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Review Commentary

Vicarious nucleophilic substitution of hydrogen. Mechanism and orientation

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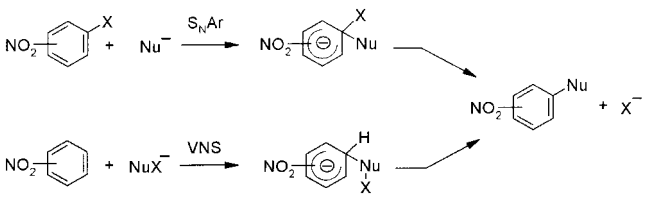
ABSTRACT: Hydrogens located at activated positions in electrophilic arenes, e.g. *ortho* and *para* hydrogens in nitrobenzenes, can be replaced with a nucleophile moiety provided there is at least one nucleofuge X connected to the nucleophilic centre. As the group really leaving in this hydrogen substitution process is not the hydride anion but X, the reaction has been named vicarious nucleophilic substitution of hydrogen (VNS). The concepts on the mechanism of the reaction and their experimental background are presented. Reactivity and orientation—the fundamental questions concerning synthetical applications of VNS—are discussed in light of the supposed mechanistic picture.

KEYWORDS: vicarious nucleophilic substitution; hydrogen; mechanism; orientation

INTRODUCTION

The introduction of substituents into electrophilic aromatic rings *via* replacement of a nucleofugal group X with a nucleophilic agent Nu proceeds as a rule *via* addition of the nucleophilic agent to the aromatic ring in positions occupied by the leaving group, resulting in the formation of short-lived intermediate σ^X-adducts, followed by departure of this group with an electron pair.[1] The nucleofugal character of the leaving group X, i.e. its ability to depart with a negative charge and low energy of the C—X bond, is essential for the reaction, thus halogens, NO_2, OR, SR, etc., can be substituted efficiently with nucleophiles. As was shown in kinetic studies of the S_NAr substitution reaction with anionic nucleophiles, the departure of such leaving groups from the intermediate σ^X-adducts is usually a fast step whereas the nucleophilic addition is a slow, rate-determining step of the overall reaction.[1] Since there is no doubt that the ability of nitroarenes to add nucleophilic agents is due to the activating effect of the nitro group, one would expect that the addition can also occur at the activated positions occupied by hydrogen to give σ^H-adducts. There are early reports on some reactions proceeding apparently *via* such σ^H-adducts,[2] but the general possibility of such a process was neglected.[1b] On the basis of these early observations and also the known chemistry of stable anionic adducts to polynitroarenes,[3] we considered that the addition of nucleophiles in positions occupied by hydrogen should be a relatively fast process, hence σ^H-adducts should be readily formed short-lived species. They are as a rule unable to form products of nucleophilic substitution of hydrogen because hydride anions cannot depart as such.[1b] Looking for a general way of converting such anionic σ^H-adducts into products, we hypothesized that when α-halocarbanions were used as nucleophiles, their further transformation can occur *via* departure of the halogen anion from the carbanion moiety with a simultaneous 1,2-hydride shift, giving products of nucleophilic substitution of hydrogen.



Scheme 1.

In a short communication published in 1978, we reported that indeed the carbanion of chloromethyl phenyl sulfone reacts with nitroarenes replacing hydrogen in *ortho* and *para* positions with a phenylsulfonylmethyl group.[4] Moreover, it was also shown that in halonitroarenes, the nucleophilic substitution of hydrogen proceeded faster than the conventional S_NAr reaction of halogens. This new reaction was named vicarious nucleophilic substitution (VNS) of hydrogen because it

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proceeds *via* departure of the halogen anion from the carbanion moiety instead of H^- from the aromatic ring (Scheme 1). Thus, the halogen acts here as a vicarious leaving group.

In further studies, it was shown that the reaction does not proceed *via* a hydride shift but *via* base-induced β-elimination of hydrogen chloride, but this does not change the general scheme and stoichiometry of this process.[5]

