The Thermal Reaction of Sterically Hindered Nitroxyl Radicals with Allylic and Benzylic Substrates: Experimental and Computational Evidence for Divergent Mechanisms

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Abstract: The reaction of stable sterically hindered nitroxyl radicals with benzylic and allylic substrates was investigated. An allyloxyamine derivative was obtained by the reaction of 2 molar equiv of a nitroxyl radical with an unactivated alkene. Experimental and computational evidence is consistent with a low-energy pathway involving addition of the nitroxyl radical to the double bond followed by H-atom abstraction from the intermediate by another equivalent of nitroxyl radical.

Sterically hindered nitroxyl radicals, for example, 2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO), are generally considered to be both kinetically and thermodynamically stable free radicals that do not typically undergo hydrogen atom abstraction reactions with hydrocarbon substrates. Hydrogen-atom-abstraction reactions of photochemically excited TEMPO and 4-hydroxy-2,2,6,6tetramethylpiperidine-N-oxyl, **1a**, are known.¹⁻³ Isolated reports on thermally initiated hydrogen-atom-abstraction reactions by sterically hindered nitroxyl radicals have recently appeared. Hazeldine and co-workers reported that bis(trifluoromethyl)nitroxide abstracts hydrogen atoms from various substrates including alkylbenzenes.⁴ Scaiano⁵ and Opeida⁶ have reported on the mechanism and kinetics, respectively, of the reaction of TEMPO with benzylic substrates.

The reaction of alkoxy radicals with cyclic alkenes in the presence of a nitroxyl trapping agent was reported by Busfield et al.⁷ In a control experiment in the absence

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SCHEME 1. Alkoxyamine Derivatives Synthesized by the Reaction of Nitroxyl Radicals with Benzylic Substrates



of alkoxy radicals, Jenkins observed the formation of a product that was formally the cross-coupling of an allylic cyclohexenyl radical with nitroxide.⁸ Jenkins made the reasonable suggestion that this cyclohexenyl radical was the result of allylic hydrogen atom abstraction by a nitroxyl radical. In this paper we report experimental and computational results that strongly suggest that the hindered nitroxyl radicals **1** $\mathbf{a}-\mathbf{c}$ react with allylic substrates by a stepwise addition:hydrogen-atom-abstraction mechanism.

The reaction of 1a-c with the benzylic substrates 2a-c at 130-143 °C (reflux temperature or pressure vessel) for 2-3 days gave good yields of the corresponding alkoxyamine derivatives 3a-e and hydroxylamines **4a**–**c**. The reactions were carried out with excess alkylbenzene as the reaction solvent. The products formed are consistent with the previously established mechanism for this reaction (rate determining benzylic hydrogen atom abstraction by nitroxyl radical followed by trapping of the benzylic radical with another mole of nitroxyl radical).⁵ The reaction of **1a** with ethylbenzene at 133 °C gave a low yield of the corresponding alkoxyamine derivative 5 (6% recrystallized) and a greater than theoretical yield of the corresponding hydroxylamine 4a. This is consistent with the known decomposition of similar secondary benzylic alkoxyamine derivatives at the reaction temperature of this study.⁹ Attempts to prepare a bis-adduct by the reaction of 2 equiv or more of **1a** with **2a** (in melt) or **2b** (chlorobenzene solvent)

⁽¹⁾ Presented in part at the 221th National Meeting of the American Chemical Society, San Diego, CA, April 1–5, 2001; American Chemical Society: Washington, DC, 2001; Abstract ORG 527.

⁽²⁾ Johnston, L. J.; Tencer, M.; Scaiano, J. C. *J. Org. Chem.* **1986**, *51*, 2806.

⁽³⁾ Keana, J. F. W.; Dinerstein, R. J.; Baitis, F. J. Org. Chem. 1971, 36, 209.

^{(4) (}a) Banks, R. E.; Haszeldine, R. N.; Justin, B. J. Chem. Soc. (C) 1971, 2777. (b) Banks, R. E.; Choudhury, D. R.; Haszeldine, R. N. J. Chem. Soc., Perkin Trans. 1 1973, 1092. (c) Banks, R. E.; Birchall, J. M.; Brown, A. K.; Haszeldine, R. N.; Moss, F. J. Chem. Soc., Perkin Trans. 1 1975, 2033.

