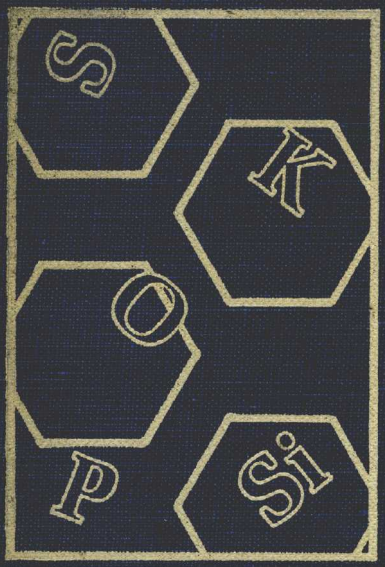

Aromatic Substitution by the $S_{RN}1$ Mechanism

ACS Monograph 178

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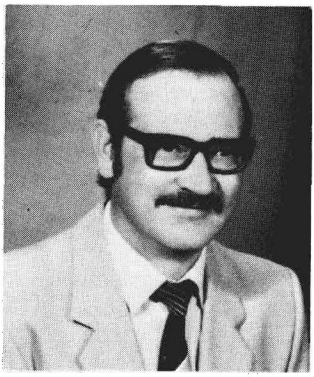
FOREWORD

ACS MONOGRAPH SERIES was started by arrangement with the interallied Conference of Pure and Applied Chemistry, which met in London and Brussels in July 1919, when the American Chemical Society undertook the production and publication of Scientific and Technologic Monographs on chemical subjects. At the same time it was agreed that the National Research Council, in cooperation with the American Chemical Society and the American Physical Society, should undertake the production and publication of Critical Tables of Chemical and Physical Constants. The American Chemical Society and the National Research Council mutually agreed to care for these two fields of chemical progress.

The Council of the American Chemical Society, acting through its Committee on National Policy, appointed editors and associates to select authors of competent authority in their respective fields and to consider critically the manuscripts submitted. Since 1944 the Scientific and Technologic Monographs have been combined in the Series. The first Monograph appeared in 1921, and up to 1972, 168 treatises have enriched the Series.

These Monographs are intended to serve two principal purposes: first to make available to chemists a thorough treatment of a selected area in form usable by persons working in more or less unrelated fields to the end that they may correlate their own work with a larger area of physical science; secondly, to stimulate further research in the specific field treated. To implement this purpose the authors of Monographs give extended references to the literature.

ABOUT THE AUTHORS



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To our daughter and son,
Gabriela and Enrique

PREFACE

THE FIELD OF NUCLEOPHILIC AROMATIC SUBSTITUTION began with the discovery that aryl compounds with an appropriate leaving group and strong electron withdrawing groups in the *o*- or *p*- positions could react with nucleophiles under mild conditions by a two-step mechanism that involves the formation of a Meisenheimer complex.

For a long time it was generally believed that unactivated aromatic compounds could not react with nucleophiles unless submitted to drastic conditions such as high temperature and pressure. About 30 years ago it was found that unactivated aryl halides could be substituted through a benzyne intermediate and a great amount of work has been done in this area. Arynes can be generated by several means and their reactions are interesting routes to the synthesis of important compounds.

In 1970 Bunnett and Kim proposed a new mechanism for nucleophilic aromatic substitution of unactivated aryl compounds, and during the last 12 years a number of studies in the field have demonstrated the generality of the mechanism in regard to the variety of substrates and nucleophiles.

This monograph is intended to compile the information available regarding these nucleophilic aromatic substitution reactions. Literature through December 1980 is cited as well as some papers that appeared in 1981 and were made available to us through the courtesy of the authors. We tried to be objective in the presentation of the results. The explanations given are in some cases based on concepts firmly established, but in others the interpretation is speculative and attempts to stimulate more research in the area.

