Direct Observation of the Intermediate in Vicarious Nucleophilic Substitutions of Hydrogen^{**}

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In memory of Janusz Baran

Vicarious nucleophilic substitution has proven to be a general method for the direct replacement of hydrogen atoms in electron-deficient aromatic rings.^[1] As shown in Scheme 1, the reaction has been postulated to proceed through the energetically high-lying intermediate σ^{H} adduct **3**.^[2] Depending on the reagents and reaction conditions, nucleophilic addition (formation of **3**) or 1,2-elimination (formation of **4**) may be the rate-determining step.^[2b]



Scheme 1. Vicarious nucleophilic substitution of hydrogen.[1]

This mechanism is in accord with all experimental evidence so far acquired, including substituent effects,^[2a] kinetic isotope effects,^[2b,c] and leaving-group dependence.^[2d,e] However, σ^{H} adducts have generally been considered as short-lived intermediates^[2a] which have never been directly observed.^[3]

Herein we report the first UV/Vis and NMR spectroscopic observation of σ^{H} adducts from an α halogen-substituted carbanion and mononitro-substituted benzene derivatives, which allows us to observe directly the individual steps of vicarious nucleophilic substitutions and to determine the rates of the addition steps.

Nucleophilic addition: Addition of 4-nitroanisole (5) to colorless solutions of 7–50 equivalents of the carbanion $6^{[4]}$

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the most intensively studied carbanion in vicarious nucleophilic substitutions (Scheme 2), results in the formation of a yellow product with $\lambda_{max} = 408$ nm (Figure 1). Since the intensity of the final absorbance does not depend on the concentration of **6**, the conversion of **5** into the σ^{H} adduct **7** must be complete.



Scheme 2. Stepwise formation of **8** by vicarious nucleophilic substitution from the chloro-4-tolylsulfonyl methyl anion **6** and nitroanisole (**5**).



Figure 1. Formation of the σ^H adduct 7 from 6 (0.01 M) and 5 $(2 \times 10^{-4} \text{ M})$ in DMF at -40° C.

When the reactions were run with $[6]_0 \ge [5]_0$ (pseudo-firstorder conditions), linear plots of $\ln(A_{\infty}-A_t)$ versus *t* were observed, which indicate first-order kinetics with respect to arene. From the slopes of these plots, the pseudo-first-order rate constants $k_{1\psi}$ were derived, which were plotted against [6] to yield the second-order rate constant k_2 (Figure 2).

To confirm the identity of the σ^{H} intermediate, the reaction of **5** with **6** was also investigated by NMR spectroscopy. A 0.02 M solution of **7** was obtained by adding equimolar amounts of *t*BuOK and of **5** dissolved in [D₈]THF successively to a solution of TsCH₂Cl (Ts = tosyl) and [18]crown-6 in [D₈]THF at -78 °C. The ¹H NMR (400 MHz) spectrum taken at -40 °C indicated the presence of two diastereoisomers in a 1:3 ratio, which are tentatively assigned the molecular structures shown in Scheme 3. The structure of the major diastereoisomer could further be corroborated by its ¹³C NMR spectrum.^[5]

Elimination: When the solution of **7** is produced from **5** $(2 \times 10^{-4} \text{ M})$ with excess of **6** $(5 \times 10^{-3} \text{ M})$ in DMF at -40 °C, the

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Figure 2. Pseudo-first-order rate constants of the addition reactions of **5** with **6** in DMF at -40 °C ([**6**]₀ \ge [**5**]₀).



Scheme 3. Chemical shift values from ¹H NMR spectroscopy of a 1:3 mixture of the two diastereoisomers of **7** assigned by a COSY experiment (-40 °C, [D₈]THF, δ [ppm], in parentheses: *J* [Hz]).

UV/Vis spectra show a slow decrease of the absorbance of **7** at $\lambda_{max} = 408$ nm (<10% within 30 min), which is accompanied by the appearance of a new absorption band with $\lambda_{max} = 534$ nm arising from the elimination process **7**→**8** formulated in Scheme 2. The small value of the absorbance at $\lambda = 534$ nm in Figure 1 indicates that this subsequent reaction is almost negligible during the formation of **7** from **5** and **6**.

In accord with previous investigations,^[2b] the conversion of **7** into **8** can be accelerated by the addition of extra base, for example *t*BuOK, the standard base for vicarious nucleophilic substitution on a preparative scale. Figure 3 illustrates that **7** and **8** have comparable absorption coefficients at λ_{max} of both ions, and the observation of the isosbestic point demonstrates the absence of further long-lived intermediates. Since the rate of the conversion of **7** into **8** does not increase linearly with the concentration of *t*BuOK, rate constants for this process have not been determined.

NMR spectroscopic investigation of the conversion of **7** into **8** showed different behavior of the two diastereoisomers. When a 0.02 \times solution of the potassium [18]crown-6 salt of **7** in [D₈]THF was warmed to -20 °C, slow disappearance of the signals of the minor diastereoisomer of **7** and the growth of signals arising from **8** was observed, while the signals of the major diastereoisomer of **7** remained unaffected. Conversion of both diastereoisomers of **7** into **8** occurred when **7** was treated with an excess of *t*BuOK at approximately -40 °C and warmed to room temperature.



