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Effect of Base Concentration on the Rate of the Vicarious Nucleophilic Substitution of Hydrogen and on the Kinetic Isotope Effect.

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Abstract: Varying concentration of the chloromethyl tolyl sulfone carbanion influences the rate of its VNS reaction with 2-fluoro-4-bromonitrobenzene and changes the mechanistic scheme from thermodynamic to kinetic control. Both primary and secondary kinetic isotope effects are observed and are clearly connected with particular kinetic relations. © 1999 Elsevier Science Ltd. All rights reserved.

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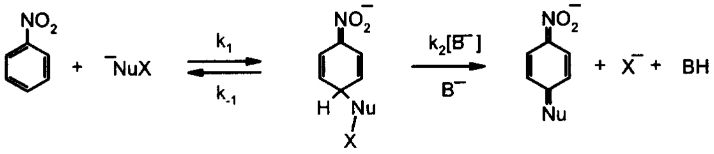
Vicarious Nucleophilic Substitution of Hydrogen (VNS), a general method for introduction of functionalized substituents onto electrophilic aromatic rings, has a very broad scope with respect to the electrophilic arenes and nucleophiles.[1] Nucleophilic agents such as carbanions containing leaving groups (X = halogens, ArO, RO, ArS, etc), anions of alkyl hydroperoxides and a variety of aminating agents enter this reaction with substitution of hydrogen in *ortho*- or *para*- positions to the nitro group in practically all carbo- and heterocyclic nitroarenes.



Scheme 1

The presently accepted mechanistic scheme of the VNS reaction (scheme 1) was formulated on the basis of semiquantitative observations of an effect of base on the reaction rate.[2] In experiments during which competition of S_NAr of fluorine and VNS was studied, it was found that the ratio of the products of these processes was governed by base concentration, namely high base concentration favored VNS.[3] Since the rates of nucleophilic addition of α-halocarbanions to the nitroaromatic ring in a position occupied by hydrogen or by fluorine, and the rate of departure of F^- seem to be not affected by the base concentration, it was concluded that the second step of the VNS is the base-induced β-elimination of HX from the σ^H-adduct.

Applying the steady-state approximation to the reaction as in scheme 1 leads to the equation (1) which expresses the relationship of the observed rate of VNS and concentration of the base, assuming constant concentration of the other substrates.

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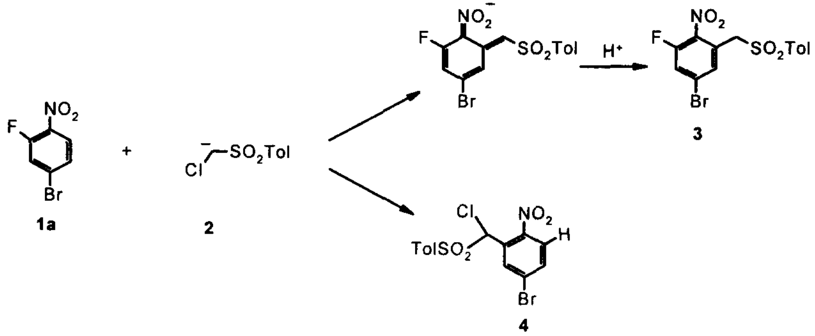
$$k_{VNS} = \text{rate}/[\text{ArH}][\text{Nu}] = k_1 k_2[\text{B}^-]/(k_{-1}+k_2[\text{B}^-]) \tag{1}$$

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

$$k_{VNS} = k_1 \qquad \text{when } k_2[\text{B}^-]/k_{-1} >> 1 \tag{3}$$

From this equation it is clear that, generally speaking, there is not a linear relation between the observed reaction rate and base concentration and, under appropriate conditions, ensuring a sufficiently fast elimination step, equation 1 is reduced to equation 3 and the overall rate of the VNS reaction becomes independent of the base concentration. This case, which can be considered as kinetic control of the reaction, was believed to be observed in some hydroxylation[4] and amination[5] reactions when strong base, in high concentration, was present, although this opinion was derived from observed changes in orientation pattern rather than those in the reaction rate.

In order to learn more about the mechanism of the VNS reaction, and particularly the relation of rates of addition and β-elimination steps we have been studying effects of base concentration on the overall rate of VNS. As a part of these studies we have examined competition between S_NAr replacement of fluorine and VNS of hydrogen in a model compound: 2-fluoro-4-bromonitrobenzene **1a** reacting with chloromethyl tolyl sulfone **2** as a function of base concentration.



Scheme 2

The nitroarene examined possesses fluorine and hydrogen atoms in equivalent positions *ortho* to the nitro group, both susceptible to nucleophilic substitution with a chlorosulfone carbanion under the applied conditions. Assuming that fluoride replacement occurs according to the commonly accepted mechanism[6] in which the observed reaction rate is determined by the slowest, irreversible first step of the reaction ($k^F_{-1} << k^F_2$) and that the kinetics of the VNS reaction is described by eq.1, the ratio of rates rates of the both reactions in the competitive experiments is a function of the base concentration as in eq. 4.

$$V_{VNS} / V_{S_NAr} = k^H_1 k^H_2 [\text{B}] / k^F_1 (k^H_{-1} + k^H_2 [\text{B}]) \tag{4}$$

A graphical representation of this equation is shown in figure 1. The very first part of the curve corresponds to the simplified equation (2) and the so-called thermodynamic control region, under which the rate of the VNS depends on the equilibrium constant of the addition and the rate of the second step and it increases with growing base concentration. The final, flat part of the curve goes to the asymptote which represents the situation when rate of the β-elimination is sufficiently high to make the overall rate of the VNS independent of the base concentration, thus the reaction is in the kinetic control region (equation 3) and consequently $V_{VNS} / V_{S_NAr} = k_1^H / k_1^F$.

