Nucleophilic substitution in nitroarenes: a general corrected mechanism

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Abstract

Nucleophilic substitution in electron-deficient arenes is one of the fundamental processes in organic chemistry; however, its mechanism as presented in textbooks does not adequately describe the process. According to this generally accepted mechanism, it is limited to substitution of halogens via nucleophilic addition at positions occupied by halogens. The possibility of addition at positions occupied by hydrogen is totally ignored. Research papers have shown that nucleophilic addition at positions occupied by hydrogen is a fast and reversible process, and σ^H adducts are initially formed as intermediates. These σ^H adducts can be converted into products of nucleophilic substitution of hydrogen in a few different ways or dissociate so that substitution of halogen can proceed. This general picture is confirmed by many examples presented.

Keywords Arenes · Nitro compounds · Nucleophilic substitution · Aromatic substitution · Carbanions

Introduction

Nucleophilic aromatic substitution in electron-deficient arenes, particularly nitroarenes, S_NAr , is a fundamental process of organic chemistry widely used in research laboratories and industrial organic synthesis. According to common knowledge, the reaction consists in the replacement of halogens or other leaving groups X by oxygen, nitrogen, sulfur, carbon, etc., nucleophiles [1, 2]. Due to great practical value and wide application, the reaction has been the subject of thorough mechanistic studies [1–3] and also ab initio calculations [4]. According to the commonly accepted mechanism (Scheme 1) formulated by Bunnett [3], the substitution proceeds via addition of nucleophiles to the electron-deficient rings at positions occupied by X to form σ^X adducts, followed by departure of X^- . Since the addition is associated with dearomatization, whereas departure of X^- recovers the aromaticity of the ring, the addition is the slow, rate-determining step. For instance, replacement of fluorine proceeds faster than chlorine. The addition–elimination mechanism shown in Scheme 1 is presented in textbooks, monographs and numerous review articles [1–8].

Recently, on the basis of detailed mechanistic studies and calculations, a conclusion was drawn that in some cases, due to the high rate of the departure of X^- , the lifetime of the hypothetical intermediate σ^X is negligible, and hence the reaction proceeds as a concerted process and the σ^X adducts are in fact transition states [5–8].

Thanks to detailed mechanistic experimental and computational studies, the many fine features of the process are clarified; nevertheless, an important question is surprisingly omitted. It is evident that electron deficiency of the ring of halonitrobenzenes is due to the presence of the nitro group; hence, in the halonitroaromatic rings, all positions *ortho*- and *para*- to the nitro group are susceptible to the addition of nucleophiles, regardless of whether they are occupied by halogens or hydrogen, and therefore nucleophiles can add to *p*-chloronitrobenzene at *ortho* positions as well [12–14]. Moreover, reactions that proceed via this addition mode have been known for many years. For instance, the von Richter reaction between *p*-chloronitrobenzene and cyanide anions reported in 1871 proceeds via the formation of σ^H adducts that are subsequently converted into *m*-chlorobenzoic acid [12] (Scheme 2).

Even more instructive is the reaction of this nitroarene with the carbanion of phenylacetonitrile, which proceeds via addition of the carbanion at the *ortho* (in protic media) and *para* (in polar aprotic media) positions (Scheme 3) [14].

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Scheme 1 The mechanism of S_NAr reaction **Scheme 2** Von Richter reaction proceeds via nucleophilic addition at positions occupied by hydrogen **Scheme 3** Carbanion of phenylacetonitrile adds to *p*-chloronitrobenzene at the *ortho* (b) or *para* (a) positions

Key hypothesis

Addition at the position occupied by chlorine (path a) is an irreversible process; therefore, the reaction shown in path 3b can proceed only when the addition at positions occupied by hydrogen proceeds faster and is a reversible process. Generalization of this observation leads to the hypothesis that this is a general situation, as presented in Scheme 4.

This hypothesis, when confirmed, shall significantly expand the scope and versatility of the nucleophilic aromatic substitution, which should embrace nucleophilic substitution of hydrogen and halogens. Moreover, it should require revision of the commonly accepted mechanism of this reaction. This hypothesis can be confirmed provided

that processes for fast conversion of the initially formed σ^H adducts into products of substitution of hydrogen are designed and executed. Unlike halogen anions that depart spontaneously from the σ^X adducts (Scheme 4, path a), spontaneous departure of the hydride anion from the σ^H adducts does not occur; thus it should be removed in a separate operation. Direct removal of hydride anions from organic molecules proceeds under the action of oxidants, and hence one could expect that treatment of the σ^H adducts with external oxidants should result in the formation of the products of oxidative nucleophilic substitution of hydrogen (ONSH). Alternatively, the hydrogen can be removed from the anionic σ^H adducts in the form of protons. This seemingly paradoxical process can be realized by means of base-induced β -elimination.

