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# Substituent Effects on the Electrophilic Activity of Nitroarenes in Reactions with Carbanions

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**Abstract:** The effect on electrophilic activity of substituents located *para*, *ortho*, and *meta* to the nitro group of nitrobenzenes was determined by using vicarious nucleophilic substitution of hydrogen (VNS) with the carbanion of chloromethyl phenyl sulfone (**1**) as the model process. Values for the relative activities of substituted nitroarenes are given relative to nitrobenzene, which was taken as the standard. This process was chosen as a model reaction because it meets key criteria, such as the wide range of substituents that can be present on the nitrobenzene ring, a low sensitivity to steric hindrance, and in particular the possibility of ensuring conditions in which the overall relative rates of reaction in competitive experiments are equal to the relative rates of nucleophilic addition. The values of relative rates of addition, which were taken to be a measure of electrophilic activity, were determined by competitive experiments in which pairs of nitroarenes competed for the VNS reaction with carbanion of **1**. A comprehensive set of data for effects of substituents on the electrophilic activity of nitroarenes is presented for the first time.

**Keywords:** carbanions · competitive experiments · electrophilic activity · nitroarenes · nucleophilic substitution

## Introduction

The introduction of substituents into aromatic rings by electrophilic substitution is one of the most important processes in organic synthesis. Reactions such as nitration, halogenation, sulfonation, and Friedel–Crafts-type reactions of arenes are widely used for the manufacture of commercially important compounds and can be considered to be primary processes for the functionalization of aromatic rings.[1]

Early studies into the effects of substituents on the rates and orientation of electrophilic substitution in benzene, using mainly nitration, laid the foundations for the formulation of the concept of electronic effects of substituents and the general rules that govern the reactivity of organic compounds.[1–3] Furthermore, the effects of substituents on reaction rates were quantified by development of the linear free energy relationship represented by the Hammett equation.[4] In recent years, the most general and successful approach to quantitative characterization of electrophilicity and nucleophilicity was elaborated by Mayr et al.,[5] who constructed a general scale of such activities.

On the other hand, much less is known about the effects of substituents on reactions between nucleophilic agents and arenes. First, only electron-deficient aromatic rings, such as those in nitroarenes,[6] transition-metal complexes of arenes,[7] azulenes,[8] and azines,[9] can add nucleophilic agents, a process paralleling the first, rate-limiting step of electrophilic substitution. Second, to form substitution products, the adducts of nucleophiles to electron-deficient arenes should lose substituents with an electron pair that, for obvious reasons, cannot be hydride anions.

Thus, contrary to reactions of electrophiles that replace hydrogen that departs from the intermediate adduct as a proton, the main reaction of nucleophilic agents with nitroarenes was considered to be the replacement of a leaving group, such as F, Cl, or MeO, *ortho* or *para* to the nitro group, which proceeds by an $S_NAr$ addition–elimination mechanism.

The kinetic characteristics of this process appear to be suitable for determination of the effects of substituents on electrophilic activity because, as a rule, the addition is the rate-limiting step.[6,10] There are numerous papers reporting the effects of substituents on the rate of $S_NAr$ reactions,

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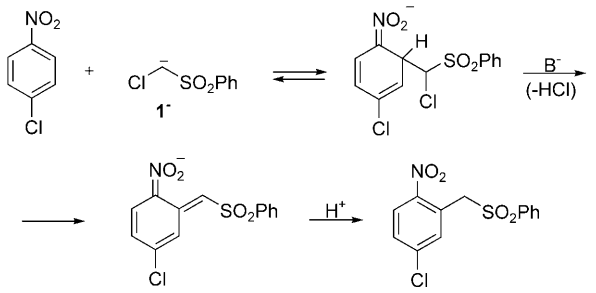
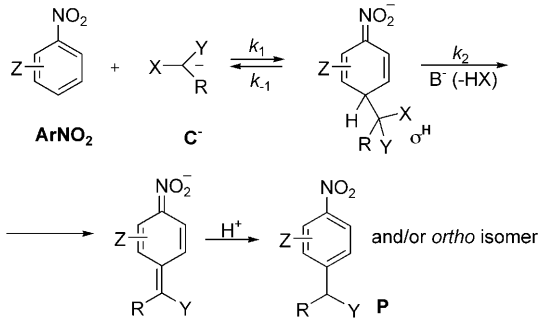
which are collected in the monographs of Miller[11] and Terrier,[6] but the reported results are of limited value as a measure of the electrophilic activity of nitroarenes for several reasons: 1) the rate of $S_NAr$ depends strongly on the nature of the leaving group, thus the substituent effect can be compared only for replacement of the same leaving group, 2) leaving groups should be located *ortho* or *para* to the nitro group, which limits the possibility of varying the positions of the substituents studied, and 3) the most important limitation is due to the fact that formation of the key intermediates, $\sigma^X$ adducts (X = halogen or other leaving group), is a secondary process that proceeds more slowly than the formation of $\sigma^H$ adducts. In spite of many early observations that nucleophiles add to nitroarenes in positions occupied by hydrogen faster than in similarly activated positions occupied by halogens,[12] this general rule was recognized only about 30 years ago. On this basis, a new reaction, called the vicarious nucleophilic substitution of hydrogen (VNS),[13] and a few other variants of nucleophilic substitution of hydrogen were found.[14]

The VNS is a reaction between nucleophiles that contain a leaving group X at the nucleophilic center, for instance α-halocarbanions, and electron-deficient arenes, mainly nitroarenes. It proceeds by the addition of such nucleophiles to nitroaromatic rings in positions occupied by hydrogen to give $\sigma^H$ adducts that, upon base-induced β-elimination of HX followed by acidic treatment, give products in which hydrogen is replaced with the nucleophile moiety. The reaction is exemplified in Scheme 1.The VNS reaction is quite general with respect to carbanions and electron-deficient arenes. All carbanions containing nucleofugal groups X (X = Cl, Br, OR, SPh, $N^+R_3$, and so on) at the carbanionic center that can be eliminated from the $\sigma^H$ adducts by base-induced β-elimination of HX can react with sufficiently electrophilic arenes along the VNS pathway.[15] In addition, O and N nucleophiles that contain leaving groups, such as alkylhydroperoxide anions,[16] anions of hydrazine, hydroxylamine,[17] and sulfenamide[18] derivatives, can be used in this reaction to give nucleophilic hydroxylation and amination processes.




Scheme 1. The VNS of 4-chloronitrobenzene with the carbanion of chloromethyl phenyl sulfone.

Mechanistic studies confirmed that VNS proceeds by two distinct steps: formation of the $\sigma^H$ adducts of nucleophiles ($Nu-X^-$) to arenes, followed by conversion of these $\sigma^H$ adducts by the base-induced β-elimination of HX, as shown in Scheme 2.[19]




Scheme 2. Mechanistic picture of the VNS reaction with α-X-carbanions (X = nucleofugal group).

Experiments with a fast radical clock suggest that formation of the $\sigma^H$ adducts proceeds as a one-step nucleophilic addition, not a two-step single-electron transfer and anion radical radical coupling.[20] The overall mechanistic picture of the VNS reaction with carbanions is shown in Scheme 2.