⁽⁵⁾ Connolly, T. J.; Scaiano, J. C. *Tetrahedron Lett.* **1997**, *38*, 1133.
(6) Opeida, I. A.; Matvienko, A. G.; Ostrovskaya, O. Z. *Kinet. Catal.* **1995**, *36*, 441.

⁽⁷⁾ Busfield, W. K.; Grice, D. L.; Jenkins, I. E.; Thang, S. H. Aust. J. Chem. 1991, 44, 1407.

⁽⁸⁾ Bottle, S. E.; Busfield, W. K.; Jenkins, I. D. J. Chem. Soc., Perkin Trans. 2 1992, 2145.

^{(9) (}a) Hawker, C. J.; Barclay, G. G.; Orellana, A.; Dao, J.; Devonport, W. *Macromolecules* **1996**, *29*, 5245. (b) Devonport, W.; Michalak, L.; Malmström, E.; Mate, M.; Kurdi, B.; Hawker, C. J.; Barclay, G. G.; Sinta, R. *Macromolecules* **1997**, *30*, 1929.

gave extensive decomposition with the chromatographic isolation of trace amounts of **6a** and **6b**, respectively. A reasonable explanation for this observation is that the rate of the reaction of nitroxyl radical with the substituted benzylic hydrogen is greater than that with the methyl hydrogen atom in the intermediate alkoxyamines **3a,b**, which leads to decomposition and rearrangement products.



Scaiano reported that the bis-adduct **7** is formed by the reaction of 2 mol of TEMPO with styrene.⁵ Jenkins observed the formation of **8** in the reaction of a 1*H*isoindol-2-yloxyl radical with the allylic proton containing substrate cyclohexene (**9**). The reaction of **1a** with **9**, 1-octene (**10**), or cyclooctene (**11**) gave the corresponding allylic derivatives **12**, **13**, and **14**, respectively. The acyclic alkene derivative **13** was obtained as a 30:70 cis:trans isomer mixture. Excess alkene was used as the reaction solvent. In the reaction of **1a** with **9**, no evidence was observed for the formation of the vicinal bis-adduct **15** as in the case of styrene, nor was the formation of the diadduct **16** observed as a result of reaction at both allylic positions.





FIGURE 1. Potential (a) H-abstraction, (b) stepwise nitroxyl addition–elimination, and (c) nitroxyl addition–H-atom-abstraction pathways for the reaction of **1a** with **9**.



FIGURE 2. Calculated E_a for H-atom abstraction and nitroxyl addition pathways.

However, unlike the benzylic substrates which required reaction temperatures greater than 100 °C, the reaction of 1a with 9 proceeded at 70 °C to give 12. Indeed, the formation of **12** was observed to slowly form upon stirring **1a** with **9** at room temperature. The reaction of **1a** with an equimolar mixture of **9** and **2b** at 70 °C gave only **12** without any evidence for the formation of **3b**. In a more revealing experiment, heating a mixture of cyclohexene and ethylbenzene that have secondary allylic and benzylic protons, respectively, at 45 °C led only to the formation of 12 with no observable 5. These observations are unexpected if the mechanism of the reaction is hydrogen atom abstraction by nitroxyl radical for both benzylic and allylic substrates because the bond dissociation energy for allylic and benzylic C-H bonds is expected to be nearly the same.¹⁰

In an effort to provide some further mechanistic insight, the activation enthalpies of three potential reaction pathways were evaluated utilizing semiempirical UHF/AM1 calculations (see Figure 1). For the purposes of the calculations, TEMPO was used as a general model for compound **1a**. As pathways b and c have a common intermediate, the transition states for allylic H-atom abstraction and nitroxyl radical addition to the double bond were located (see Figure 2). The calculated enthalpic barrier to allylic H-atom abstraction from **9** was 37.5 kcal/ mol for the pseudoaxial H-atom. It is noteworthy that the pseudoaxial abstraction was slightly favored (by about 1 kcal/mol) over abstraction of a pseudoequatorial

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^{(10) (}a) Benson, S. W. J. Chem. Educ. **1965**, 42, 502. (b) Kerr, J. A. Chem. Rev. **1966**, 66, 465.

