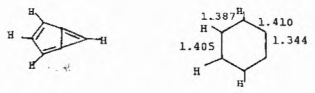
39 **40** **41**

that of benzene, lead to the conclusion that (1) o-benzyne has a singlet groundstate while m- and p-benzyne have triplet groundstates [92,93], (2) that the order of stability is **39** > **41** > **40** [94], and (3) that the heat of formation of o-benzyne is 72.6 kcal/mole [95]. The calculated heat of formation differs substantially from the two experimental estimates of 118 ± 5 kcal/mole [96] and of 100 kcal/mole [97] obtained by mass spectrometry.

A MINDO/2 calculation by *Haselbach* [98] with complete optimization of the geometry led to $\Delta H_f = 107$ kcal/mole which is much closer to the experimental estimates.



42 **43**

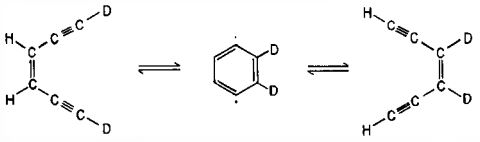


44 **45**

A more recent MINDO/3 calculation [99] suggests the geometry shown in **42** for o-benzyne and a ΔH_f of 118.4 kcal/mole (or 114.2 kcal/mole with configuration interaction). The same study also concludes that m-benzyne has a singlet groundstate which is in contrast to earlier studies [92, 93] but in agreement with *Hess* and *Schaad* [100], and that m-benzyne has a stability similar to that of o-benzyne.

The most recent calculations by an ab initio method using an extended basis (4–31G) level concludes that the relative energies are definitely in the order ortho (0.0) < meta (14.5) < para (23.3) (relative energies in kcal/mole given in parentheses) with o- and m-benzyne definitely having a singlet groundstate while the energies of the two states of p-benzyne are too close to differentiate between a singlet and a triplet [101]. Thus, as far as m-benzyne is concerned, its structure is probably best represented as bicyclo[3.1.0]hexa-1,3,5-triene **44**, a view which has received experimental support [102, 103]. The geometry of o-benzyne is shown in **43**.

Experimental evidence for p-benzyne is scarce. An example where p-benzyne has been postulated as an intermediate is in the isomerization reaction 35 [104]; for other examples see *Bergman* [105] and *Breslow* [106].



(35)

Another approach in calculating the structure of o-benzyne has been to carry out a normal coordinate analysis [107] of the matrix IR spectrum reported by *Chapman* et al. [87]. The structure is as shown in **45**; the authors conclude that o-benzyne is properly viewed as a cycloalkyne rather than as a resonance hybrid with considerable cumulene character [98].

In the area of hetarynes extended *Huckel* Theory calculations on pyridynes indicate that 3,4-pyridyne is more stable than 2,3-pyridyne [108]; this result has been confirmed recently by MNDO calculations [109].

46 **47**

48 **49**

The calculations of *Adam* et al. [108] further show that the anion formed by deprotonation of 3-halopyridine at the 4-position is more stable than at the 2-position. Both factors would tend to favor the formation of 3,4-pyridyne from 3-halopyridines. This is in fact observed [110–112]; the 2,3-pyridyne can only

be obtained if the 4-position is blocked by an alkyl group [113].
The higher stability calculated for **48** is also in agreement with the observation that base catalyzed deuterium exchange of 3-chloropyridine predominates at the 4-position over the 2-position [114].

S_N1 Mechanism

The aromatic S_N1 mechanism which has only been shown to occur with arenediazonium ions was first proposed by *Waters* in 1942 [115]. The reactions of arenediazonium ions with nucleophiles have been studied for over 80 years [116] but it is only recently that a detailed understanding of this mechanism has emerged.