Scheme 4 Hypothetical relation of the rates of nucleophilic addition

Regardless of how the conversion of the σ^H adducts occurs in subsequent processes, it is feasible when the equilibrium 4b ensures sufficient concentration and lifetime of the σ^H adducts. The position of the equilibrium is a function of the electrophilic activity of arenes and the nucleophilicity of the nucleophiles, as well as the reaction conditions—solvents, and particularly temperature. Due to the entropy effects, low temperature favors the addition; thus many processes of $S_N\text{ArH}$ are realized at low temperatures.

Oxidation of the anionic σ^H adducts

The removal of the hydride anions from anionic σ^H adducts via oxidation by external oxidants encounters substantial obstacles. First, the σ^H adducts are usually short-lived species, produced in reversible processes. Thus, taking into account that nucleophiles themselves are sensitive to oxidation, the addition of oxidants to an equilibrated system nitroarene—nucleophile, e.g. 4b, can result in simple oxidation of the nucleophile. The desired oxidation of the σ^H adducts can proceed provided that:

- nucleophiles are resistant towards oxidation;
- the addition equilibrium is shifted towards adducts, and in an extreme case the addition proceeds irreversibly; and
- the rates of oxidation of the σ^H adducts are higher than the oxidation of nucleophiles.

Case A Treatment of *p*-chloronitrobenzene dissolved in liquid ammonia with KOH, source of OH^- anion, a nucleophile resistant towards oxidation and oxygen, results in oxidation of the σ^H adducts to form 2-nitro-5-chlorophenol in high yield [15] (Scheme 5). As shown in textbooks, $S_N\text{Ar}$ of chlorine by OH^- anions proceeds at elevated temperatures.

Scheme 5 Oxidative nucleophilic hydroxylation of *p*-chloronitrobenzene

Liquid ammonia is a moderately active nucleophile and also an excellent solvent for KMnO_4 to produce a stable solution. Dissolution of 2,4-dinitrochlorobenzene in such solution results in efficient oxidative amination to give 3-chloro-4,6-dinitroaniline (Scheme 6) [16].

Case B Methinic, moderately stabilized carbanions add to nitrobenzenes selectively at *para* positions due to steric effects. At low temperatures, the equilibrium is fully shifted towards the adducts. Oxidation of the σ^H adducts by potassium permanganate in liquid ammonia or by dichlorodicyanobenzoquinone (DDQ) or dimethyldioxirane (DMD) in DMF/THF results in the formation of products of ONSH, usually in high yields (Scheme 7) [17, 18].

Other kinds of anionic nucleophiles, including anilide anions and potassium diphenylphosphide, are less sterically demanding, so they can add at *ortho* and *para* positions to form σ^H adducts that can be subsequently oxidized to give products of ONSH. Addition at positions occupied by halogens proceeds much slower (Scheme 8) [19, 20].

Scheme 6 Oxidative amination of 2,4-dinitrochlorobenzene **Scheme 7** Oxidative substitution of hydrogen in *o*-fluoronitrobenzene with methinic carbanion**Scheme 8** Oxidative substitution of hydrogen in *p*-fluoronitrobenzene with phosphorus and nitrogen nucleophiles

Primary alkyl magnesium bromides add to nitroarenes and also to *p*- or *o*-chloronitrobenzenes to irreversibly form σ^H adducts that can be subsequently oxidized, giving products of oxidative nucleophilic alkylation (Scheme 9) [21, 22].

Sufficiently nucleophilic methylenic carbanions of acetonitriles, ethyl arylacetates, some ketones, esters of benzyl phosphonic acids, etc., can add at the *ortho* and

para positions of nitroarenes. The produced σ^H adducts can be efficiently oxidized by a variety of oxidants. Even in 2,4-dinitrofluorobenzene, the Sanger reagent in which S_NAr of fluorine is a very fast process, ONSH with carbanions proceeds faster than the replacement of fluorine (Scheme 10) [23].

Particularly interesting and attractive is oxidation with oxygen, which proceeds efficiently in the presence of an

excess of base, apparently upon deprotonation of the σ^H adducts; hence dianions are actually oxidized [24]. For instance, the reaction of esters of arylacetic acids with nitroarenes in the presence of an excess of base and air results in the formation of substituted nitrobenzophenones (Scheme 11) [25].

Taking into account the scope and versatility of oxidative nucleophilic substitution of hydrogen, ONSH is presently a valuable methodology in organic synthesis. A few examples presented above unambiguously confirm the hypothesis shown in Scheme 4b.

