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Vicarious nucleophilic substitution of hydrogen

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ABSTRACT. The reaction involving the vicarious nucleophilic substitution of hydrogen in aromatic nitro-compounds and certain electrophilic heterocycles is discussed. The applications of the reaction, its limitations, the problems concerning its mechanism and mode, as well as the possibilities of the practical application of this new method in organic synthesis are examined.

The bibliography includes 101 references.

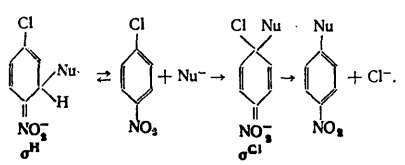
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I. Introduction

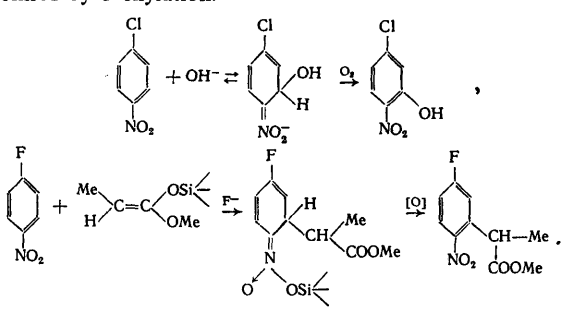
Reactions involving nucleophilic substitution in an aromatic ring[1–5] differ from aliphatic nucleophilic substitution reactions not only by a greater variety of mechanisms but also by the wide variety of groups which can be substituted by nucleophiles. Such a group can be even the hydride ion, but, despite numerous examples,[6,7] the general method for the nucleophilic substitution of hydrogen in aromatic systems has been lacking hitherto, if one disregards the Chichibabin reaction, whose applications are limited to the amination of individual heterocycles.[8] The known instances of the nucleophilic substitution of hydrogen described in the literature are fairly specific and their mechanisms differ very greatly.[7,9–12]

At the end of the 1970s, the present author began to develop a new method for the direct substitution of hydrogen in aromatic nitro-compounds and other electrophilic arenes on the basis of reactions with carbanions. The starting point in our research was the most general reaction involving the nucleophilic substitution of the halogens and other leaving groups in nitroarenes, which proceeds via an addition–elimination mechanism.[1,2] For example, the interaction of a nucleophile with *p*-chloronitrobenzene begins with the addition of the reactant to the carbon atom linked to chlorine whereupon an anionic σ^{Cl}-adduct (frequently called the Meisenheimer complex) is formed and then decomposes rapidly into chloride ion and the nucleophilic substitution product:



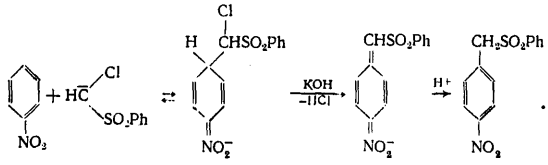
Evidently the formation of the σ^{Cl}-adduct is due to the presence of the nitro-group, which is capable of delocalising effectively the negative charge. For this reason, the nucleophile can also add to the carbon atom in the *ortho*-position relative to the nitro-group. Although the examples of the formation of such σ^{H}-adducts are known,[11,13] the latter are usually incapable of further reactions because of the impossibility of the elimination of the hydride ion.

It follows from the numerous investigations into the chemistry of stable σ-adducts of polynitro-compounds that the addition of nucleophiles to an unsubstituted carbon atom is faster than the addition to one linked to substituents, even substituents such as halogens. On the other hand, the σ-adducts formed in the latter reaction are usually thermodynamically more stable.[14,15] When these observations are extended to the short-lived σ-adducts of mononitro-compounds, one arrives at the conclusion that in most instances of the nucleophilic substitution of a halogen in nitroarenes, the nucleophile adds initially to the carbon atoms linked to hydrogen and σ^{H}-adducts are formed. Since the latter are in general unable to react further because of the impossibility of the elimination of the hydride ion, the formation of such adducts has been unremarked even in the numerous kinetic investigations[1] and the observed reaction is the substitution of the halogen via the slower formation of the σ^{X}-adduct. Hence it follows that the development of a general method for the nucleophilic substitution of hydrogen in nitroarenes is entirely feasible and useful and should be based on the rapid subsequent conversion of the σ^{H}-adducts, including the hydrogen abstraction process. The seemingly most evident approach to this problem, namely the oxidation of the σ^{H}-adducts, cannot have a general importance in view of the reversibility of the addition, the unfavourable equilibrium position, and, usually, the sensitivity of nucleophiles to oxidation. Nevertheless, such a process can be carried out by using non-oxidisable nucleophiles[9] or by ensuring a high concentration of the σ^{H}-adducts. This occurs for polynitro-compounds,[16] in the reactions of organomagnesium compounds with nitroarenes,[17] and also when the resulting σ-adducts of carbanions are stabilised by *O*-silylation:[18]



Our approach to the solution of this problem was based on the hypothesis that the σ^{H}-adducts, formed by carbanions containing a leaving group X (for example, chlorine) at the carbanionic centre,

can undergo further reaction via the elimination of the X^- anion as a result of the 1,2-migration of the hydride ion from the ring to the carbon atom of the entering substituent. This should result in the formation of the product of the substitution of hydrogen by the dehalogenated carbanion residue. The formation of σ-halogeno-carbanions is frequently accompanied by autocondensation and in the first attempt to carry out this process we therefore chose as the reagent chloromethyl phenyl sulphone, which is fairly stable in this respect.[19] The reaction of nitrobenzene with this sulphone in the presence of powdered potassium hydroxide in dimethyl sulphoxide occurred with an intense exothermic effect and was accompanied by the development of a very deep blue-violet colour of the reaction mixture. This resulted in the formation of a mixture of *o*- and *p*-nitrobenzyl phenyl sulphones in a satisfactory yield:[20]



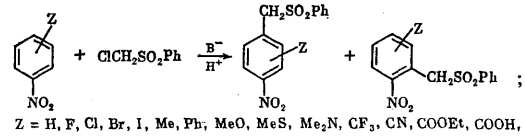
The hydrogen atom in the *o*- and *p*-positions relative to the nitro-group was substituted in this reaction by the carbanion residue, but, from the point of view of the stoichiometry, the halide ion and not the hydride ion was eliminated from the intermediate σ^H-adduct. Thus the halogen plays the role of the leaving group instead of the ring hydrogen, which is incapable of being eliminated in the form of the anion. We therefore designated this process in English as "vicarious nucleophilic substitution of hydrogen (VNS)"†. The study of the reaction mechanism showed that the σ-adducts are converted into the final products not via the hydride complex, as postulated initially, but as a consequence of the β-elimination of hydrogen chloride (or HX in the general case).[21] The earlier important hypothesis of the faster addition of the nucleophile to the unsubstituted rather than the halogen-substituted ring carbon atom has been fully confirmed. In the reactions of *p*- and *o*-chloronitro-benzenes with chloromethyl sulphone in the presence of an excess of a base, hydrogen is substituted exclusively; chlorine substitution products were not detected.[20] The higher rate of the VNS of hydrogen, usually exceeding the rate of the usual substitution of a halogen, is one of the most significant features of this reaction. Here one should note that several examples of VNS had also been known previously. These include the methylation of nitroarenes and certain heterocycles by carbanions derived from DMSO[22–24] and from methyl sulphone[25] and dimethylsulphonium[26] and sulph-oxonium[27,28] ylides as well as the dichloromethylation of *p*-halogeno-nitrobenzenes by trichloromethyllithium.[29] The amination of certain nitroarenes by hydroxylamine in the presence of bases[30,31] also belongs to reactions of this type. However, these few obser-vations were not developed further, since the general character of these reactions was not discovered and the proposed speculative mechanisms were not usually correct.[25,27,31] In our subsequent studies, the general character of this new reaction was demonstrated and its specific features, the principal elements of its mechanism, direction rules, as well as the conditions necessary for its successful performance were found.[32–34]

†Vicarious = substituting another, acting for another.

