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Azide Ion Trapping of the Intermediate in the Bamberger Rearrangement. Lifetime of a Free Nitrenium Ion in Aqueous Solution

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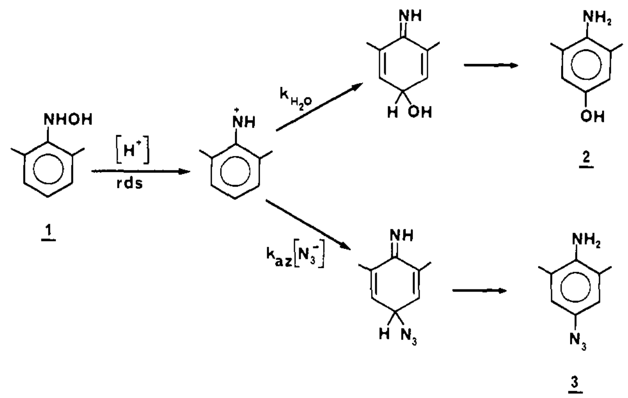
The carcinogenicity and mutagenicity of certain arylamines have been attributed to the ability of their *N*-hydroxy derivatives to form electrophilic nitrenium ions which subsequently react with nucleic acid.[1] There is evidence, in the form of large negative ρ values and in the form of trapping studies, consistent with the intermediacy of nitrenium ions in a variety of model chemical reactions.[2] However, the possibility of ion pairing in some systems obscures the exact nature of the intermediate. The lifetimes of nitrenium ions under reaction conditions have yet to be determined. This quantity is of particular importance because it has been demonstrated for a number of reaction types that the choice of mechanism is largely determined by the lifetimes of the intermediates.[3] We report here a study of the rearrangement and substitution reactions of the known mutagen[4] *N*-(2,6-dimethylphenyl)hydroxylamine (**1**). This work establishes a free nitrenium ion intermediate in aqueous solution, which reacts with water with a rate constant of 7×10^8 s^{-1}.

The Bamberger rearrangement of **1** (Scheme I) has been studied and readily occurs under mildly acidic conditions.[2b] Under our conditions,[5] analysis by HPLC shows that the expected rearrangement product **2**[6] is formed in greater than 96% yield. Experiments in azide buffer reveal two additional products being formed at the expense of **2**, with the major new product being identified as 4-azido-2,6-dimethylaniline (**3**).[7] Figure 1A shows the changes in the relative yields of **2** and **3** as a function of azide ion concentration. In all cases these two species account for more than 94% of the products.

The kinetics in azide buffers were monitored at 310 nm (absorbance increase), with first-order behavior being observed to 95% of completion. As shown in Figure 1B, k_{obsd} increases less than 13% from zero buffer concentration (extrapolated value) to the highest azide concentration.[8] In this solution however, the azide adduct **3** represents 73% of the products. Thus we conclude that azide ion is trapping the nitrenium ion intermediate after the rate-limiting step of the reaction. A second-order mechanism for the azide ion reaction requires a 3-fold increase in k_{obsd} in order to account for the products.

Scheme I



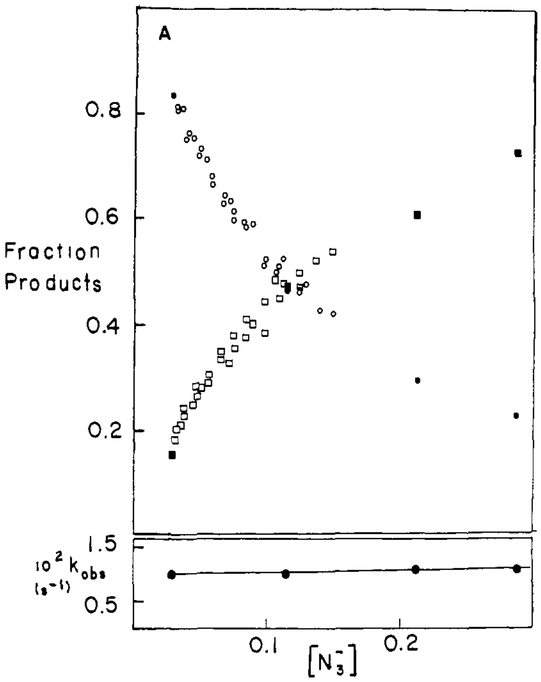


Figure 1. (A) Fractions of **2** (circles) and **3** (squares) for reactions of **1** at 40 °C, $\mu = 1.0$, in azide buffers ($[NH_3]/[N_3^-] = 5.7$ (○, □) and 2.3 (●, ■, analysis following kinetic runs). (B) Values of k_{obsd} at $[NH_3]/[N_3^-] = 2.3$, pH = 4.03.