Conversion of the σ^H adducts into substituted nitrosoarenes

The σ^H adducts of some carbanions, particularly arylacetoneitriles, generated in protic media undergo protonation–dehydration to form substituted nitrosoarenes that are active compounds and usually react further (Scheme 3). A similar reaction can be promoted when σ^H adducts of methinic carbanions are treated by trimethyl chlorosilane in the presence

of triethylamine. *O*-silylation of the oxygen atoms of the nitro group followed by 1,6-elimination of the silanol results in the formation of stable substituted nitrosoarenes [17], exemplified in Scheme 12.

Similarly, the addition of anilide anions to nitroarenes at low temperature followed by protonation of the σ^H adducts results in the formation of nitrosodiarylamines, usually in high yields (Scheme 13) [26].

Removal of hydrogen from the anionic σ^H adducts in the form of protons via base-induced β -elimination

All these reactions of the anionic σ^H adducts—elimination of water upon protonation or silanol upon silylation—can be considered as a stepwise removal of the hydride anions in the form of protons. Such a process in a direct form is the key step of the most important variant of the nucleophilic substitution of hydrogen—vicarious nucleophilic substitution (VNS) [27]. σ^H adducts of nucleophiles that contain nucleofugal groups X at the nucleophilic centers,

Scheme 9 Oxidative nucleophilic alkylation of *p*-chloronitrobenzene

Scheme 10 ONSH with methylenic carbanions in the Sanger reagent

Scheme 11 Nucleophilic benzoylation of nitroarenes via ONSH

particularly α -chlorocarbanions, undergo base-induced β -elimination of HX at the expense of the ring hydrogen to form nitrobenzylic carbanions, which upon protonation give products of the substitution. The reaction of carbanion of chloromethyl phenyl sulfone with *p*-fluoronitrobenzene can be considered a model case of VNS (Scheme 14) [28, 29].

When this reaction is carried out at room temperature or lower in the presence of excess *t*-BuOK, VNS at the *ortho* position proceeds exclusively (path a). On the other hand, under conditions that favor equilibration and disfavor β -elimination, as for example in the slow addition of a

solution of the carbanion to *p*-fluoronitrobenzene at temperatures above 20 °C, S_NAr of fluorine is the main process (path b) [28, 29]. These simple experiments unambiguously confirm that even in the case of *p*-fluoronitrobenzene, the addition of the carbanion at position *ortho* occupied by hydrogen is the fast primary and reversible process and that conversion of the σ^H adducts proceeds via base-induced β -elimination of HCl. Detailed mechanistic studies have provided further pieces of evidence of this picture [30].

VNS is a general reaction that takes place between a great variety of α -chlorocarbanions and a practically unlimited

Scheme 12 Conversion of anionic σ^H adducts into nitrosoarenes via silylation

Scheme 13 Synthesis of nitrosodiarylamines in the reaction of anilines with nitroarenes

Scheme 14 Vicarious substitution of hydrogen versus S_NAr of fluorine in *p*-fluoronitrobenzene

variety of electron-deficient arenes: carbocyclic and heterocyclic nitroarenes and arenes of high electrophilic activity due to electronic configuration—particularly azines [27, 31]. When the arenes contain halogens in activated positions, VNS of hydrogen proceeds faster as a rule than S_NAr of halogens. Some examples of VNS with α -chlorocarbanions are presented in Scheme 15 [32–34].

α -Chlorocarbanions are rather unstable entities; hence, in some cases, VNS proceeds better with carbanions containing other leaving groups, such as RO or RS (Scheme 16) [32].

The examples presented in Schemes 13, 14, 15 and 16 indicate that VNS proceeds with similar stoichiometry but opposite polarity to the Friedel–Crafts reaction. Indeed, because the result of both of these reactions is that a

hydrogen atom in an aromatic ring is replaced by a carbon substituent—however, via the addition of either nucleophilic or electrophilic agents—it is justified to consider VNS as an umpolung of the Friedel–Crafts reaction. This relation can be convincingly exemplified by nucleophilic benzylation and α -chlorobenzylation of nitroarenes [35], as shown in Scheme 17.

VNS is not limited to carbanionic nucleophiles. Anions of *t*-butyl and cumyl hydroperoxides add to nitroarenes to form σ^H adducts. Subsequent base-induced β -elimination of alcohols provides nitrophenols. This is a general process of nucleophilic hydroxylation of electron-deficient arenes (Scheme 18) [36].