The VNS reaction is now a well established general method for the introduction of substituents into electrophilic aromatic rings. Its scope with respect to the arenes is very broad—derivatives of nitrobenzene and nitronaphthalene enter this reaction irrespective of other substituents present in the ring provided that there is a hydrogen atom in a *para* or *ortho* position to the nitro group.[6a] The same situation applies in heterocyclic nitroarenes[7] such as nitrothiophene,[8] nitrofuran,[8] nitroimidazole,[9a] nitrothiazole,[9b] nitropyridine[10] and nitroquinoline.[10c–f,11] Many electrophilic heterocyclic systems such as 1,2,4-triazine,[12] pteridine[13] and benzothiazole[12a] enter this reaction without the presence of any activating group. The VNS reaction is of equally broad scope with respect to nucleophilic agents. Virtually any carbanion of general structure ^-CRXY can react with any electrophilic arene along the VNS pathway provided that at least one substituent (X) can be eliminated as HX from the intermediate σ^H-adducts. In the reported examples, carbanions containing leaving groups X such as F, Cl, Br, OMe, OAr, SAr, R_2NCSS, SMe, SO_2CF_3 and Py^+ were found to enter the VNS reaction.[6a,10c,14] Substituents R and Y should provide adequate stabilization of the carbanion, but there are no limits as to their nature. Some limitations concerning the carbanions are due to their instability under the reaction conditions or insufficient nucleophilicity when substituents R, Y and X are efficient carbanion-stabilizing groups [e.g. in $ClCH(COOEt)_2$]. Nevertheless, even such weakly nucleophilic carbanions give the VNS products with sufficiently electrophilic arenes.[9b]

VNS is not limited to the introduction of carbon substituents *via* the reaction with carbanions. Anions of alkyl hydroperoxides such as *tert*-BuOOH or cumene hydroperoxide react with a large variety of nitroarenes to produce nitrophenols.[15] Similarly, hydroxylamine[16] and hydrazine[17] derivatives and sulfenamides[18] afford efficient VNS amination of nitroarenes.

From this introduction, it is evident that the VNS reaction is a general and versatile process allowing the introduction of a variety of C, O and N substituents into a virtually unlimited range of electrophilic aromatic rings.[6a,7,19]

On the other hand, mechanistic features of this process and factors governing its orientation are much less well known. Its mechanistic picture is essentially based on qualitative studies and observations made during exploratory research in this field.

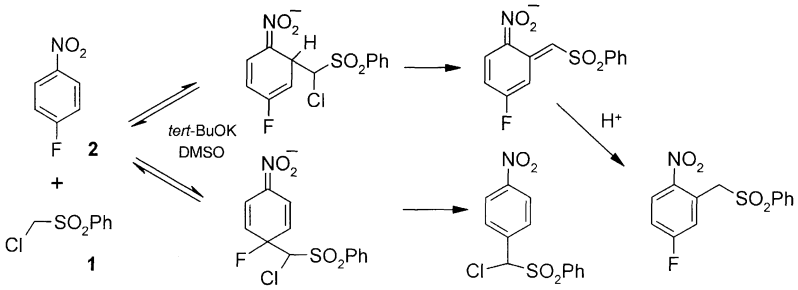
MECHANISM OF THE VNS REACTION

The VNS reaction is unquestionably a multi-step process which includes the formation of the σ^H-adducts of the carbanion to nitroarene and their transformation into the final products. Hence a few important questions should be addressed: how does the formation of the σ^H-adducts proceed, how does the transformation of the σ^H-adducts into products proceed, what are the relationships for the rates of the nucleophilic addition and dissociation of the σ^H-adducts to the starting components and their conversion into the products?

The formation of the anionic σ-adducts of nucleophiles to nitroarenes is a common initial step for the VNS reaction, S_NAr reactions of halogens and many other processes. In general, two pathways are considered for this process: direct nucleophilic addition and a two-step process proceeding *via* single electron transfer (SET) from the nucleophile to the nitroarene, giving radicals and radical anions, followed by coupling of these paramagnetic species. The latter process was recently often favored as a route to the formation of σ^X-adducts, intermediates in the S_NAr reactions of halogens.[20] This aspect has not been studied for the VNS reaction, but there are no observations indicating that σ^H-adducts are not formed via direct nucleophilic addition.[21a]

In this paper we will discuss mainly mechanistic problems of the conversion of σ^H-adducts into VNS products and effects of some factors on the orientation of this reaction. The VNS reaction was designed on the basis of the hypothesis that σ^H-adducts of α-halocarbanions to nitroarenes can be converted into the products *via* a hydride shift promoted by the simultaneous departure of the halogen anion. A similar mechanism was proposed earlier for the amination of *m*-dinitrobenzene with hydroxylamine,[22] although it appears to be incorrect. A reasonable mechanistic alternative for this process appears to be a base-induced β-elimination of hydrogen halide.

