Elucidation of the Vicarious Nucleophilic Substitution of Hydrogen Mechanism via Studies of Competition between Substitution of Hydrogen, Deuterium, and Fluorine

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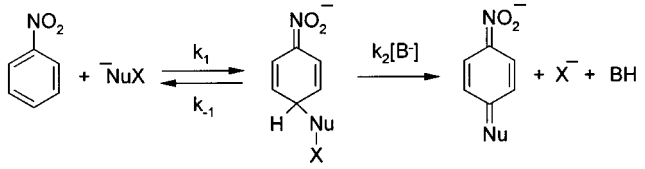
Received June 12, 2001

Relations of rates of the vicarious nucleophilic substitution of hydrogen (VNS) and S_NAr substitution of fluorine in 2-fluoronitrobenzenes with chloroalkyl aryl sulfone carbanions were determined from competitive experiments carried out at various concentrations of base. The observed dependence of the VNS/S_NAr rate ratio on the base concentration confirmed the two-step mechanism of the VNS, which consists of reversible formation of σ^H adducts of the α-chlorocarbanion to nitroarene, followed by base-induced β-elimination of HCl. It was also evidenced that both of these processes can be the rate-limiting steps: the β-elimination at low base concentration and the nucleophilic addition at high base concentration. Consistent with that conclusion is the finding that the kinetic isotope effect in the VNS reaction decreases from 4.2 (a value typical of a primary KIE) to 0.8 (a value typical of a secondary KIE) with increasing base concentration. Also reported is our discovery that the S_NAr substitution of the 2-fluoronitrobenzenes studied in this work was subject to base catalysis under some of the experimental conditions employed in our competitive experiments.

Introduction

Nucleophiles possessing leaving groups at the nucleophilic center react with nitroarenes and some other electron-deficient arenes replacing hydrogen with the nucleophile moiety. The reaction, known as vicarious nucleophilic substitution of hydrogen VNS,[1] proceeds with a variety of nucleophiles such as carbanions containing halogen, alkoxy, thioalkoxy, etc. leaving groups, alkyl hydroperoxide anions,[2] and many amination reagents.[3,4] Thus, VNS is a general method for introduction of C, O, and N substituents via direct replacement of hydrogen in electron-deficient aromatic rings. A large body of investigations has been devoted to clarify the essential features of the reaction and its applications in organic synthesis.[5] Much less comprehensive remains our knowledge of the reaction mechanism,[6] mainly because of the experimental complexity of kinetic investigations. The generally accepted mechanistic pathway of VNS is shown in Scheme 1.

Scheme 1



The reaction proceeds via addition of the nucleophile $^-$NuX to an ortho or para position of the nitroarene and subsequent base-promoted β-elimination of HX from the intermediate σ^H-adduct. Since direct kinetic data have not yet been accumulated, this mechanistic picture is based on the results obtained in competitive experiments where changes in the product ratio of the VNS and a reference reaction were examined.[2a,3,7,8] In particular, nice information has been derived from a competition between VNS and S_NAr substitution of a halogen atom (F, Cl) located in similarly activated positions of the same nitroarene molecule.[7] Thus, it was found that the VNS/S_NAr product ratio increases when a strong soluble base, e.g., t-BuOK, was used in high concentrations. Should the base concentration not affect the rate of the S_NAr process—a reasonable assumption in many cases—the results imply that the base must play an important role in determining the rate of the VNS reaction. On this ground, it was concluded that the base-promoted β-elimination of HX is the rate-limiting step of the reaction, whereas the nucleophilic addition is a fast and reversible

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10.1021/jo010590z CCC: $22.00
Published on Web 12/29/2001

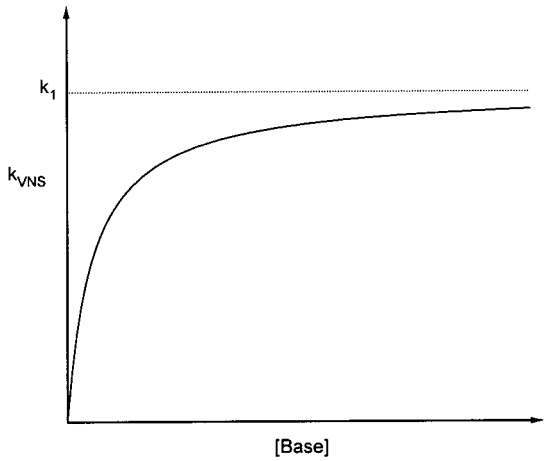

Figure 1. Value of k_{VNS} as a function of base concentration calculated according eq 1.

process. Support for this reasonable conclusion has also come from the determination of notable kinetic isotope effects for the VNS reactions of some carbanions[9] and oxygen nucleophiles[2a] with 1,3-dinitrobenzene (k^H/k^D = 3.9 and 7.0, respectively). In contrast with this mechanistic picture, KIE values close to unity were observed in other systems.[7] Also, numerous examples of competition experiments in which the VNS/S_NAr ratio does not depend appreciably on the strength and concentration of the base have been found. This situation clearly called for further experiments in mechanistic studies.