The carbanion is usually generated directly in the reaction mixture in the presence of an aromatic nitro-compound by treatment of the corresponding CH acid with a base. Since the elimination requires a second equivalent of the base, the base is required in at least a twofold excess relative to the other reactants. The reaction products are formed as intensely coloured nitrobenzyl carbanions derived from strong CH acids. They are protonated only on treating the reaction mixture with an acid. The success of the reaction depends on the nature of the base, the character of the solvent, temperature, and other conditions. The base must ensure the deprotonation of the CH acid and rapid elimination, while the solvent must ensure a high reactivity of the carbanion and the base. Satisfactory results were obtained when the carbanions are present as solvate-separated ion pairs, so that sodium hydroxide, potassium hydroxide, potassium t-butoxide, and sodium methoxide in dimethyl sulphoxide, dimethylformamide, liquid ammonia, and sometimes in tetrahydrofuran are most often used. The carbanions derived from the initial CH acids and the products are frequently unstable, which makes it necessary to carry out the reaction at low temperatures and to neutralise the reaction mixture immediately when the reaction has reached completion.

II. Applications of the reaction

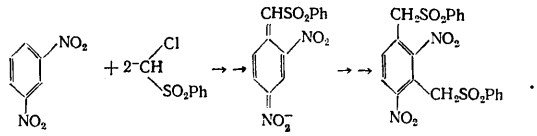
Both reactants participate in the VNS reaction, so that its applications must be determined by their character, namely the electrophilicity of the arenes (usually nitroarenes) and the stability of their carbanions, i.e. ultimately their structure. In order to deter-mine the structural requirements as regards nitroarenes, chloro-methyl sulphone has been used. As stated above, it does not undergo autocondensation in the presence of bases[19] and its conjugate carbanion is fairly stable. This sulphone reacts very effectively with nitrobenzene and its substituted derivatives, forming the products of the substitution of hydrogen in the *ortho*- and *para*-positions relative to the nitro-group:[20,35]



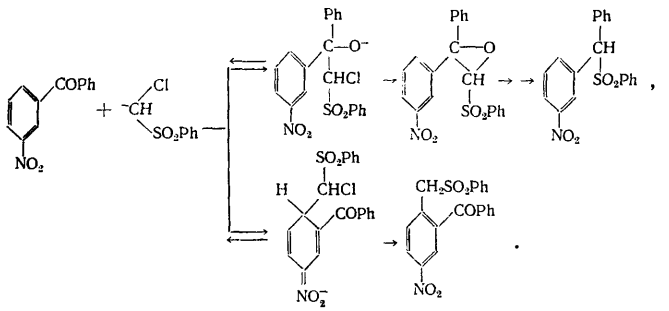
Z = H, F, Cl, Br, I, Me, Ph, MeO, MeS, Me_2N, CF_3, CN, COOEt, COOH, SO_3H, SO_2Me, NO_2, $CH(OR)_2$, COPh, etc.

In the case of *p*-halogenonitrobenzenes (Z = *p*-halogen), only the *ortho*-substitution product is formed. Only when Z = F is the VNS reaction accompanied by the nucleophilic substitution of fluorine. As shown below, this process can be suppressed by carrying out the reaction under special conditions.[21,36] Naturally, when the substituent Z is in the *ortho*- and *meta*-positions relative to the nitro-group, there is a possibility of the formation of two or even three isomeric substitution products. The character of the substituents in the aromatic nitro-substituted ring which do not prevent the reaction is virtually unlimited but there is no doubt about their influence on the rate of the reaction and the site of substitution. The few substituents inhibiting the VNS include also those which are deprotonated under strongly basic reaction conditions with formation of anions containing a free electron pair in the position conjugated with the aromatic ring and the nitro-group, such as, for example, the hydroxy-group in nitrophenols, the mercapto-group in nitrothiophenols, etc. In the case of the substituents COO^- [37] and SO_3^-,[38] where there is no conjugation of this kind, their presence

does not prevent the VNS. Since the VNS products exist in the reaction mixture as nitrobenzyl carbanions, this reaction is very selective in relation to monosubstitution. The inhibiting effect of conjugated negatively charged substituents can be compensated by the presence of a second nitro-group. Whereas nitrophenols do not enter into the VNS reaction, the substitution in dinitrophenols proceeds fairly smoothly.[39] The activating effect of the second nitro-group has also been demonstrated by the reaction of *m*-dinitrobenzene with an excess of a sulphone, which leads to disubstitution products, while in 1,3,5-trinitrobenzene there is even a possibility of trisubstitution:[39]

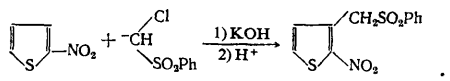


It must be emphasised that the rates of substitution of the first, second, and third hydrogen atoms in polynitroarenes differ greatly, which ensures the process selectivity. Certain limitations in VNS may arise as a consequence of the presence of substituents capable of reacting with carbanions. For example, in the reaction with nitrobenzophenones the mode of reaction is determined principally by the structure of the substrate: the *para*-isomer enters exclusively into the Darzens condensation, the *ortho*-isomer is involved in the VNS reaction, while in the case of the *meta*-isomer the two reactions compete and the conditions ensuring a high concentration of the base promote the substitution of hydrogen:[40]

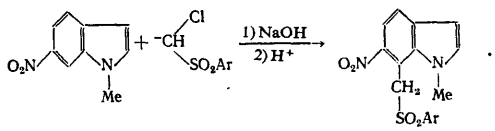


Presumably there is a possibility of the VNS of hydrogen not only in a monosubstituted but also in any nitroarene having at least one hydrogen atom in the *ortho*- or *para*-position relative to the nitro-group. Here it must be emphasised that in all these cases the VNS of hydrogen is faster than the usual nucleophilic substitution of a halogen, as has been observed, for example, in the reactions of chloronitrobenzoic[37] and chloronitrosulphonic acids.[38]