$$ArN_2^+ \xrightarrow{\text{slow}} Ar^+ + N_2 \qquad (36a)$$

$$Ar^+ + Y^- \xrightarrow{\text{fast}} Ar-Y \qquad (36b)$$

The early evidence in favour of an S_N1 process, eq. 36, has been summarized by *Bunnett* [117]; it included observations that the reaction was kinetically of the first order and that the rate was essentially independent of the nature and concentration of added metal halide salts even though at high concentrations of such salts the product was to a large extent the aryl halide. These findings clearly exclude a transition state in which the nucleophile participates.
Nevertheless, in 1969 *Lewis* et al. [118] suggested an S_N2-type one-step mechanism instead. They based their proposal on the fact that the rate of decomposition of several arenediazonium salts increases linearly with the concentration of nucleophiles such as SCN^-, Br^- and Cl^-.
Additional support for the idea of a direct nucleophilic displacement came from a kinetic demonstration of nucleophilic participation in the arylation of toluene, benzene, trifluoromethylbenzene and anisole with benzenediazonium tetrafluoroborate in trifluoroethanol [116, 119]. The alternative S_NAr mechanism, consistent with the rate law, was dismissed because strongly electron withdrawing substituents in the ortho and para positions of the arenediazonium ion do not accelerate hydroxydediazoniations [116].
In 1975 *Swain* et al. [120–122] published the results of several experiments aimed at clarifying the confused state of the field. For example, they observed that the rate constant for hydrolysis of benzenediazonium ion varies less than 2% when the medium is changed from 80 to 105% H_2SO_4 despite the fact that the activity of water changes more than 1000 fold just from 80 to 98% H_2SO_4 [120]. This clearly shows that covalent bond formation between carbon and water (or HSO_4^-) is extremely small or absent in the transition state.
Other evidence in favor of an S_N1 process includes a very large α-^{15}N kinetic isotope effect ($k^{14}/k^{15} = 1.038$) indicating very extensive C–N bond breaking in the transition state [122], and a large secondary kinetic hydrogen isotope effect of 1.22 for each ortho hydrogen, pointing to substantial carbonium ion character of the transition state [121]. Entropies of activation [120] and substituent effects on the rate [120] were also shown to be consistent with the S_N1 mechanism.
An interesting question is whether the first step (loss of N_2) is reversible to a measurable extent. Two experiments were performed aimed at clarifying this point. One involved the demonstration of isotopic rearrangement, eq. 37.

$$\underset{\alpha\ \beta}{Ar-\overset{+}{N}\equiv\overset{15}{N}} \rightleftarrows Ar^+ + \underset{\alpha\ \beta}{N\equiv\overset{15}{N}} \rightleftarrows \underset{\alpha\ \beta}{Ar-\overset{+}{N}\equiv\overset{15}{N}} \qquad (37)$$

An early demonstration of 1–2% rearrangement in the dediazoniation of benzene and toluene diazonium ion by *Lewis* [124, 125] was first suspected to be an artifact [126] but was later confirmed [127] and considerably strengthened by observations in more suitable systems where the extent of rearrangement is much higher [128–130]; with 2,4,6-trimethylbenzenediazonium ion, after 70% dediazoniation, rearrangement reaches 20.9% and 36.9% in trifluoroethanol and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), respectively [129, 130].
The other experiment was to show that ^{15}N-labeled diazonium ions are able to exchange their nitrogen with external $^{14}N_2$ [128–130]. This exchange is quite modest in the case of the

$$Ar\text{-}{}^*N_2^+ + N_2 \rightarrow Ar\text{-}N_2^+ + N_2{}^* \qquad (38)$$

benzenediazonium ion (2.46% after 70% dediazoniation in trifluoroethanol under 300 atm of N_2) [128] but becomes appreciable (17.75%) in the case of 2,4,6-trimethylbenzenediazonium ion in HFIP [129]. It should be noted here that quite apart from their relevance to the S_N1 mechanism these latter experiments are of much broader significance because they constitute the first known examples of a reaction of a nitrogen molecule with a purely organic reagent in solution [128].
The simplest mechanism which seems to accomodate the above results would be the one shown in eq. 39

$$Ar\text{-}N_2^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Ar^+ + N_2 \qquad (39a)$$

$$Ar^+ + Nu^- \rightarrow Ar\text{-}Nu \qquad (39b)$$

with the steady state rate law

$$-\frac{d[Ar\text{-}N_2^+]}{dt} = \frac{k_1 k_2 [Nu^-]}{k_{-1}[N_2] + k_2[Nu^-]} \qquad (40)$$