Assuming that the steady-state approximation applies, the observed rate constant k_{VNS} for formation of the VNS product according to Scheme 1 is given by eq 1. As shown in Figure 1, this equation predicts a curvilinear dependence of k_{VNS} upon the base concentration with the possible observation of two limiting situations corresponding to the reduced equations (2) and (3) at low and high base concentrations, respectively:

$$\frac{\text{Rate}}{[\text{ArH}][\text{Nu}]} = k_{VNS} = \frac{k_1 k_2[\text{B}]}{k_{-1} + k_2[\text{B}]} \quad (1)$$

$$k_{VNS} = K_1 k_2[\text{B}] \quad (2)$$

$$k_{VNS} = k_1 \quad (3)$$

Equation 2 relates to a thermodynamically controlled process that prevails when the intermediate σ-adduct is formed in a fast preequilibrium step ($k_{-1} \gg k_2[\text{B}]$). In this instance, the β-elimination step is rate-limiting and the rate of the overall VNS reaction will depends linearly on the strength and concentration of the base B.

Conversely, eq 3 describes a kinetically controlled process that is operating when the nucleophilic addition step is rate limiting ($k_2[\text{B}] \gg k_{-1}$). Then, the β-elimination step is so fast that the formation of the intermediate σ^H adduct can be considered as an irreversible process.

Each of these limiting situations is believed to have been observed in individual instances of VNS reactions. For a full confirmation of Scheme 1, it was important, however, to design suitable model reagents and reaction conditions that would allow coverage of the entire range of kinetic situations predicted by eq 1. This should also help in clarifying the role that kinetic isotope effects (KIE) can possibly play as a diagnostic tool for the understanding of the mechanism of VNS reactions.

We have succeeded in delineating all the reactivity facets of Scheme 1 by carrying out a detailed study of the reactions of the fluoronitroarenes **1a**−**d** with the halocarbanion **C-2** to afford competitively the S_NAr and VNS substitution products **3a**−**d** and **4a**−**d** (or **5a**−**d**), respectively. Following a communication of preliminary promising results,[10] we report here a full and comprehensive account of this work that, for clarity, we will discuss in a point-to-point approach.

Results and Discussion

Scheme 2 describes our competitive strategy with the observed rates of the VNS and S_NAr reactions being given by eqs 4 and 5 where the various rate constants k_1, k_{-1}, k_2, and k'_1, k'_{-1}, k'_2 refer to the depicted individual steps. That the steady-state approximation also applies with $k'_2 \gg k'_{-1}$ for the S_NAr pathway is an assumption that reflects the most commonly reported situation for mononitroactivated arenes.[11] In eqs 4 and 5, **1** and **C-2** refer to the fluoronitroaromatic and the carbanion at hand, respectively, while P^H and P^F represent the products of the hydrogen and fluorine substitutions, respectively; i.e., we will express the product distribution as $[P^H] = [\mathbf{3}]$ and $[P^F] = [\mathbf{4}] + [\mathbf{5}]$.

$$\frac{\text{d}[P^H]}{\text{d}t} = \frac{k_1 k_2[\text{B}]}{k_{-1} + k_2[\text{B}]}[\mathbf{1}][\mathbf{C\text{-}2}] \quad (4)$$

$$\frac{\text{d}[P^F]}{\text{d}t} = \frac{k'_1 k'_2}{k'_{-1} + k'_2}[\mathbf{1}][\mathbf{C\text{-}2}] = k'_1[\mathbf{1}][\mathbf{C\text{-}2}] \quad (5)$$

For experiments conducted at a constant base concentration ($[\text{B}]_t = [\text{B}]_o$), a standard treatment of eqs 4 and 5 affords eq 6, which shows that the $[P^H]/[P^F]$ ratio must depend curvilinearly on $[\text{B}]_o$, as does the rate of the VNS substitution alone (Figure 1). However, the plateau will now correspond to the ratio k_1/k'_1 and not to k_1.

$$\frac{[P^H]}{[P^F]} = \frac{k_1 k_2[\text{B}]_0}{k'_1(k_{-1} + k_2[\text{B}]_0)} \quad (6)$$

Model Reagents and Reaction Conditions. The 4-X-substituted 2-fluoronitrobenzenes **1a**−**d** and the carbanion of chloromethyl *p*-tolyl sulfone **C-2** have been selected as the most appropriate model reagents to study Scheme 2. Apart from a similar activation by the *o*-nitro group, the C_2−F and C_6−H positions of **1a**−**d** are symmetrically located with respect to the X substituent. Changing the nature of X should therefore equally affect the two electrophilic centers, allowing us to disclose how a variation in the overall electron-deficiency of the benzene ring affects the competition between the S_NAr and VNS processes.

On the above grounds, Scheme 2 was investigated by mixing DMF solutions of the two reagents at −40 °C. The reacting concentration of the nitroarene **1** was 3×10^{-3}