Nitronaphthalenes are distinguished by an especially high reactivity in the VNS reaction, which is undoubtedly associated with the increased stabilisation of the σ-adducts by the second aromatic ring. 1-Nitronaphthalene forms a mixture of 2- and 4-substituted products in which the 2-isomer greatly predominates. The substitution of hydrogen in 2-nitronaphthalene takes place exclusively in the 1-position.[41] VNS reactions are characteristic also of heterocyclic compounds. The nitro-derivatives of aromatic heterocycles are usually very reactive in the reaction with the chloromethyl phenyl sulphone carbanion. Thus the VNS reaction proceeds readily and affords substitution products in satisfactory yields for **2-, 3-, and 4-nitropyridines and also their chloro-, ethyl-, and** methoxy-derivatives.[42] In the case of chloronitropyridines, in which the nucleophilic substitution of chlorine is known to proceed at a high rate, the VNS of hydrogen is observed exclusively.[42] The VNS reaction takes place very smoothly in nitro-derivatives of five-membered heterocycles: 2-nitrothiophen,[43] 2-nitrofuran and its derivatives,[43] *N*-substituted 2- and 3-nitropyrroles,[43] and nitroimidazoles,[44] for example:

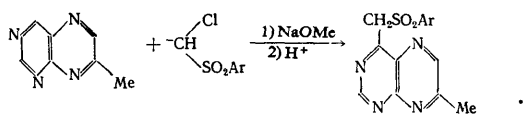


Nitroquinolines are very reactive in the VNS reaction and, as in nitronaphthalenes, mainly or exclusively the hydrogen atom in the *ortho*-position relative to the nitro-group is substituted; for example, in the 6-, 5-, and 7-positions respectively in 5-, 6-, and 8-nitroquinolines.[45] The substitution of hydrogen via the VNS mechanism can also be carried out in *N*-derivatives of nitroindoles:[46]



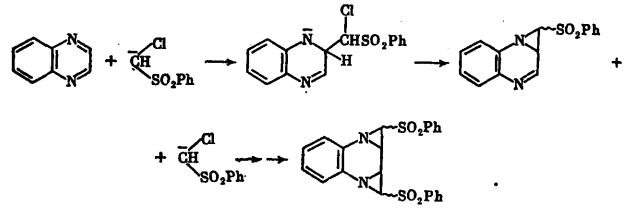
Certain heterocycles are sufficiently electrophilic for the occurrence of the VNS reaction even in the absence of the nitro-group. Thus the methylation of acridine, quinoline, and certain other heterocycles by DMSO and methyl phenyl sulphone anions was noted previously.[23,25]

The chloromethyl phenyl sulphone carbanion is less nucleophilic than the two carbanions used previously, but it is also capable of substituting the hydrogen in acridine, benzothiazole, and benzoxazole.[147] 1,2,4-Triazine and its derivatives are especially interesting, since in this instance nucleophilic attack may be directed to the 5-, 3-, or even 6-positions in the ring, the reactivity of the hydrogen atoms relative to nucleophiles decreasing in the sequence 5-H > 3-H > 6-H.[48] Using the corresponding substituted triazines, it is possible to carry out the VNS reaction in all these positions.[48,49] Pteridine derivatives exhibit a comparatively high reactivity in the VNS reaction. The reaction with unsubstituted pteridine could not be carried out apparently as a consequence of the instability of the ring under the highly basic reaction conditions, but the reaction with 5-methyl- and 5-phenyl-pteridines proceeds fairly readily:[50]

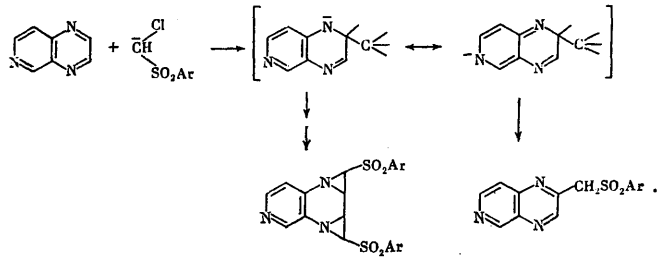


The attempts to extend the VNS reaction to certain other electrophilic heterocycles without the nitro-group, such as quinoxaline and naphthyridines, were unsuccessful: the reaction occurred in a different direction, namely via the bisannelation pathway.[51] The first stage of this process—the formation of a σ-adduct—is undoubtedly common to the VNS, but its subsequent reaction pathway is different. Instead of β-elimination, intramolecular nucleophilic substitution of chlorine takes place and the monoannelation product

formed, containing a reactive aliphatic C=N double bond, reacts rapidly with a second carbanion:

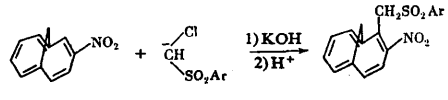


As a consequence of the partial delocalisation of the negative charge in the σ-adduct of quinoxaline, the neighbouring nitrogen atom has fairly pronounced nucleophilic properties promoting substitution and at the same time hindering β-elimination. This situation is absent in quinoxaline *N*-oxide, which forms a σ-adduct with a low negative charge on the nitrogen atom, as a result of which VNS takes place exclusively.[52] The negative charge density on the N(1) atom in the corresponding σ-adduct is reduced as a consequence of the conjugation with the N(6) atom, as a result of which competition is observed between the VNS and bisannelation reactions; the mode of the reaction of the σ-adduct can be controlled by varying the reaction conditions. A high concentration and an excess of the base as well as a low temperature promote bimolecular elimination, leading to VNS, while reduction of the base concentration and an increase in temperature promote bisannelation:[53]



Similar phenomena have been observed when the substituents in the substrate were varied. Thus the interaction of 1-cyanonaphthalene with the chloromethyl phenyl sulphone carbanion leads to the exclusive formation of the bisannelation product. The introduction of a second CN group increases the delocalisation of the negative charge in the σ-adduct, which promotes β-elimination and VNS; thus the mode of reaction is susceptible to control.[52]

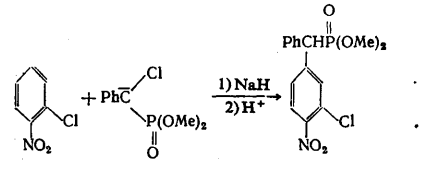
Finally, one should note that sufficiently electrophilic nonbenzenoid aromatic systems are also capable of VNS. The most interesting example is provided by derivatives of 1,6-methano-[10]annulene, which is an analogue of naphthalene as regards properties.[54] Thus in the reactions of 2- or 3-nitro-1,6-methano-[10]annulenes with chloromethyl phenyl sulphone, the hydrogen atom in the 3- and 2-positions respectively is substituted. Cyanomethanoannulenes are less reactive in this reaction. However, cyano-1,6-difluoromethano[10]annulenes undergo VNS, although the yields of the product are low.[55]



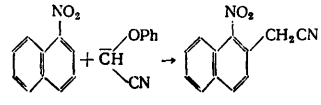
The possibility of VNS in the tropylium cation has been demonstrated in a few instances.[56]

The VNS concept can also be extended to electrophilic alkenes (the so called Michael acceptors). These compounds react with α-halogenocarbanions usually via an addition–intramolecular substitution mechanism with formation of cyclopropane derivatives.[57] By selecting the alkene and the reaction conditions, it is nevertheless possible to induce β-elimination in the adducts and to carry out the VNS of the hydrogen also in aliphatic systems.[58]

