# Reviews

## Electrophilic and nucleophilic aromatic substitution: analogous and complementary processes

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Analysis of many variants of nucleophilic aromatic substitution of hydrogen proceeding according to an addition—elimination pattern reveals that this is the major reaction pathway, whereas nucleophilic replacement of halogen or another nucleofugal group is the secondary process, *i.e.*, *ipso*-substitution. In this respect electrophilic and nucleophilic aromatic substitution can be considered as analogous processes.

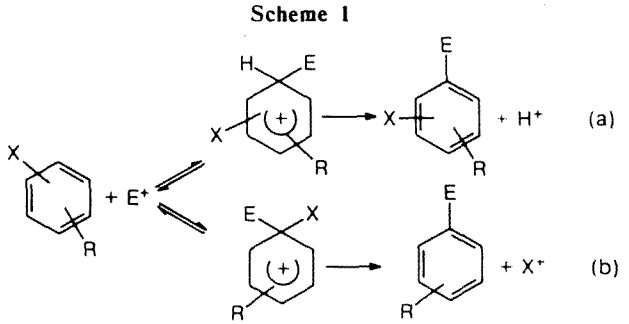
**Key words:** nitroarenes, carbanions, *O*-nucleophiles, *N*-nucleophiles, vicarious substitution, oxidative substitution

### Introduction

Aromatic rings are relatively stable entities due to favorable electronic configuration, which provides a substantial energy gain, often termed the aromatization energy.[1] Because of this particular stabilizing effect, reactions of aromatic compounds proceed, as a rule, with conservation of the rings, *i.e.*, as substitution processes. Chemical properties of aromatic rings are determined by their π-electron systems, therefore they should be susceptible to reactions with electrophilic agents. Indeed the most characteristic and important reaction type of aromatic compounds is electrophilic substitution, a process which occurrs according to general Scheme 1.[2,3]

The mechanistic pathway of this reaction involves two major steps: 1) addition of an electrophilic agent to the aromatic ring with the formation of a cationic intermediate that can be considered a cationic $\sigma_H$- or

**Scheme 1**

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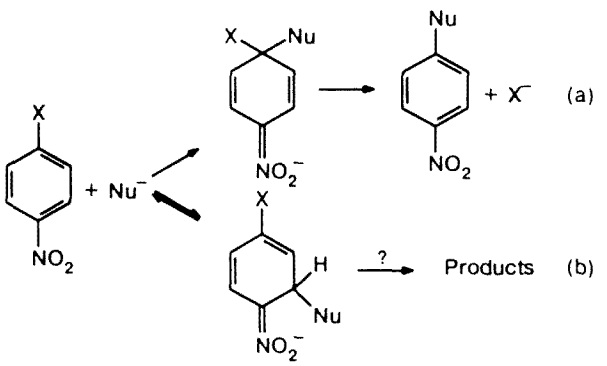
$\sigma_X$-adduct in which the aromaticity is destroyed, and 2) elimination of a proton or other cationic species to give the substitution product whose aromaticity is recovered. There are numerous reactions that proceed according to this general mechanism; it is sufficient to mention such important processes as nitration, sulfonation, halogenation, many variants of the Friedel—Crafts reactions, *etc.*[2,3] Of course each of these reactions has fine mechanistic features characteristic of the given process, nevertheless, the general mechanism presented in Scheme 1 is applicable to all of them. It is also necessary to stress that the vast majority of electrophilic aromatic substitution reactions proceed as substitution of hydrogen (Scheme 1, path a). This reaction course is considered as the "normal" process. There is, however, a possibility that substituents other than hydrogen can be replaced in the electrophilic process (Scheme 1, path b). These reactions are termed "*ipso*" substitution and are much less frequent.[2] The preference for "normal" electrophilic substitution of hydrogen is perhaps due to the higher rate of electrophilic addition to the carbon atom bearing hydrogen and particularly facile elimination of a proton from the cationic $\sigma_H$-adducts.

Aromatic π-electron systems, which favor addition of electrophilic agents hence promote the electrophilic aromatic substitution and hinder reactions of a nucleophilic agent with arenes. Moreover, since in nucleophilic substitution the replaced substituent X should, generally speaking, eliminate with an electron pair, this process is usually limited to replacement of halogen or other nucleofugal groups. It is the cause of a common opinion that electrophilic and nucleophilic aromatic substitution reactions differ in all aspects.[2,3] In spite of the difficulties in reactions of nucleophiles with aromatic compounds nucleophilic aromatic substitution does occur, but often along indirect pathways such as elimination—addition *via* arynes, single-electron transfer, transition metal catalysis, *etc.*[2—4] Only one of the mechanisms of nucleophilic aromatic substitution, *viz.*, addition—elimination is somewhat related to the electrophilic aromatic substitution. This mechanism operates in reactions of nucleophilic agents with highly electrophilic aromatic rings and consists of addition of nucleophilic agents to the aromatic ring at a position occupied by a leaving group X followed by elimination of an $X^-$ anion from the intermediate $\sigma_X$-adduct. In majority of cases formation of $\sigma_X$-adducts is the slow, rate-determining step of the overall process. This conclusion follows from the relation of the rates of substitution of various halogens X, which usually reduce in the row $F \gg Cl \geq Br \approx I$, opposite to that observed in typical aliphatic $S_N2$ substitution. This order indicates that the C—X bond breaking is not the rate-determining step, thus, it should be a fast process and the bond energy is not a decisive factor.[5—7]

The reaction type under discussion takes place in electron-deficient aromatic rings which are active as electrophilic partners in reactions with nucleophilic agents. Electrophilic character of aromatic rings can be caused by the presence of an electron-withdrawing substituent particularly the nitro group, specific electronic structure of some heterocyclic rings, complexation of arene rings with transition metals or electron deficiency of nonbenzenoid aromatic rings. Electron-withdrawing effect of a leaving group, although contribute to some extent to the total electrophilicity of the ring, is usually not a decisive factor in the nucleophilic addition process. This situation can be exemplified by reaction of *p*-halonitrobenzenes with nucleophilic agents (Scheme 2).

**Scheme 2**

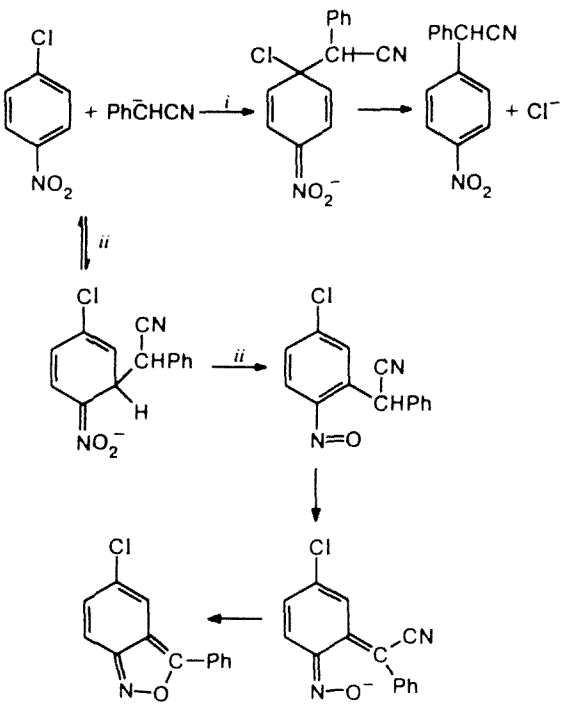



$k_H > k_X$

The electrophilic character of these arenes and their ability to form the $\sigma_X$-adducts in the reaction with a nucleophilic agent is due to the presence of the nitro group. It is therefore a reasonable expectation that nucleophiles can also add to *p*-halonitrobenzenes at another conjugated position (*ortho*) which is occupied by hydrogen atom to form $\sigma_H$-adduct (Scheme 2, path b). These adducts being isomers of the $\sigma_X$-adducts are however unable to loose unstable $H^-$ anion to form products of nucleophilic substitution of hydrogen. Nevertheless there are a few reports in the literature on reactions proceeding obviously *via* such $\sigma_H$-adducts to *p*-chloronitrobenzene.[8—10] An example of such a process is shown in Scheme 3.