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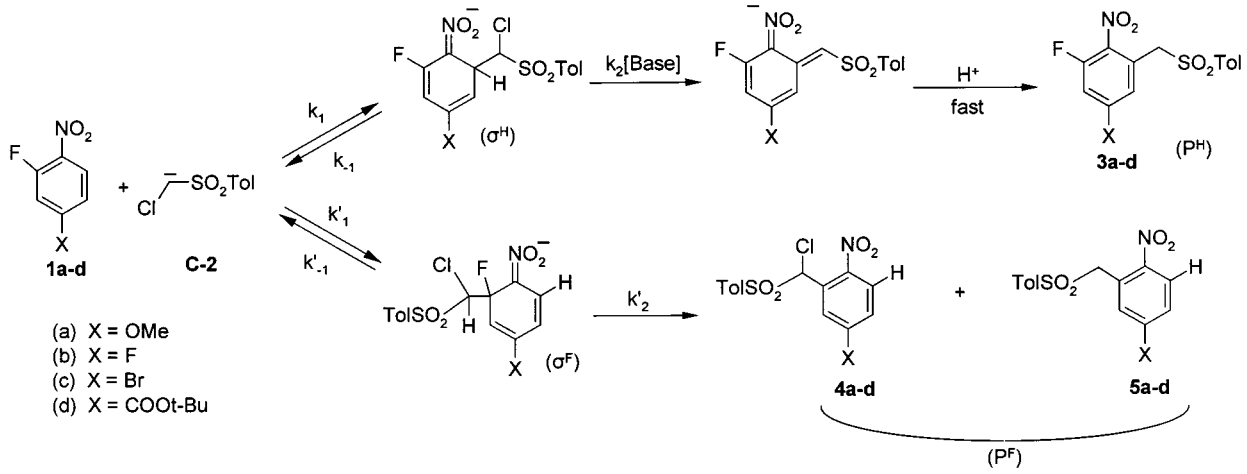
Scheme 2



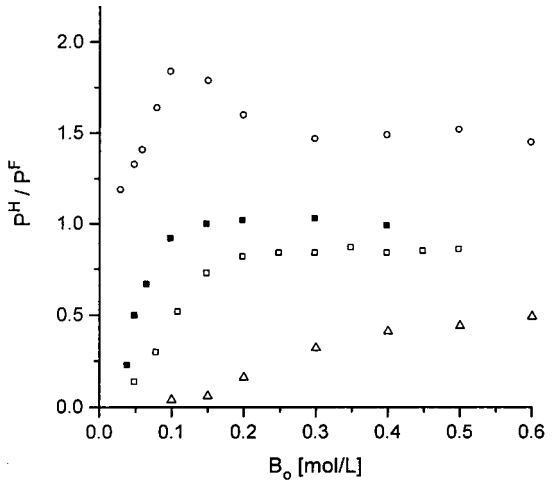


Figure 2. VNS/S_NAr product ratio vs concentration of carbanion **C-2** in the reactions of 4-substituted 2-fluoronitrobenzenes: **1a** (△), **1b** (□), **1c** (■), **1d** (○).

mol L^{-1} while that of the carbanion **C-2** varied in the range 2×10^{-2} to 0.6 mol L^{-1}, being therefore in a sufficient excess to consider $[B]_o$ as essentially constant during the course of a given experiment. After 10 s, the reaction mixtures were quenched with strong acid and analyzed by using a reversed-phase HPLC or GC technique. This analysis confirmed the complete disappearance of the starting nitroarene and the formation of products arising from the expected VNS and S_NAr processes.

Formation of some amounts of nitrobenzyl sulfones **5a**−**d** indicates that some decomposition of the chloromethyl moiety of the S_NAr products **4a**−**d** has occurred under the experimental conditions; however, no difference in the product distribution was observed when the reaction mixtures were quenched after longer times, e.g., 60 s.[12] The sum of the concentrations of **4a**−**d** and **5a**−**d** was therefore taken as representative of the efficiency of the S_NAr pathway.

In the case of the difluoronitroarene **1b**, some competitive S_NAr substitution of the *p*-fluorine atom also occurred to a measurable extent. Figure 2 expresses the results obtained, showing how the ratio $[P^H]/[P^F]$ of the VNS and S_NAr products—only the S_NAr^{ortho} product was considered for **1b**—depends for each of the nitroarenes studied on the sulfone anion concentration.

The Reactions of 1a−**c.** As can be seen, the shape of the product profiles obtained for **1b** and **1c** fits well the curvilinear behavior predicted by eqs 1 and 6 with the observation of the two limiting situations expected for a thermodynamically controlled VNS process at low base concentrations and a kinetically controlled process at high base concentrations. Interestingly, the $[P^H]/[P^F]$ ratio levels off close to unity in the case of the bromonitroarene **1c**. This implies that the addition of **C-2** occurs at essentially similar rates at the C_6−H and C_2−F positions ortho to the NO_2 group of **1c**. Carrying out the reactions under different experimental conditions, e.g., mixing equimolar amounts of **1c** and **C-2** in the presence of a large excess of a strong base like *t*-BuOK (in the concentration range 0.05−0.3 mol L^{-1}), did not change the product distribution, thereby confirming the conclusion that $k_1 \sim k'_1$ for the **1c** system. The situation is not actually very different for the **1b** system with a k_1/k'_1 ratio of about 0.8.