We are greatly indebted to Joseph F. Bunnett: he introduced us to the field, he has had many enlightening discussions with us, and he has had the courtesy to read this monograph and give us many valuable suggestions. In addition, this monograph could not have been finished without the help of Marjorie C. Caserio who took the task of correcting and proofreading the manuscript. We also thank Architect Tómas Vargas for doing the original drawings for the figures.

ROBERTO ROSSI

RITA HOYOS DE ROSSI
Universidad Nacional de Cordoba
Cordoba, Argentina

December 1982

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Aromatic Nucleophilic Substitutions

Mechanisms

During the last three decades, and after the landmark review of Bunnett and Zahler (*1*), organic chemists have recognized that aromatic compounds can undergo nucleophilic substitution just as easily as they undergo electrophilic substitution. The available mechanisms vary greatly depending on the aromatic moiety, the nucleophile, and the reaction conditions. Generally these aromatic nucleophilic substitution mechanisms can be summarized as shown in Scheme I.

Intermediates **1–4**, after one or several reaction steps, lead to the substitution product, as in Reaction 5 (*2*, *3*).

Although a one-step mechanism is formally possible, present evidence does not indicate a concerted one step mechanism. On the other hand, the literature contains abundant evidence for multistep mechanisms of nucleophilic aromatic substitutions.

Aromatic substrates bearing nitrogen as the leaving group, such as diazonium salts seem to be the only compounds able to form aryl cations **1**. Consequently, only **5** has been found to react by this mechanism (reaction 6) (*4*, *5*).

Formation of aryl carbanions **2** as precursors of benzyne intermediates takes place in strongly basic solution. Although benzynes can be formed by several other means, these do not involve a carbanion intermediate. Reactions involving benzyne intermediates have the drawback that more than one product is obtained (Reactions 7, 8). However, their advantage is that they are quite general regarding the substituent in the aromatic moiety. Thus, nucleophilic substitution by this mechanism has been observed with substrates bearing both electron-withdrawing and electron-releasing substituents (*6*, *7*, *8*).

With substrates bearing an electron-withdrawing group, the most popular mechanism involves the formation of a σ-complex such as **3**.