Scheme 15 Examples of VNS by α -chlorocarbanions in various halonitrobenzenes

Scheme 16 VNS in *p*-fluoronitrobenzene with carbanion of phenoxyacetonitrile

Similarly, *N*-anions generated via deprotonation of some sulfenamides, hydrazine and hydroxylamine derivatives enter VNS reaction with electron-deficient arenes (Scheme 19) [37, 38].

As a rule, both of these reactions, VNS hydroxylation and amination, proceed faster with halonitroarenes than substitution of chlorine.

Summary: initial formation of anionic σ^H adducts is confirmed

Numerous examples of the conversion of the σ^H adducts of nucleophiles to nitroarenes and also halonitroarenes into products of nucleophilic substitution of hydrogen via oxidative and eliminative processes that proceed efficiently with a plethora of halonitroarenes provide unambiguous proof that the hypothesis formulated in Scheme 4 is correct. Therefore, it is necessary to accept that nucleophilic substitution of hydrogen proceeds faster than that of halogens, and to reject the commonly accepted mechanism of the S_NAr reaction

and formulate the following corrected general mechanism. The initial step of the reaction between nucleophiles and electron-deficient arenes is a fast and reversible addition at positions occupied by hydrogen to form σ^H adducts. When, due to the type of educts and conditions, further rapid conversion of the σ^H adducts into products of the substitution of hydrogen does not proceed, the σ^H adducts dissociate, and slower addition at positions occupied by halogens leads to conventional replacement of halogen. On the other hand, when, thanks to the nature of the educts and conditions, σ^H adducts can be rapidly converted into products of nucleophilic substitution of hydrogen, this process is dominant. Therefore, nucleophilic substitution of hydrogen is the fast primary process, whereas nucleophilic substitution of halogens is the secondary *ipso* reaction [39, 40]. Of course, the substitution of halogens is a secondary process with respect to rates, not to the importance of these processes. This mechanistic picture of S_NAr reactions formulated on the basis of numerous experimental observations and studies is fully confirmed by ab initio calculations. The calculated rates of the addition of some nucleophiles at positions occupied by

Scheme 17 Nucleophilic benzylation and α -chlorobenzylation of nitroarenes via VNS

Scheme 18 VNS hydroxylation of 2,4-dinitrochlorobenzene

Scheme 19 VNS amination of *p*-chloronitrobenzene

hydrogen of *p*-halonitrobenzenes are higher than the rates of addition at positions occupied by halogens [41, 42]. It should be mentioned that in the quantum chemical calculations of nucleophilic aromatic substitution published in numerous reports [4, 9–11], the possibility of the addition of nucleophiles to halonitrobenzenes at positions occupied by hydrogen is totally ignored. In my opinion, calculations of the reactions between two partners should search for a pathway with the lowest energy barrier, the lowest free energy of the transition state; thus these calculations, in spite of the high theoretical level, have a conceptual deficiency.

Does the addition proceed directly or via single-electron transfer (SET)?

To present a complete picture of nucleophilic aromatic substitution, the question of how the addition proceeds should also be discussed. It is well known that nitroarenes are active single-electron acceptors, and the exposure of nitroarenes to some nucleophiles and/or strong bases generates nitroaromatic anion radicals detected by electron spin resonance (ESR) spectroscopy [43]. On the basis of these and related observations, a concept was formulated that the addition of nucleophiles to nitroarenes often proceeds not directly, but as a two-step process—SET—followed by anion-radical–radical coupling [44–47]. Such a pathway was confirmed, for instance, for addition of the primary alkyl magnesium bromides to nitroarenes to form σ^H adducts on the basis of the radical clock criterion [47].

An interesting effect of conditions on the reaction pathway between carbanions of diphenylacetonitrile and *o*-chloronitrobenzene was observed [48].

The carbanions of diphenylacetonitrile in dipolar aprotic solvent DMSO and DMF or protic solvent methanol (Scheme 20a, b) are in the form of loose ion pairs and add directly to the ring, giving products of the substitution

of hydrogen and chlorine. In cases a and b, initial addition proceeds at the *para* position to form σ^H adducts. In case a, the adduct dissociates, and slower addition at the position occupied by chlorine results in S_NAr . In protic media, case b, the σ^H adduct is converted into the nitrosoarene (as in Scheme 12). The subsequent addition of the carbanion to the nitroso group gives the final product. On the other hand, in nonpolar solvent, the carbanions are in the form of tight pairs with the counterions, and hence they exhibit low nucleophilic activity. Therefore, SET dominates, which leads to dimerization of the carbanion and reduction of the nitroarene (Scheme 20). In order to clarify whether SET participates in the VNS and other reactions of α -chlorocarbanions with nitroarenes, experiments with a fast radical clock were carried out (Scheme 21) [49].