According to this mechanism, the rate of formation of the $\sigma^H$ adduct is expressed in Equation (1):

$$V_{\sigma^H} = k_1[ArNO_2][C^-] - k_{-1}[\sigma^H] \quad (1)$$

whereas the rate of formation of the product (P) is:

$$V_P = k_2[\sigma^H][B^-] \quad (2)$$

and the rate of dissociation of the σ adduct to the starting material:

$$V_D = k_{-1}[\sigma^H] \quad (3)$$

Depending on the conditions and the kind of carbanion and nitroarene used, the relative rates of these processes, that is, nucleophilic addition, dissociation of the σ adducts into starting reagents, and the β-elimination of HX (i.e., the relationship between $k_1$, $k_{-1}$, and $k_2$), can vary greatly, and the relative rates obviously also depend on the position in the nitroaromatic ring at which the addition takes place. Because VNS can proceed in two or even three positions in many nitroarenes, the ratio of isomers depends on the relationship between these rate constants and the conditions. Herein, we can consider two borderline cases. The first case occurs when the rate of conversion of the σ adduct into product P is much higher than the rate of its dissociation (i.e., $k_2[\sigma^H][B^-] \gg k_{-1}[\sigma^H]$), all $\sigma^H$ adducts are converted into products once produced, regardless of the rates of their formation. In this case, the orientation of substitution is determined by the relation of rates of addition in different positions, and the process is kinetically controlled. The second borderline case occurs when $k_2[\sigma^H][B^-] \ll k_{-1}[\sigma^H]$; in this case, the $\sigma^H$ adducts are in equilibrium with the starting ma-

terials and the orientation is governed by the relative concentrations of isomeric $\sigma^H$ adducts, the value of $k_1^i/k_{-1}^i = K^i$ ($K^i$ denotes equilibrium constants), and the relation of the rate constants $k_2^i$ (Curtin–Hammett principle), so this process is thermodynamically controlled.[21]

These characteristics of VNS make this process an appropriate tool for estimating the effects of substituents on the electrophilic activity of arenes. Indeed, becuase VNS proceeds by the addition of nucleophiles in positions occupied by hydrogen *ortho* or *para* to the nitro group and this addition is the primary process, the nitroarene ring may contain a variety of substituents located *ortho*, *meta*, or *para* to the nitro group, and therefore, *meta*, *ortho*, and/or *para* to the reaction sites. Consequently, there are wide possibilities to study effects of these substituents on the rate of nucleophilic addition and therefore, the electrophilic activity of the nitroarenes.

## Results and Discussion

Herein, we present the results of our studies on the effects of substituent on the electrophilic activity of nitroarenes in reactions with nucleophiles by using VNS as a model process. For these studies, a proper model nucleophile was needed, that is, one with sufficient stablity to be handled without decomposition, sufficient nucleophilicity to react with moderately active nitroarenes, low steric bulk, and a leaving group X that can assure rapid elimination of HX from the intermediate $\sigma^H$ adducts. Taking these criteria into account, we chose the carbanion of chloromethyl phenyl sulfone (**1**) because, contrary to other α-halocarbanions, it is relatively stable in the absence of air and humidity at low temperatures. Thus, the $K^+$ salt of this carbanion decomposed only to a low extent at −40 °C in DMF (less than 5 % after 0.5 h; DMF = *N*,*N*-dimethylformamide). Although $SO_2Ph$ is rather a bulky group, $\mathbf{1}^-$ does not experience sterical difficulties during addition to nitroarenes; for example, it reacts readily in the 2-position of 3-halonitrobenzenes.[22] We have already observed that *t*BuOK is a sufficiently strong base to deprotonate **1** and to promote rapid elimination of HCl from the $\sigma^H$ adducts, and DMF is a good solvent for this reaction.[19]

For technical reasons we have chosen to determine the relative rate constants of addition of this carbanion to nitroarenes by performing competitive experiments relative to nitrobenzene, which was used as the standard. Competitive experiments consist of treatment of a mixture of two different nitroarenes with a small quantity of $\mathbf{1}^-$ and excess base, followed by GLC analysis of the mixture of VNS products. The composition of the mixture reflects the relationship between the rates of VNS of the two competing nitroarenes, and consequently the relationship between the rate constants of the addition reaction, provided that the reaction proceeds under kinetic control, namely, that the conditions assure that the rate of conversion of the intermediate $\sigma^H$ adducts into products of the VNS reaction is faster than the reverse reaction. According to the VNS mechanism shown in Scheme 2 and the kinetic equations [Eqs. (1), (2), and (3)], the value of $k_2[B^-]$ should be much higher than that of $k_{-1}$ so all $\sigma^H$ adducts are converted into VNS products once formed. The second requirement is that the concentrations of the competing nitroarenes should be in excess relative to $\mathbf{1}^-$ during the reaction.

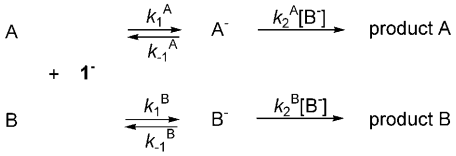
Under conditions that assure kinetic control (i.e., $k_2[B^-] \gg k_{-1}$), there is a high possibility that $k_1[C^-] > k_2[B^-]$, which means the rate of addition exceeds that of elimination, and thus the rate of formation of the VNS products does not reflect the rate of addition. In this situation, $\sigma^H$ adducts accumulate in the reaction mixture and the rate of VNS determined in kinetic experiments cannot be used as a measure of the rate of addition. The accumulation of $\sigma^H$ adducts was observed experimentally and used to execute the cine substitution of the nitro group.[23] On the other hand, in this situation the ratio of the VNS products determined in competitive experiments precisely reflects the ratio of the rates of addition because $\sigma^H$ adducts, once formed, are converted into the VNS products.

Competitive experiments provide a convenient way to determine relative rate constants. The experimental technique is simple, does not require advanced spectral instrumentation for recording the kinetics of fast reactions, and can be used for nitroarenes that form more than one isomeric product and differ substantially in activity. Moreover, competitive experiments, unlike spectral measurements, can be carried out in concentrations similar to those used in preparative procedures.

It should be noted that in one of our preceding papers we have already presented an application of this method for determining the effects of halogens on the electrophilic activity of a narrow range of halonitrobenzenes.[24]

For identification of the VNS products and quantitative analysis of the mixtures produced in the competitive experiments, samples of all expected products were synthesized in advance by preparative-scale VNS reaction of **1** with individual nitroarenes. Most of these VNS products have been described in our earlier papers.[25,26] Details of the analytical and spectral data of new compounds are given in the Experimental Section and Supporting Information. These compounds were used for the calibration necessary for quantitative GLC analyses of the reaction mixtures produced in the competitive experiments.

After some preliminary experiments, we found conditions that assured kinetic control and gave reproducible results. These conditions are essentially the same as reported earlier.[24] The procedure for the competitive experiments is shown in simplified way in Scheme 3.

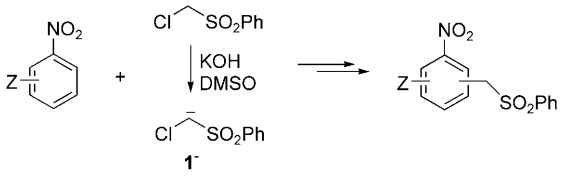



Scheme 3. Schematic procedure of the competitive experiments.

A solution of *t*BuOK (4 mol per mole of **1**) in DMF was added to a solution of **1**, a mixture of two competing nitroarenes A and B (2–6 M excess w.r.t. **1**), and diphenyl sulfone (internal standard) in DMF at −40 °C. The mixture was stirred at −40 °C for 15 s, quenched with aqueous HCl, extracted with methylene chloride, and analyzed by GLC. The experiments were repeated 3 or 4 times and the results were averaged. Under these conditions, the reaction of **1** with nitrobenzene gave two isomeric products of VNS in positions 2 and 4 in a ratio of ≈2.9. It should be stressed that addition of carbanion $\mathbf{1}^-$ to nitrobenzene preferentially proceeds *ortho* to the nitro group. Because the rates of reaction of substituted nitroarenes differ substantially, to keep the concentrations of the competing arenes constant and maintain comparable concentrations of products, the starting concentrations of the competing arenes were chosen according to their relative activity. The methods of calculation of relative rates of addition based on GLC analysis of the mixture of products are presented in Supporting Information. Moreover, because quantitative GLC analysis of the products mixtures is unfeasible when the activities of competing nitroarenes differ substantially, in the majority of cases the relative activities of substituted nitrobenzenes were determined not in direct competition with nitrobenzene, but with other nitrobenzenes with less different activities. To verify the results, the relative activities of particular nitroarenes were determined in competing experiments with two different nitroarenes. The results of competing experiments between particular pairs of substituted nitrobenzenes are given in the Supporting Information. The relative activities determined by competition between two different nitroarenes differ slightly, thus two values are listed in the Supporting Information, whereas the averaged values are given in the main body of this paper. In the case of nitrobenzene and 2- and 3-substituted nitrobenzenes, two or even three isomeric VNS products are formed, therefore in further discussions of the substituent effects we will use values for the partial activity of a given position in substituted nitrobenzenes relative to the *ortho* position in nitrobenzene and also values for the overall activity. These numbers represent the rates of addition of $\mathbf{1}^-$ to all active positions in substituted nitrobenzenes relative to the combined rates of addition of $\mathbf{1}^-$ in the *para* and both *ortho* positions of nitrobenzene. In further discussion we will consider that the nitro group always occupies position 1, and the positions of substituents will be numbered accordingly.