The somewhat different shape of the product profile in the case of **1a** can be explained in terms of the electron-donating +M effect of the OCH_3 group to the ring.[15] This will reduce the stability of the intermediate σ-adduct by increasing k_{-1} appreciably while making at the same time the β-elimination pathway more difficult (k_2 decreases). Accordingly, the $k_2[B]_0/k_{-1}$ ratio should be smaller for **1a** (X = OCH_3) than for **1b** (X = F) or **1c** (X = Br), accounting for the greater difficulty to reach the kinetic control region. On the other hand, the possible conjugation of the 4-OCH_3 group with the NO_2 group in **1a** must also reduce the electron-withdrawing effect of this substituent and, hence the overall electrophilic reactivity of the nitroarene. This will in turn reinforce the ipso effect of the fluorine atom, leading to a relatively faster nucleophilic addition of the carbanion **C-2** at the fluoro-bearing carbon C_2 than at the unsubstituted carbon C_6, i.e., $k'_1 > k_1$.[16]

(12) This indicates that the initially formed neutral S_NAr product **4** is transformed into the stable anionic form of **4** and **5** via action of **C-2** on a proton or a "positive" chlorine at the position α, promoting proton- or halogen-exchange reactions, respectively. Halogen exchange between carbanions and their chlorinated analogues is a common process, observed most frequently when carbanions of halogenated sulfones are concerned.[13,14]

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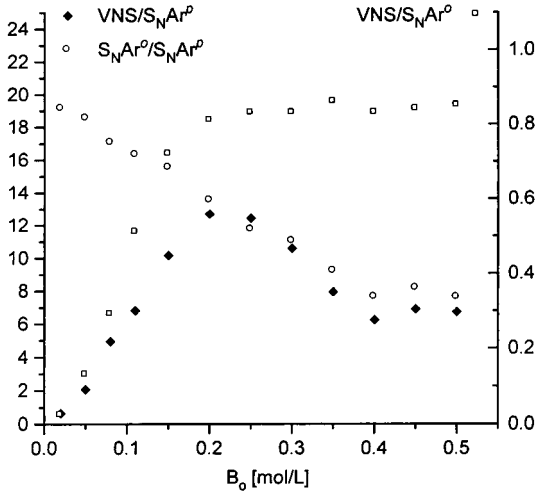


Figure 3. Product ratios: VNS/S_NAr^{para} (◆), VNS/S_NAr^{ortho} (□), and $S_NAr^{ortho}/S_NAr^{para}$ (○) versus concentration of carbanion **C-2** in the reaction with **1b**.

The Reaction of 1d. Base Catalysis of the S_NAr Reactions. The product profile obtained for **1d** (X = COO-*t*-Bu) is rather unexpected. Following a rapid increase at low base concentrations, the $[P^H]/[P^F]$ ratio is seen to decrease with increasing $[B]_0$, reaching a plateau corresponding to a k_1/k'_1 value of about 1.5 at $[B]_0 = 0.3$ mol L^{-1}. A similar product profile with a more pronounced maximum was obtained when the effect of the concentration of **C-2** on the reactivity of **1d** studied at 0 °C.

Keeping with the model, the observed decrease in the $[P^H]/[P^F]$ ratio for **1d** in the intermediate $[B]_0$ range can be viewed as the result of a decrease in the rate of the VNS substitution and/or an increase in that of the S_NAr substitution. Obviously, it is difficult to visualize how an increase in $[B]_0$ can have an inhibiting effect on the VNS substitution since the base is necessarily a partner of the β-elimination step. It follows that the decrease observed in the $[P^H]/[P^F]$ ratio must reflect an acceleration of the S_NAr process. This conclusion means that, contrary to the assumption made in deriving eq 5, the substitution of the fluorine atom by carbanion **C-2** may be a base-catalyzed reaction. A reconsideration of the results obtained for **1b** supports this proposal.

As mentioned earlier, the reaction of **C-2** with difluoronitroarene **1b** afforded not only the VNS and S_NAr^{ortho} products related to Scheme 2 but also some amount of the product of the S_NAr^{para} substitution of the *p*-nitro-activated fluorine atom (**4b′** and dechlorinated **5b′**). Taking account of this latter reaction, the base dependence of the VNS/S_NAr^{ortho}, VNS/S_NAr^{para}, and $S_NAr^{ortho}/S_NAr^{para}$ product ratios can be compared (Figure 3). Contrary to the $VNS/S_NAr^{ortho} = [P^H]/[P^F]$ ratio which fits well the overall behavior depicted in Figure 1, the VNS/S_NAr^{para} ratio is subject to a base dependence that closely resembles that observed for the VNS/S_NAr ratio for **1d**. This is really an unexpected behavior if the S_NAr reactions proceed through a rate-limiting nucleophilic addition step, as we had originally assumed and is commonly accepted for most S_NAr systems. In fact, the above findings can only be understood if the departure of F^- from our substrates **1a**−**d** is assisted by the base reagent. In the case of **1b**, this assistance seems to be more effective for the displacement of the para than the ortho fluorine atom, accounting for the observed regular decrease of the $S_NAr^{ortho}/S_NAr^{para}$ ratio at $[B]_0 < 0.4$ mol L^{-1}.

(16) In as much as a fluorine atom has a much greater −I effect but a much smaller +M effect than a OCH_3 group, the similarly possible through-the-ring conjugation of the NO_2 group with the *p*-fluoro atom in **1b** is not expected to affect the k_1/k'_1 ratio at a major extent.[17]

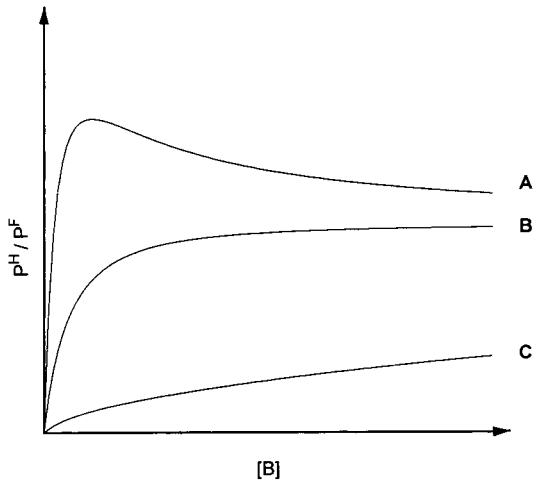


Figure 4. $[P^H]/[P^F]$ as a function of $[B_0]$ (eq 8) for a given k_{-1}/k'_{-1} ratio and $k_2^A > k_2^B > k_2^C$.