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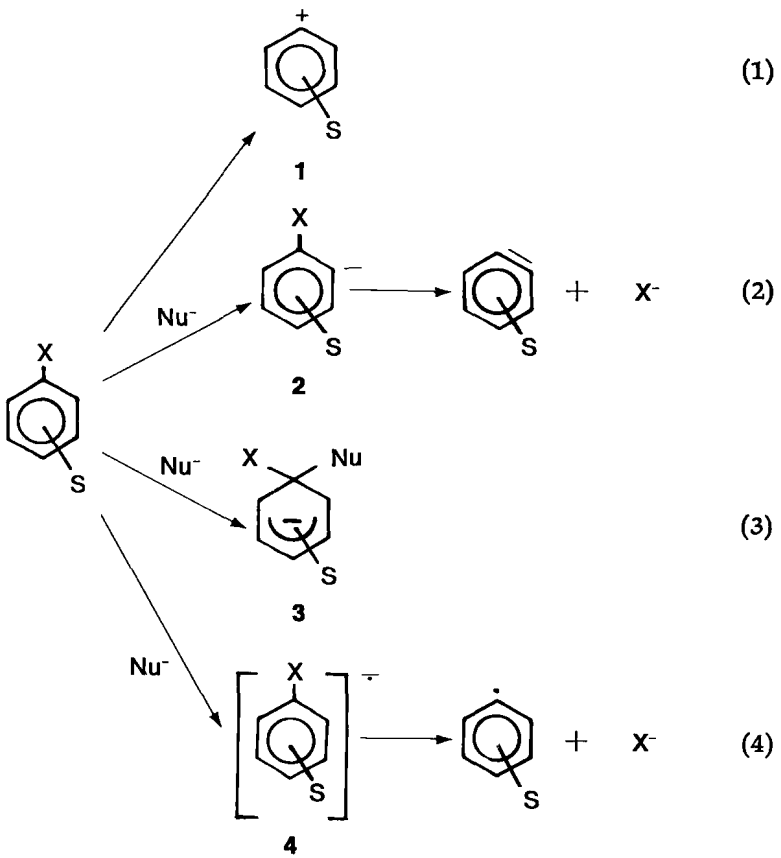
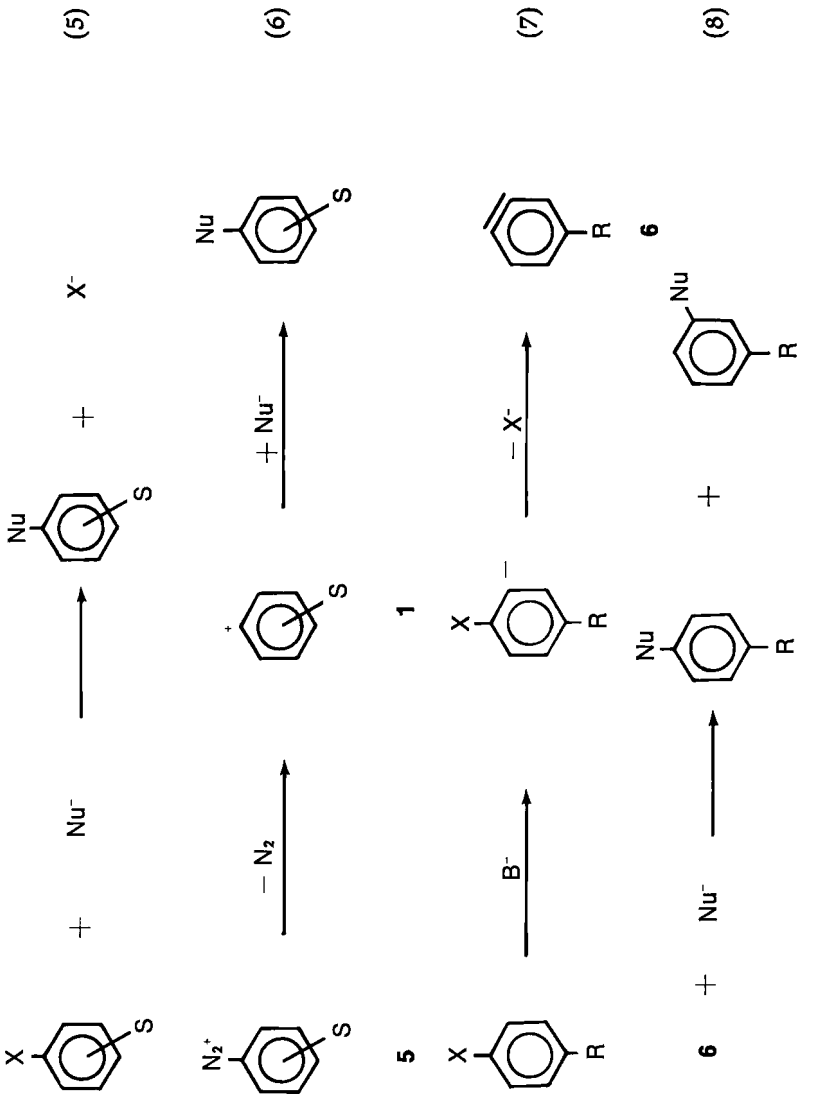


Scheme I

Historically, this was the first mechanism proposed for nucleophilic aromatic substitution, and the subject has been reviewed frequently (*1, 4, 5, 9, 10*). A restrictive condition for this mechanism seems to be the presence of an electron-withdrawing group in the aromatic ring. However, an unsubstituted aromatic substrate does react apparently by this mechanism under drastic conditions, such as high temperature, or in dipolar aprotic solvents (*11*).