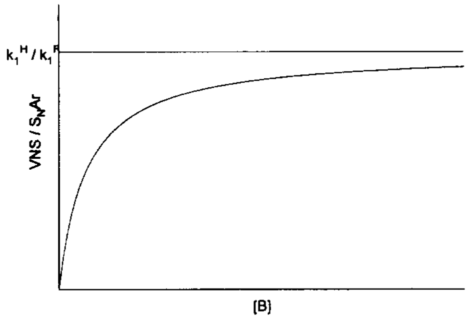


fig.1

The goal of the studies required the use of a rather weak base, soluble at a wide range of concentration and which are the only base in the reaction medium. To meet these requirements the starting sulfone carbanion, which is always present in the reaction mixture, was used in a large excess as the actual base. The carbanions were generated *via* deprotonation of **2** with *tert*-BuOK, which was always used in some deficit in relation to the sulfone so no free butoxide was present in the system. The carbanion of **2** was used at least in 10-fold excess over the nitroarene, thus the concentration of the base was constant during the reaction. Starting concentration of the nitroarene was 0.003M and that of the chlorosulfone anion was altered in range 0.02 to 0.6M. The reactions were carried out in DMF at -40±0.2 °C. The reaction mixtures were quenched after 10s at -40 °C and analysed using a reversed-phase HPLC technique. The experiments were performed 2-4 times for each base concentration and the results were averaged. The product of S_NAr reaction (**4**) was accompanied with small amount of a dechlorinated derivative, being a result of subsequent processes, so they both were accounted as products of the fluorine substitution.

The results of the VNS / S_NAr ratio *versus* concentration of the sulfone carbanion for nitroarene **1a** are given on figure 2 by open circles.

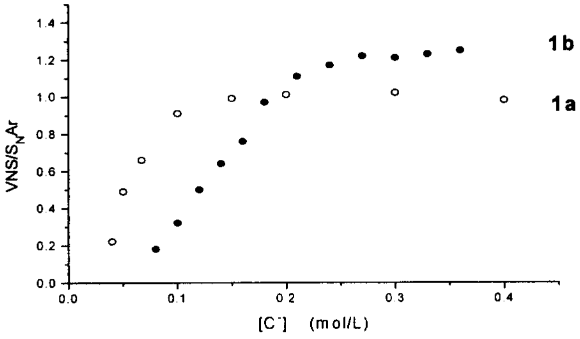


fig. 2

Two distinct regions of the base concentration can be recognized on the curve: first, the initial phase, in which the ratio V_{VNS} / V_{S_NAr} depends strongly on the base concentration, and the second phase, at higher base concentration, where this dependence is practically absent and the ratio V_{VNS} / V_{S_NAr} achieves its highest, constant value, close to 1. Since the rate of S_NAr process is considered to be independent of base concentration, the relation of the V_{VNS} / V_{SNAr} ratio as a function of $[B^-]$ represents that of V_{VNS} itself. Thus, in the applied range of the carbanion concentration the reaction of **1** with chloromethyl tolyl sulfone changes its mechanistic scheme from thermodynamic (eq. 3) to kinetic (eq. 2) control.

Substantial support for the mechanistic picture presented came from measurements of the kinetic isotope effect in the reaction of **2** with 4-bromo-6-deuterio-2-fluoronitrobenzene **1b**, an analog of **1a** in which the VNS reaction leads to substitution of deuterium instead of hydrogen. This compound was subjected to the reaction with carbanion of **2** at various base concentration, as for **1a**, and the results are shown as solid circles on figure 2.

The effect of deuterium on the V_{VNS} / V_{SNAr} ratio is significant and beyond experimental error. Assuming negligible influence of deuterium on the rate of fluorine substitution, it is evident that in the range of low base concentration deuterium is substituted a few times slower, whereas at high base concentration substitution is slightly faster than hydrogen. This observation is in full agreement with expectations for the reaction being in both kinetic (eq. 2) and thermodynamic (eq. 3) control regions. This is the first case of detection of the primary KIE in the VNS reaction in mononitroarenes with secondary carbanions. Until now this effect was reported only in VNS in dinitrobenzenes,[7] whereas in mononitrobenzene derivatives it was found for reactions with some bulky, tertiary carbanions.[8]

The secondary kinetic isotope effect, which is connected with formation of σ^H-adducts, was observed earlier in the VNS reaction in nitrobenzene[3] but its correct interpretation was not possible as it could have originated either from $k_1^H / k_1^D < 1$ under kinetic control or from $K^H / K^D < 1$ under thermodynamic control. The latter case is possible when a primary isotope effect, connected with the elimination step, is not observed due to the non-symmetric transition state. In the case presented here, both isotope effects are separated and clearly connected with particular kinetic relationships (eq. 2 and 3).

Acknowledgments

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