Figure 3. Formation of the anion **8** by treatment of the σ^{H} adduct **7** $(2 \times 10^{-4} \text{ M})$ with *t*BuOK $(2 \times 10^{-2} \text{ M}; \text{ DMF}, -40 \text{ °C})$. The color of the reaction mixture changes from yellow to purple.

While *anti*-elimination of HCl converts the minor diastereoisomer of **7** directly into the *E* isomer of **8**, the corresponding *Z* isomer of **8** is expected to be formed by *anti*-elimination from the major diastereoisomer. It is not clear whether the exclusive formation of the *E* isomer of **8** is a result of stereoisomerization at the stage of **7** (by deprotonationreprotonation of **7** at the CHCl position) or a result of baseinduced isomerization of the *Z* isomer of **8** into the thermodynamically more favorable *E* isomer of **8**. Stereomutation of the two stereoisomers of **7** by retroaddition $(\rightarrow 5 + 6)$ is excluded because the formation of **8** from the major stereoisomer requires the presence of a higher concentration of base.

Treatment of the purple solution of **8** with trifluoroacetic acid (TFA) led to decolorization because of the formation of **9**, which gave spectra consistent with those in the literature (Scheme 4).^[6]



Scheme 4. Chemical shift values from ¹H NMR spectroscopy of the nitrotosyl-substituted benzyl anion **8** and its protonation product, **9** (in $[D_8]$ THF).

Since the same reaction cascade, quantitative formation of a σ^{H} adduct followed by slow elimination of HCl was also observed by the reaction of **6** with 4-bromonitrobenzene, it is concluded that in contrast to current opinion^[2a] the initially formed σ^{H} adducts are often not high-energy intermediates, but are usually formed in exergonic reactions of α halocarbanions with nitroarenes.

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- [1] a) M. Mąkosza, J. Winiarski, Acc. Chem. Res. 1987, 20, 282-289;
 b) M. Mąkosza, Synthesis 1991, 103-111; c) M. Mąkosza, Pol. J. Chem. 1992, 66, 3-23; d) M. Mąkosza, Chem. Unserer Zeit 1996, 30, 134-140; e) M. Mąkosza, Russ. Chem. Bull. 1996, 45, 491-503; f) M. Mąkosza, K. Wojciechowski, Liebigs Ann. 1997, 1805-1816; g) F. Terrier, Nucleophilic Aromatic Displacement: The Influence of the Nitro Group, VCH, New York, 1991; h) O. N. Chupakin, V. N. Charushin, H. C. van der Plas, Nucleophilic Aromatic Substitution of Hydrogen, Academic Press, San Diego, 1994; i) S. Ostrowski, Pol. J. Chem. 2001, 75, 1661-1687; j) O. V. Donskaya, G. V. Dolgushin, V. A. Lopyrev, Chem. Heterocycl. Compd. 2002, 38, 371-383; O. V. Donskaya, G. V. Dolgushin, V. A. Lopyrev, Khim. Geterotsikl. Soedin. 2002, 435-449.
- [2] a) M. Mąkosza, A. Kwast, J. Phys. Org. Chem. 1998, 11, 341–349;
 b) M. Mąkosza, T. Lemek, A. Kwast, F. Terrier, J. Org. Chem. 2002, 67, 394–400; c) T. Glinka, M. Mąkosza, J. Org. Chem. 1983, 48, 3860–3861; d) S. Ostrowski, M. Mąkosza, Tetrahedron 1988, 44, 1721–1726; e) M. Mąkosza, T. Ziobrowski, M. Serebriakov, A. Kwast, Tetrahedron 1997, 53, 4739–4750.
- [3] For reactions of carbanions, which contain leaving groups, with highly electrophilic arenes yielding stable σ^H adducts which do not undergo β elimination, see: a) G. P. Stahly, B. C. Stahly, J. R. Maloney, J. Org. Chem. 1988, 53, 690–692; b) G. P. Stahly, J. Fluorine Chem. 1989, 45, 431–433; c) S. Ostrowski, M. Mąkosza, J. Organomet. Chem. 1989, 367, 95–100; d) P. Müller, G. Bernardinelli, S. Motallebi, Helv. Chim. Acta 1990, 73, 1242–1249; see also: e) F. Terrier, R. Goumont, M. J. Pouet, J. C. Halle, J. Chem. Soc. Perkin Trans. 2 1995, 1629–1637.
- [4] The carbanion **6** ($\lambda_{max} = 317 \text{ nm}$) formed instantaneously (<0.1 s) when a solution of *t*BuOK (0.2 mmol) in THF (0.8 mL) was added to a solution of 1 equivalent of chloro 4-tolylsulfonyl methane and 1 equivalent of [18]crown-6 in DMF (20 mL) at -40 °C.
- [5] ¹³C NMR ([D₈]THF, 100.7 MHz): δ = 21.77 (q, CH₃), 41.98 (d), 54.56 (q, OCH₃), 74.09 (d), 87.99 (d), 109.59 (d), 113.27 (s), 127.13 (d), 129.68 (d), 130.67 (d), 136.73 (s), 145.92 (s), 157.97 ppm (s).
- [6] a) W. Verboom, E. O. H. Orlemans, H. J. Berga, H. W. Scheltinga,
 D. N. Reinhoudt, *Tetrahedron* 1986, 42, 5053-5064; b) M.
 Mąkosza, Z. Wróbel, J. Prakt. Chem. 1992, 334, 131-134.