The results presented make it clear that the VNS of hydrogen in electrophilic aromatic compounds is of an extremely general character. Similarly, the carbanions of t-butyl chloromethyl, t-butyl *p*-tolyl, and t-butyl chloromethyl sulphones react with various electrophiles like the chloromethyl phenyl sulphone carbanion,[35] but it has to be stated that other alkyl chloromethyl sulphones are not usually employed in this reaction as well as other reactions proceeding via carbanions because they undergo rapid Ramberg–Baecklund rearrangements.[59] Other chloromethanesulphonyl compounds, namely *NN*-dialkylamides[35] and the phenyl or neopentyl ester of chloromethanesulphonic acid,[65] are also satisfactory precursors of carbanions in the VNS reaction. The tertiary carbanions formed from α-chloroalkyl or α-chlorobenzyl sulphone react with nitroarenes in accordance with the VNS mechanism but differ from the chloromethyl derivatives of sulphones by their reactivity and especially by the preferential substitution in the *para*-position.[35] In carbanions stabilised by sulphonyl groups, chlorine is the most convenient leaving group; other halogenomethanesulphonyl compounds are less easily available and undergo side reactions more readily.[35] Not only halogens but also certain other substituents, such as PhS, Me_2NCS_2, or PhO are capable of β-elimination, but the applicability of the corresponding substituted sulphones in VNS reactions is limited as a consequence of the low rate of elimination, which frequently leads to the preferential elimination of benzenesulphonic acid.[53] Chlorine is the most convenient and effective leaving group also in other carbanions stabilised by benzenesulphinyl,[61] diphenylphosphine oxide, and diethoxyphosphonyl[62] groups. For example, dimethyl α-chlorobenzylphosphonate reacts effectively with many nitroarenes, affording esters of *p*-nitrophenyl(phenyl)methylphosphonic acids:[62]



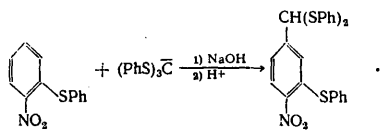
Despite the fact that α-chloronitriles, especially chloroacetonitrile, are fairly unstable in the presence of bases, they are capable of undergoing the VNS reaction but satisfactory results are obtained only in reactions with reactive nitroarenes.[63,64] Thus the cyanomethylation of chloronitrobenzenes or nitronaphthalene by chloroacetonitrile proceeds with a satisfactory yield. In the reaction with nitrobenzene, moderate yields have been achieved, while less reactive alkoxynitrobenzenes do not react with chloroacetonitrile via the VNS mechanism.[63,64] The cyanomethylation of the less reactive nitroarenes can be achieved with the aid of substituted nitriles such as $PhSCH_2CN$ or $PhOCH_2CN$, which are more stable in the presence of bases:[63–65]



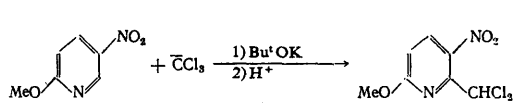
The reaction of α-chloropropionitrile with many nitroarenes usually leads to VNS products in satisfactory yields.[63,64]

The carbanions derived from chloroacetic,[66] dichloroacetic,[67] and α-chloroalkanoic acids[68] are fairly reactive in the alkoxycarbonylalkylation of nitroarenes via the VNS mechanism, but the process is very sensitive to the reaction conditions and the electrophilicity of arenes. Here too the more stable esters containing PhS or Me_2NCS_2 leaving groups have found more general application.[64] An example of the alkoxycarbonylmethylation reaction, in which the leaving group is the ammonium substituent, is known.[69]

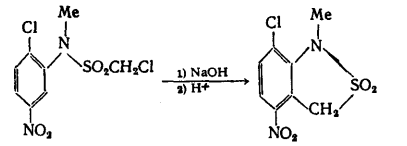
The majority of leaving groups stabilise the corresponding carbanions, so that many of these compounds are fairly strong CH acids capable of being deprotonated on treatment with bases and then reacting further with nitroarenes via the VNS mechanism. For example, PhS is a group of this kind. In fact tri(phenylthio)-methane substitutes the hydrogen atom in the *para*-position relative to the nitro-group in many nitroarenes, forming diphenyl dithioacetals of *p*-nitrobenzaldehydes:[70]



The similar reactions of the diphenyl dithioacetals of aldehydes or of benzyl phenyl sulphides with nitroarenes lead to the formation of nitrobenzyl phenyl sulphides[71] and diarylmethane derivatives.[72] There is no doubt that the VNS reaction with trihalogenomethyl-carbanions is of greatest interest in view of the ready availability of the initial haloforms as well as the possibility of further reactions of the dihalogenomethyl groups introduced. In analysing the possibilities of these reactions, account must be taken of the instability of the trihalogenomethyl anions, which dissociate rapidly with formation of dihalogenocarbenes,[73] and also of the instability of nitrobenzylidene dichloride carbanions.[74] As already mentioned above, McBee et al.[29] carried out the dichloromethylation of *p*-halogenonitrobenzenes by trichloromethyllithium at temperatures in the range –100 to –65 °C and proposed a carbene reaction mechanism.[29] We have found that, when potassium t-butoxide is used in a tetrahydrofuran–dimethylformamide mixture at temperatures in the range –65 to –70 °C, it is possible to achieve the dichloromethylation and even the dibromomethylation of many nitroarenes by the corresponding haloforms frequently in high yields.[75,76] The dihalogenomethylation reaction is very sensitive to the conditions and the reactivity of the nitroarenes. There is no doubt that it proceeds via a mechanism typical for the VNS reaction–the addition of the CX_3^- anions and the elimination of HX from the σ-adduct formed:[76]

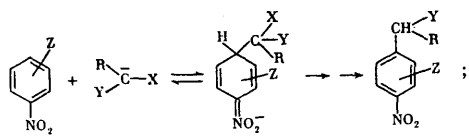


Instances of VNS occurring with ring opening or closure are known. Thus the carbanions of phenylcyanooxirans react with nitronaphthalene to form σ-adducts, the subsequent reaction involving β-elimination from them and being accompanied by the opening of the oxiran ring.[77] Examples of intramolecular processes leading to ring formation are more numerous. They include the intermolecular VNS in chloromethanesulphonamides formed from *m*-nitrobenzylamine and *m*-nitroaniline derivatives:[78]



The synthesis of tetracyclic derivatives of anthraquinone via intramolecular VNS which follows Michael addition is extremely interesting.[79]

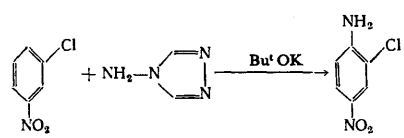
It is evident from the examples quoted above that the range of carbanions suitable for VNS reactions is wide. A necessary requirement which must be met by the structure of the carbanions is the presence at the carbanionic centre of a group X capable of undergoing β-elimination in the form of HX from the intermediate σ-adduct under the influence of bases. Thus carbanions capable of undergoing the VNS reaction can be represented by the general formula X–$\bar{C}$YR, where X is the leaving group, Y the group stabilising the carbanion, and R its substituent. A mechanism of VNS is presented below in a general form (examples of the group Z were presented above):



X = Cl, Br, PhO, PhS, Me_2NCS_2, etc;
Y = SO_2Ar, SO_2OPh, SOPh, CN, COOEt, $P(O)Ph_2$, Cl, PhS, etc;
R = H, Alk, Ar, Cl, PhS, etc.