Assuming that such a base catalysis is actually operative to some extent in the reactions of **C-2** with **1a**−**d**, the results obtained should fit Scheme 3 rather than Scheme 2 with the rate of the S_NAr substitution being in this instance given by eq 7.

$$\frac{d[P^F]}{dt} = \frac{k'_1k'_2 + k'_1k'_3[B]}{k'_{-1} + k'_2 + k'_3[B]}[\mathbf{1}][\mathbf{C\text{-}2}] \qquad (7)$$

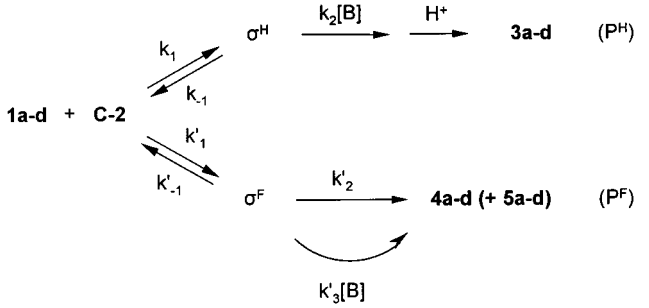
$$\frac{[P^H]}{[P^F]} = \frac{k_1k_2k'_3[B]_0^2 + (k_1k_2k'_{-1} + k_1k_2k'_2)[B]_0}{k'_1k'_3k_2[B]_0^2 + (k'_1k'_3k_{-1} + k'_1k'_2k_2)[B]_0 + k'_1k'_2k_{-1}} \qquad (8)$$

$$\frac{k'_3}{k'_{-1}} < \frac{k_2}{k_{-1}} \qquad (9)$$

Combining eqs 7 and 4 affords eq 8 for the $[P^H]/[P^F]$ ratio. As a matter of fact, a mathematical analysis of this complicated equation predicts that the $[P^H]/[P^F]$ ratio can exhibit a maximum value provided that the inequality expressed in eq 9 is obeyed. Working out eq 8 with increasing k_2 at a given k_{-1}/k'_{-1} ratio, i.e., $k_2^A > k_2^B > k_2^C$, thus afforded the family of curves drawn in Figure 4, which shows that a maximum is present only when eq 9 is fulfilled. Similar changes in the shape of the $[P^H]/[P^F]$ function from C to A are induced when decreasing the k_{-1}/k'_{-1} ratio at a given k_2 value. Interestingly, these trends appear to be consistent with the expected influence of the X-substituent on the rate parameters.

Obviously, the above results point to the occurrence of base-catalyzed fluoride anion departure in the S_NAr pathways involved in the reactions of **C-2** with **1a**−**d**, as depicted in Scheme 3. While such a situation has been described for the reactions of fluoronitroarenes with

Scheme 3



neutral nucleophiles such as secondary amines,[18] we are not aware of works reporting a similar behavior in S_NAr reactions involving anionic nucleophiles, especially carbanions. Only to be noted is a report by Leffek and Tremaine that the rate of reaction of 2,4-dinitrofluorobenzene with diethyl malonate anion increases regularly with increasing the carbanion concentration.[19] However, this phenomenon was not recognized as arising from base catalysis of the departure of F^-.

Why the S_NAr reactions of Scheme 3 are subject to base-catalysis is therefore an interesting question. This behavior requires two major conditions: (1) ability of the σ^F adduct to return to the starting materials, thus some reversibility of the addition step, i.e., k'_{-1} being at least of the same order of magnitude as k'_2; (2) the hydrogen atom bonded at the C_α carbon of σ^F must be sufficiently acidic to allow base-promoted elimination of HF. Regarding the first condition, a key point is that we are here dealing with reactions carried out in DMF, a dipolar aprotic solvent where the solvation of small ions with a localized negative charge like F^- is rather poor[20] while that of highly delocalized anionic species such as σ-adducts is very much favored. As a result, fluoride anion departure of σ^F may be rather difficult, accounting for k'_2 comparable to k'_{-1}. The fact that the reaction must proceed with replacement of a small fluorine atom by a bulky nucleophile may also contribute to this inequality. On the other hand, it seems reasonable to anticipate that having a base-catalyzed concerted E−2-type breaking of the C_α-H_α and C_2−F bonds in σ^F should not be very different from having the base-catalyzed E-2 elimination of HCl in the σ^H adduct.

The Reaction of 1d with a Tertiary Carbanion. Definitive evidence that our reasoning regarding the course of the S_NAr reactions expressed in Scheme 3 is actually correct was obtained by studying of the reaction of **1d** with the tertiary carbanion **C-6** derived from the deprotonation of 1-chloroethyl phenyl sulfone **6**. Since the low stability of **C-6** precluded its use as the excess base reagent, Scheme 4 was investigated by mixing equimolar amounts of **1d** and **6** in the presence of *t*-BuOK in a large excess, a procedure shown to afford reliable results in the reaction of **1c** with **C-2** (vide supra). In this reaction, the VNS products **7** and **9** were formed, and the latter was produced via dechlorination of the initial S_NAr product **8**. A separate experiment using an authentic sample of **8** confirmed that the decomposition of this product readily occurs in basic medium to give **9**.