**Comparison of results of VNS under kinetic and thermodynamic control**: The values of relative rate constants determined in competitive experiments can reflect electrophilic activities of nitroarenes only when they are carried out under conditions that assure kinetic control of the reaction; $k_2[B^-] \gg k_{-1}$ [Eqs. (2) and (3)]. To show the importance of these conditions and the differences in the reaction course under conditions that assure the reversibility of $\sigma^H$ adduct formation (i.e., thermodynamically controlled), we reacted $\mathbf{1}^-$ with nitroarenes under conditions that assure a low rate for the β-elimination step, which thus allows equilibration of the addition step. For this purpose, the potassium salt of $\mathbf{1}^-$ in DMSO (dimethyl sulfoxide) was slowly added to solutions of nitroarenes in DMSO at room temperature (Scheme 4). Under these conditions, β-elimination is induced by the carbanion being a much weaker base than *t*BuOK, thus the value of $k_2$ is low and, moreover, the carbanion is in low concentration, so the $k_{-1} \gg k_2[B^-]$ condition is assured. The results are given in Table 1 for comparison with orientation under kinetic control.




Scheme 4. The VNS reaction of $\mathbf{1}^-$ with nitroarenes under thermodynamic control.

Table 1. Orientation of the VNS of some substituted nitrobenzenes with **1** under kinetic and thermodynamic control (Scheme 4).

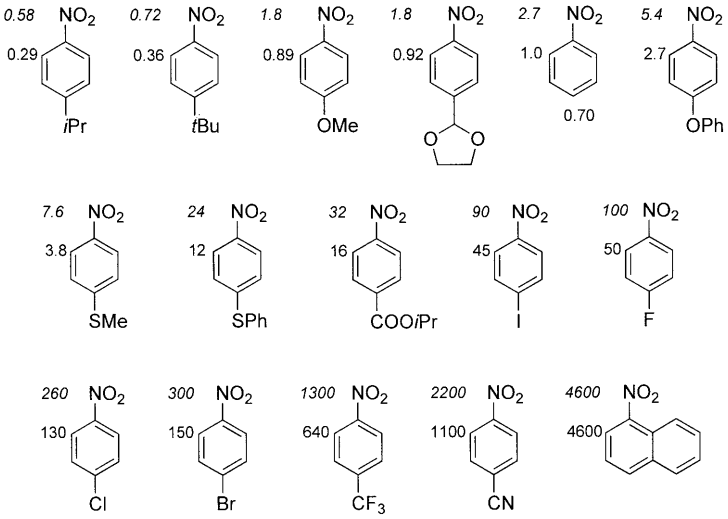
| Entry | Nitroarene, Z | Kinetic products | | Thermodynamic products | |
|---|---|---|---|---|---|
| | | position | [%] | position | [%] |
| 1 | H | 2, 4 | 74, 26[a] | 4 | 100 |
| 2 | 4-F | 2 | 100 | 4[b] | 100 |
| 3 | 3-Cl | 2, 6 | 85, 15[a] | 4 | 100 |
| 4 | 1-nn[c] | 2 | 100 | 2, 4 | 85, 15[a] |

[a] Ratio of isomers. [b] $S_NAr$ of F. [c] 1-Nitronaphthalene.

Under thermodynamic control, reaction of $\mathbf{1}^-$ with nitrobenzene proceeds only in position 4, whereas the 2-isomer dominates under kinetic control (Table 1, entry 1). In 4-fluoronitrobenzene, only an $S_NAr$ reaction of fluorine took place instead of VNS in position 2 (Table 1, entry 2) and in 3-Cl-nitrobenzene only the 4-isomer was formed, whereas under kinetic control only 2- and 6-isomers were produced (Table 1, entry 3). Similar dramatic differences in the reaction course under kinetically and thermodynamically controlled conditions have already been observed in the VNS hydroxylation of 1-nitronaphthalene with *tert*-butyl hydroperoxide, that is, substitution in position 2 under kinetically controlled conditions and in position 4 under thermodynamically controlled conditions.[16]

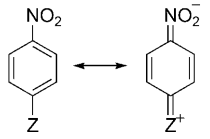
**Effects of substituents in 4-substituted nitrobenzenes on the relative rate of nucleophilic addition of $\mathbf{1}^-$**: The results of competitive experiments with 4-substituted nitrobenzenes are given in Scheme 5. These data show, for instance, that 4-*t*Bu-nitrobenzene reacts with $\mathbf{1}^-$ three times more slowly than nitrobenzene, whereas 4-chloronitrobenzene reacts 130 times faster. Halogens in 4-halonitrobenzenes affect the electrophilicity of the reaction site (position 2) by inductive effects that should increase in the order I < Br < Cl < F; how-




Scheme 5. Partial and overall (italic) relative activities of 4-substituted nitrobenzenes in the VNS reaction with **1**.

ever, the determined order of activity is $I \approx F < Cl < Br$. This is because the free p-electron pairs of the halogens in 4-halonitrobenzenes are conjugated with the strongly electron-accepting nitro group, as can be pictured by using resonance structures.



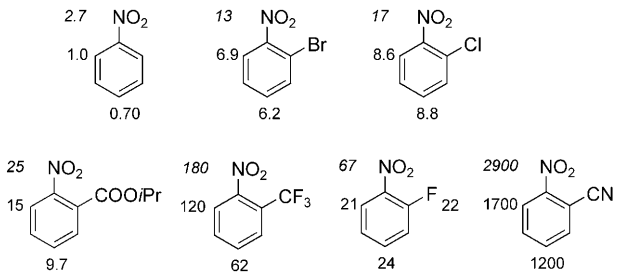

This effect does decrease the electron-withdrawing action of the nitro group and thus, the activity of the ring towards nucleophilic addition. This neat observed result is an interplay between the electron-withdrawing inductive and electron-donating conjugative effects of the halogens. Although the inductive effect of fluorine is the strongest, the conjugation of fluorine with the nitro group is also the most efficient because of smaller differences between the orbital sizes of fluorine and carbon. Similarly, the inductive effect of chlorine is stronger than bromine, but due to a smaller difference between the orbital sizes of chlorine and carbon, conjugation of chlorine with the nitro group is more efficient and 4-chloronitrobenzene is somewhat less active than 4-bromonitrobenzene. A similar but less clear-cut effect was observed earlier in the $S_NAr$ reaction of 2-chloro-4-Z-nitrobenzenes with piperidine. Halogens Z accelerated substitution in a similar order $k_H/k_Z = 34.5$ (Br), 32.3 (Cl), 24.9 (I), although the differences in the effects are much smaller. The rate for Z = F could not be measured because fluorine was substituted.[27]

Similar reasoning can be applied for 4-MeO-, 4-PhO-, 4-MeS-, and 4-PhS-nitrobenzenes. Although oxygen shows a stronger inductive accepting effect than sulfur, due to the efficient conjugation between the methoxy and nitro groups, its electron-withdrawing effect becomes weak and 4-MeO-nitrobenzene is less active, whereas because of its less efficient conjugation, 4-MeS-nitrobenzene is more active than nitrobenzene. 4-PhO- and 4-PhS-nitrobenzenes are more active than the methyl analogues and nitrobenzene itself because of competing conjugation of the p electrons of oxygen and sulfur with the phenyl group.