Taking into account that ionic dissociation of C—Hal bond is a much faster process than that of C—C bond the formation of $\sigma_X$-adducts is practically an irreversible process, therefore the formation of products *via* transformations of $\sigma_H$-adducts to *p*-chloronitrobenzene can be observed provided the addition at positions occupied by the halogen occurs slower than at those occupied by hydrogen. Higher rates of nucleophilic addition at positions occupied by hydrogen than in those occupied by other substituents are unambiguously established for polynitroarenes which form relatively stable long-living σ-adducts.[11,12] These early observations allow one to extrapolate the firmly established relation of the

**Scheme 3**




*i.* Py
*ii.* MeOH

addition rates in polynitroarenes onto mononitroarenes for which direct measurements cannot be made. Thus the general picture shown in Scheme 2 should be amended to include the rate constants $k_H > k_X$.

Naturally, the question should arise: is it possible to design a general process for fast conversion of the $\sigma_H$-adducts into products of nucleophilic substitution of hydrogen? Such general possibility would be of a great practical value and open new horizons in understanding chemistry of aromatic compounds. In this review some routes to solution of this question will be discussed that lead to a general conclusion concerning relation of reactions of nucleophilic and electrophilic agents with aromatic compounds.[13]

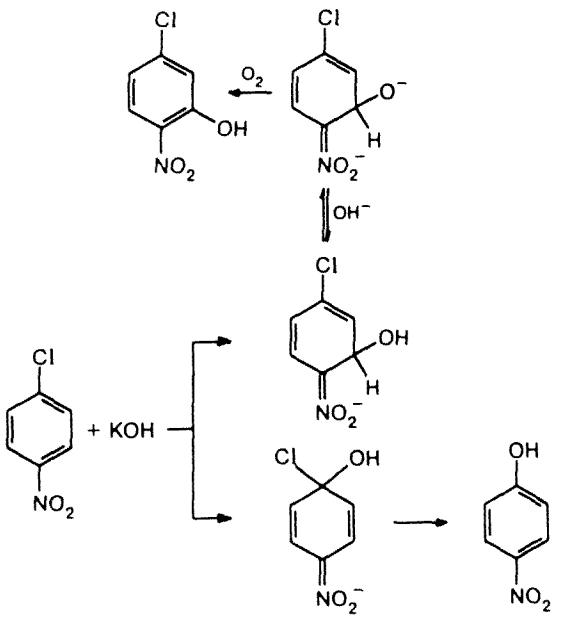
## Oxidative nucleophilic substitution of hydrogen

From the stoichiometry of the processes presented in Scheme 2 it follows that the $H^-$ anion should be removed from the $\sigma_H$-adduct in order to afford the nucleophilic substitution; hence the obvious way of its conversion to the product appears to be an oxidation reaction. This possibility is, however, severely limited for a few reasons. First of all the addition is a reversible process, and in the most common cases of mononitroarenes the addition equilibrium is shifted to the left so there is only a low concentration of $\sigma_H$-adducts and a high concentration of nucleophiles. Consequently the latter, being usually susceptible towards oxidation, are oxidized. Moreover, those oxidants that are active $H^-$ acceptors are usually strong electrophiles; hence, they exhibit a high tendency to capture nucleophiles at the expense of $\sigma_H$-adduct formation. Nevertheless there are numerous examples of such oxidative nucleophilic substitution of hydrogen (ONSH), resulting from serendipitous observations or intentional design.[14] The feasibility of this process can be generalized by formulating a few *a priori* rules (a—c) or guidelines concerning the starting materials, oxidants, *etc.*[13]

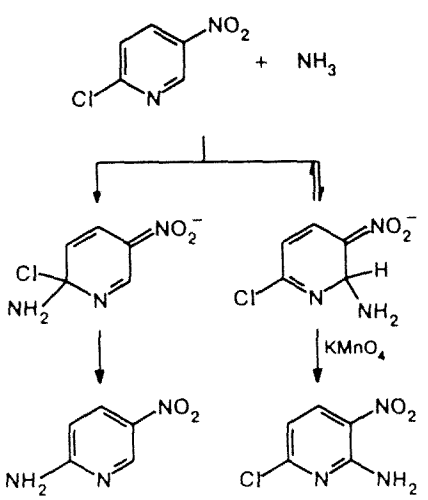
(a). First of all, it appears that such a process can occur when nucleophiles are resistant towards oxidation, and therefore, in spite of an even much higher concentration of $Nu^-$ than of $\sigma_H$-adducts, the latter are oxidized to form the desired products. The most typical representative of strong nucleophiles resistant towards oxidation is the hydroxide anion $OH^-$. Indeed, oxidative nucleophilic substitution of hydrogen in nitroarenes, so-called hydroxylation, with sodium or potassium hydroxides has been known for more than 100 years and was used for manufacturing of nitrophenols, even those containing chlorine atoms as substituents in the activated positions.[15] The most clear-cut cases of a competition between ONSH and the $S_NAr$ reaction in halonitroarenes with hydroxide anions were recently reported in a few papers by Malykhin and Shteingarts.[16] The reaction of KOH with *p*-chloronitrobenzene and oxygen carried out in liquid ammonia gave exclusively 5-chloro-2-nitrophenol (ONSH), whereas under the same conditions in the case of *p*-fluoronitrobenzene the halogen is exclusively replaced. Although it is well known that hydroxide anions hydrolyze *p*-chloronitrobenzene to *p*-nitrophenol, the above-mentioned results indicate that for $Nu^- = OH^-$ $k_H > k_{Cl}$; it is not clear, however, whether $k_H < k_F$ since the observed exclusive $S_NAr$ reaction of F could be due to reversibility of the formation of the $\sigma_H$-adduct combined with an insufficient rate of its oxidation. It is surprising that there are no reports on ONSH with halide anions, particularly with the fluoride ion, which is a strong nucleophile resistant towards oxidation. Also there are no reports on efficient oxidative alkoxylation of nitroarenes with the alkoxide anion. It appears that in order to be readily oxidized with oxygen the $\sigma_H$-adducts formed from $OH^-$ and nitroarenes should be deprotonated as shown in Scheme 4.