In the absence of a C_α−H bond in the σ^F adduct, no base catalysis of the S_NAr pathway was expected to affect the VNS/S_NAr competition of Scheme 4. As shown in Figure 5, the VNS/S_NAr profile (open circles) fits very well the simple curvilinear base dependence predicted by eq 6 with a rapid access to the plateau associated with the occurrence of a kinetically controlled VNS process. A most noteworthy feature, however, is that this plateau corresponds to a much larger predominance of the VNS reaction, i.e., $[P^H]/[P^F] \sim 25$, than that found in the reactions of **1d** with the secondary carbanion **C-2** under the same conditions where $[P^H]/[P^F] \sim 1.1$ was observed (solid circles).

In this regard, the available evidence is that the reactivity of **C-6** is commonly 3−4 times greater than that of **C-2** in covalent addition processes at C−H ring positions.[21] Since the ring C−H and C−F positions of **1a**−**d** are rather similar in terms of steric demand,[22] there is no reason why this relative reactivity should be modified on going from σ^H to σ^F adducts. It follows that the quite different $[P^H]/[P^F]$ ratios observed here in the systems involving **C-2** and **C-6** must be a consequence of different rates of the fluoride ion departure, which appears to be the rate-limiting step in the reaction of **C-6**. The possible acceleration of the S_NAr reaction of **1d** with **C-2** but not that with **C-6** by the base reagent is a reasonable explanation of this observation, although steric hindrances caused in this step by tertiary **C-6** may also contribute to this effect.

Althought the occurrence of base catalysis in the S_NAr reactions of Schemes 2 and 3 can only be taken into account within the complicated mathematical formalism of eq 8, the competitive VNS/S_NAr strategy—developed in this work to get a better understanding of the VNS reaction—remains actually useful for the two following reasons:

(1) Notwithstanding the fact that it is difficult to differentiate between the parameters responsible for the observed variations of the $[P^H]/[P^F]$ ratio in the low base region, the initial increase of this ratio with increasing $[B]_0$ implies necessarily that the rate of the VNS reaction is accelerated by the base reagent. Thus, the VNS reaction proceeds with formation of the σ^H adduct in a fast equilibrium step that is followed by a rate-limiting base-catalyzed β-elimination step.

(2) The plateau at high $[B]_0$ strongly suggests that the two VNS and S_NAr processes are both occurring with rates independent from the base concentration. In regard to the VNS, it means that this process is under kinetic control with a rate-limiting formation of the σ^H adduct. Less definite conclusions can be made for the S_NAr reaction. It is also kinetically controlled, the overall kinetic behavior being identical to the one predicted by the simple competitive model of Scheme 2, i.e., $[P^H]/[P^F] = k_1/k'_1$, or it is controlled by the k'_1/k'_{-1} ratio and the rate of F^- departure k'_2. The latter case seems to be working in the reaction of Scheme 4.

Isotope Effects. The two major conclusions presented above have been further consolidated by a study of the

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(19) Leffek, K. T.; Tremaine, P. H. *Can. J. Chem.* **1973**, *51*, 1659.

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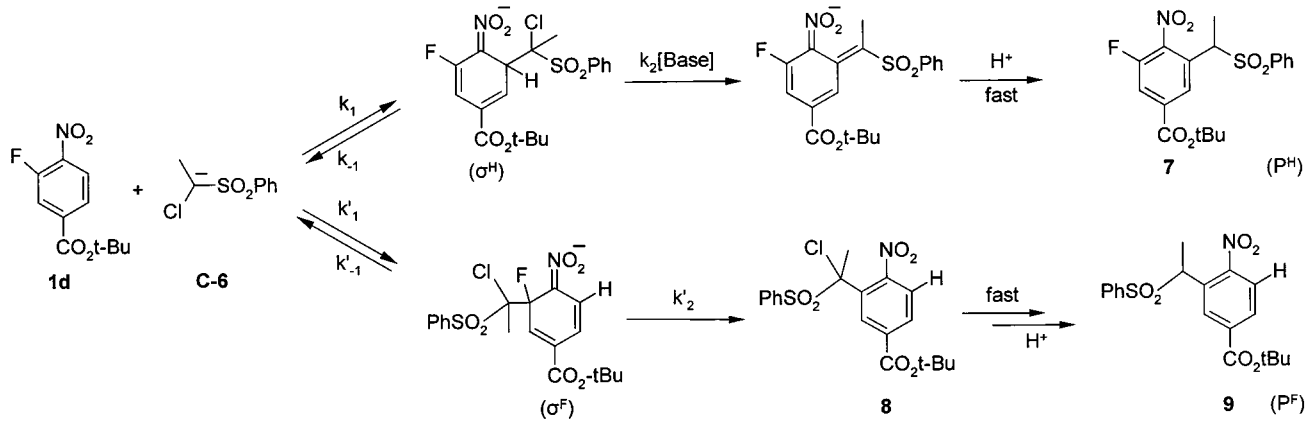
(21) Mudryk, B.; Mąkosza, M. *Tetrahedron* **1988**, *44*, 209.