As expected, strongly electron-accepting substituents CN and $CF_3$ show a large activating effect, whereas COO*i*Pr (isopropyl ester was used to avoid transesterification) is only moderately activating, six times weaker than chlorine! A similar observation was made for the $S_NAr$ reaction of 2-chloro-4-COOEt-nitrobenzene with piperidine, the ratio of rates for 4-Cl/4-COOEt was 6.1. No explanation has been proposed for this unexpected observation.[27] Speculative rationalization of this surprising result can be based on assumption of two electron-accepting effects of COOR, that is, moderate inductive and strong conjugative effects. In 4-COOR-nitrobenzene, this substituent is located *meta* to the reaction site so the addition is accelerated by only the moderate inductive effect. This assumption is supported by the high activity observed for 3-COOR-nitrobenzene, which is much higher than 3-Cl-nitrobenzene (vide infra). In 3-COOR-nitrobenzene, this group is located *para* and *ortho* to the reaction site so the addition is accelerated by the strong conjugative effect.

1-Nitronaphthalene exhibits higher activity than any of the 4-substituted nitroarenes. This high activity is due to the aromaticity of the naphthalene ring system being lower than that of benzene, so addition to the ring of 1-nitronaphthalene which destroys the aromatic system is more facile (less energy demanding) than to nitrobenzene derivatives.

**Effects of substituents in 2-substituted nitrobenzenes on relative rates of nucleophilic addition of $1^-$**: Scheme 6 shows the relative activities of 2-substitued nitrobenzenes. The activating effect of electron-withdrawing substituents in position 2 relative to the nitro group is, as a rule, much weaker than in position 4. This is due to the secondary steric effect of these substituents, which hinders the coplanarity of the nitro group with the ring necessary for the formation and stabilization of the $\sigma^H$ adducts. This is particularly evident when the effects of halogens in the 4- and 2-positions are compared. The secondary steric effects of a large iodine atom *ortho* to the nitro group dominates over other effects, so the rate of VNS in 2-iodonitrobenzene is too small to be measured by competitive experiments, even against the least



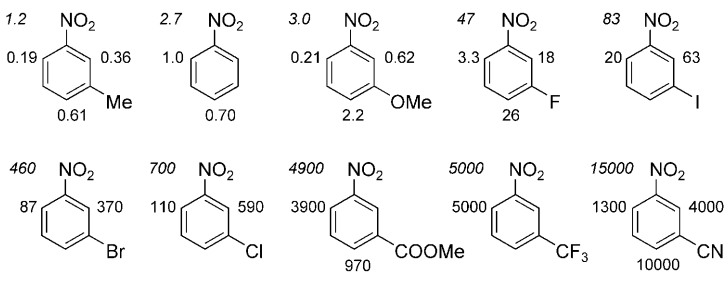

Scheme 6. Partial and overall (italic) relative activities of 2-substituted nitrobenzenes in the VNS reaction with **1**.

active 4-*tert*-butylnitrobenzene. Nevertheless, in spite of the slow rate of nucleophilic addition, 2-iodonitrobenzene undergoes VNS in a preparative experiment to give both isomers of the VNS product (in positions 4 and 6) in reasonable yields (see the Experimental Section). Similarly, the rates of the VNS reaction of $\mathbf{1}^-$ with 2-MeO- and 2-*t*BuO-nitrobenzenes are too low to be measured by competitive experiments, although the VNS reaction of **1** with these nitroarenes does proceed.[25]

Contrary to 4-halonitrobenzenes in which the order of activity was $I \approx F < Cl < Br$, for 2-isomers the order of activity is $I \ll Br < Cl < F$. The observed results originate from the interplay of at least three effects: the inductive effect and the conjugation of p electrons of halogens with the nitro group, as discussed above, and the secondary steric effect, which is the decisive one. The most interesting case is that of 2-fluoronitrobenzene in which, as well as two isomeric VNS products in positions 4 and 6, a 2-F $S_NAr$ product was formed at an equal rate. It should be mentioned that the reaction of $\mathbf{1}^-$ with 4-fluoronitrobenzene under kinetically controlled conditions exclusively gave the VNS product without any traces of the $S_NAr$ reaction, as shown in Scheme 5. One can suppose that formation of the $\sigma^F$ adduct, an intermediate of the $S_NAr$ reaction in 2-fluoronitrobenzene, is facilitated because it eliminates steric interaction between fluorine and the nitro group that hinders coplanarity of the latter with the ring (an example of steric assistance). Due to the small secondary steric effects of the fluorine atom, addition of $\mathbf{1}^-$ in positions 2, 4, and 6 of 2-fluoronitrobenzene is faster than in 2-chloro- and 2-bromonitrobenzenes, but slower than in 4-halonitrobenzenes. Amongst the 2-substituted nitrobenzenes, only 2-cyanonitrobenzene reacts in a similar rate to the 4-isomer; due to its linear shape, the cyano group does not create secondary steric hindrances. Interestingly, 2-COO*i*Pr-nitrobenzene is somewhat more active than the 2-Cl analogue, contrary to the results for the respective 4-isomers.

**Effects of substituents in 3-substituted nitrobenzenes on relative rates of nucleophilic addition of $\mathbf{1}^-$**: 3-Z-Substituted nitroarenes in a VNS reaction with **1** can form three isomeric products of substitution in positions 2, 4, and 6, so the activity of particular positions (i.e., orientation of the substitution) is of additional interest (see Scheme 7). The reactions



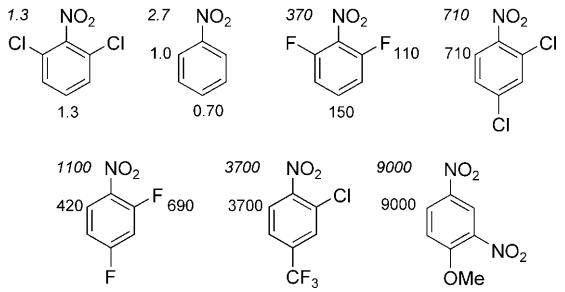

Scheme 7. Partial and overall (italic) relative activities of 3-substituted nitrobenzenes in the VNS reaction with **1**.

of **1** with 3-halonitrobenzenes gave interesting and somewhat unexpected results, and the order of activity is $F < I < Br < Cl$. Moreover, in the case of 3-iodo-, 3-bromo-, and 3-chloronitrobenzenes, the fastest reaction occurred in the most sterically hindered 2-position and only two isomeric VNS products in position 2 and 6 were formed, whereas 4-isomers were not produced. In the case of all 3-halonitrobenzenes, the activity of position 2 was higher than position 6, and the ratios of 2/6 for F, Cl, Br, and I were 5.5, 5.5, 4.1, and 3.1, respectively. This peculiar orientation pattern, namely, the preference for substitution in the most sterically hindered position 2 over 6 in the VNS reaction, was already observed in preparative experiments.[22] A reasonable explanation for this observation is that the halogens exert the strongest accepting inductive effect on the vicinal (*ortho*) positions 2 and 4 and the most efficient donating conjugation with p electrons on the *para* (6) position. The preference of position 2 over position 4 is perhaps due to the strong tendency of the kinetically controlled VNS reaction to proceed *ortho* (positions 2 and 6) to the nitro group. It should be mentioned that under conditions that assure thermodynamic control of the VNS reaction of $\mathbf{1}^-$ with 3-chloronitrobenzene, only the 4-isomer was formed! (See Table 1, entry 3.)

Because 3-halonitrobenzenes form two or even three isomeric products, it is reasonable to compare their overall activities: F 18, I 31, Br 170, and Cl 260. It is interesting to note that 3-F activates nitrobenzene nine and fourteen times more weakly than 3-Br and 3-Cl, respectively. 3-chloro- and 3-bromonitrobenzenes are $\approx$3 and 1.7 times more active and 3-fluoronitrobenzene is two times less active than their 4-isomers. Perhaps most interesting is a comparison of the overall activities of nitrobenzenes that contain a COOR group in position 3 or 4; the 3-isomer is $\approx$160 times more active! Relative values for other substituents are: Cl 3, Br 1.7, CN 7, $CF_3$ 4. The activating effect of the 3-COOR group is similar to that of 3-$CF_3$ and only three times weaker than CN. This unexpectedly large difference in activity between 3- and 4-COOMe nitrobenzenes can be rationalized by taking into consideration the moderate inductive and strong conjugative effects of COOR, as discussed earlier. Of particular interest are the reactions of $\mathbf{1}^-$ with dinitrobenzenes. Data for *para*-dinitrobenzene are not included in the appropriate place because its reaction with $\mathbf{1}^-$ produces a number of sideproducts. On the other hand, the reaction of $\mathbf{1}^-$ with *meta*-dinitrobenzene proceeds efficiently,[25,26] but with such a high rate that it cannot be determined, even in competition with the most active 3-cyanonitrobenzene.