An important example of a nucleophilic agent resistant towards oxidation is ammonia. It is a moderately strong nucleophile stable in the presence of such strong oxidant as $KMnO_4$ which forms solutions in liquid ammonia. In such solutions one can afford efficient oxidative nucleophilic amination with ammonia and even potassium or sodium amide.[14,17] This oxidative variant of the Chichibabin reaction, which was developed by van der Plas, follows the general rule concerning the relation of rates of nucleophilic addition, $k_H > k_{Cl}$, as can be seen in Scheme 5.[18]

**Scheme 4**

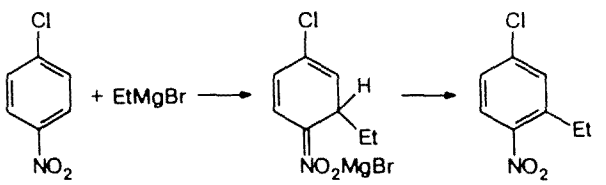


**Scheme 5**



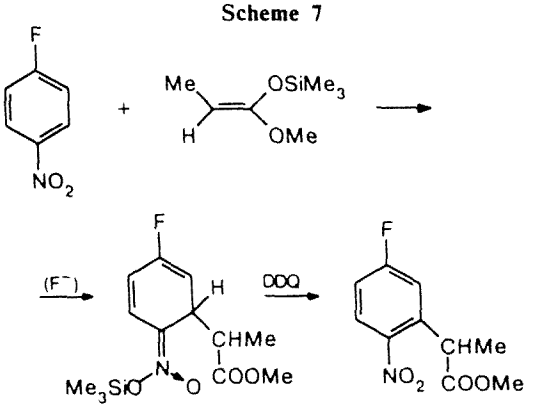
(b). The second case is to use starting materials or conditions that assure a high concentration of $\sigma_H$-adducts and only a negligible concentration of $Nu^-$. There are a few ways to provide a high concentration of $\sigma_H$-adducts and a low concentration of nucleophiles in the system. The simplest is the case when the addition equilibrium is favorable owing to high electrophilicity of arenes. This can be exemplified by the known Zimmerman reaction of the acetone enolate anion with an excess of *m*-dinitrobenzene, the latter acting also as an oxidant; thus 2,4-dinitrophenylacetone is produced.[19] Due to the high equilibrium constant of the addition, many other external oxidants are efficient in this reaction. Reactions of a similar type occur between many other nucleophiles and electrophilic arenes.[14] A high concentration of $\sigma_H$-adducts to mononitroarenes can be also produced when the latter are treated with such nucleophilic agents as alkyllithium[20] or Grignard reagents[21] (Scheme 6). In numerous papers Bartoli has shown the possibility of direct oxidative nucleophilic alkylation of nitroarenes in the reaction with Grignard reagents followed by oxidation with 2,3-dichloro-5,6-dicyanoquinone (DDQ) and even $KMnO_4$.[21] In many examples of such reactions with nitroarenes containing leaving groups (halogens, alkoxy groups, *etc.*) addition at positions bearing hydrogen and consequently OSNH was the dominant process. Stability of the intermediate $\sigma_H$-adducts in these cases is apparently connected with the partially covalent character of the bond between oxygen of the nitro group and magnesium or lithium, particularly because heterolytic dissociation of the C—C bond in the $\sigma_H$-adducts to produce unstabilized carbanions is a highly unfavorable process.

**Scheme 6**



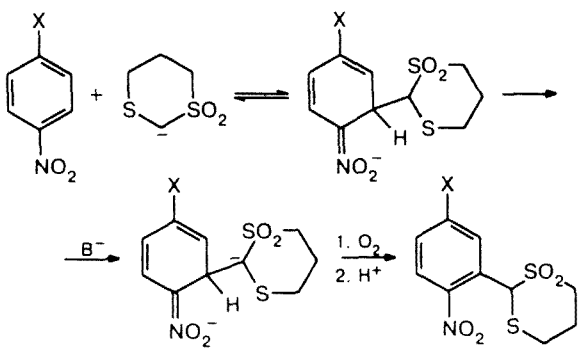
An efficient way of stabilizing the $\sigma_H$-adducts formed by such nucleophiles as carbanions with $ArNO_2$ is O-silylation of the negatively charged nitro group resulting in stabilization of the cyclohexadiene nitronate structure. The $\sigma_H$-adducts stabilized in this way can be subsequently oxidized with external oxidants hence ONSH with the carbanion moiety is achieved. This principle is exemplified in papers by RajanBabu et al.[22] and Beletskaya *et al.*[23] in which the reactions of silyl enol ethers or sililated ketene acetals with nitroarenes catalyzed by fluoride anions are described (Scheme 7). Again it should be stressed that even in *p*- and *o*-fluoronitrobenzenes the addition occurs exclusively at carbon atoms bearing hydrogen.

**Scheme 7**



(c). Finally, one can imagine the use of selective oxidants so the rate constant of oxidation of the $\sigma_H$-adducts becomes higher than that of the competing oxidation of nucleophiles. Of course the latter case is somewhat related to the first one because such characteristics as resistance or susceptibility towards oxidation depend greatly on the mechanism of oxidation and type of oxidizing agent. The most complicated is the question of selective oxidants that are able to oxidize $\sigma_H$-adducts but not nucleophiles in spite of the sensitivity of the latter toward oxidation and their high concentration in the system. There are many reports on ONSH in mononitroarenes with carbanions for which the nature of the oxidizing agents (atmospheric oxygen, nitroarene, DMSO as the solvent, *etc.*) was not firmly established,[24] although, in a majority of cases, it is believed that oxygen was the main oxidant.[25] Nevertheless there are clear-cut examples in which $ArNO_2$ acted as the oxidant.[26] We have recently shown that in the ONSH reaction of *p*-halonitrobenzenes with the dithiane-1,1-dioxide carbanion the oxidation with oxygen was promoted by excess base, indicating that the deprotonated $\sigma_H$-adducts were actually oxidized[27] (Scheme 8).

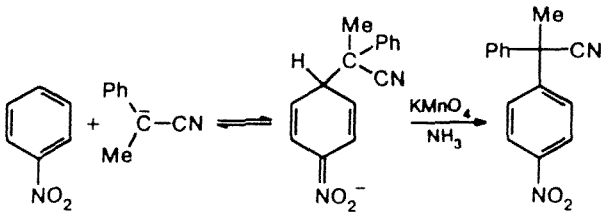
**Scheme 8**



One could suppose that due to electrostatic repulsion oxidation of strong anionic nucleophiles with anionic oxidants should be somewhat slower than that of corresponding $\sigma_H$-adducts because the negative charge in the latter is delocalized. Indeed, we have observed that the reaction of some nitroarenes with carbanions of 2-alkyl-substituted phenylacetonitriles and $KMnO_4$ carried out in liquid ammonia gives ONSH products in high yield[28] (Scheme 9).

Oxidation of the $\sigma_H$-adducts appears to be the main conversion pathway in the reactions of nucleophiles with some transition metal $\eta^6$-complexes of arenes.[29] Arenes, upon complexation with Cr, Fe, Mn *etc.*, acquire strongly electrophilic character: such complexes as $Ar{\rightarrow}Cr(CO)_3$, $Ar{\rightarrow}Fe^+CpBF_4^-$ in reactions with nucleophiles behave as electrophilic nitroarenes. Since these complexes are readily oxidized themselves there are even more severe restrictions concerning $\sigma_H$-adducts

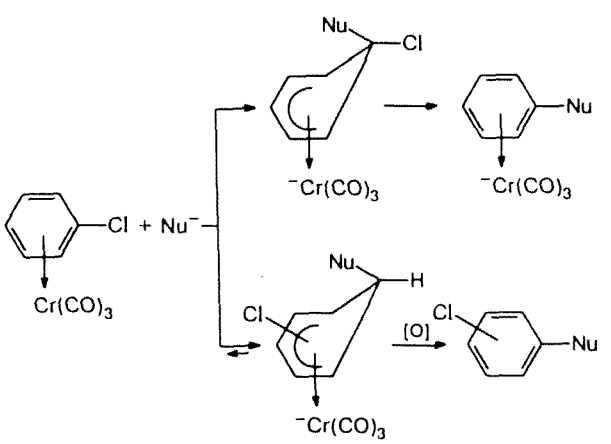
**Scheme 9**



concentration providing ONSH to be a feasible process.[30,31] However, the oxidation not only converts the $\sigma_H$-adducts into products of ONSH but also liberates the arene from the complexing metal; thus the sequence can serve as an indirect method of nucleophilic substitution of hydrogen in arenes *via* activation of the latter by complexation.