Virtually any combination of X, Y, and R presented in the scheme gives rise to a carbanion capable of reacting in accordance with the VNS mechanism. Certain limitations in the use of such carbanions are associated with the tendency of some of them to undergo autocondensation ($ClCH_2CP$) or to decompose (CCl_3^-). Such carbanions react smoothly only with reactive nitroarenes. In addition, appreciable stabilisation induces a reduced nucleophilicity of the carbanions, which can also prevent the reaction. Finally, bulky tertiary carbanions (R ≠ H) are frequently incapable of undergoing the hydrogen substitution reaction in the *ortho*-position relative to the nitro-group or to other bulky substituents, principally as a result of the steric hindrance in the elimination stage.

The VNS of hydrogen is not limited to the reactions of carbon-based nucleophilic carbanions. The amination of nitroarenes by hydroxylamine and, especially effectively, by 1-amino- and 1-alkylamino-1,3,4-triazoles takes place via the same addition–β-elimination mechanism:[80,81]



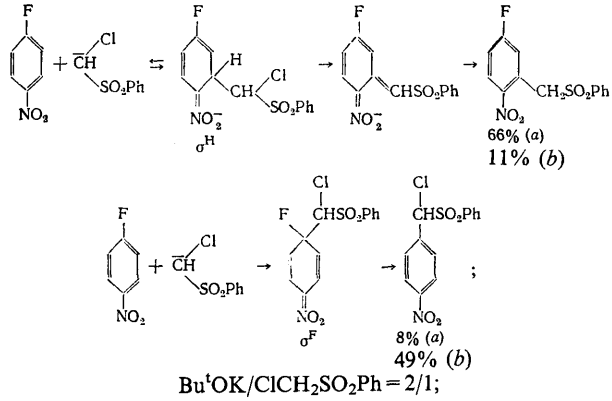
III. The reaction mechanisms

The VNS reaction is undoubtedly a multistage process including, in the first place, the formation of the σ-adduct of the carbanion and the nitroarene and its further reactions. Thus the reaction

mechanism must provide answers to the following questions: how is the σ-adduct formed and in what way is it converted into the product. Furthermore, it is necessary to determine the ratios of the rates of these stages.

σ-Adducts can be formed via two alternative pathways: as a result of the direct nucleophilic attack or in two stages via electron transfer from the carbanion to the nitroarene with subsequent recombination of the radical-anion and the radical formed.[82] The question via which pathway the σ-adducts are formed in the VNS reaction has not been studied in detail but certain observations and preliminary experiments suggest that here we are dealing with direct nucleophilic attack. For example, the *ortho*-directing effect in the VNS reactions, determined by the existence of the carbanions as close ion pairs,[36] while the formation of the σ-adducts of organomagnesium compounds with nitroarenes via one-electron transfer[17,83] usually affords a statistical mixture of the *ortho*- and *para*-isomers, leads to the same conclusion. The hypothesis that the VNS proceeds via the direct addition of the nucleophile and not as a one-electron transfer has been confirmed by the results of studies of reactions using the so called free-radical clocks, because these reactions occur without appreciable competition with free-radical processes.

In our view, the question of the way in which the σ-adducts are converted into the VNS products is more important. Among the various possibilities, the 1,2-hydride shift with the concerted elimination of the X^- anion and the base-induced β-elimination of HX appeared most likely. The study of the influence of the concentration of the base on the rate of reaction led to the conclusion that the VNS proceeds via the elimination pathway.[21] The influence of the base on the rate of reaction was studied by the method of competing reactions—the competition between the fluorine and hydrogen substitution reactions in *p*-fluoronitrobenzene was studied:



$Bu^tOK/ClCH_2SO_2Ph = 2/1$;
(*a*) high concentration of Bu^tOK,
(*b*) low concentration of Bu^tOK.

The rates of formation of the σ^F- and σ^H-adducts as well as the rate of conversion of the σ^F-adduct into the fluorine-substitution product are independent of the base concentration, like the rate of conversion of the σ^H-adduct into the product via hydride transfer, while the rate of conversion of the σ^H-adduct into the product via the β-elimination of HCl should be directly proportional to the base concentration. Thus an increase in the concentration of the base should appreciably increase the fraction of the hydrogen-substitution products, which has in fact been observed. Similarly, when there is intermolecular competition between the substitution of *p*-H in nitrobenzene and *p*-F in *p*-fluoronitrobenzene by the phenylphenoxyacetonitrile carbanion (this tertiary carbanion substitutes only the hydrogen in the *para*-position relative to the nitro-group), the mode of reaction is determined by the base concentration. In the absence of an excess of the base, the usual fluorine substitution has been observed, while in the presence of an excess of the base the exclusive formation of the products of the VNS of hydrogen in nitrobenzene has been observed, while *p*-fluoronitrobenzene remained unaltered[21]!

These results show not only that the conversion of the σ^H-adducts into the VNS products is accelerated by the base and hence that it proceeds via the pathway involving the β-elimination of HX but also that the formation of σ-adducts is a reversible and rapid process compared with β-elimination and that the rate of formation of σ^H-adducts is higher than that of σ^F-adducts. Numerous kinetic studies of nucleophilic aromatic substitution have shown that the rate of substitution of fluorine is much higher than the rate of substitution of chlorine and other leaving groups, which increases still further the ratio of the rates of formationof σ^H-adducts and other corresponding adducts.[1]

On the basis of this ratio, one can control the mode of reaction of chloromethyl phenyl sulphone with *m*-nitrobenzophenone[40] and azaquinoxaline:[53] a high concentration of the base promotes the VNS, while the use of more dilute solutions and the absence of an excess of bases lead to other processes.

Important data concerning the mechanisms of the reactions involving the dissociation of a C–H bond have been obtained in the study of the kinetic isotope effect.[84] For the two-stage VNS process, in which a C–H bond is cleaved (as shown above) in the second stage, which limits the overall rate of reaction, we expected the appearance of a distinct primary effect where the ratio $k_H/k_D > 1$. Unexpectedly, the ratio k_H/k_D for *p*-nitro[D]benzene {determined by comparing the ratios of the *o*- and *p*-isomers in reactions of chloromethyl phenyl sulphone with *p*-nitro[D]benzene and nitrobenzene} proved to be less than unity, amounting to 0.9. Thus a secondary isotope effect is observed. This is possible in the addition stage but not in the elimination stage. These at first sight contradictory results can be accounted for by analysing the energy profile of the process, which in the case of mononitro-derivatives, when the latter are stable, involves the formation of an unstable intermediate (σ-adduct). The subsequent β-elimination of HCl converts this adduct into the highly stabilised nitrobenzyl carbanion and the structure of the early transition state in this stage should therefore be asymmetric.