(22) Manderville, R. A.; Durst, J. M.; Buncel, E. *J. Phys. Org. Chem.* **1996**, *9*, 515.

Scheme 4



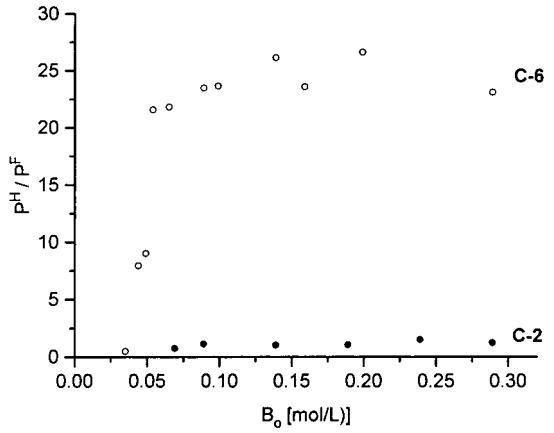


Figure 5. VNS/S_NAr ratio in the reactions of secondary and tertiary carbanions **C-2** (●) and **C-6** (○) with **1d** versus concentration of *t*-BuOK.

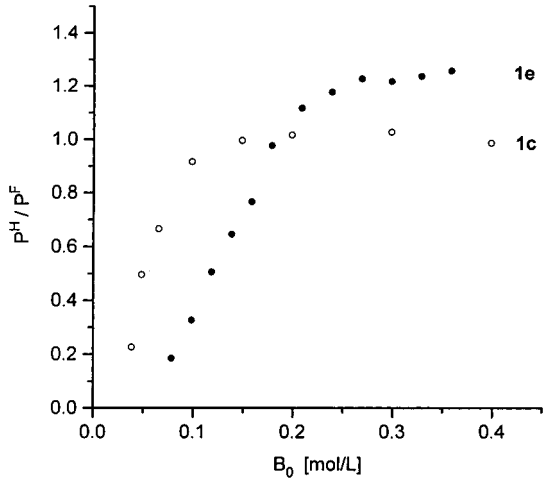
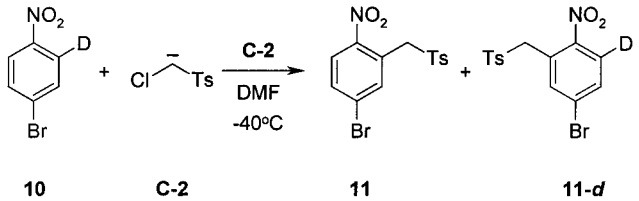


Figure 6. VNS/S_NAr product ratio vs concentration of carbanions **C-2** in the reaction of **1c** (○) and its deuterated analogue **1e** (●).

kinetic isotope effects associated with the reaction of **C-2** with 4-bromo-6-deuterio-2-fluoronitrobenzene **1e**. The kinetic behavior of this compound was studied under the same experimental conditions as those used for its protio analogue **1c**. The related $[P^H]/[P^F]$ profiles are compared in Figure 6.

Contrary to those for the fluorine S_NAr process, all the parameters of the VNS reaction may be affected by the replacement of H by D with a primary effect on the β-elimination step ($k_2^{DCl} < k_2^{HCl}$) and possible secondary effects on the rate constants for formation and dissociation of the σ^H adduct ($k_1^H/k_1^D \leq 1$; $k_{-1}^H/k_{-1}^D \geq 1$; $K_1^H < K_1^D$). As can be seen, Figure 6 reflects a reasonable reverse secondary isotope effect of $k_1^H/k_1^D \sim 0.8$ and shows that the VNS reaction of **1e** proceeds at a much lower rate than that of **1c** in the low to moderate $[B]_0$ region. The situation is fully consistent with the idea that the VNS reaction is now controlled by the β-elimination step and that the relative values of the $[P^H]/[P^F]$ ratios for **1c** and **1e** are governed by a primary kinetic effect: $k^H/k^D \sim 4.2$ at $[B]_0 \sim 0.08$ mol L^{-1}, the higher value of which should be expected at lower $[B]_0$, being in agreement with the following estimation made for a pure thermodynamically controlled VNS reaction: $k^H/k^D = k_1^H k_2^H k_{-1}^D/k_1^D k_2^D k_{-1}^H \sim 8$ with $k_1^H/k_1^D \sim 0.8$, $k_{-1}^H/k_{-1}^D \sim 1.2$, and $k_2^H/k_2^D \sim 12$ at −40 °C.[23] This suggests the view that the base-induced β-elimination step of the VNS reaction of **1c** with **C-2** proceeds via an E2-like transition state. More importantly, this suggests that measuring KIE effects may be particularly valuable tool for the mechanistic analysis of VNS substitutions.

As a test for this approach, the reaction of 4-bromo-2-deuterionitrobenzene **10** with carbanion **C-2** to afford a mixture of the protio and deuterio VNS products **11** and **11**-*d* has been studied (eq 10). In this instance, the KIE values were calculated as the product ratios [**11**-*d*]/[**11**] which were measured at different base concentrations using mass spectroscopy.