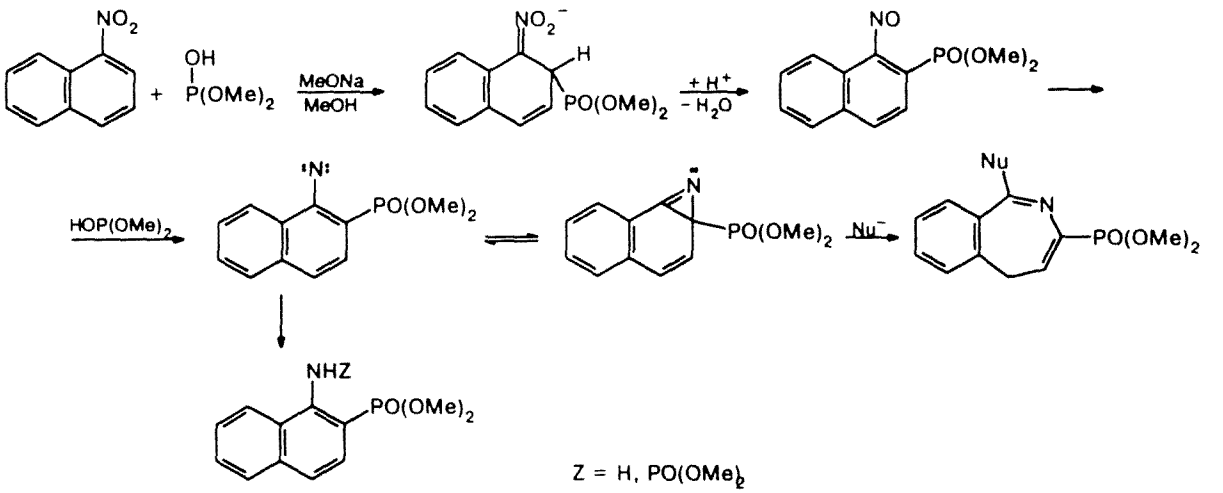
There is a close analogy between nitroarenes and complexes of arenes with transition metals concerning relation of rates of the nucleophilic addition at positions occupied with hydrogen and with other substituents, including halogens. For example the initial addition of nucleophiles to chromium tricarbonyl complexes of chloro- or fluorobenzenes takes place at carbon connected with hydrogen predominantly *meta* to the halogen. When such $\sigma_H$-adducts are sufficiently stable the oxidation with $I_2$ or other oxidants gives the corresponding substituted halobenzenes. If the equilibrium is shifted to the left, slow $S_NAr$ reaction of the halogen occurs. Such process dominates with weaker nucleophiles which do not form adducts sufficiently stable for being oxidized[31] (Scheme 10).

**Scheme 10**



Thus one can conclude that $\sigma_H$-adducts of many nucleophiles to nitroarenes, electrophilic heteroarenes, and arene $\pi$-complexes of transition metals can be oxidized to form products of ONSH. In many cases such processes occur faster than nucleophilic substitution of halogen if the latter is present in the ring.

**Scheme 11**




### Conversion of $\sigma_H$-adducts into nitroso compounds

In protic media $\sigma_H$-adducts of some nucleophiles to nitroarenes are converted into the corresponding nitroso compounds apparently *via* protonation of the negatively charged nitro group and elimination of water. The nitroso compounds are very active electrophiles and enter a variety of further reactions. This way of transformation was reported by Davis, for the reaction of arylacetonitriles with nitroarenes (Scheme 3).[8]

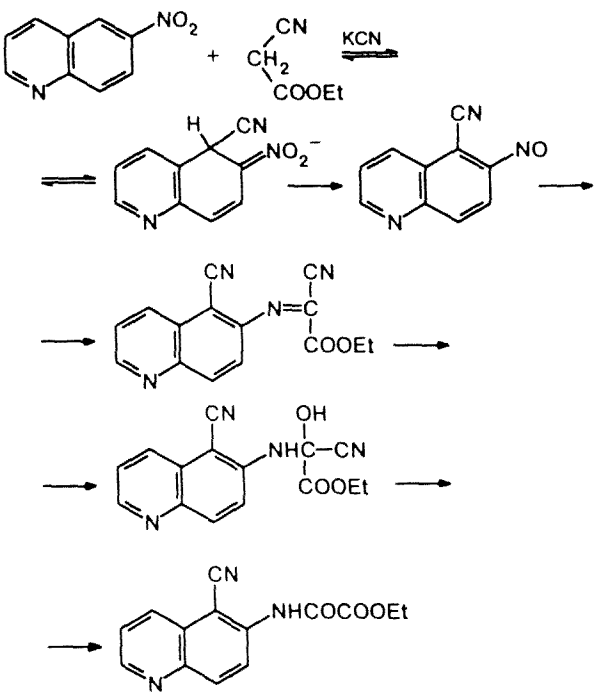
Also the reaction of diphenylacetonitrile carbanion with nitroarenes carried out in protic medium results in the formation of the nitroso compounds which are subsequently converted to nitrones.[15] It should be stressed that when both of these reactions were carried out in a polar aprotic solvents (pyridine or DMSO) conventional nucleophilic substitution of the halogen takes place.

Conversion of the $\sigma_H$-adducts into nitroso compounds was observed in the reaction of the dimethyl phospite anion with bicyclic nitroarenes.[32] The nitroso compounds are then deoxygenated by phosphite to form nitrenes which subsequently react further according to the pathways described earlier by Cadogan for thermal deoxygenation of nitroarenes with trialkyl phosphites. Strong preference for the $\sigma_H$-adduct formation in these reactions is evidenced by the fact that 4-chloro-1-nitronaphthalene enters the same reaction whereas 2-chloro-1-nitronaphthalene is inactive under these conditions and can be recovered (Scheme 11).

Even the $\sigma_H$-adducts of hydroxide anion to some nitroarenes can undergo similar transformation to the nitroso compounds as exemplified by the reaction of nitrobenzoic acid with concentrated alkali.[33]

Many highly electrophilic nitroarenes particularly of bicyclic structure react with ethyl cyanoacetate to produce derivatives of cyanoarenes.[34] Although in the papers in which these reactions are reported no mechanistic scheme is proposed it appears reasonable to suppose that also in these cases the $\sigma_H$-adducts are converted into the nitroso compounds which undergo further transformation. This hypothetical mechanistic picture is shown in Scheme 12.

**Scheme 12**



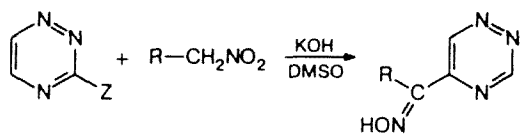

Treatment of the $\sigma_H$-adducts of the Grignard reagents to nitroarenes with protic acids also results in formation of the nitroso compounds, undoubtedly along a similar pathway. Since in these cases the reaction steps are separated in time, *i.e.*, addition occurs in aprotic medium, whereas formation of the nitroso compound

*via* protonation-elimination takes place in the absence of nucleophiles, the nitroso compound can be isolated.[21]

One can also suppose that the well documented mechanism of the von Richter reaction[10,35] can be slightly modified because it is viable to postulate that the initially formed *p*-chloronitrobenzene—$CN^-$ $\sigma_H$-adduct is subsequently converted in the protic medium to the *ortho*-nitrosonitrile. Addition of the hydroxide anion to the nitroso group results in further transformations leading to *m*-chlorobenzoic acid as the ultimate product.

In the reaction of 1,2,4-triazines with alkylnitronate anions, oximes of 5-acyl-1,2,4-triazines are produced in good yields. This reaction proceeds through the formation of the $\sigma_H$-adducts which then undergo conversion to the oximes (more stable isomers of nitrosoalkenes) apparently *via* a pathway similar to that discussed above, although in this case the nitro group of the nucleophile participates in the transformation (Scheme 13).[36]

**Scheme 13**




In spite of many examples of conversion of $\sigma_H$-adducts into nitroso compounds it is not a general process so far; in particular no rules can be formulated concerning the selection of nucleophiles entering this reaction.