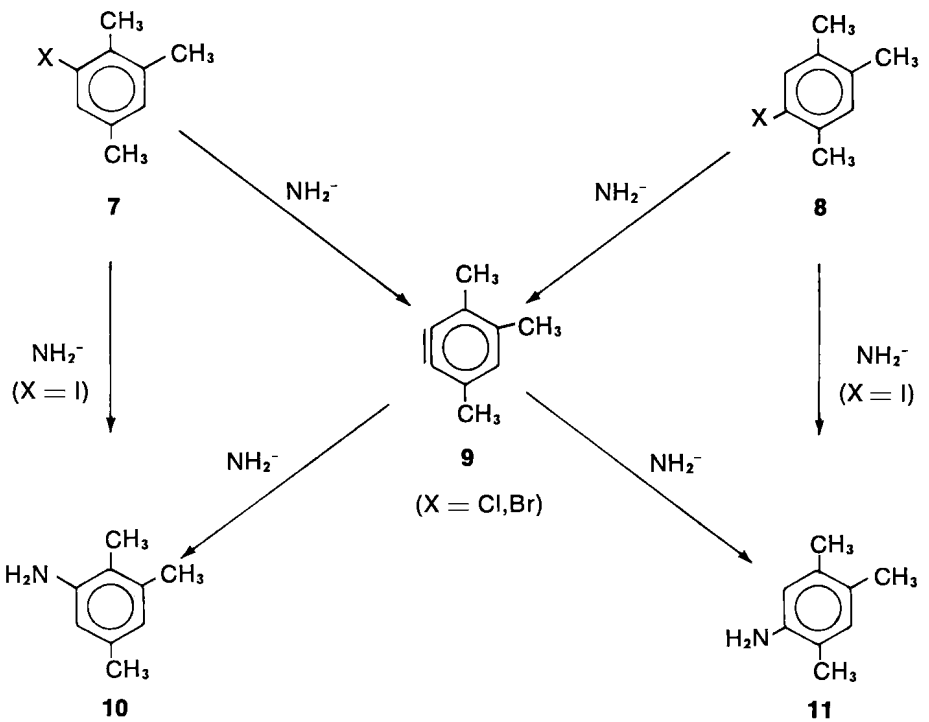
Most studies have been carried out with substrates containing at least one activating group; the mechanism amy be different for unactivated substrates. While studying reactions of unactivated aryl halides with amide ion in liquid ammonia Bunnett and Kim (*12*) observed some unusual results that could not be explained by the proposed benzyne mechanism. The reaction under study was the formation of 5- and 6-


(5)
(6)
(7)
(8)
X
S
Nu⁻
Nu
X⁻
N₂⁺
− N₂
+ Nu⁻
B⁻
− X⁻
R
Nu
5
1
6
6

amino-1, 2, 4-trimethylbenzenes from 5- and 6-halo -1, 2, 4-trimethylbenzenes, (**7** and **8**, Scheme II).

Both isomers **7** and **8** were expected to give the same ratio, **10:11**, of products, and the ratio was expected to be independent of the halogen (X) employed. This expectation was fulfilled with X being a chloro or bromo leaving group, where the product ratio of **10:11** was 1.46. However, with an iodo leaving group, the mixture of aminotrimethylbenzenes obtained was always enriched in the product in which the amine group assumed the same position as the leaving iodide. That is, **7** gave more of **10** and **8** gave more of **11.**

A mechanism involving σ-complexes (as in Reaction 3) was considered unlikely at the low temperatures at which the reactions were carried out.