For differentiation of these alternative processes, the effect of base on the reaction rate should be informative. The rate of the base-induced β-elimination should depend on the kind and concentration of base whereas the hydride shift should be insensitive to these changes under the reaction conditions. The influence of base on the rate of the VNS reaction was studied using competitive experiments in which the rate of the VNS reaction was compared with that of a competing process independent of a base. For example, in the model reaction of *p*-fluoronitrobenzene with the carbanion of chloromethyl phenyl sulfone (Scheme 2), the rates of its addition in *para* and *ortho* positions giving σ^F- and σ^H-adducts and the rate of fluoride ion departure from the σ^F-adduct and also the hydride shift in σ^H-adduct should not depend on the base concentration. On the other hand, the β-elimination of HCl from the σ^H-adduct should be sensitive to base concentration. The observed strong



tert-BuOK added slowly to **1**+ **2**	49	11
2 added to **1** + *tert*-BuOK (1eq)	12	14
2 added to **1** + *tert*-BuOK (2eq)	8	66

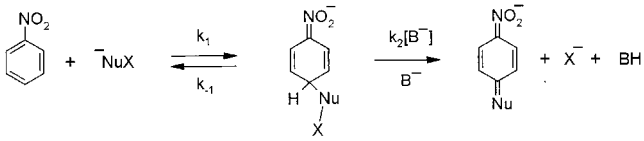
Scheme 2.

influence of the base concentration on the ratio of S_NAr and VNS products indicates that the base accelerates the formation of the latter product and thus conversion of the σ^H-adduct.[5]

From these simple experiments, it was concluded that the conversion of the σ^H-adduct proceeds as a base-induced β-elimination, that the second step is kinetically important for the overall reaction rate and that the first step, formation of the σ^H-adduct, is a fast and reversible process.

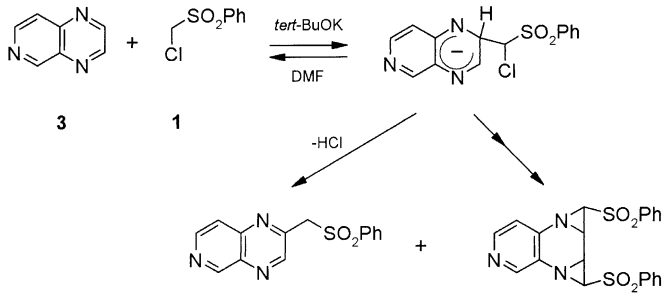
A similar effect of the base concentration on the rate of the VNS reaction monitored by the competition with S_NAr of halogens has been observed in many other cases. For instance, the reaction of chloromethyl phenyl sulfone carbanion with 2-nitro-3-bromothiophene proceeds as VNS of hydrogen in position 5 when base is used in an excess or as S_NAr of 3-Br in the absence of an additional base.[8b] The VNS hydroxylation of 4-nitrochlorobenzene with cumene or *tert*-butyl hydroperoxide proceeds when base is used in excess, whereas in the absence of additional base the alkyl hydroperoxide anions replace mainly halogen in this nitroarene,[15a] etc.

For mechanistic clarification of the VNS reaction, of substantial importance is the observation that the σ^H-adduct of chloromethyl phenyl sulfone carbanion to 6-azaquinoxaline can react in two ways depending on the base concentration (Scheme 3).[23] When additional base is absent it undergoes intramolecular nucleophilic substitution to give an aziridine derivative, which reacts with the next carbanion molecule to give the bis-annulation product. On the other hand, an excess of base promotes base-induced β-elimination, resulting in the VNS reaction. This observation is of particular value because here the same σ^H-adduct enters two competing processes, so reversibility of its formation and the kinetic significance of the second step do not affect the results.



Scheme 4.

Based on these and numerous other observations, the mechanistic picture of the VNS can be presented as shown for *para*-substitution in nitrobenzene in Scheme 4. Deprotonation of the nucleophile precursor and pro-



3 added to **1** + *tert*-BuOK (1 eq.)	17	50
3 + **1** added to tert-BuOK (1 eq.)	30	36
3 + **1** added to *tert*-BuOK (6 eq.)	60	14

Scheme 3.

tonation of the anionic products are not shown because they are not kinetically important under the applied conditions.

Since it can be assumed that the σ^H-adducts are short-lived intermediates, the steady-state approximation can be applied, so the second-order rate constant of VNS reaction at a given base concentration [B^-] is represented by Eqn (1), which can be simplified under certain conditions to Eqn (2) or (3):

$$k_{VNS} = \text{rate}/[\text{ArH}][\text{Nu}] = k_1k_2[B^-]/(k_1 + k_2[B^-]) \quad (1)$$

$$k_{VNS} = (k_1/k_{-1})k_2[B^-] \qquad \text{when } k_2[B^-]/k_{-1} \ll 1 \quad (2)$$

$$k_{VNS} = k_1 \qquad \text{when } k_2[B^-]/k_{-1} \gg 1 \quad (3)$$

In the first case [Eqn (2)], the reaction rate is of first order in base concentration and it depends also on its strength *via* the value of k_2. In the second case [Eqn (3)], the base does not affect the overall rate and the VNS rate constant is identical with that of the addition (formation of the σ^H-adduct). In the intermediate cases these simplifications are not allowed and the effect of base on the rate of the VNS is not linear.