However, two pieces of evidence suggest a mechanism involving not just one but at least two intermediates: (1) After 70% conversion of 2,4,6-trimethylbenzenediazonium ion in HFIP, N_α-N_β rearrangement has proceeded more than twice as fast (37%) as the ex-

change with external N_2 (16.5%) [129]. (2) The rate of dediazoniation, determined as a function of N_2 pressure cannot be fitted to eq. 40 [130]. These results are consistent with mechanism 41; the first intermediate is a molecule-ion pair

$$\text{Ar-N}_2^+ \rightleftarrows |\,\text{Ar}^+\text{N}_2\,| \rightleftarrows \text{Ar}^+ + \text{N}_2 \xrightarrow{\text{Nu}^-} \text{Products} \qquad (41)$$

(Nu⁻ also adds to the molecule-ion pair)

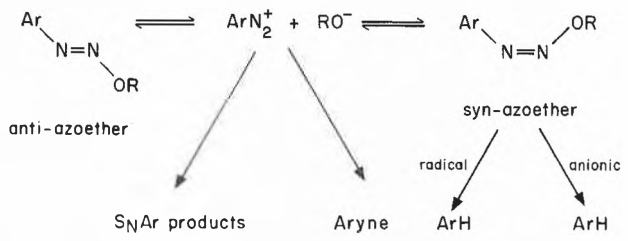
and N_α-N_β rearrangement can occur not only with the free aryl cation but within the molecule-ion pair. On the other hand, exchange with external nitrogen occurs only with the free aryl cation.

Just as the structure of arynes, the structure of aryl cations poses interesting problems for the theoretical chemist. Although originally assumed to be a triplet [131] there seems general agreement now that the phenyl cation is a singlet [132]. According to a recent ab initio calculation [132] the singlet phenyl cation is of comparable energy to the vinyl cation and is highly distorted, with a CCC angle of 145°.

The situation with substituted phenyl cations changes in that calculations show that strong π-donors such as the NH_2 and OH group in the para position stabilize the triplet to such an extent that it becomes the ground-state [133]. This prediction has been experimentally confirmed by ESR spectroscopy on aryl cations generated by UV irradiation at 77°K of arenediazonium salts substituted at the 4-position by dialkylamino groups [134].

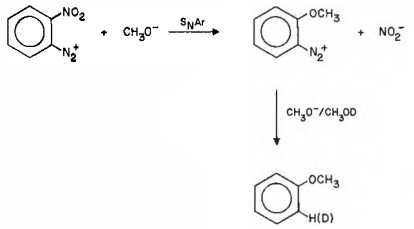
Reactions of arenediazonium ions in basic solution, most thoroughly studied in methanolic NaOMe, open up additional possibilities. Dediazoniation occurs by a radical as well as a carbanion mechanism [135, 136] although according to recent views these reactions proceed via the syn-arylazo methyl ether rather than directly from the arenediazonium ion [137, 138]. S_NAr displacements of a ring substituent activated by the diazonio group has been known to occur [116]; new examples have been reported recently along with cases of aryne formation by elimination of the diazonio group and an adjacent proton [133].

Scheme 5:

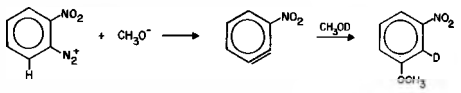


Scheme 5 summarizes the various competing reactions [137–139] which sometimes can all be observed simultaneously [139]. An example is the reaction of 2-nitrobenzenediazonium ion in $NaOCH_3/CH_3OD$ which leads to 11.1% anisole, 56.6% nitrobenzene and 2.75% 3-nitroanisole, with the nitrobenzene and anisole monodeuterated to the extent of 15.5% and 19.0%, respectively, and the 3-nitroanisole 87% monodeuterated [139]. These products can be accounted for as follows: nitrobenzene is formed by dediazoniation partly through the radical (no deuterium uptake) and partly through the carbanionic mechanism (15.5% deuterium uptake). Anisole arises by S_NAr displacement of the nitro group, followed by dediazoniation, again via the two competing mechanisms, Scheme 6.

Scheme 6:



3-Nitroanisole is presumably formed via an aryne, eq. 42.



(42)

Concluding Remarks

Zoltewicz's recent review [85] of nucleophilic aromatic substitution ends with the phrase "Clearly, aromatic nucleophilic substitution continues to remain a diverse, rapidly expanding area of chemistry with a promising future". The developments over the last few years bear out and strengthen this view.

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