### Direct nucleophilic replacement of hydride anions

As was mentioned above, in contrast to $\sigma_X$-adducts, the $\sigma_H$-adducts are in general unable to form final products *via* direct elimination of hydride anions since they are unstabilized species and because of high energy of the C—H bond. Nevertheless, there are some cases when nucleophilic substitution of hydrogen in aromatic rings occurs along this pathway. The most important example of such processes is the Chichibabin amination of azines with $KNH_2$.[14,37] It appears that in these reactions splitting off the hydride anions is facilitated by deprotonation of the initial $\sigma_H$-adducts and is promoted by association with the counter ion, $K^+$ or $Na^+$. Also alkylation of some azines with alkyllithium reagents can, in some cases, proceed *via* removal of $H^-$ in the form of LiH, which deprotonates the product and so liberates the hydrogen.[14] Since $H^-$ elimination is a slow and difficult process, often requiring high temperature, it cannot compete with nucleophilic substitution of halogen if it is present in the ring.

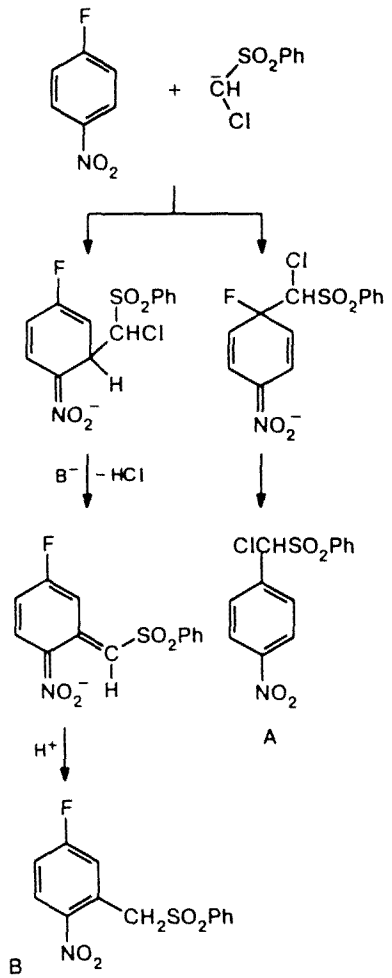
### Vicarious nucleophilic substitution

The most general possibilities of transformation of $\sigma_H$-adducts of nucleophiles to nitroarenes into products of nucleophilic replacement of hydrogen exist when the nucleophiles contain leaving groups X at the nucleophilic centers. Anionic $\sigma_H$-adducts formed by such nucleophiles, *e.g.*, α-halocarbanions, can subsequently undergo base induced β-elimination of HX at the expense of the ring hydrogen atom; under favorable conditions this process can proceed at a high rate. Experimental verification of this hypothesis resulted in the discovery that, in fact, carbanions containing leaving groups X at the carbanion centers react rapidly with nitroarenes, replacing with the carbanion moiety the hydrogen atom in *para*- or *ortho*-position to the nitro group.[38] The reaction proceeds *via* addition of carbanions to the carbon atoms bearing hydrogen, followed by base induced β-elimination of HX from the resulting $\sigma_H$-adducts. The elimination results in highly stabilized nitrobenzyl carbanions, which give final products upon protonation during a work-up procedure.[39] In this process, instead of the hydride anion of the ring, the $X^-$ anion of the carbanion splits off from the $\sigma_H$-adduct, thus acting as a vicarious leaving group. For this reason the process was termed "vicarious nucleophilic substitution" (VNS) of hydrogen. The most important and characteristic feature of this reaction is that in nitroarenes containing such leaving groups as halogens *etc.*, it usually proceeds much faster than the conventional nucleophilic replacement of these groups ($S_NAr$). This is due to the much faster addition of the carbanions to carbon bearing hydrogen than to that bearing other substituents (including F) and also to the relatively high rate of elimination of HX from the $\sigma_H$-adducts under appropriate conditions (an excess of base effecting the elimination). The relation between VNS and a conventional $S_NAr$ reaction of halogen is shown in Scheme 14.

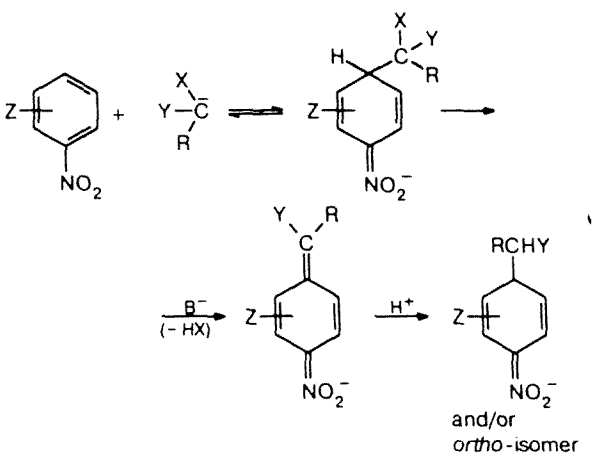
Even such active nitroarylating agents as *o*- and *p*-fluoronitrobenzenes, fluoro-2,4-dinitrobenzene (Sanger reagent) or chloronitropyridines enter VNS with α-halocarbanions faster as compared to the $S_NAr$ reaction of halogens.[39-41]

VNS is a general process with respect to both partners: nitroarenes and carbanions. Even if there is only one hydrogen in *o*- or *p*-position to the nitro group in nitroarenes it can be replaced in the VNS reaction regardless of the other substituents present in the ring. Some limitations are due to the deactivating effects of the negatively charged substituents, steric hindrances by bulky substituents on the addition and, particularly, on the elimination process. A similar generality claim is true for carbanions, for which the only necessary requirement is the presence at the carbanionic centers of substituents X, such as halogens, ArO, RS, *etc.*, that are able to be eliminated from the $\sigma_H$-adducts as HX in the base-induced β-elimination process (Scheme 15).[41] Some limitations with respect to the carbanions can be imposed by the low nucleophilicity of highly stabilized carbanions, by steric hindrances when they are bulky, or by instability of some α-halocarbanions when the reaction with less active nitroarenes is desired.[42]

**Scheme 14**

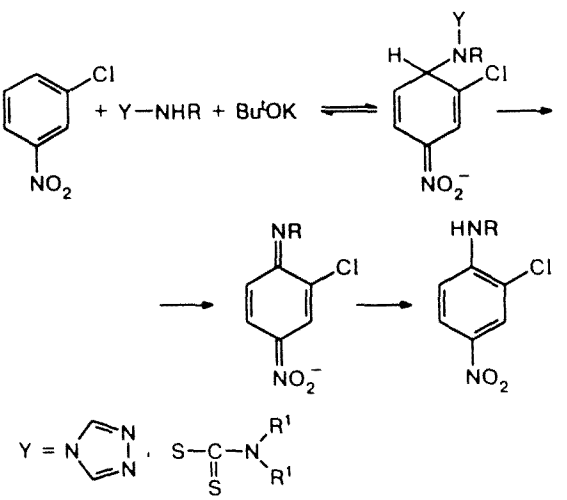


**Scheme 15**



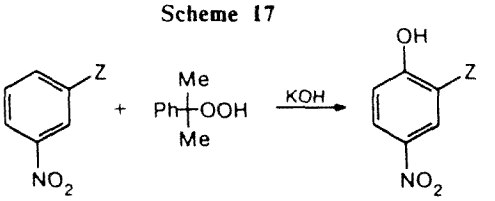
The VNS reaction is not limited to the carbanion nucleophiles. The process of amination of nitroarenes with hydroxylamine in alkaline medium proceeds apparently along a similar pathway,[43] although the hydride shift was also erroneously postulated for this reaction.[44] Since this process is limited to a few cases of highly electrophilic arenes, a better aminating agent, 4-amino-1,2,4-triazole was recently proposed by Katritzky.[45] This variant of the VNS amination is more general, and can be applied also for some monocyclic nitroarenes; nevertheless, it is still severely limited. Our recent finding that sulfenamides react efficiently in alkaline medium with nitroarenes to replace hydrogen with the amino group offers a simple and general method for direct nucleophilic amination of such compounds.[46] Preliminary mechanistic studies revealed that the reaction proceeds *via* deprotonation of sulfenamides YSNHR, reversible addition of the *N*-anion to nitroarenes, followed by base induced β-elimination of YSH from the intermediate $\sigma_H$-adducts (Scheme 16). Since Y and R in the sulfenamides can be varied a proper design is possible to introduce a number of the desired NHR groups into a variety of nitroarenes.