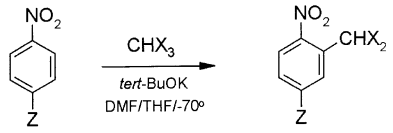
Equation (2) describes the reaction the rate of which is proportional to the equilibrium constant of the addition, $K^H = k_1/k_{-1}$, hence it can be considered as a thermodynamically controlled process, whereas Eqn (3) represents kinetic control of the reaction.

Recognition of a kinetic model of a given VNS reaction is essential for the proper interpretation of the results and for understanding the crucial questions of VNS, i.e. electrophilic reactivity of arenes and orientation of the process. Direct kinetic and thermodynamic data for σ^H-adducts formation in arenes of medium electrophilicity, such as mononitrobenzene derivatives, are not available, hence the VNS reaction may provide some information on relative rates or relative equilibrium constants of the nucleophilic addition to such arenes.

EFFECT OF ELECTROPHILICITY OF ARENES ON THE VNS REACTION

The electrophilicity of arenes can be expressed in terms of the rate of addition of nucleophilic agents to the arene rings and, in the case of its reversibility, of the addition equilibrium. When S_NAr and VNS reactions are compared it appears that the latter is more sensitive to the electrophilicity of the arenes. In contrast to S_NAr, where the addition in a position occupied by a leaving group X produces σ^X-adducts from which X^- usually departs in a fast process, the second step in the VNS reaction is of critical importance. The base-induced elimination of HX from the σ^H-adducts, especially in the case of weaker electrophiles (large k_{-1}), may be the slowest step (k_2[B]/$k_{-1} \ll 1$) of the whole process. As a consequence of low stabilization of the negative charge in σ^H-adducts, the equilibrium constant $K^H = k_1/k_{-1}$ and probably also k_2 are both very small, hence the value of $K^Hk_2[B^-]$ (the overall rate) becomes extremely small. In other words, the formation of σ^X-adducts is necessary and sufficient for a typical S_NAr process, whereas the formation of σ^H-adducts is necessary but not a sufficient requirement for VNS. Accumulated data indicate that σ^H-adducts are initial short-lived species produced when nitroarenes react with nucleophiles and their formation precedes the formation of σ^X-adducts;[1c,6] however, for VNS some additional requirements should be satisfied: nucleophiles should contain leaving groups and both the σ^H-adduct and the base should be present at concentrations sufficient to ensure a fast elimination process. Since the stability of nucleophiles such as α-halocarbanions is usually low, the slow rate of the VNS in the case of weakly electrophilic arenes precludes this reaction because decomposition of the nucleophiles occurs faster. There is no such general limitation for S_NAr reactions.

An interesting possibility for evaluating the electrophilicity of nitroarenes in the light of these requirements provides the VNS reaction with trihalomethyl carbanions.[24] These anions can form σ^H-adducts to nitroarenes provided that the addition proceeds faster than their dissociation into dihalocarbenes. Since all substituents at the carbanion center are good leaving groups, the β-elimination of the HX from these σ^H adducts should be a particularly facile and rapid process. It appears, therefore, that the yields of the VNS dihalomethylation products are a result of competition between dissociation of these carbanions into dihalocarbenes and addition to nitroarenes. Thus, taking additionally into account that the dissociation of CBr_3^- proceeds faster than that of CCl_3^-,



Z	Yield	
	X = Cl	X = Br
Cl	94	69
CF_3	76	64
OTs	50	48
H	52(13)[a]	16(15)[a]
OPh	59	-[b]
F	59	-[b]
OMe	-[b]	-[b]

[a] *ortho* isomer (*para* in brackets)
[b] dihalomethylathion not observed

Scheme 5.

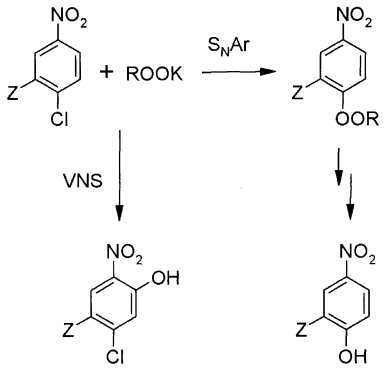
the yields of the dichloromethylated and dibromomethylated products can be used as a qualitative measure of the electrophilic activity of nitroarenes.[24] Some selected results of VNS in 4-substituted nitrobenzenes are shown in Scheme 5. Although they confirm the expected effects of substituents *para* to the nitro group on the electrophilic reactivity of the ring, the lower reactivity of derivatives in which lone electron pairs of the heteroatoms can be conjugated with the nitro group of the substrate such as 4-OMe and 4-F is noteworthy.