Scheme II

An important observation was that the reactions were catalyzed by solvated electrons from dissolution of alkali metals in liquid ammonia. This fact provided a clue to the mechanism, which was subsequently suggested to involve radicals and radical anions (Scheme III) (*13*).

$$ArI + e^- \rightarrow (ArI)^{\cdot-} \quad (9)$$

$$(ArI)^{\cdot-} \rightarrow Ar^{\cdot} + I^- \quad (10)$$

$$Ar^{\cdot} + NH_2^- \rightarrow (ArNH_2)^{\cdot-} \quad (11)$$

$$(ArNH_2)^{\cdot-} + ArI \rightarrow ArNH_2 + (ArI)^{\cdot-} \quad (12)$$

Scheme III

where ArI = 5- or 6-iodo-1,2,4-trimethylbenzene.

It was postulated that in the initiation step (Reaction 9), the aryl halide captures an electron. The radical anion formed dissociates to form an aryl radical and iodide ion (Reaction 10). This aryl radical reacts with amide ions to form a new radical anion (Reaction 11) which, by electron transfer reaction to the substrate aryl iodide, gives the substitution product and the radical anion of the substrate (Reaction 12). Reactions 10–12 are the propagation steps of the chain mechanism. Adding Reactions 10–12, we have the substitution process (Reaction 13). Although the overall reaction is a nucleophilic aromatic substitution, it involves radicals and radical anions as intermediates.

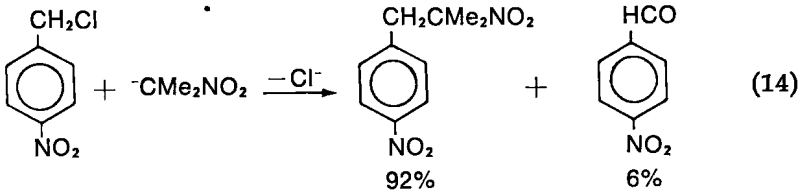
$$ArX + NH_2^- \rightarrow ArNH_2 + X^- \quad (13)$$

This mechanism was termed *Substitution Radical Nucleophilic, Unimolecular*, or $S_{RN}1$, due to its similarity to the S_N1 mechanism.

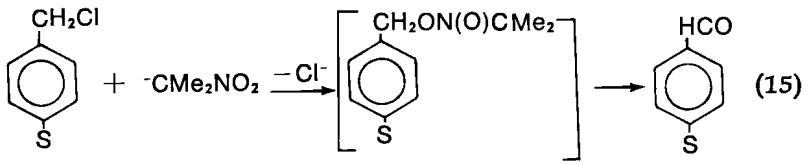
$$\frac{S_N1}{ArN_2^+ \rightarrow Ar^+ + N_2} \qquad \frac{S_{RN}1}{(ArX)^{\cdot-} \rightarrow Ar^{\cdot} + X^-}$$

A radical nucleophilic substitution mechanism, with reaction steps similar to Reactions 9–12, was suggested by Kornblum (*14*), and Russell (*15*), independently. For example, it was known that *p*-nitrobenzyl chloride reacts with the sodium salt of 2-nitropropane to yield 92% of the C-alkylated product and only 6% of the O-alkylated product (isolated as *p*-nitrobenzaldehyde) (Reaction 14). However, the usual reaction of this nucleophile with alkyl halides leads to O-alkylation (Reaction 15) (*16*).

Kornblum et al. found that the C-alkylation product not only depends on the *p*-nitro group, but also on the leaving group. In addition, the C-alkylation reaction is inhibited with very good electron acceptors,

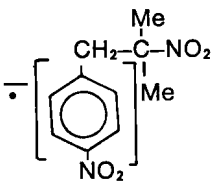


(14)



(15)