**Scheme 16**

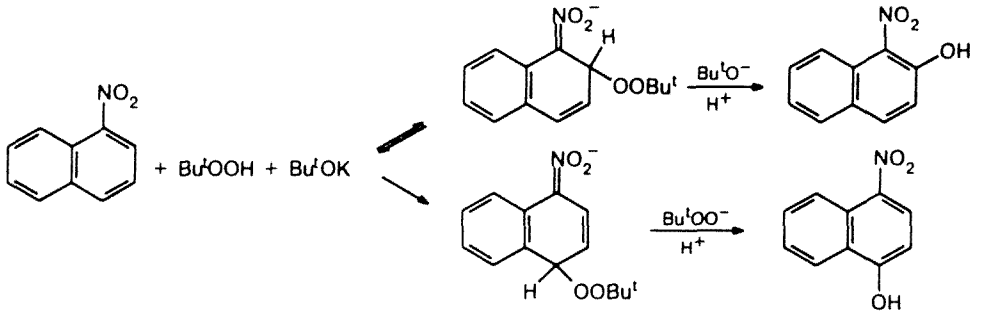


The VNS type reaction can also be applied for direct hydroxylation of nitroarenes. Readily available and relatively stable t-butyl and particularly cumyl hydroperoxides t-BuOOH and $PhMe_2COOH$ easily form relatively nucleophilic anions in which the leaving RO groups are attached to the nucleophilic center. In basic medium these alkylhydroperoxides react with nitroarenes *via* addition—β-elimination pathway (ROH being eliminated) to produce nitrophenols (Scheme 17).[47]

**Scheme 17**



**Scheme 18**

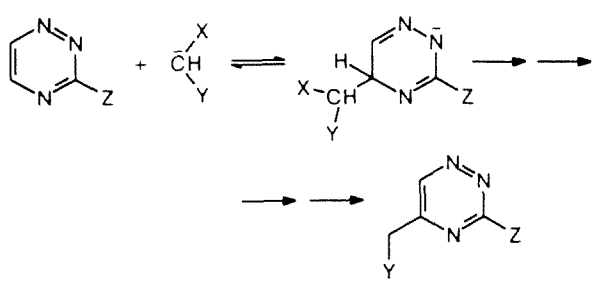


The VNS hydroxylation proceeds efficiently with mono- and bicyclic nitroarenes bearing a variety of substituents as well as with many heteroaromatic compounds. This process is undoubtedly the most general and simple method for the synthesis of nitrophenols and can be easily applied for large scale operations. In some cases orientation of the hydroxylation can be controlled by the conditions applied. For example, the hydroxylation of 1-nitronaphthalene with t-BuOOH in the presence of an excess of t-BuOK proceeds mainly at C-2; however, when t-BuOOH and t-BuOK are used in equimolar amounts preferential hydroxylation at C-4 takes place (Scheme 18). In the former case the orientation is kinetically controlled, whereas in the latter one slow elimination induced by a weak base ($ROO^-$) leads to thermodynamic control.

For both cases of VNS reactions of heteronucleophiles, *viz.*, amination with sulfenamides and hydroxylation with alkyl hydroperoxides, it was shown by competitive experiments that the $\sigma_H$-adducts of the corresponding anions are converted into the products *via* base-induced β-elimination and that in general the rate of this reaction is higher than that of the related $S_NAr$ reaction of halogen.

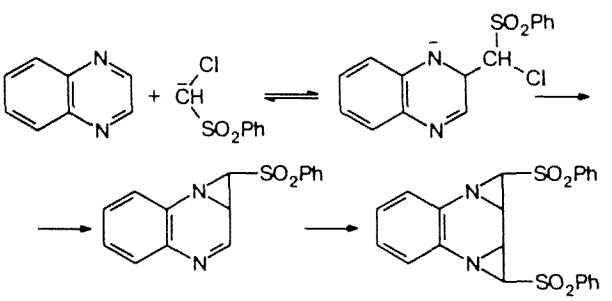
The VNS with α-halocarbanions proceeds efficiently not only in carbo- and heterocyclic nitroarenes but also in highly electrophilic heteroarenes which do not contain electron-withdrawing substituents. For example 1,2,4-triazines,[48] pteridines,[49] pyridazines,[50] *etc.* react with a variety of such carbanions according to the addition—β-elimination scheme to give products of the VNS of hydrogen (Scheme 19).

**Scheme 19**



In some cases further conversion of the $\sigma_H$-adducts of α-halocarbanions to electrophilic arenes took another course; instead of the β-elimination intramolecular nucleophilic substitution proceeded giving rise to the formation of aziridine and/or cyclopropane rings and to an overall annulation process. For example this type of the reaction was observed for carbanions of α-haloalkyl aryl sulfones on their interaction with quinoxalines[51] and their derivatives (Scheme 20) as well with cyanonaphthalenes.[52] The reason for this change in the reaction course appears to be much less efficient delocalization of the negative charge in the anionic $\sigma_H$-adducts. In the adducts formed by quinoxalines the charge is located mainly on the vicinal nitrogen atom that becomes highly nucleophilic and enters rapidly intramolecular substitution, whereas for the same reason the base-induced β-elimination is hindered.

**Scheme 20**



The correctness of this rationalization was shown in a few ways. Quinoxaline *N*-oxide enters the normal VNS reaction with chloromethyl aryl sulfone carbanions (because in the corresponding $\sigma_H$-adduct the negative charge resides mostly on the *N*-oxide oxygen atom).[53] In this respect particularly convincing are experiments with 6-azaquinoxaline in which the ultimate course of the reaction of the chloromethyl sulfone carbanion is governed by the conditions (concentration, amount of base, temperature, *etc.*). When the conditions favor bimolecular base induced β-elimination (high concentration, excess of base, low temperature), VNS becomes

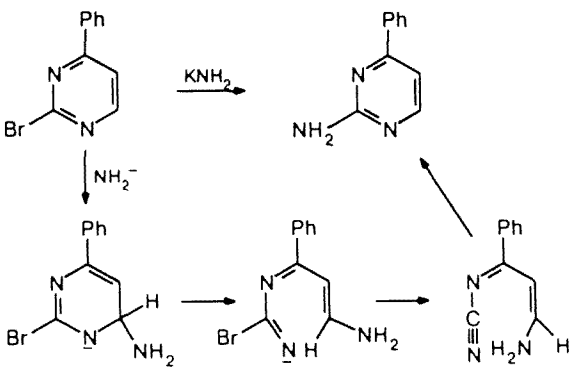
the main process, whereas general low concentration, no excess of base and higher temperature (which favor monomolecular conversion of the $\sigma_H$-adducts) result in formation of the bis-annulated quinoxalines as virtually the only products.[54]

It must be particularly stressed that the addition of such carbanions to 2-chloroquinoxaline takes place initially at C-3 atom. Owing to the reversibility of the addition the final results depend on the rate of transformation of the initially formed $\sigma_H$-adduct; usually the major reaction product is derived from this $\sigma_H$-adduct.