Analysis of the general kinetics of VNS [Eqns (1)–(3)] indicates that an increase of electrophilicity of nitroarenes should be more favorable for VNS than for S_NAr reactions. For moderately electrophilic arenes, the competition between S_NAr and VNS is controlled by the relationship between the rates of dissociation of σ^H-adducts (k_{-1}) and β-elimination ($k_2[B^-]$):

$$V_{VNS}/V_{S_NAr} = \frac{k_1^H}{k_1^X} k_2[B^-]/k_{-1} \qquad (4)$$

When the former constant is high, $k_2[B^-]/k_{-1}$ is much smaller than unity and the S_NAr process may be faster than VNS despite the fact that ${k_1}^H > {k_1}^X$ [Eqn (4)]. The increasing electrophilicity of the arene probably does not influence the ${k_1}^H/{k_1}^X$ ratio but the value of k_{-1} becomes substantially smaller, resulting an increase in V_{VNS}/V_{S_NAr} ratio and also in a progressive change in the kinetic model of the VNS reaction [Eqns (2) and (3)]. In the most convincing way, such a situation can be observed in the VNS hydroxylation of 4-nitro- and 2,4-dinitrochlorobenzene with alkyl hydroperoxides (Scheme 6).[15a]

In the presence of both weak (ROOK) and strong (*t*-BuOK) base, the VNS/S_NAr product ratio is much higher



t-BuOK / *t*-BuOOK	VNS / S_NAr product ratio	
	Z = H	Z = NO_2
0	<0.05	2.5
1	1.0	>93
4	2.9	-
4[a]	10.4[a]	-

[a] $PhCMe_2OOK$ was used instead of *t*-BuOOK

Scheme 6.

in the case of the dinitroarene. Moreover, the observed effects of the strength and concentration of the base and the kind of leaving group on this reaction strongly suggest thermodynamic control in the case of mononitroarene hydroxylation, whereas in the case of the more electrophilic chloro-2,4-dinitrobenzene the VNS model changes so that in the presence of strong base the β-elimination becomes the fast step ($k_2[B^-]/k_{-1} \gg 1$) of the reaction. This conclusion was drawn from kinetic isotopic effect measurements, revealing ${k_{VNS}}^H/{k_{VNS}}^D = 6.0 \pm 0.3$ and 0.98 ± 0.01 for the reaction of 1-D-2,4-dinitrobenzene induced by weak and strong base, respectively.[15b]

ORIENTATION OF THE VNS REACTION

In contrast to the conventional S_NAr of halogens in electrophilic arenes, which proceeds at the site where the halogen is located, hence orientation is a minor issue, the VNS reaction can usually proceed in more than one position of the arene ring, forming isomeric products. Orientation of the VNS reaction is therefore an important question.

The orientation can be considered as the relationship between the rates of the reaction at different positions of the aromatic ring, hence all parameters affecting these rates should influence the observed orientation. From a phenomenological standpoint one would expect the orientation to be a function of the following factors: (1) structure of the electrophilic arene—aromacity and symmetry of the ring and substituents in the ring; (2) structure of the nucleophilic agents—nucleophilicity, steric demands, kind and number of leaving groups; and (3) reaction conditions—solvent, counterion, strength and concentration of the base, temperature, etc.

Generally, these parameters can influence the VNS rate in both addition and β-elimination steps and, depending on the details of the mechanism, this effect can be different. Numerous experimental observations confirmed that all these factors exert substantial effects on the orientation of VNS which, in certain cases, can be controlled over a wide range.

There are electrophilic arenes in which structural elements responsible for the electrophilic character of the arene ensure selective activation of certain positions in the aromatic ring. In polyazaheterocycles such as 1,2,4-triazine,[12] acridine,[12a] 5- and 6-azaquinoxalines[23,25] and benzothiazole,[12a] the location of the electronegative heteroatoms defines possible sites of nucleophilic addition, hence the VNS reaction proceeds selectively in such positions. More complicated is the orientation problem in arenes activated by a nitro group, which activates strongly all conjugated *ortho* and *para* positions of the ring. Only in intrinsically non-symmetric aromatic systems with considerably different bonds multiplicities and the nitro group located in specific positions is the

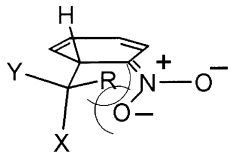


Figure 1.