S = CN, CF_3, N^+Me_3Cl, MeCO, Me, Br



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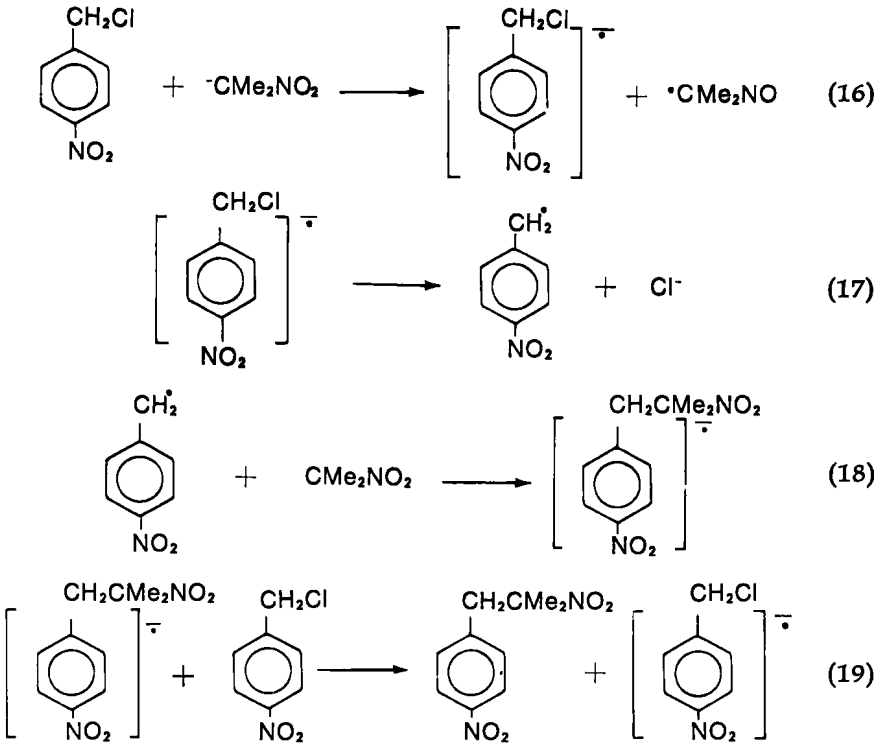
whereas the O-alkylation reaction becomes relatively important. Thus, in the presence of 0.2 equivalent of *p*-dinitrobenzene the yield of C-alkylation decreased to 6%, but the O-alkylation increased to 88% yield (*17*).

This evidence suggested that O-alkylation of the sodium salt of nitroalkanes is actually a direct nucleophilic displacement of chloride from the alkylating agent by the oxygen of the nitroparaffin anion. Also, an alternative mechanism that leads to the C-alkylation product in the *p*-nitrobenzyl series competes with the direct displacement mechanism. The competing mechanism proposed involves radical and radical anions as intermediates and is depicted in Reactions 16–19.

Based on a different approach, the same mechanism was proposed concurrently by Russell and Danen (*15*). They showed that the coupling reaction between the 2-nitro-2-propyl anion and *p*-nitrobenzyl chloride, or 2-chloro-2-nitropropane, is catalyzed by light, and the radical anion of the *p*-nitrobenzyl-2-nitro-2-propyl coupling product (**12**) was detected by electron spin resonance (ESR) spectroscopy in ethanol or dimethylformamide solution.

The subject of $S_{RN}1$ reactions at aliphatic sites has been reviewed by Kornblum (*16*), and others (*18*). Thus we will deal briefly with some



aspects of the mechanism in Chapter 10. The discussion hereafter deals mainly with $S_{RN}1$ reactions at aromatic sites.

Steps in the $S_{RN}1$ Mechanism

The main steps that comprise the $S_{RN}1$ mechanism are the initiation step, the chain propagation steps, and the termination steps (*see* Scheme IV).

The first reactive intermediate of this mechanism, a radical anion, is formed when an aromatic substrate with an appropriate nucleofugal group receives an electron (Reaction 20). This occurs either by reaction with a solvated electron from dissolution of alkali metals in liquid ammonia, or from a cathode, or by electron transfer from another radical anion, or by some other chemical reaction.

In Step 21 of the propagation cycle, the radical anion dissociates to form an aryl radical and the anion of the nucleofugal group. If the substrate ArX is a cation, the nucleofugal group leaves as a neutral species.