Because of the absence of fluorine in the nitroarene molecule, the reactions were very clean, allowing measurements over a wider base concentration range. Also, as the H/D competition in **10** is of intramolecular nature, the results of the KIE measurements are much more reliable than those derived from a comparison of the two compounds **1c** and **1e**. As can be seen in Figure 7, the KIE profile for **10** resembles that drawn for the **1c**/**1e**

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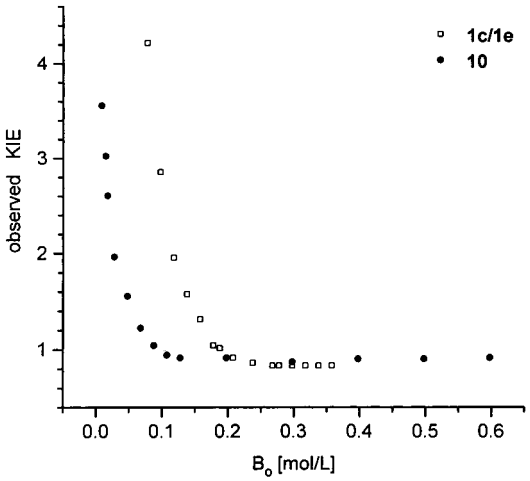

Figure 7. Dependence of the observed kinetic isotope effects (KIE) in the VNS reaction of **C-2** on concentration of base.

pair with a strong dependence of $[B]_0$ in the low concentration range and a plateau corresponding to a k_1^H/k_1^D value of about 0.9 at high $[B]_0$ values.

These results leave no doubt that the VNS reactions of mononitrobenzene derivatives with the secondary carbanion of chloromethyl tolyl sulfone occur according to the mechanism shown in Scheme 1. Base-promoted E2-type elimination of HCl from the intermediate σ^H-adduct is rate-limiting at low base concentrations. Nucleophilic addition of **2** at the nitro-activated unsubstituted position becomes rate-limiting at high base concentrations.

Experimental Section

General Procedure for the Reactions of Carbanions C-2 or C-6 with Nitroarenes 1a−e or 10 under the Conditions of Specified Base Concentrations (Schemes 2 and 4, Eq 10). The reactions were performed in a 10 mL round-bottom flask, dried at 100 °C prior to use, equipped with a magnetic bar and a septum with an inlet and an outlet needle for dry argon. The appropriate amount of freshly sublimed *t*-BuOK was placed in the flask and then dissolved by addition of dry DMF (8.0 mL) while in a thermostatic bath. The mixture was stirred for 5 min at −40 ± 0.2 °C, and then a solution of the carbanion precursor (**2** or **6)** in DMF (1.0 mL) was added. The mixture was stirred for 1 min, and then a solution of the nitroarene (**1a**−**e**) in DMF (1.0 mL) was added at once. After 10 s (or 1 min for reactions of **6**) of a vigorous stirring the reaction was quenched by quick addition of a small excess of concentrated HCl_{aq}. The mixture was subjected to HPLC, or—after neutralization with solid sodium bicarbonate—to GLC analyses. The reactions were repeated two to five times for each base concentration $[B]_0$. The chromatographic analyses were repeated three times for each reaction and the results were averaged.

Reactions Performed with an Excess of C-2 (Scheme 2, Figures 2, 3, and 6). According to the general procedure, 0.30−7.0 mmol of *t*-BuOK, 1.01 equiv in respect to *t*-BuOK of **2**, and 0.03 mmol of nitroarene **1a**−**e** were used. The calculated concentration of *t*-BuOK was employed as a concentration of **C-2** ($[B]_0$).

Reactions Performed in the Presence of an Excess of *t*-BuOK (Scheme 4, Figure 5). According to the general procedure, 0.41−2.95 mmol of *t*-BuOK was used. Amounts of the other reagents used (0.05−0.1 mmol of sulfone **2** or 0.04−0.05 mmol of **6**, and 0.02−0.04 mmol of **1d**) were appropriate to provide a sufficient excess of *t*-BuOK in all experiments. The $[B]_0$ values (Figure 5) were calculated from the initial amount of *t*-BuOK used, diminished by that, consumed for deprotonation of the sulfone.

Kinetic Isotope Effect in the Reaction of 10 with C-2 (Eq 10, Figure 7). According to the general procedure, 0.11−6.0 mmol of *t*-BuOK, 1.01 molar equiv with respect to *t*-BuOK of **2**, and 0.01 mmol of **10** were used. After the reaction was quenched, the mixture was diluted with water and extracted three times with CH_2Cl_2. The extract was washed with water and dried with Na_2SO_4, and the solvent was evaporated. The reactions were repeated three times for each base concentration. The crude products were subjected to GCMS analysis. The isotope-ratio measurements were made for fragment ions 214/215 ($M^+ - Ts$) and 323/324 ($M^+ - NO_2$) as the parent ion of the product was too small. Both ions gave very similar isotope ratios; thus an isotope effect of fragmentation was assumed to be negligible if any, and the KIE values on Figure 7 are for 323/324 ions. The calculated concentration of *t*-BuOK was employed as B_0 of **C-2**.

Identification of the products and calibrations for HPLC and GC analyses were performed using authentic samples of compounds synthesized independently.

Acknowledgment. This work was supported by the State Committee for Scientific Research (KBN) (Grant No. PBZ 6.01). M.M. thanks the Foundation of Polish Sciences for a Professorial Subsidy. This work was a product of collaboration between PAN (Polish Academy of Sciences) and CNRS.

Supporting Information Available: Procedures for the preparation of starting materials and samples of the products including characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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