**Effects of two substituents in nitrobenzenes on the relative rates of nucleophilic addition**: The activity of some nitroarenes that contain two substituents in the VNS reaction with **1** are presented in Scheme 8. In 2,6-dichloronitrobenzene, a strong deactivating secondary steric effect is observed. This effect is much weaker in 2,6-difluoronitrobenzene, so the electron-withdrawing inductive effect dominates and 2,6-difluoronitrobenzene is $\approx$300 times more active than its di-




Scheme 8. Partial and overall (italic) relative activities of disubstituted nitrobenzenes in the VNS reaction with **1**.

chloro analogue. The additivity of the substituent effects is observed in 2,4-disubstituted nitrobenzenes.

Due to the deactivating effect of the methoxy group, the activity of 3-nitro-4-methoxynitrobenzene (2,4-dinitroanisole) can be measured in competition with 3-cyanonitrobenzene.

**Correlation of the effects of substituents on the activity of nitroarenes with the Hammett constants**: The relative activities of nitroarenes presented in Schemes 5, 6, and 7 are of the same character as $k/k_0$ in the Hammett equation. Thus, the next step in our studies involved examining the correlation between the log of the activities of substituted nitroarenes ($\log k_Z/k_0$) and the Hammett $\sigma$ ($\sigma_m$) constants of the substituents. In 4-Z-nitrobenzenes, the substituents are located in the *meta* position relative to the reaction site, thus the relative activities should correlate with the $\sigma_m$ constants

The correlation between $\log k_Z/k_0$ and the $\sigma_m$ constants is presented in Figure 1. In an ideal case, the points should form a straight line through the origin and the slope would give the value of the reaction constant, $\rho$. As one can see, the points are quite dispersed, the correlation is poor ($r=$ 0.89), and the value of $\rho$ is about 5.0. This poor correlation indicates that effects of substituents are not limited to the action on the reaction site. Interactions between substituents and the nitro group that change its activating effect undoubtedly contributes significantly to the overall activity and seems to be responsible for this poor correlation. Because the main reaction course of $\mathbf{1}^-$ with the majority of 3-substituted nitroarenes resulted in substitution at positions 2 and 4, there were no reasons to attempt correlation of the log of the relative rates of these nitroarenes with the Hammett $\sigma_p$ constants, which should affect substitution in position 6.

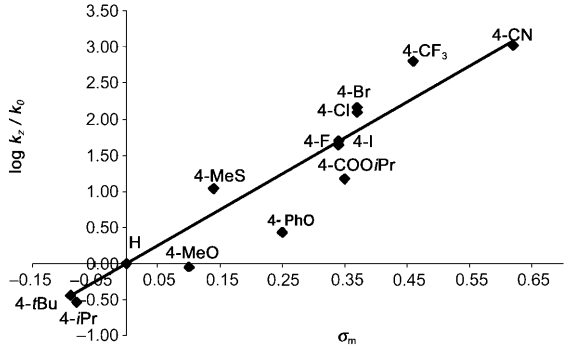



Figure 1. Correlation between $\log k_Z/k_0$ of 4-Z-nitrobenzenes and the Hammett $\sigma_m$ constants of Z; $y=5.0x$, $r=0.89$. The values of $\sigma_m$ were taken from reference [4].

**Verification of the values of relative electrophilic activities of nitroarenes**: To verify the values of the relative electrophilic activities determined for the VNS reaction of substituted nitroarenes with **1** by competitive experiments, we have determined rate constants for the addition of $\mathbf{1}^-$ to some nitroarenes by direct kinetic experiments. The kinetics of addition of $\mathbf{1}^-$ to selected nitroarenes were studied by using a previously reported method.[19b] Details of these experiments are reported in an earlier paper.[28] Although the conditions for these kinetic experiment measurements were not identical to those used in the competitive experiments, the results obtained by these different approaches are in good agreement (Table 2).

Table 2. Comparison of the relative activities determined from competitive experiments and direct kinetic measurements.

| Compared nitroarenes | Relative activities[a] | Relative rates[b] |
|---|---|---|
| 4-Cl/4-MeO | 140 | 124 |
| 2,4-$Cl_2$/4-MeO | 390 | 850 |
| 4-MeO/4-*t*Bu | 2.4 | 4.55 |

[a] On the basis of competitive experiments in this work. [b] On the basis of direct kinetic measurements reported in ref. [28].

Another way of verifying the values for the relative activities of nitroarenes was by using competitive experiments analogous to those described herein, but with other α-halocarbanions. For this purpose, the carbanions of chloromethyl *p*-chlorophenyl sulfone and bromomethyl phenyl sulfone were chosen. The carbanions of these sulfones exhibit similar nucleophilicity to $\mathbf{1}^-$, so the relative rate constants for the addition of these carbanions to nitroarenes should be similar to that determined in the VNS reaction with $\mathbf{1}^-$. Indeed, experiments in which nitroarenes competed for the VNS reaction with carbanions of chloromethyl *p*-chlorophenyl sulfone and bromomethyl phenyl sulfone under conditions assuring kinetic control gave results very similar to those reported herein. These results are reported elsewhere.[29]

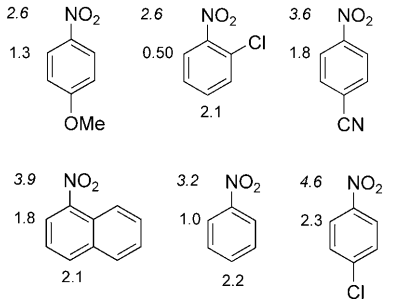
**Effects of substituents in nitroarenes on the rates of addition of Grignard reagents**: Primary alkyl Grignard reagents add to nitroarenes in positions *ortho* and *para* to the nitro group to form relatively stable $\sigma^H$ adducts that can be efficiently oxidized with $KMnO_4$ to give alkylated nitroarenes.[30,31] This oxidative nucleophilic substitution of hydrogen (ONSH) is a valuable process for introducing alkyl groups into nitroaromatic rings. It was of interest to learn whether the relative rates of addition of the Grignard reagents to substituted nitrobenzenes follow a similar pattern to the rel-

ative rates of the addition of carbanion of $\mathbf{1}^-$ that results in the VNS reaction.

The addition of these nucleophiles to nitroarenes is an irreversible process because dissociation of the $\sigma^H$ adducts to starting nitroarenes and the Grignard reagents would proceed by heterolytic C–C bond splitting with the electron pair taken by the alkyl group, which is highly unfeasible. Thus, relative rates for the oxidative nucleophilic alkylation of nitroarenes with Grignard reagents can be conveniently studied by using competitive experiments. To complement the results of our studies into the effects of substituents in nitroarenes on the rates of nucleophilic addition by using VNS as the model reaction, we have made similar studies of the ONSH reaction with *n*BuMgCl. The procedure was as follows: a small quantity of *n*BuMgCl in THF was added to a mixture of equimolar quantities of two nitroarenes in THF at −78 °C, followed by addition of solid $KMnO_4$ and liquid ammonia. The liquid ammonia was added to dissolve the $KMnO_4$.[31] After a few minutes, the mixture was quenched with solid $NH_4Cl$ and the ammonia was evaporated, then the mixture was treated with acidified water containing $Na_2SO_3$ and products were extracted and analyzed by GLC.

The products, *ortho* and *para n*-butyl nitroarenes, were described earlier,[31] and samples for the calibration necessary for quantitative GLC analyses were prepared as reported. The results of these competitive experiments are presented in Scheme 9.




Scheme 9. Partial and overall (italic) relative rates of addition of *n*BuMgCl to substituted nitrobenzenes relative to nitrobenzene.