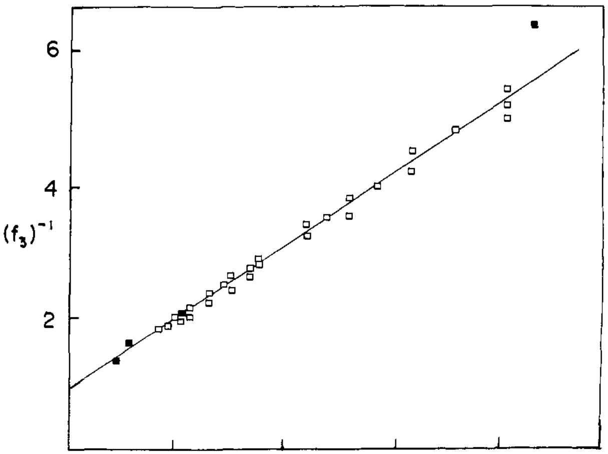


Figure 2. Double reciprocal plot for fraction of **3** as a function of azide ion.

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[1] Miller, E. C. *Cancer Res.* **1978**, *38*, 1479.

[2] (a) Sone, T.; Tokudo, Y.; Sakai, T.; Shinkai, S.; Manabe, O. *J. Chem. Soc., Perkin Trans. 2* **1981**, 298. (b) Sone, T.; Hamamato, K.; Seija, Y.; Shinkai, S.; Manabe, O. *Ibid.* **1981**, 1596. (c) Gassman, P. G.; Campbell, G. A. *J. Am. Chem. Soc.* **1972**, *94*, 3891. (d) Gassman, P. G.; Campbell, G. A.; Frederick, R. C. *Ibid.* **1972**, *94*, 3884. (e) Gassman, P. G.; Granrud, J. E. *Ibid.* **1984**, *106*, 1498, **1984**, *106*, 2448. (f) Novak, M.; Pelecanou, M.; Roy, A. K.; Andronico, A. F.; Plourde, F. M.; Olefirowicz, T. M.; Curtin, T. J. *Ibid.* **1984**, *106*, 5623. (g) Novak, M.; Roy, A. K. *J. Org. Chem.* **1985**, *50*, 4884. (h) Pelecanou, M.; Novak, M. *J. Am. Chem. Soc.* **1985**, *107*, 4499. (i) Novak, M.; Pelecanou, M.; Pollack, L. *Ibid.* **1986**, *108*, 112. (j) Shudo, K.; Ohta, T.; Okamoto, T. *Ibid.* **1981**, *103*, 943. (k) Hashimoto, Y.; Shudo, K.; Okamoto, T. *Ibid.* **1982**, *104*, 7636.

[3] Jencks, W. P. *Chem. Soc. Rev.* **1981**, *10*, 345.

[4] Nohmi, T.; Yoshikawa, K.; Nakadate, M.; Miyata, R.; Ishidate, M. *Mutat. Res.* **1984**, *136*, 159.

[5] Reactions were carried out at 40 °C, 1 M ionic strength, with 0.1–2 mM **1** in a nitrogen atmosphere. Experiments with no buffer were carried out in 3×10^{-4} M $HClO_4$. HPLC analysis was performed with a Waters C^{18} column using buffered methanol/water as the eluting solvent.

[6] Prepared by scaling up the reaction conditions.[5] **2**: mp 190 °C dec; ^1H NMR ($CDCl_3/D_2O$) δ 2.10 (s, 3 H), 6.40 (s, 3 H). Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.89; H, 8.01; N, 10.36. This product was inferred in ref 2b, on the basis of UV spectral evidence only.

[7] Isolated by chromatographic separation. **3**: mp 46.5–47.5 °C; ^1H NMR ($CDCl_3$) δ 2.20 (s, 3 H), 3.53 (s, 1 H), 6.63 (s, 1 H); MS, exact mass calcd for $C_8H_{10}N_4$ 162.0905, found 162.0906. Anal. Calcd for $C_8H_{10}N_4$: C, 59.24; H, 6.21; N, 34.54. Found: C, 59.16; H, 6.15; N, 34.48.

[8] It is unlikely that this represents a small S_N2' component because there is a similar increase in the presence of a similar concentration (0.4 M) of the much weaker nucleophile chloride ion (ionic strength 1 M with $NaClO_4$).