SET from carbanions of sulfone A to a substituted nitrobenzene should result in the formation of short-lived cyclopropylmethyl radical $\cdot A$, which rearranges with the rate constant 10^9 s^{-1} . As shown in Scheme 21, VNS by this carbanion proceeds without traces of rearrangement; hence intermediacy of the radical $\cdot A$ is excluded, and the addition proceeds directly and not via SET.

General analysis concerning the participation of SET as a means of nucleophilic addition to nitroarenes is presented in Scheme 22.

The addition of nucleophiles to *p*-chloronitrobenzene, a model chloronitroarene, can proceed directly (paths a^H and a^{Cl}) to produce σ^H and σ^{Cl} adducts, or via SET, which initially produces nitroaromatic anion radical and radical $Nu^\cdot$ followed by the combination of these paramagnetic species path b^H and b^{Cl} to produce σ^H and σ^{Cl} adducts identical to those produced via direct addition. According to the microscopic reversibility principle, dissociation of these σ adducts to form educts should proceed via identical transition states (identical pathways). Therefore, in the case of both of the σ adducts formed via SET, pathways b^H and b^{Cl} , the dissociation of C–Nu and C–Cl bonds, should proceed via homolysis

Scheme 20 Effects of conditions on reactions of carbanions with nitroarenes

Scheme 21 Experiments with a fast radical clock indicate that VNS does not proceed via SET

Scheme 22 Comparison of direct addition and SET as the pathway of nucleophilic aromatic substitution

to produce nitroaromatic anion radicals and radical Nu[•] and chlorine atoms followed by SET from nitroaromatic anion radicals to Nu[•] and Cl[•]. Such a pathway of dissociation of the σ^H adducts, while possible, seems unlikely. However, homolysis of C–Cl bonds in anionic σ^{Cl} adducts and generation of

chlorine atoms is highly improbable. On the other hand, in my opinion, different routes for the conversion of the σ^{Cl} adducts via dissociation of C–Nu and C–Cl bonds in terms of the microscopic reversibility principle are difficult to accept. It appears, therefore, that when the S_NAr of halogens

Scheme 23 General picture of nucleophilic substitution in halonitroarenes

Scheme 24 Carbanion of phenoxyphenylacetonitrile can react with *o*-chloronitrobenzene in five! different ways with high selectivity

in halonitroarenes is preceded by reversible addition of the nucleophiles at positions occupied by hydrogen, and such reversibility can be confirmed, SET as the reaction pathway can be excluded.

Consequences and advantages of the use of the general mechanism of substitution

On the basis of the general mechanism discussed above, it was possible to determine the true effects of substituents on the electrophilic activity of nitroarenes. The effect of

substituents on rates of nucleophilic substitution of halogens in halonitroarenes has been the subject of numerous studies [1–4]. However, the results, although practically useful, cannot be considered as a measure of electrophilicity of nitroarenes, for two main reasons: (a) the rates of the substitution were dependent on the nature of the leaving groups, and (b) the substitution is a secondary process preceded by fast and reversible addition at positions occupied by hydrogen and formation of the σ^H adducts. The true effects of substituents on the electrophilic activity of nitroarenes were determined by measuring of the rates of nucleophilic addition at positions occupied by hydrogen [50, 51].

The general mechanism of nucleophilic aromatic substitution in electron-deficient arenes and its specific features presented in this paper reveal a much wider scope, versatility and diversity of the reactions between nucleophiles and nitroarenes. First, according to the general mechanism, nucleophilic substitution is not limited to halonitroarenes, but can proceed in a variety of nitroarenes that do not contain a leaving group, and hence so far had not been taken into consideration for reactions with nucleophiles. Moreover, the reactions of nucleophiles with halonitroarenes are not limited to simple replacement of the halogens, but offer a few processes for conversion of the σ^H adducts into a variety of products of the substitution of hydrogen. It should be pointed out that nucleophilic substitution of hydrogen in nitroarenes and in a variety of other electron-deficient arenes, particularly azines, is presently a rich and important chapter of organic chemistry [27, 31, 52–55]. Thus a general picture of such reactions is shown in Scheme 23.

Furthermore, since there are a few variants of conversion of the σ^H adducts, it is possible to observe situations in which a given nucleophile–nitroarene pair can react in a few ways to give different products [20, 26, 56]. A striking example of such a case is shown in Scheme 24.

I certainly hope that the general mechanism presented in this paper will find a way to classrooms and textbooks and will be helpful in solving many synthetic problems. I also hope that the examples and reasoning presented in the paper will promote wider application of these processes in practical organic synthesis and will inspire the design of new reactions.

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