Surprisingly, the rates of addition of *n*BuMgCl to various nitroarenes are negligibly different. For instance, addition to 4-MeO- and 4-CN-nitrobenzenes proceeds at the same rate, whereas addition of $\mathbf{1}^-$ to 4-CN-nitrobenzene proceeds 1200 times faster than to 4-MeO-nitrobenzene. One can rationalize these unexpected results in two ways: 1) the addition is a very fast, diffusion-controlled process, thus there is no observed selectivity or 2) the formation of $\sigma^H$ adducts does not proceed by nucleophilic addition, but as a two-step process, that is, a single-electron transfer (SET) and subsequent coupling of anion radicals of nitroarenes with the alkyl radicals. The participation of the SET mechanism in the addition of Grignard reagents to nitroarenes was postulated and confirmed experimentally by Bartoli et al.[32] However, the rates of the SET processes should correlate with the redox potential of nitroarenes, hence some selectivity should be observed. Lack of selectivity indicates that the addition of Grignard reagents is a fast, diffusion-controlled process.

## Conclusion

The relative rate constants of the VNS reaction of a series of substituted nitroarenes with the carbanion of chloromethyl phenyl sulfone **1** were determined by using competitive experiments. The obtained data represent a consistent set of effects of substituents on the electrophilic activity of nitroarenes on reaction with nucleophiles. It should be stressed that the observed effects are a superposition of direct electronic and steric effects on the addition site and also indirect (secondary) effects, that is, the electronic and steric interactions of substituents with the nitro group that affect its activation power. These secondary effects are often stronger than the direct effects, and this is particularly the case when steric effects are concerned. For instance, the bulky iodine atom does not hinder addition in its vicinity; in 3-iodonitrobenzene, addition in position 2 (*ortho* to iodine) is 3.1 times faster than in position 6 (*para* to iodine), whereas the rate of the reaction of 2-iodonitrobenzene is too slow to be measured by competitive experiments due to a strong secondary steric effect.

These results are not only of theoretical significance, in that they provide new insight into factors that influence the course of nucleophilic substitution, but they also allow the outcome of future reactions of this type to be predicted, which is important for planning successful experiments.

The relative rate constants can be considered as semiquantitative measures of the effects of substituents on electrophilicity of substituted nitrobenzenes. These results reveal that in many cases our simplified intuitive approach to the activities of nitroarenes in reactions with nucleophiles as based on textbook knowledge are misleading. The presented electrophilicity values can supplement the extensive scale of electrophilic activities elaborated by Mayr et al.[5] In fact, determination of the absolute rate constants for addition of $\mathbf{1}^-$ and other carbanions to some nitroarenes, as reported in a separate paper,[28] allows incorporation of these results in this scale.

## Experimental Section

**General**: $^1H$ and $^{13}C$ NMR spectra were recorded by using Varian Mercury 400 (400 MHz) or Brucker AM-500 (500 MHz) instruments. Chemical shifts are expressed in ppm referenced to TMS and coupling constants are in Hz. Mass spectra were recorded by using AMD 604 Inectra GmbH (EI ionization) and Mariner (ESI ionization) spectrometers. GLC analyses were performed by using a HP 6890 chromatograph equipped with a HP-5 capillary column. Melting points are uncorrected. Silica gel Merck 60 (230–400 mesh) was used for column chromatography. Aluminum foil Kieselgel 60/$F_{254}$ (Merck) was used for TLC. All solvents used for column chromatography, extraction, and recrystallization were distilled. DMF was purified by distillation over $CaH_2$, THF was distilled

over benzophenone potassium, and extra-pure DMSO was used. All reactions were carried out under an argon atmosphere.

Most of the reagents were commercially available (Aldrich). Isopropyl 4-nitro- and 2-nitrobenzoates were obtained from the appropriate acids according to a known procedure.[33] Chloromethyl phenyl sulfone was synthesized according to a known procedure.[25]

**General procedure for the VNS reaction of nitroarenes with sulfone 1**: A solution of chloromethyl phenyl sulfone (0.570 g, 3 mmol) and nitroarene (3 mmol) in THF or DMF (1 mL) was added to a solution of *t*BuOK (1.02 g, 9 mmol) in THF or DMF (5 mL) cooled to −78 °C (THF) or −40 °C (DMF). After 20 min, the reaction mixture was quenched with acetic acid (3 mL) or aqueous HCl (1:10, 5 mL), diluted with water (100 mL), and extracted with $CH_2Cl_2$. The combined extracts were washed with water and dried over $Na_2SO_4$. The products were isolated and purified by column chromatography and/or recrystallization.

**The VNS reaction under thermodynamic conditions**: The carbanion of chloromethyl phenyl sulfone was generated from a solution of sulfone **1** (1.9 g, 10 mmol) in DMSO (20 mL) passed through a layer of ground KOH, and then added to a solution of nitroarene (1 mmol) in DMSO (5 mL) at RT over 10 min. The mixture was acidified with aqueous HCl (1:10) and the products were isolated in the same way as in the preceding procedure.

**Examples of preparative VNS reactions**

**Reaction of 2-fluoronitrobenzene with 1 (3 products)**

*(3-fluoro-2-nitro)benzyl phenyl sulfone*: Yield 25 %; m.p. 220–221 °C (hexane/ethyl acetate); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 4.36 (s, 2H), 7.07 (br d, $J$ = 8.32 Hz, 1H), 7.12 (dd, $J$ = 11.0, 1.79 Hz, 1H), 7.52–7.57 (m, 2H), 7.67–7.74 (m, 3H), 7.98 ppm (t, $J$ = 8.32 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 61.81, 120.76 (d, $J$ = 21.4 Hz), 126.25 (d, $J$ = 2.6 Hz), 126.87 (d, $J$ = 4.3 Hz), 128.46, 129.42, 134.50, 136.66 (d, $J$ = 7.8 Hz), 137.38, 155.11 ppm (d, $J$ = 265.7 Hz); MS (EI): *m/z* (%): 249 (6), 154 (100), 141 (15), 107 (29), 96 (61), 77 (80), 51 (46); HRMS (ESI): *m/z* calcd for $C_{13}H_{10}NO_4FNaS$: 318.02068 [$M^+$]; found: 318.02052.

*(3-fluoro-4-nitro)benzyl phenyl sulfone*: Yield 30 %; m.p. 217–219 °C (hexane/ethyl acetate); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 4.60 (s, 2H), 7.28–7.33 (m, 2H), 7.48–7.55 (m, 3H), 7.66–7.69 (m, 1H), 7.70–7.74 ppm (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 57.48 (d, $J$ = 2.6 Hz), 118.29 (d, $J$ = 19.8 Hz), 123.69, 128.40, 128.57 (d, $J$ = 3.5 Hz), 129.46, 132.53 (d, $J$ = 8.6 Hz), 134.49, 135.41, 137.57, 154.52 ppm (d, $J$ = 258.9 Hz); MS (EI): *m/z* (%): 295 (15) [$M^+$], 154 (55), 141 (70), 124 (34), 107 (46), 96 (30), 77 (100), 51 (41); HRMS (EI): *m/z* calcd for $C_{13}H_{10}NO_4FS$: 295.03146 [$M^+$]; found: 295.03254.

*(2-nitrophenyl)chloromethyl phenyl sulfone*: Yield 11 %; m.p. 120–122 °C (hexane/ethyl acetate); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.12 (s, 1H), 7.35–7.40 (m, 2H), 7.63 (ddd, $J$ = 8.01, 7.61, 1.52 Hz, 1H), 7.70–7.77 (m, 4H), 8.11–8.78 ppm (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 89.01, 125.21, 129.90, 130.91, 131.42, 132.00, 132.43, 133.50, 145.95, 148.93 ppm; MS (EI): *m/z* (%): 170 (100), 155 (19), 112 (62), 91 (85); HRMS (ESI): *m/z* calcd for $C_{13}H_{10}NO_4ClNaS$: 334.02776 [$M^+$]; found: 334.02538.