activation limited to one position. For example, in 2-nitronaphtalene[26] the reaction proceeds only in position 1, and similarly in 3-nitrothiophene,[8a,b,27] 3-nitrofuran and 3-nitropyrrole[8b] only position 2 is activated for nucleophilic addition and hence for the VNS. High regioselectivity has also been found in VNS reactions of chloromethyl phenyl sulfone with nitroquinolines.[11,28] Except for the 2-nitro isomer, all mononitroquinolines reacted exclusively in one specific position. Similar selectivity was found for 2-X-3-nitro-1,8-naphthyridines.[28b] Calculations of the π electron stabilization energy showed that the reaction is controlled by the interactions of HOMO of the nucleophile and LUMO of the substrate as these energy values, contrary to the formal electron charges, were in full accord with the observed orientation.[28]

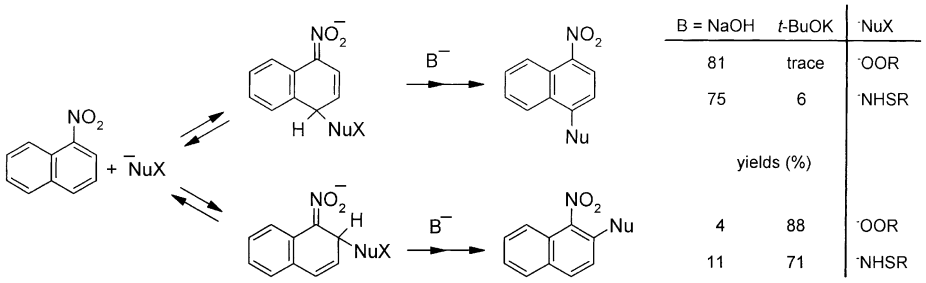
In general, however, positions activated by the nitro group are not sufficiently differentiated for selective VNS, hence the observed orientation is a result of interplay of other factors affecting the reaction rates in different positions.

The VNS reaction is very sensitive to steric hindrance created by the nitro group or other substituents in the ring. Carbanions and other nucleophiles with substantial steric demands tend to react in positions *para* to the nitro group or in positions in which the steric hindrance is smallest. Thus, for VNS reactions of nitrobenzene with carbanions CHXY the *ortho*/*para* ratio decreases in the order X = F, Cl, Br, I and also in the order Y = CN, SO_2OR, SO_2Ar.[29] More drastic effects on orientation are exerted by additional substituents at the carbanionic centre. When both *ortho* and *para* positions are available, more bulky tertiary carbanions usually replace exclusively *para* hydrogen atoms.[29a] Although steric hindrance operates on the addition and elimination steps, it appears that the latter effect is particularly important, as the bulkiness of the nucleophile moiety should considerably hinder the antiperiplanar conformation in the *ortho* σ^H-adduct required for the β-elimination (Fig. 1)

Indeed, whereas under typical weak-base conditions (KOH in DMSO—because of the insolubility of KOH the carbanion of the substrate is the operating base) tertiary 1-chloroethyl phenyl sulfone replaces only *para* hydrogen in nitrobenzene and does not react at all when this position is occupied, under strong-base conditions (*tert*-BuOK, DMF) at low temperature *ortho*-substitution in nitrobenzene is also observed (*ortho*/*para* ratio = 1:16) and in *para*-substituted derivatives it occurs efficiently.[30]

When all substituents in tertiary carbanions are good leaving groups, the steric hindrance is counterbalanced by a statistical factor favoring the β-elimination. Trichloromethyl carbanions in the *tert*-BuOK–DMF–THF ($-70\,^\circ C$) system replace *ortho*-hydrogens in nitrobenzene four times faster than *para*-hydrogens. 1-Nitronaphthalene and 2-nitrothiophene are dichloromethylated exclusively in the *ortho* position.[24]

These and many other observations show that factors which favor fast β-elimination, such as the presence of efficient or more than one leaving group in the nucleophile and a high concentration of a strong base, favor *ortho* orientation of VNS. The tendency for *ortho* orientation is enhanced at low temperature when all reactions, but particularly dissociation of the σ^H-adducts, and thus equilibration, are decelerated. It appears that the initial addition of nucleophiles to nitroarenes proceeds *ortho* to the nitro group; however, the produced σ^H-adducts are less stable than the corresponding *para* isomers ($k^o_1/k^p_1 > 1$; $K^o/K^p < 1$). When the elimination step is not sufficiently fast ($k_2[B^-]/k_{-1} \ll 1$, thermodynamic control), the *ortho* σ^H-adducts rearrange via a dissociation–addition process to produce *para* σ^H-adducts. On the other hand, when $k_2[B^-]/k_{-1} \gg 1$ and thus $k_{VNS} = k_1$ (kinetic control), *ortho* substitution becomes the dominant process.