## ANRORC reactions*

In many halogenated electrophilic heterocyclic systems halogen in the rings can be replaced in the reactions with such strong nucleophilic agent as $NH_2^-$ to give products in which the $NH_2$ group occupies the position of the replaced halogen. However in many cases the reaction course is not as simple as it appears. Close investigations of such processes revealed that they begin from addition of the nucleophilic agent in a position occupied with hydrogen, not with halogen, to form $\sigma_H$-adducts. A series of transformations of these $\sigma_H$-adducts, *i.e.*, ring opening, elimination of HX and ring closure, give the expected, apparently «normal», products of the replacement of halogen. However, in these products the nitrogen atom of amino group originates from the ring whereas that from the $NH_2^-$ of reagent is located in the ring (Scheme 21).

**Scheme 21**



This process, for which the term Addition of Nucleophile—Ring Opening—Ring Closure (ANRORC) was coined, was thoroughly investigated by van der Plas. Even the reactions of some chloronitropyridines with potassium amide proceed to a substantial extent *via* the ANRORC mechanism.[56] This process can be considered as another general transformation pathway of the $\sigma_H$-adducts and supports the general concept presented in this paper that the addition of nucleophiles to the aromatic rings is faster when it occurs at C—(H) than at C—(X).

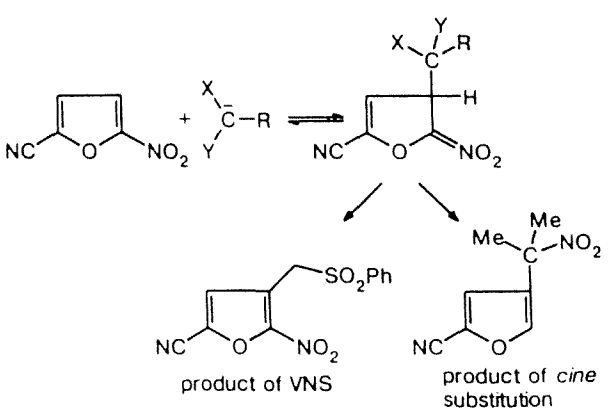
## *Cine* and *Tele* substitution

The anionic $\sigma_H$-adduct of nucleophiles to electrophilic arenes can be converted into stable products also by elimination of a leaving group located at another atom of the ring or in a side chain. Two major cases can be considered here: 1) when the leaving group connected with an atom vicinal to the addition site is eliminated, the process is termed *cine* substitution, 2) when the elimination of the leaving group takes place from a more remote position, then the term *tele* substitution is applied.

Among many examples of the *cine* substitution, one can mention the reaction of 3,4-dinitrothiophene with thiolate anions yielding 2-alkylthio-4-nitrothiophene,[57] or 2,3-dinitronaphthalene with alkoxides or carbanions, in which nucleophiles replace 1-hydrogen whereas 2-$NO_2$ group is eliminated.[58] The case of 5-cyano-2-nitrofuran appears to be most interesting in this respect. Addition of nucleophiles to this nitroarene occurs initially at the C-3 atom to give the $\sigma_H$-adducts, which, depending on the kind of nucleophile and on the reaction conditions, can be stabilized in two ways: 1) by elimination of the nitro group to yield the product of *cine* substitution,[59,60] or 2) when α-halocarbanions were used as nucleophiles, VNS of hydrogen in position 3 takes place[61] (Scheme 22). Finally, alkoxides or thiolate anions, unable to react along the above-mentioned pathways, replace 2-$NO_2$ group in a typical $S_NAr$ process, although under conditions favorable for the *cine* substitution the latter nucleophiles give some amounts of 3-alkylthio-5-cyanofurans.

*Tele* substitution occurs most frequently in di- and trichloromethyl derivatives of electrophilic arenes. For example, the ethoxide anion reacts with 2-dichloro-

**Scheme 22**

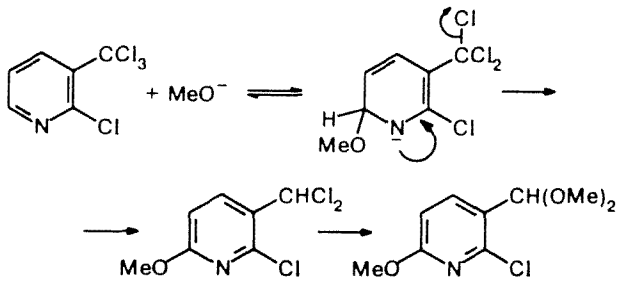



X, R, Y = Cl, H, $SO_2Ph$ (VNS)
X, R, Y = Me, Me, $NO_2$ (*cine* substitution)

* ANRORC is an acronym of the term Addition of Nucleophile—Ring Opening—Ring Closure.

methyl-3-chloropyridazine to yield 2-chloromethyl- or 2-ethoxymethyl-3-chloro-5-ethoxypyridazine.[62] A similar strong preference of *tele* substitution over the $S_NAr$ reaction of halogen was observed for chloro(trichloromethyl)pyridines[63] (Scheme 23).

**Scheme 23**



## Conclusions

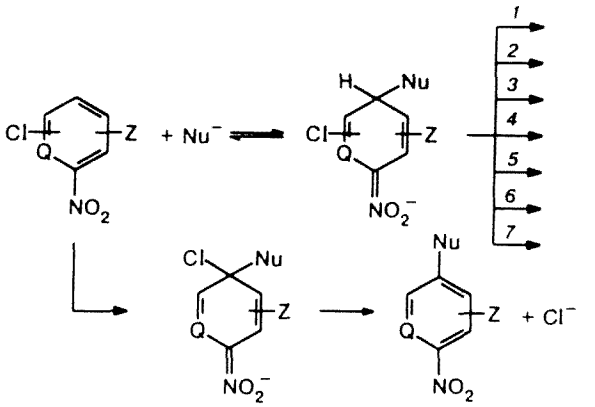
This short review of the reactions of nucleophilic agents with electrophilic arenes makes it evident that independently of the kind of the arene, *viz.*, nitroarenes, electrophilic azines, nonbenzenoic electrophilic arenes, π-arene complexes of transition metals, *etc.*, nucleophilic agents add initially at positions occupied by hydrogen. Even in cases when the electrophilic aromatic ring contains halogen and hydrogen located at equally activated positions the addition of nucleophilic agents occurs faster at the positions occupied with hydrogen, to give $\sigma_H$-adducts. These adducts, although, generally speaking, unable to form products *via* direct departure of the hydride anion, have many available ways for further transformations. These ways, which depend on the structure of the nucleophiles and electrophilic arenes and the conditions, have been discussed in this paper. They provide a possibility of achieving direct or indirect nucleophilic replacement of hydrogen, sometimes leading to more complicated products.

This situation is presented in an abbreviated form in Scheme 24, where routes 1—7 represent a variety of transformations of the $\sigma_H$-adducts discussed above: oxidative nucleophilic substitution of hydrogen (1), conversion of $\sigma_H$-adducts into nitroso compounds (2), direct nucleophilic replacement of hydride anions (3), vicarious nucleophilic substitution (4), ANRORC reactions (5), *cine* substitution (6), and *tele* substitution (7).

The nucleophilic addition is a reversible process; hence when none of transformations 1—7 proceed at a sufficient rate the dissociation of the initially formed $\sigma_H$-adducts results in slower formation of $\sigma_X$-adducts, which irreversibly lose $X^-$ anions, yielding the products of the conventional $S_NAr$ reaction of halogen.