The difference between the rates of cleavage of C–H and C–D bonds in such processes is known to be insignificant. In other words, in this case $k_H/K_D \simeq 1$ for β-elimination, as a result of which a secondary isotope effect can be manifested in the addition stage. In fact, the addition of the carbanion to the nitrobenzene ring is accompanied by a change in the hybridisation of the ring carbon atom from sp^2 (in the initial nitrobenzene) to sp^3 (in the σ-adduct), which is known to be promoted by the replacement of hydrogen by deuterium. Since the addition is reversible while deuterium retards the dissociation, the equilibrium constant, which determines the concentration of the σ-adducts, is higher for the σ^D-adduct, i.e. $k_D > k_H$.

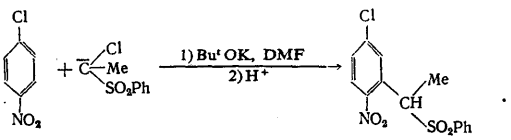
In the absence of the isotope kinetic effect in the elimination stage, the observed rate of substitution of deuterium exceeds the rate of substitution of hydrogen, i.e. $k_H/k_D \simeq 0.9$. These considerations, which are partly speculative, have been confirmed by the results of

the study of the kinetic isotope effect for the VNS reactions in which the elimination proceeds via a symmetrical transition state. The kinetic effects, i.e. the ratios k_H/k_D, reach appreciable values (3–7) in specific examples.[85,86]

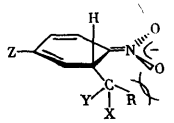
The above conclusions concerning the characteristic features of the VNS mechanism are a result of so far fairly simple studies at a qualitative level. They require further revisions and corrections, especially those based on quantitative measurements. In particular, many observations indicate that the ratios of the rates of addition and elimination found above can vary.

IV. The problem of the reaction site

Although the proposed VNS mechanism is of a preliminary character, nevertheless it indicates effectively the complexity of the problem of the reaction site. As a rule, the reaction proceeds via the rapid and reversible formation of σ-adducts, which then undergo the slower β-elimination. The relative rates of substitution of hydrogen in different positions in the nitroarene therefore depend on the ratios of the rates of formation of the isomeric σ-adducts, the corresponding equilibrium constants, and the elimination rate constants. The overall picture is complicated by the fact that carbanions can also act as bases in the elimination step, while their concentration varies during the reaction. Furthermore, the problem of the reaction site can be approached phenomenologically by analysing the influence of the principal variable parameters on the reaction site: the structure of the carbanions, the structure of the nitroarenes, and the reaction conditions. The ratio of the products of *ortho*- and *para*-substitution, formed in the VNS of the hydrogen atoms in nitrobenzene by the carbanions of α-halogenoalkyl phenyl sulphones depends greatly on the steric effects. Secondary carbanions of the type $X\bar{C}HSO_2Ph$ (X = halogen) substitute the hydrogen atom in the *ortho*- and *para*-positions relative to the nitro-group, the fraction of the *ortho*-isomer diminishing with increase in the size of the halogen, i.e. in the sequence F > Cl > Br > I, whereas tertiary carbanions $Cl\bar{C}RSO_2Ph$ (R = Me, Ph, etc.) give rise exclusively or mainly to *para*-substituted products.[35,87] This does not mean that tertiary carbanions are incapable of substituting hydrogen in the *ortho*-position relative to the nitro-group. In the case of *para*-substituted nitrobenzenes, for example, *p*-chloronitrobenzene, the α-chloroethyl phenyl sulphone carbanion,[87] and certain other tertiary carbanions substitute smoothly the hydrogen atom in the *ortho*-position:[64,66]



The substitution by tertiary carbanions in the *ortho*-position relative to the nitro-group has also been observed in nitrobenzene derivatives having a bulky group in the *meta*-position.[87] Many observations have shown that the VNS is more sensitive to steric hindrance than the classical nucleophilic substitution of a halogen. One can therefore postulate that steric hindrance in the VNS reaction has a greater effect in the elimination stage and not in the addition stage. Since the transition state in the elimination step requires an antiperiplanar disposition of the hydrogen atom and the leaving group, the sensitivity of this process to the size of the groups R and Y is evident.



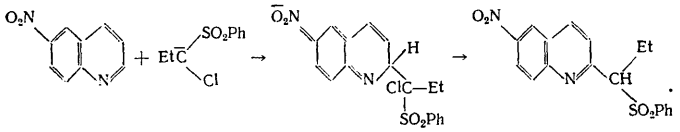
The steric effects in elimination from *ortho*-σ-adducts formed by tertiary carbanions can usually be compensated by the increased nucleophilicity of such carbanions (which increases the equilibrium constants of the addition reactions) and also by the presence of several leaving groups, etc. A good example is provided by the substitution reaction with participation of the tertiary trichloromethyl carbanion, which occurs preferentially in the *ortho*-position relative to the nitro-group even in the interaction with nitrobenzene.[76]

The conditions where the carbanions are present as solvate-separated ion pairs are most favourable for VNS. This happens for the sodium and potassium salts of deprotonated nucleophiles in DMSO, dimethylformamide (DMF), liquid ammonia, etc. in the presence of an excess of a soluble base. Under these conditions, the ratio of the *ortho*- and *para*-substitution products depend little on the nature of the cation and the solvent and is determined mainly by the structure of the carbanion and the nitroarene. The nature of the base can also have a significant influence on the reaction site under these conditions. For example, the NaOH and KOH frequently employed are almost insoluble in these solvents, so that they are used in the powdered state in a large excess. One must postulate that in such cases the elimination occurs mainly on the surface of the solid phase and partly under the influence of the carbanion as a base. It has been demonstrated experimentally that, depending on the character of the base, the ratio of the *ortho*- and *para*-isomers (the products of the VNS of the hydrogen in nitrobenzene by the potassium salt of chloromethyl phenyl sulphone) varies from 1.80 (when the elimination takes place under the influence of the excess Bu^tOK) to 0.86 (when it is induced by the excess carbanion).[88]

The degree of association of the ion pairs has a very powerful influence on the ratio of the *ortho*- and *para*-substitution products in VNS. Thus virtually only *ortho*-substitution is observed in the reaction of chloromethyl phenyl sulphone with nitrobenzene in the Bu^tOK–THF system. The product of the substitution of the second ortho-hydrogen atom is formed exclusively even in the case of *o*-chloronitrobenzene.[36] Similar effects have also been observed in reactions with other carbanions.[89] These phenomena are induced by the intense association of the cation–carbanion ion pairs in a moderately solvating solvent of the type of THF. The K^+ cation in this close ion pair is attracted to the negatively charged oxygen atoms of the nitro-group, which leads to the formation of the *ortho*-σ-adduct and *ortho*-substitution. The solvation character of this effect has been demonstrated by adding to the system an equimolar amount of crown-ether, which strongly binds the K^+ cation in a complex and this entails the formation of a mixture of *ortho*- and *para*-substitution products characteristic of dipolar solvents.[36]