B = NaOH	*t*-BuOK	·NuX
81	trace	·OOR
75	6	·NHSR
yields (%)		
4	88	·OOR
11	71	·NHSR

conditions: KOH/DMSO/rt or *tert*-BuOK /DMF/rt for the amination (R= 2-benzothiazolyl)
NaOH or *tert*-BuOK/$NH_{3\,liq}$/-33°C for the hydroxylation (R= *tert*-butyl)

Scheme 7.

Under thermodynamic control, the reaction rate $k_{VNS} = Kk_2[B^-]$ thus depends also on the rate of the elimination which could be responsible for the observed preference for *para*-substitution, regardless of the K^o/K^p value, if $k^p{}_2 \gg k^o{}_2$. The results of amination[21b] and hydroxylation[15b] of 1-nitronaphthalene (Scheme 7) apparently clarify this uncertainty.

In contrast to the reaction promoted by *tert*-BuOK, the use of insoluble NaOH, hence the nucleophile anion as the only acting base, leads to predominant *para* substitution.[15a] Taking into account the low steric demands of the nucleophiles, the differences in the rates of the elimination step in these reactions should be negligible ($k^p{}_2 \approx k^o{}_2$). These results suggest that the orientation ($k^p{}_{VNS}/k^o{}_{VNS}$) under thermodynamic control conditions really represents the K^p/K^o relationship and that it is much greater than unity.

The tendency for kinetic or thermodynamic control of the VNS reaction depends also on the nucleophilicity of the carbanions. High nucleophilicity shifts the addition equilibrium towards σ^H-adducts and thus favors kinetic control, and vice versa, orientation of VNS with carbanions of lower nucleophilicity is usually thermodynamically controlled.

The orientation of VNS can be strongly affected by the state of the carbanions in the solution. Under the conditions typical for VNS (NaOH, KOH or *tert*-BuOK in DMSO, DMF or liquid NH_3), carbanions and counterions form loose ion pairs. Under such conditions, the orientation of VNS in nitrobenzene with $ClCH_2SO_2Ph$ depends on factors discussed earlier and the *ortho*/*para* ratio varies in range 0.4–2.1. On the other hand, this reaction carried out in the presence of *tert*-BuOK in THF results in the exclusive formation of the *ortho*-substituted product.[31] A similar effect has been observed with many other nitrobenzene derivatives and also for cyanomethylation reactions.[32] This *ortho* effect can be rationalized as follows. In THF, where tight ion pairs exist, nucleophilic addition in the *ortho* position is strongly favored owing to the interactions between cations and the nitro group oxygens in the cyclic transition state (Fig. 2). Hence $k^o{}_1/k^p{}_1 \gg 1$ and VNS takes place preferentially in the *ortho* position. This supposition is confirmed by the observation that the addition of crown ethers, efficiently solvating K^+, eliminates the preference for an *ortho* orientation.[31] Since this directing effect is of kinetic nature and can operate only on the first step of the VNS, it appears that this reaction in THF is kinetically controlled.

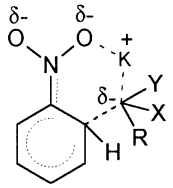


Figure 2.

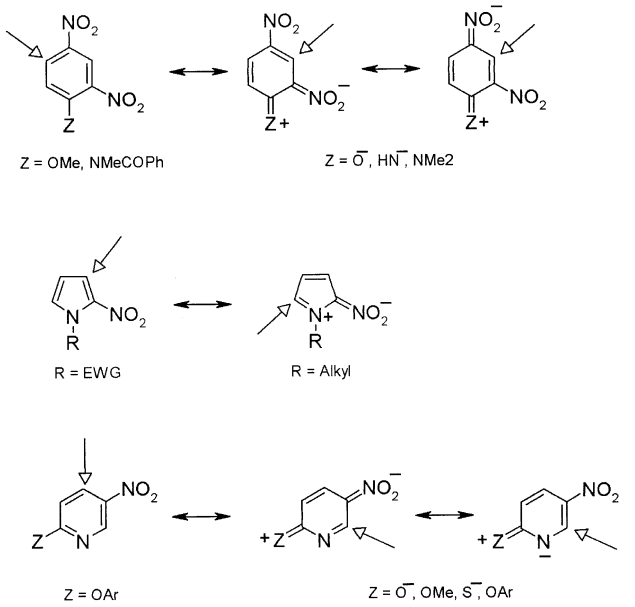
An issue of similar nature is the copper-promoted VNS substitution selectively in position 2 of 1,3-dinitrobenzene with secondary and even tertiary α-halocarbanions.[33] The chelation involving copper cation, two nitro groups and the leaving halogen is believed to be the reason for such an orientation.