**Reaction of 2-iodonitrobenzene with 1 (2 products)**

*(3-iodo-2-nitro)benzyl phenyl sulfone*: Yield 28 %; m.p. 170–171 °C (EtOH); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 4.39 (s, 2H), 7.21 (t, $J$ = 7.90 Hz, 1H), 7.51–7.55 (m, 2H), 7.58 (dd, $J$ = 7.90, 1.10 Hz, 1H), 7.66–7.72 (m, 3H), 7.92 (dd, $J$ = 7.90, 1.20, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 57.94, 86.21, 122.24, 128. 45, 129.37, 131.48, 132.66, 134.50, 137.50, 141.26 ppm; MS (EI): *m/z* (%): 403 (2) [$M^+$], 357 (20), 262 (100), 245 (9), 204 (19), 77 (68); HRMS (EI): *m/z* calcd for $C_{13}H_{10}NO_4IS$: 402.93753 [$M^+$]; found: 402.93899.

*(3-iodo-4-nitro)benzyl phenyl sulfone*: Yield 34 %; m.p. 187–189 °C (EtOH); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 4.30 (s, 2H), 7.28 (dd, $J$ = 8.35, 1.60 Hz, 1H), 7.54–7.60 (m, 2H), 7.65–7.72 (m, 3H), 7.70 (d, $J$ = 1.60 Hz, 1H), 7.77 ppm (d, $J$ = 8.35 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 61.34, 125.37, 128.56, 128.89, 129.39, 131.34, 134.16, 134.47, 136.3, 136.8, 143.98 ppm; MS (EI): *m/z* (%): 403 (13) [$M^+$], 262 (60), 232 (58), 77 (49), 71 (76), 57 (100); HRMS (EI): *m/z* calcd for $C_{13}H_{10}NO_4IS$: 402.93753 [$M^+$]; found: 402.93838.

**Reaction of 2,4-difluoronitrobenzene with 1 (2 products)**

*(3,5-difluoro-2-nitro)benzyl phenyl sulfone*: Yield 39 %; m.p. 158–161 °C (EtOH); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 4.61 (s, 2H), 7.02–7.09 (m, 2H), 7.51–7.62 (m, 2H), 7.68–7.78 ppm (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 57.41, 106.62 (dd, $J$ = 25.86, 24.14 Hz), 115.96 (dd, $J$ = 24.14, 3.45 Hz), 125.92 (dd, $J$ = 25.00, 4.32 Hz), 126.69 (d, $J$ = 11.21 Hz), 129.09, 130.04, 134.70, 137.40, 155.64 (dd, $J$ = 263.81, 12.93 Hz), 162.80 ppm (dd, $J$ = 258.63, 12.07 Hz); MS (EI): *m/z* (%): 188 (10), 172 (51), 141 (41), 77 (100), 51 (34); HRMS (ESI): *m/z* calcd for $C_{13}H_9NO_4F_2NaS$: 336.01126 [$M^+$]; found: 336.01273.

*[(5-fluoro-2-nitro)phenyl]chloromethyl phenyl sulfone*: Yield 50 %; m.p. 166–168 °C (EtOH); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.19 (d, $J$ = 1.1 Hz, 1H), 7.30 (ddd, $J$ = 9.36, 6.79, 2.75 Hz, 1H), 7.58–7.63 (m, 2H), 7.29–7.70 (2H), 7.90–7.93 (m, 2H), 8.17 ppm (dd, $J$ = 9.18, 4.95 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 68.62, 118.25 (d, $J$ = 22.84 Hz), 119.27 ($J$ = 26.29 Hz), 128.25 (d, $J$ = 9.48 Hz), 128.40 (d, $J$ = 9.06 Hz), 129.39, 129.90, 134.93, 135.15, 144.97, 164.68 ppm (d, $J$ = 257.50 Hz); MS (EI): *m/z* (%): 188 (100), 130 (44), 107 (28), 77 (87), 51 (43); HRMS (ESI): *m/z* calcd for $C_{13}H_9NO_4FNaSCl$: 351.98171 [$M^+$]; found: 351.98063.

**General procedure for the preparative ONSH reaction of nitroarenes with *n*BuMgCl**: A solution of *n*-butylmagnesium chloride (1.5 mL, 2 M) in THF (3 mL) was added dropwise to a solution of nitroarene (2.0 mmol) in THF (10 mL) cooled to −78 °C. After 5 min, powdered $KMnO_4$ (0.4 g, 2.5 mmol) and liquid $NH_3$ (5 mL) were added, then after 1 min the reaction mixture was treated with powdered $NH_4Cl$ (0.5 g), and then the ammonia was evaporated. The crude reaction mixture was decolorized with water and $Na_2SO_3$, then treated with aqueous HCl (1:10), extracted with $CH_2Cl_2$ (100 mL), and washed with water. The extracts were dried over $MgSO_4$ and the products were isolated and purified by column chromatography.

**Procedures for the competitive experiments**

*VNS reaction with sulfone **1***: *t*BuOK (0.6 M) in THF (0.8 mL; stock solution kept at −40 °C) was rapidly added to a solution of competing nitroarenes A and B (0.2–0.6 mmol), chloromethyl phenyl sulfone (0.023 g, 0.12 mmol), and diphenyl sulfone (internal standard; ≈0.005 g, 0.02 mmol) in DMF cooled to −40 °C. After 15 s, the reaction mixture was quenched at −40 °C with aqueous HCl (1:10, 3 mL), then diluted with water (70 mL) and extracted with $CH_2Cl_2$ (5 mL). The extracts were dried over $Na_2SO_4$ and analyzed by using GLC with an internal standard and calibration procedures. The reaction was repeated 3 times for each pair of nitroarenes and the results were averaged.

*ONSH reaction with nBuMgCl*: A 2 M solution of *n*BuMgCl (1 mmol) in THF (0.5 mL) was added to a solution of competing nitroarenes A and B (2.0–2.5 mmol) and diphenyl sulfone (internal standard; ≈0.05 g, 0.2 mmol) in THF (10 mL) cooled to −78 °C. After 5 min, powdered $KMnO_4$ (0.18 g, 1.1 mmol) and liquid $NH_3$ (5 mL) were added. Oxidation was carried out for 1 min, then powdered $NH_4Cl$ (0.5 g) was added and the ammonia evaporated. The crude reaction mixture was decolorized with water containing $Na_2SO_3$, treated with diluted HCl (1:10), extracted with $CH_2Cl_2$ (50 mL), and washed with water. Extracts were dried over $Na_2SO_4$ and analyzed by using GLC with an internal standard and calibration procedures. The reaction was repeated 3 times for each pair of nitroarenes and the results were averaged.

**Calculation of total relative activities of competing nitroarenes**

Equation (4) gives the relative activities of competing nitroarenes:

$$\frac{k_B}{k_A} = \frac{\ln\left(\frac{[B_0]-[P_B]}{[B_0]}\right)}{\ln\left(\frac{[A_0]-[P_A]}{[A_0]}\right)} \quad (4)$$

in which $k_A$ is the relative rate constant of the addition of the carbanion to nitroarene A, $k_B$ is the relative rate constant of the addition of the carbanion to nitroarene B, $[A_0]$ is the starting concentration of nitroarene A, $[B_0]$ is the starting concentration of nitroarene B, $[P_A]$ is the final concentration of product(s) formed from nitroarene A, and $[P_B]$ is the final concentration of product(s) formed from nitroarene B.

**Example calculation of partial relative activities with A = *o*-$Z_1$-nitrobenzene and B = *o*-$Z_2$-nitrobenzene**:

$$\frac{k_B^{(2\text{-iso})}}{k_A^{(2\text{-iso})}} = \frac{k_B^{(4\text{-iso})+(2\text{-iso})}}{k_A^{(4\text{-iso})+(2\text{-iso})}} \frac{1+({}^{(4\text{-iso})}_{(2\text{-iso})})_A}{1+({}^{(4\text{-iso})}_{(2\text{-iso})})_B} \quad (5)$$

in which 2-iso and 4-iso indicate the 2- and 4-isomers, respectively. The $k_B^{(4\text{-iso})+(2\text{-iso})}/k_A^{(4\text{-iso})+(2\text{-iso})}$ term is equal to $k_B/k_A$ calculated from Equation (4).