In considering the influence of the structure of nitroarenes on the reaction site, it is necessary to consider the electronic structure of the ring and the influence of substituents. The ratios of the *ortho*- and *para*-substitution products in the VNS reactions with nitrobenzene and nitropyridines differ insignificantly as a consequence of the

similar electronic structures of these aromatic systems. In less symmetrical aromatic systems, the ratio usually changes in favour of the *ortho*-isomer, which happens, for example, in the bicyclic naphthalene and quinoline systems. In the case of 1-nitronaphthalene[41] and 5- and 8-nitroquinolines,[45] the reaction takes place preferentially in the *ortho*-position relative to the nitro-group, i.e. at the C(2), C(6), and C(7) atoms respectively. The *para*-isomers are formed only in small amounts. On the other hand, 2-nitronaphthalene and 6-nitroquinoline react exclusively in the 1- and 5-positions respectively and only with secondary carbanions. The reaction does not take place with tertiary carbanions apparently because of the significant steric hindrance induced by the nitro-group and the hydrogen atom in the *peri*-position. For the same reason, the product of the VNS of the hydrogen atom at the C(2) atom was obtained in a low yield in the reaction of 6-nitroquinoline with α-chloropropyl *p*-tolyl sulphone:[45]

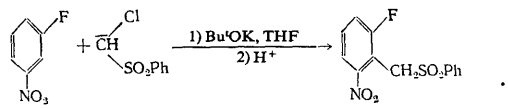


The preferential or exclusive *ortho*-directing effect in the VNS reaction with nitro-derivatives of bicyclic arenes is caused by the significant double bond character of the C(1)–C(2) bonds in naphthalene and also the C(5)–C(6) and C(7)–C(8) bonds in quinoline, which induces the preferential addition of nucleophiles to the positions indicated above in the corresponding *nitro*-derivatives. The addition to the C(3) and C(7) atoms in 2-nitronaphthalene and 6-nitroquinoline is also very much less favourable, because the stabilisation of the σ-adduct by conjugation with the nitro-group would lead to the breakdown of the aromaticity of the second ring. A similar situation arises in five-membered heterocycles such as thiophen, pyrrole, furan, etc. in which the C(2)–C(3) and C(4)–C(5) bonds have an appreciable double bond character. Therefore in 2-nitro-derivatives the VNS takes place preferentially at C(3), while in 3-nitro-derivatives it takes place exclusively at C(2).[43] It must be **emphasised that this "*ortho*"-direction occurs also in reactions with tertiary carbanions, which is promoted by the geometry of the five-membered ring** in which the steric effects of the neighbouring substituents are weaker than in the six-membered ring.

The question of the influence of the substituent Z in the nitrobenzene ring on the site of the VNS is fairly complex. This problem is naturally absent in the 4-Z-nitrobenzenes and can be solved fairly simply in 2-Z-nitrobenzenes. The ratio of the *ortho*- and *para*-substitution products in the latter case changes mainly as a result of the statistical factor. Sterically bulky substituents can prevent the reaction, hindering the coplanarity of the ring and the group, which is essential for the effective stabilisation of the σ-adduct (the so called secondary steric effect). Nevertheless, the reaction proceeds with a satisfactory yield even with *o*-nitrobenzoic and *o*-nitrobenzenesulphonic acids.[37,38]

The site of the reaction in 3-Z-nitrobenzenes, where one may expect, in principle, the formation of three isomeric products of the substitution of hydrogen in the 2-, 4-, and 6-positions, constitutes the most complex problem. The relative amounts of these isomers depend on the nature of the substituent Z and the carbanion and on the reaction conditions, which leads to a fairly complex picture. In the reaction series with participation of chloromethyl sulphone as the source of the carbanion, the substituents Z promote, regardless of conditions, substitution at either the neighbouring C(2) or C(4) atom (first group) or at the more remote C(6) atom (second group).[35,36,42,90] The halogens, Me, MeO, Me_2, etc. belong to the first group and CF_3, COOEt, NO_2, etc. belong to the second group.

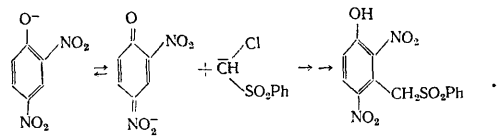
Such influence of the substituents on the reaction site is observed also in reactions with certain other secondary carbanions.[64,89] Bearing in mind that the use of Bu^tOK in THF leads to *ortho*-substitution, it is possible in many cases to synthesise 2,3-disubstituted nitrobenzene derivatives:[36]



The influence of the substituent Z on the reaction site can be determined by its influence on the rate of addition, the equilibrium constant, the rate of elimination, and the electronic and steric factors. The influence of the substituent Z on the electronic effects can be illustrated by a quantum-chemical calculation, which reveals a correlation between the parameters of the lowest unoccupied MO of the substrate and the character of the reaction site; however, better results were obtained when classical electronic effects were resorted to in order to explain this influence.[90] Overall, the effects indicated can account for the influence of the substituent Z on the rate of addition of the nucleophile and, to a lesser extent, on the equilibrium constant, but its influence on the rate of addition of the nucleophile, which can be explained on the basis of steric effects, is less understandable from the standpoint of electronic effects.

The attempts to explain the strong directing effect of the substituents of the first group (Me, MeO) indicated above in terms of the polarisabilities (the so called Bunnett–Reinheimer effect[91]) were unsuccessful, since many non-polarisable substituents (for example, F) have a similar effect.

The influence of substituents with a strong electron-donating activity on the reaction site is very interesting. As already mentioned previously, in contrast to mononitrophenols, dinitrophenols enter into the VNS reaction.[39] Unusual reaction sites are observed in such cases. Thus, substitution in 2,4-dinitrophenol takes place at the C(3) atom, whereas in 2,4-dinitroanisole it occurs at the C(5) atom. In the latter case, the hydrogen atom substituted is in the *para*-position relative to one nitro-group and in the *ortho*-position relative to the other, as for substitution at the C(4) atom in 1,3-dinitrobenzene.[35] The unusual VNS reaction site in 2,4-dinitrophenol is induced by the fact that in a fairly basic medium the phenol reacts as the dinitrophenoxide anion whose negative charge is delocalised, mainly between the oxygen atoms of the nitro-groups:



Hence it is evident that the nucleophilic attack must be directed to the C(3) atom.[35] For the same reason, 1,3-di(benzenesulphonyl)-methyl-2,4-dinitrobenzene is formed in the reaction of *m*-dinitrobenzene with an excess of chloromethyl phenyl sulphone; in this case, the substitution of the second hydrogen atom takes place in the dinitrobenzyl anion whose electronic structure is similar to that of the 2,4-dinitrophenoxide anion.[35] The characteristic features of the VNS reaction sites in the amino-derivatives of dinitrobenzene,

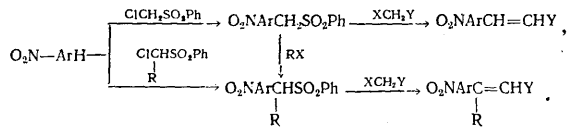
alkoxynitropyridines, *N*-alkyl-2-nitropyrroles, and other structurally related compounds can be explained similarly.