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Based on Scheme I[9] and neglecting the unknown product, the equation below is obtained in which f_3 is the fraction of product accounted for by **3**. The double reciprocal plot is shown in Figure

$$\frac{1}{f_3} = \left(\frac{1}{[N_3^-]}\right)\left(\frac{k_{H_2O}}{k_{az}}\right) + 1$$

2 and does have the correct form. The inverse of the slope gives a selectivity ratio k_{az}/k_{H_2O} of 7.5 M^{-1}. This value is some 6 orders of magnitude smaller than the selectivity observed for activation limited reactions with stable cations and can be interpreted as evidence that the reaction with azide ion is diffusion controlled.[10] Choosing a value for the rate constant for a diffusion-limited reaction, and thus for k_{az}, of 5×10^9 M^{-1} s^{-1} (limits 1–10 × 10^9),[11] the rate constant for the reaction with water is 7×10^8 s^{-1} (limits 1.3–13 × 10^8).[12]

Thus, for the hydroxylamine **1**, both the rearrangement reaction and the substitution reaction involving the powerful nucleophile azide occur via a short-lived but free nitrenium ion intermediate. From a biological point of view this study establishes that such electrophiles can form under aqueous conditions. However, the short lifetime indicates that little DNA modification is to be expected by the cation of this study unless it is formed in the immediate vicinity of the target. We are currently investigating the reactions of other nucleophiles with **1** and reactions of other phenylhydroxylamines to determine whether and how the selectivities of nitrenium ions change.

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[9] A control experiment shows that azide ion is likely acting only as a nucleophile, not as a base catalyst of hydration. Product analysis of five reactions with $[N_3^-]$ = .0544 M showed that **3**/**2** decreased by less than 5% as acetate buffer, $[HA]/[A^-]$ = 2.3, was varied from 0.19 to 0.98 M.

[10] Ta-Shma, R.; Rappoport, Z. *J. Am. Chem. Soc.* **1983**, *105*, 6089.

[11] Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 8238.

[12] From k_{az}/k_{H_2O} = 7.5 M^{-1} and $k_{az} = 5 \times 10^9$ M^{-1} s^{-1}, $k_{H_2O} = 5 \times 10^9$ M^{-1} s^{-1}/7.5 M^{-1} = 7×10^8 s^{-1}.

Reaction of C–H Bonds in Alkanes with Bis(diphosphine) Complexes of Iron

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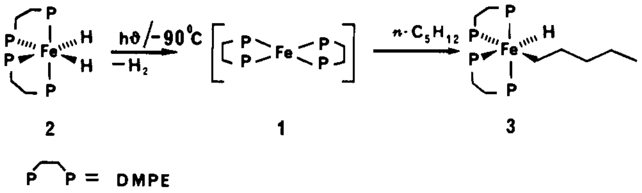
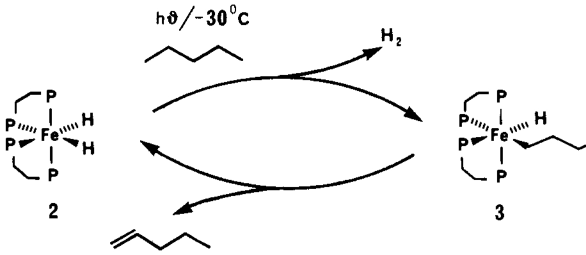
Oxidative addition of unactivated C–H bonds to transition-metal complexes has been an area of intense interest in organometallic chemistry over recent years. There have been numerous reports of complexes of second- and third-row transition metals (including Ir,[1] Rh,[2] Re,[3] and Os[4]), lanthanides,[5] and actinides,[6] which react intermolecularly with the C–H and C–C bonds in alkanes, but, to our knowledge, there have been no reports of alkane C–H activation involving complexes of first-row transition metals. In this paper we describe the reaction of alkanes with the species Fe(DMPE)$_2$ (**1**)[7] [DMPE = 1,2-bis(dimethylphosphino)ethane] in homogeneous solution.

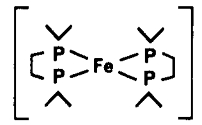
Scheme I



Scheme II



We recently reported[8] some reactions of the reactive intermediate Fe(DMPE)$_2$ (**1**) generated from FeH$_2$(DMPE)$_2$ (**2**) with



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sp^2 C–H bonds in alkenes and arenes at low temperature. In previous work, [7c–e] the species **1** has been generated by the reductive elimination of naphthalene from *cis*-FeH(Np)(DMPE)$_2$ (Np = 2-naphthyl); however, this limited the scope of reactions which could be studied to substrates with a reactivity greater than (or comparable to) that of naphthalene. In addition, to form **1** from FeH(Np)(DMPE)$_2$ necessarily required reaction temperatures close to room temperature, where any thermally labile products may not have been sufficiently stable to be observed. Generation of **1** by the photochemical elimination of dihydrogen from **2** has the advantage that **1** can be formed in the absence of compounds with which it can react readily.