The effects of substituents in the electrophilic aromatic rings on the VNS orientation can be of steric and electronic nature. As has already been mentioned, the ring substituents can exert steric hindrance to the addition of the nucleophiles and particularly to the elimination step. The steric effect on the addition process could be first or second order, namely directly affecting the addition site or hindering coplanarity of the NO_2 group with the aromatic ring necessary for efficient stabilization of the anionic σ^H-adducts.

The electronic effect of substituents on the orientation of the VNS reaction is a particularly complex question. Both steps of the VNS are affected by the substituents, often in different ways, so their overall effect can vary depending on the kinetic model of the reaction. Whereas their influence on electron density or LUMO orbital coefficients can be calculated and correlated with rates of addition and also the stability of the σ^H-adducts, nothing is known about effects of the substituents on the rate of β-elimination from the σ^H-adducts, which is crucial for the kinetic relationships of the two-step reaction. There are many interesting results and observations of the orientation of VNS reactions of 2- and 3-substituted and disubstituted nitrobenzene derivatives that suffer from a lack of reliable rationalization. The most complicated is the orientation pattern in 3-Z-nitrobenzene derivatives which can form three isomeric VNS products at positions 2, 4 and 6.[21c,29,32] Surprisingly, substituents such as Me, MeO, F, Cl, Br and NMe_2 favor substitution in their vicinity at C-2 and C-4. When the reaction is carried out in the presence of *t*-BuOK in THF the substitution occurs mainly is the most hindered position 2.[21c,31,32]

Perhaps the most interesting effect on the VNS orientation is exerted by highly electron-donating substituents conjugated with the nitro group. The conjugation of the lone electron pairs leads to reorganization of the π-electron system in the substrate and hence strongly differentiates the activated positions to the nucleophilic attack. Examples of structures for which such effects were observed, in comparison with those incapable of efficient conjugation, and preferred positions of the VNS reaction are shown in Scheme 8.

The orientation of VNS in 2,4-dinitrophenol and 2,4-dinitroanisole is different—it proceeds at position 3 in the former and at position 5 in the latter case.[34] The phenol enters the reaction as the dinitrophenolate anion represented by two resonance structures so it can be considered as a nitrocyclohexadienone system in which nucleophilic addition occurs at C-3. Such conjugation also takes place in 2,4-dinitroanisole but the corresponding dipolar structure is of much smaller weight and



Scheme 8.

cannot counterbalance the steric hindrance at C-3. The conjugation of the NMe_2 group with the nitro groups in 2,4-dinitro-*N*,*N*-dimethylaniline is much stronger, thus the dipolar structures govern the behavior of this nitroarene and the VNS occurs, as in the anionized dinitroaniline, at C-3.[21d] On the other hand, in *N*-methyl-*N*-acyl-2,4-dinitroaniline, in which the conjugation is not efficient, VNS proceeds at position 5.

Similar effects are responsible for some surprising observations concerning VNS orientation in heterocyclic nitroarenes. In five-membered heterocycles such as 2-nitrothiophene it was expected that the substitution should take place at C-3 because of the substantial double character of the C-2—C-3 bond. This tendency should be stronger in the less aromatic 2-nitropyrrole and 2-nitrofuran. Indeed, VNS in 2-nitrohiophene with $ClCH_2SO_2Ph$ occurs at position 3 whereas unexpectedly the reaction with *N*-methylpyrrole proceeds at C-5.[8b,35] It appears that in the latter case there is efficient conjugation of the ring nitrogen with the nitro group, as shown in Scheme 8, hence the nucleophilic addition takes place at C-5. This rationalization is confirmed by the observation that VNS in 2-nitro-*N*-(phenylsulfonyl)pyrrole, in which such conjugation cannot be efficient, proceeds at C-3.[8b,35]

Equally interesting observations were made in the 2-Z-5-nitropyridine series in which distribution of the isomeric VNS products at C-6 and C-4 was controlled by Z.[24] 2-Z-5-nitropyridine derivatives are similar to 1-Z-2,4-dinitrobenzenes because the pyridine nitrogen provides similar activation to NO_2, but does not create steric hindrances. As a consequence, the conjugation of the methoxy group appears sufficient to direct the VNS into position 2.[24] The most spectacular is the case of 2-ArO-5-nitropyridine in which substituents in the aryloxy group exert a substantial effect on ratio of 4- and 6-substitution.[36]

The discussion of mechanistic and orientation features of the VNS reaction is based on observations made in the course of exploratory studies and qualitative competitive experiments. Since this process is of wide scope and of substantial practical value, detailed quantitative investigations of its mechanism are necessary. We certainly hope that this paper will stimulate interest in these problems and promote mechanistic studies of this important reaction.

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