$k_B^{(2\text{-iso})}/k_A^{(2\text{-iso})}$ can be calculated from the known ratio of the total rate constants of addition to A and B and the ratio of the 4-isomer to the 2-isomer in nitroarenes A and B.

From the simple calculation the desired relations can be determined:

$$\frac{k_A^{(4\text{-iso})}}{k_B^{(2\text{-iso})}} = \frac{k_A^{(2\text{-iso})}}{k_B^{(2\text{-iso})}} ({}^{(4\text{-iso})}_{(2\text{-iso})})_A \quad (6)$$

Details of calculations are given in the Supporting Information.

## Acknowledgement

The authors are deeply indebted to Professor Herbert Mayr for very valuable discussions.

[1] R. Taylor, *Electrophilic Aromatic Substitution*, J. Wiley & Sons, New York, **1990**; J. March, M. B. Smith, *March's Advanced Organic Chemistry: Reactions, Mechanism, and Structure*, 6th ed., J. Wiley & Sons, New York, **2007**.
[2] L. M. Stock, *Prog. Phys. Org. Chem.* **1976**, *12*, 21; G. Olah, R. Malhotra, S. C. Narang, *Nitration: Methods and Mechanism*, J. Wiley & Sons, New York, **1989**.
[3] C. Ingold, *Structure and Mechanism in Organic Chemistry*, 2nd ed., Cornell Univ. Press (USA), **1969**.
[4] L. P. Hammett, *J. Am. Chem. Soc.* **1937**, *59*, 96; C. D. Ritchie, W. F. Sager, *Prog. Phys. Org. Chem.* **1964**, *2*, 323; O. Exner, *Correlation Analysis of Chemical Data*, Plenum, New York, **1988**.
[5] H. Mayr, M. Patz, *Angew. Chem.* **1994**, *106*, 990; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 938; H. Mayr, A. R. Ofial, *Pure Appl. Chem.* **2005**, *77*, 1807.
[6] F. Terrier, *Nucleophilic Aromatic Displacement: The influence of the Nitro Group*, J. Wiley & Sons, New York, **1991**.
[7] M. F. Semmelhack, G. R. Clark, J. L. Garcia, J. J. Harrison, Y. Thebtaranouth, W. Wulf, D. Yamashita, *Tetrahedron*, **1981**, *37*, 3957; F. Rose-Munch, V. Gagliardini, C. Renard, E. Rose, *Coord. Chem. Rev.* **1998**, *178–180*, 249; F. Rose-Munch, E. Rose, *Current Org. Chem.* **1999**, *3*, 445.
[8] K. Hafner, H. Weldes, *Justus Liebigs Ann. Chem.* **1957**, *606*, 90; D. Ginsburg, W. Baker, *Non-benzenoid Aromatic Compounds*, Interscience Publishers, London, **1959**; S. Hunig, K. Hafner, B. Ort, M. Muller, *Justus Liebigs Ann. Chem.* **1986**, 1222.
[9] A. R. Katrizky, A. F. Pozharskii, *Handbook of Heterocyclic Chemistry*, 2nd ed., Elsevier, Oxford, **2000**.
[10] J. F. Bunnet, R. E. Zahler, *Chem. Rev.* **1951**, *49*, 273.
[11] J. Miller, *Aromatic Nucleophilic Substitution*, Elsevier, Amsterdam, **1968**.
[12] V. von Richter, *Ber. Dtsch. Chem. Ges.* **1871**, *4*, 21; R. B. Davis, L. C. Pizzini, *J. Org. Chem.* **1960**, *25*, 1884.
[13] J. Goliński, M. Mąkosza, *Tetrahedron Lett.* **1978**, *19*, 3495.
[14] O. N. Chupakhin, V. N. Charushin, H. C. van der Plas, *Nucleophilic Aromatic Substitution of Hydrogen*, Academic Press, San Diego, **1994**; M. Mąkosza, K. Wojciechowski, *Chem. Rev.* **2004**, *104*, 2631; M. Mąkosza, *Russ. Chem. Bull.* **1996**, *45*, 491.
[15] M. Mąkosza, J. Winiarski, *Acc. Chem. Res.* **1987**, *20*, 282; M. Mąkosza, K. Wojciechowski, *Liebigs Ann./Recueil* **1997**, *9*, 1805.
[16] M. Mąkosza, K. Sienkiewicz, *J. Org. Chem.* **1990**, *55*, 4979; M. Mąkosza, K. Sienkiewicz, *J. Org. Chem.* **1998**, *63*, 4199.
[17] A. R. Katritzky, K. S. Laurenzo, *J. Org. Chem.* **1988**, *53*, 3978; P. F. Pagoria, A. R. Mitchell, R. D. Schmidt, *J. Org. Chem.* **1996**, *61*, 2934; S. Seko, N. Kawamura, *J. Org. Chem.* **1996**, *61*, 442.
[18] M. Mąkosza, M. Białecki, *J. Org. Chem.* **1992**, *57*, 4784; M. Mąkosza, M. Białecki, *J. Org. Chem.* **1998**, *63*, 4878; T. Brose, F. Holzscheiter, G. Mattersteig, W. Pritzkow, V. Voerckel, *J. Prakt. Chem.* **1992**, *334*, 497.
[19] T. Glinka, M. Mąkosza, *J. Org. Chem.* **1983**, *48*, 3860; T. Lemek, M. Mąkosza, D. S. Stephenson, H. Mayr, *Angew. Chem.* **2003**, *115*, 2899; *Angew. Chem. Int. Ed.* **2003**, *42*, 2793; M. Mąkosza, A. Kwast, *J. Phys. Org. Chem.* **1998**, *11*, 341; M. Mąkosza, T. Lemek, A. Kwast, F. Terrier, *J. Org. Chem.* **2002**, *67*, 394; M. Mąkosza, T. Lemek, A. Kwast, *Tetrahedron Lett.* **1999**, *40*, 7541.
[20] M. Mąkosza, A. Kwast, *Eur. J. Org. Chem.* **2004**, 2125.
[21] Use of the term "kinetic and thermodynamic control" in relation to an overall VNS reaction that proceeds in two distinct steps is somewhat incorrect. More precise would be descriptive terms irreversible (kinetic control) and reversible (thermodynamic control) formation of the $\sigma^H$ adduct. However, usage of these terms could be misleading because the overall VNS is an irreversible process.
[22] M. Mąkosza, T. Glinka, A. Kinowski, *Tetrahedron* **1984**, *40*, 1863.
[23] S. Błażej, A. Kwast, M. Mąkosza, *Tetrahedron Lett.* **2004**, *45*, 3193.
[24] M. Mąkosza, A. Kwast, O. Lobanova, *Tetrahedron* **2004**, *60*, 2577.
[25] M. Mąkosza, J. Goliński, J. Baran, *J. Org. Chem.* **1984**, *49*, 1488.
[26] M. Mąkosza, S. Ludwiczak, *J. Org. Chem.* **1984**, *49*, 4562.
[27] W. Greizerstein, R. A. Bonelli, J. A. Brieux, *J. Am. Chem. Soc.* **1962**, *84*, 1026.
[28] F. Seeliger, S. Błażej, S. Bernhardt, M. Mąkosza, H. Mayr, *Chem. Eur. J.* **2008**, *14*, 6108.
[29] S. Błażej, B. Wileńska, N. Vojnowa, M. Mąkosza, *Polish J. of Chem.* **2008**, *82*, 2017.
[30] G. Bartoli, M. Bosco, A. Melandri, A. C. Boicelli, *J. Org. Chem.* **1979**, *44*, 2087; G. Bartoli, *Acc. Chem. Res.* **1984**, *17*, 109.
[31] M. Mąkosza, M. Surowiec, *J. Organomet. Chem.* **2001**, *624*, 167.
[32] G. Bartoli, M. Bosco, R. Dal Pozzo, F. Ciminale, *J. Org. Chem.* **1982**, *47*, 5227.
[33] *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Longman, London, **1989**.

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