As a consequence of this generalization the following final conclusion concerning nucleophilic aromatic substitution can be formulated: nucleophilic aromatic substitution of halogen or of another leaving group *via* an addition-elimination mechanism is a secondary process, preceeded by reversible formation of $\sigma_H$-adducts.[13]

**Scheme 24**



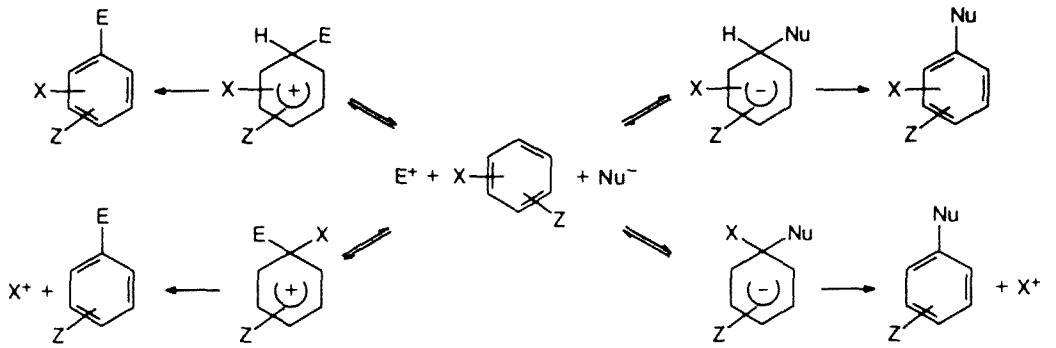
It is really surprising that this general phenomenon was not detected in numerous kinetic studies of these reactions and that the importance and generality of the processes occurring *via* $\sigma_H$-adducts was recognized only recently.[7,14,41] The preference for formation of $\sigma_H$-adducts over $\sigma_X$-adducts as well as the peculiar situation when the second step of the reaction controls the possibility of nucleophilic substitution of hydrogen allows one to claim that this is the main reaction course as compared to $S_NAr$ reaction of a nucleofugal leaving group, that is *ipso* substitution.

This situation is analogous to that in electrophilic aromatic substitution but with inverted polarities. Indeed, as was mentioned in the Introduction it is well recognized that electrophilic agents add to aromatic rings at positions occupied by hydrogen to form cationic $\sigma_H$-adducts faster than at positions occupied with other substituents. Since departure of a proton is a rapid process the normal electrophilic substitution, replacement of hydrogen, dominates over *ipso* substitution, which is much less frequent. This general rule is applicable to a majority of such important processes of electrophilic substitutions as nitration, halogenation, sulfonation, and many variants of Friedel—Crafts type reactions. The relation of electrophilic and nucleophilic aromatic substitution in this respect is presented in Scheme 25.

The electrophilic agent $E^+$ adds rapidly to the aromatic ring at a position occupied by hydrogen to form a cationic $\sigma_H$-adduct, from which a proton splits off readily to form the normal product. Much slower addition of $E^+$ at a position occupied by a substituent, *e.g.*, X, gives a cationic $\sigma_H$-adduct; subsequent elimination of $X^+$ results in the formation of the *ipso*-substitution product.

An analogous situation occurs in the case of reactions of nucleophilic agents (right side of Scheme 25). Here, for the reaction to occur the aromatic ring should

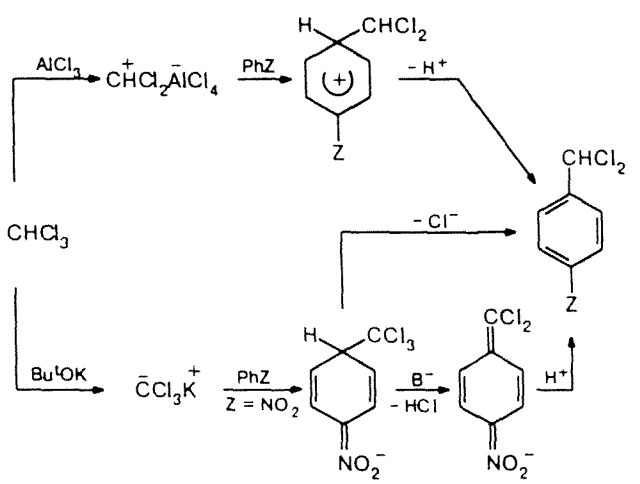
**Scheme 25**



have an electrophilic character. The initial addition takes place at the position occupied by hydrogen, to form the anionic $\sigma_H$-adduct, which, contrary to its cationic analog, cannot be stabilized by spontaneous expulsion of $H^-$. There are, however, many ways, discussed in this paper, along which the transformation of such a $\sigma_H$-adduct into a product can occur. They should be considered as the normal products. However, when owing to the kind of starting materials or conditions further transformations of the $\sigma_H$-adduct cannot proceed at a sufficient rate $\sigma_X$-adducts are produced, and then $S_NAr$ products are formed. They should be considered as *ipso* products.

This relationship of electrophilic and nucleophilic aromatic substitution (of hydrogen) can be nicely exemplified by comparison of the Friedel—Crafts type reaction and the vicarious substitution in arenes with chloroform, which can be activated by Lewis acids and bases. Treatment of chloroform, with $AlCl_3$ gives a dichloromethyl carbocation, which in the reaction with an arene produces its dichloromethyl derivative. This product reacts further and usually cannot be isolated (although there are cases in which it can be done[64]), but it is the initial product of electrophilic substitution.

**Scheme 26**



Similar treatment of chloroform with t-BuOK gives the trichloromethyl carbanion, which in the reaction with a nitroarene *via* addition—elimination also yields its dichloromethyl derivative[42] (Scheme 26).

Thus, analogous starting materials give analogous products *via* pathways with the same stoichiometry but opposite polarity and with a different sequence of events. Such as analogy can be extended to many other electrophilic reactions.

Because of the analogies between electrophilic and nucleophilic aromatic substitution discussed above it is of great interest to compare such reactions that can lead to the formation of bonds of the same type between the introduced substituents and carbon atoms of the ring. This comparison, given in Table 1, indicates a broad scope of possibilities of these processes.

The potentialities of nucleophilic substitution of hydrogen in electrophilic arenes and particularly its relation with nucleophilic substitution of halogen are practically neglected in textbooks and also in many monographs. Only recently has this process begun to be slowly recognized.[67]

**Table 1.** Comparison of electrophilic and nucleophilic aromatic substitution of hydrogen

| Bond formed | Electrophilic substitution | Nucleophilic substitution |
|---|---|---|
| C—C | Friedel—Crafts reactions | Vicarious substitution, oxidative substitution with $RMgX$, $R_3C^-$, *etc.* *Tele* and *cine* substitution, conversion into $R_3C$—ArNO |
| C—N | Nitration, nitrosation, diazo coupling, *etc.* | Vicarious substitution, oxidative amination, ANRORC |
| C—O | Few examples (see Ref. 3, p. 294) | Vicarious substitution, oxidative hydroxylation |
| C—Hal | Halogenation | Single examples[65] |
| C—S | Sulfonation | Specific cases[66] |

Taking into account the data and discussion presented in this paper it is necessary to state that, similarly to electrophilic aromatic substitution, nucleophilic aromatic substitution of hydrogen in its many variants is the major reaction course, whereas nucleophilic substitution of halogen ("*ipso*" substitution) is a secondary process. According to this approach nucleophilic substitution can be considered to be a kind of mirror reflection (resulting in inversion of polarity) of electrophilic substitution.

I certainly hope that the unifying treatment of aromatic substitution presented in this paper will stimulate interest in this field and promote discovery of new reactions.

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