V. Practical applications

The VNS of hydrogen is a new hitherto little investigated reaction in organic chemistry. Our studies were directed mainly towards the elucidation of its applications and the solution of the problems of the mechanism, reaction site, and other general questions. However, certain possibilities for the practical application of the VNS can also be inferred from these results. Readily available starting materials are necessary for the VNS reaction, the reaction does not require any complex conditions, and its result is the direct substitution of the hydrogen atom in the aromatic nitro-substituted ring by alkyl substituents containing functional groups. The prospects for the practical application of the VNS reaction therefore appear very favourable.

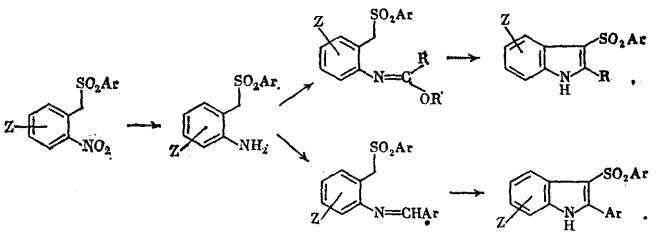
In the first place, the VNS products are fairly strong CH acids; on treatment with bases, they are readily converted into the corresponding carbanions. Despite their moderate nucleophilicity due to the very effective stabilisation, the latter are capable of entering into many reactions characteristic of carbanions. For example, the carbanions derived from nitrobenzyl sulphones and nitriles by the VNS reaction are readily alkylated and add to Michael acceptors.[92] These reactions occur particularly readily under the conditions of phase transfer catalysis.[93]

The possibility of synthesising derivatives of nitrocinnamic acid and other substituted nitrostyrenes by VNS is very interesting. The alkylation of nitrobenzyl sulphones by the esters of carboxylic α-halogenoacids and other alkylating agents containing an electron-accepting group is accompanied by the elimination of benzenesulphonic acid, which leads to the formation of nitrostyrene derivatives.[94] Thus two-stage substitution of a hydrogen atom by the vinyl residue is achieved:



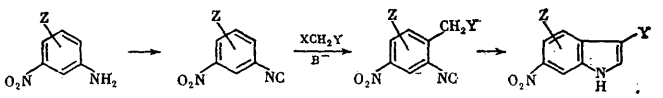
The possibility of introducing carbon-based functional groups into aromatic nitro-substituted rings by means of VNS and the subsequent reactions of the products are of significant interest. Thus the reaction with tri(phenylthio)methane leads to the formation of the dithioacetals of *p*-nitrobenzaldehydes, which afford aldehydes on hydrolysis, whilst their alkylation followed by hydrolysis leads to alkyl nitroaryl ketones.[70] An even more convenient synthesis of nitroarylaldehydes is based on the dihalogenomethylation of nitroarenes by haloforms followed by hydrolysis.[75,76] The VNS products can be readily converted into aromatic nitroacids after oxidation or hydrolytic halogenation and hence one can achieve a two-stage carboxylation of nitroarenes.[95]

By virtue of the possibility of introducing various functional group-containing substituents in the *ortho*-position relative to the nitro-group, the application of the VNS reaction in the synthesis of heterocyclic systems, especially indoles, is very promising. For example, the reduction of substituted *o*-nitrobenzyl phenyl sulphones leads, as a result of the VNS, to the corresponding amino-derivatives, which are converted into substituted indoles as a consequence of the initial conversion into isonitriles, imidates,[96] or Schiff bases[97] and the subsequent condensation in the presence of a base:



The existing method of synthesis of indoles by the catalytic hydrogenation of derivatives of *o*-nitroarylacetonitriles[98] is of limited importance because of the low availability of the initial compounds. The possibility of synthesising various *o*-nitroarylacetonitriles by direct cyanomethylation via the VNS reaction[64,65,89] makes this method of great value. All the isomeric hydroxy- and alkoxy-indoles have been synthesised in this way.[65]

Nitroindoles can be obtained directly by the VNS reaction from *m*-nitroaniline:

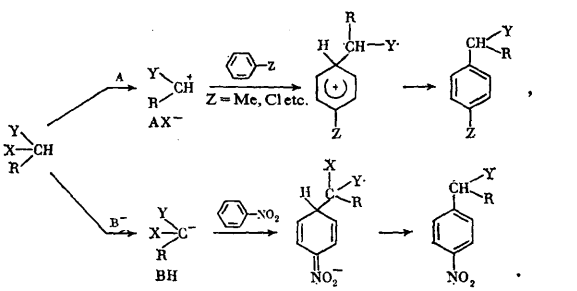


The *m*-nitrobenzoisonitrile obtained is introduced into the VNS reaction with various carbanions; the VNS products formed, in which the functional group-containing methyl substituents are in neighbouring positions relative to the isonitrile group, undergo cyclisation, which leads to nitroindole derivatives.[99]

VI. Conclusion

The data presented in this review permit the conclusion that VNS is an extremely general process for the substitution of hydrogen in electrophilic arenes (predominantly in nitroarenes) by alkyl groups containing functional groups in the α-positions. In this respect, it is possible to deduce a significant similarity between the VNS reaction and the Friedel–Crafts reaction, which takes place via an electrophilic substitution mechanism.

In fact the stoichiometries of the VNS and Friedel–Crafts reactions are similar. Also similar are the types of products obtained, but these processes differ radically in their mechanisms and in the influence of the polarity of the reactants:



Thus, as regards stoichiometry and the results, VNS can be regarded as a process analogous to the Friedel–Crafts reaction but with the reverse polarity of the reactants. It is therefore entirely appropriate to apply the term "umpolung" (reversal of polarity) introduced by Seebach[100] to define the principle of the reversal of the polarity of reactants in organic synthesis. By extending this term to reactions taking place with reversal of polarity, one may say that VNS represents the "umpolung" of the Friedel–Crafts reaction. Apart from these terminological considerations, it must be emphasised that VNS is a process complementary to the Friedel–Crafts reaction, since it makes it possible to substitute a hydrogen atom by carbon-centred substituents in those arenes which are incapable of undergoing electrophilic substitution. Thus a possibility is created for substituting hydrogen by carbon-based residues in virtually any aromatic systems. The general character of the VNS, which is much faster than the usual nucleophilic substitution of the halogens, finally demonstrates the lack of validity of the generally adopted view[1] that the nucleophilic substitution of hydrogen in aromatic systems is a possible phenomenon but is not usual. On the contrary, bearing in mind that the addition of nucleophiles to the carbon atoms of a halogen-substituted aromatic ring takes place at a high rate at the positions containing hydrogen and not halogen atoms and also taking into account the many possibilities for further reactions of the σ^H-adducts obtained in this way, the traditional nucleophilic substitution of the halogen in halogenonitroarenes can be frequently regarded as a side process, developing against the background of the reactions indicated above.[101]

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