When the dihydride **2** was irradiated[9] at low temperature (<–90 °C) in *n*-pentane solution, dihydrogen was eliminated and one major product was formed (70% yield after 60% conversion, by ^{31}P NMR) (Scheme I). We assign this as *cis*-(1-pentyl)Fe(DMPE)$_2$H (**3**). The complex **3** contains four nonequivalent phosphorus atoms and possesses a single phosphorus-coupled, iron-bound hydride which resonates at δ –13.283 in the ^{1}H NMR spectrum (Figure 1b).[10,11] The complex decomposed rapidly on warming to temperatures above –20 °C and could not be isolated.

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[1] See, for example: (a) Hoyano, J. K.; McMaster, A. D.; Graham, W. A. G. *J. Am. Chem. Soc.* **1983**, *105*, 7190–7191 and references cited therein. (b) Janowicz, A. H.; Periana, R. A.; Buchanan, J. M.; Kovac, C. A.; Stryker, J. M.; Wax, M. J.; Bergman, R. G. *Pure App. Chem.* **1984**, *56*, 13–23 and references cited therein.

[2] See, for example: Jones, W. D.; Feher, F. J. *Organometallics* **1983**, *2*, 562–563.

[3] See, for example: (a) Wenzel, T. T.; Bergman, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 4856–4867. (b) Baudry, D.; Ephritikhine, M.; Felkin, H.; Zakrewski, J. *Tetrahedron Lett.* **1984**, *25*, 1283–1286. (c) Klahn-Oliva, A. H.; Singer, R. D.; Sutton, D. *J. Am. Chem. Soc.* **1986**, *108*, 3107–3108.

[4] Graham, W. A. G. *J. Organomet. Chem.* **1986**, *300*, 81–91.

[5] See, for example: (a) Watson, P. L. *J. Chem. Soc., Chem. Commun.* **1983**, 276–277. (b) Watson, P. L. *J. Am. Chem. Soc.* **1983**, *105*, 6491–6493.

[6] See, for example: Fendrick, C. M.; Marks, T. J. *J. Am. Chem. Soc.* **1986**, *108*, 425–437 and references cited therein.

[7] For earlier studies on the chemistry of bidentate alkylphosphine complexes of iron, see: (a) Baker, M. V.; Field, L. D. *Organometallics* **1986**, *5*, 821–823. (b) Baker, M. V.; Field, L. D. *J. Am. Chem. Soc.* **1986**, *108*, 7436–7438. (c) Tolman, C. A.; Ittel, S. D.; English, A. D.; Jesson, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 4080–4089. (d) Tolman, C. A.; Ittel, S. D.; English, A. D.; Jesson, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 7577–7585. (e) Tolman, C. A.; Ittel, S. D.; English, A. D.; Jesson, J. P. *J. Am. Chem. Soc.* **1979**, *101*, 1742–1751. (f) Bergamini, P.; Sostero, S.; Traverso, O. *J. Organomet. Chem.* **1986**, *299*, C11–C14.

[8] Baker, M. V.; Field, L. D. *J. Am. Chem. Soc.* **1986**, *108*, 7433–7434.

[9] Samples (2–10 mg/mL) were irradiated in Pyrex NMR tubes, positioned ca. 10 cm from a 125-W mercury vapor lamp. The tubes were supported within a quartz cylinder and cooled by a stream of nitrogen gas.

[10] ^{31}P NMR spectra were referenced to external, neat trimethyl phosphite, taken as 140.85 ppm, at the temperature quoted. ^{1}H NMR spectra were referenced to solvent resonances. P–P splittings were measured directly from spectra and signs of P–P couplings are not implied. In protonated solvents, some regions of ^{1}H spectra were obscured by solvent resonances.

[11] **3**: ^{31}P{^{1}H} NMR spectrum (pentane, –80 °C) δ 76.41, P$_A$; 75.04, P$_B$; 64.98, P$_C$; 63.18, P$_D$ (J_{AB} = 125.4, J_{AC} = 22.7, J_{AD} = 33.2, J_{BC} = 27.0, J_{BD} = 25.1, J_{CD} = 11.3 Hz). ^{1}H NMR spectrum (pentane, –80 °C) δ –13.283, Fe–H (dddd, J = 38.4, 50.6, 60.8, 60.8 Hz); –0.190, –0.414, multiplets, FeCH_2(CH$_2$)$_3$CH$_3$.

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