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FIGURE 3. Calculated E_a of possible reaction pathways leading to **12** from the vicinal diadduct **15**.

hydrogen. This seems reasonable in light of the overlap between the developing singly occupied carbon p-orbital and the adjacent π system of the incipient allylic radical. In contrast, TEMPO addition to the double bond of **9** proceeded with a calculated enthalpic barrier of only 28.5 kcal/mol (TS1, Figure 2), 9.0 kcal/mol lower than that calculated for pathway a. These results are consistent with the formation of only product **12** when equimolar amounts of **9** and **2b** are mixed with **1a** at 70 °C, in that the calculation predicts that addition to the double bond is faster than allylic (or even benzylic) H-atom abstraction.

After the formation of the addition product, additional nitroxyl may react in a stepwise manner to form the bisproduct 15. Indeed, a transition structure for this process was located. All attempts at locating a termolecular activated complex, as a result of concerted addition of 2 mol of nitroxyl, failed, and reverted back to the bimolecular structure. The calculated activation barrier for this bimolecular coupling was 13.8 kcal/mol, which probably arises largely from the steric requirements of a hindered nitroxyl and a secondary alkyl radical. Even so, this calculated value is too high in comparison to the previously reported experimental value of 2.3 kcal/mol for the coupling of TEMPO with α-methylbenzyl radical.¹¹ Quantitative agreement between the experimental and our calculated value is not to be expected, as semiempirical methods, such as AM1, have been parametrized from ground-state structures, rather than transition states. Conversely, we have seen that the relative energetics provided by the calculations are fully consistent with the experimental results (vide infra).

The bis-adduct **15** may ultimately form product **12** through an elimination mechanism involving the β -hydrogen, in a cyclic transition structure (Figure 3). Furthermore, this hydrogen may also be abstracted by an additional nitroxyl radical, followed by homolytic fragmentation to form the olefin. Both of these pathways were calculated to be high-energy processes proceeding with barriers of 56.1 and 41.1 kcal/mol, respectively. In contrast, reversion of **15** to the mono-addition radical



FIGURE 4. Calculated E_a for nitroxyl addition-H-atomabstraction pathway.

SCHEME 2. Reaction of Nitroxyl 1b with Mono-adduct 12



product was calculated to be a relatively easy process, proceeding with a calculated barrier of only 30.8 kcal/mol.

The formation of product **12** can occur directly from the mono-addition radical product by abstraction of the H-atom adjacent to the radical site. This relatively lowenergy process, which is driven by the formation of the double bond, is calculated to proceed with an enthalpic barrier of 30.9 kcal/mol (TS3, Figure 4).

The relative energetics provided by the calculations suggest a possible mechanistic pathway for the reaction. Nitroxyl addition to the double bond, which is faster than allylic H-atom abstraction, produces the mono-addition radical product. This product can rapidly undergo a crosscoupling reaction with another nitroxyl to give the bisaddition product **15**. As the lowest energy pathway from

⁽¹¹⁾ Skene, W. G.; Belt, S. T.; Connolly, T. J.; Hahn, P.; Scaiano, J. C. *Macromolecules* **1998**, *31*, 9103.

15 is the reversion back to the mono-adduct, an equilibrium may be set up between the mono-adduct and **15**. The product **12** can then be formed through an essentially irreversible [E_a (forward) = 30.9 kcal/mol; E_a (reverse) = 45.3 kcal/mol] H-atom abstraction from the mono-adduct.¹²

In a crossover experiment designed to further ascertain whether the proposed nitroxyl addition—H-atom-abstraction mechanism is correct, an equimolar mixture of **12** and the 4-benzyloxy-substituted nitroxyl **1b** in benzene was heated together at 56 °C. Addition of **1b** to **12** should lead to the radical intermediate or transition state **17**, from which either **1a** or **1b** could eliminate (Scheme 2). Consistent with the proposed mechanism, a mixture of **1a**, **1b**, **12**, and **18** was obtained.

In general, the calculated and experimental results provide a detailed mechanistic picture that strongly supports pathway c (Figure 1), nitroxyl addition followed by H-atom abstraction, which has not been previously considered for this reaction. Of greater significance to the scientific community, the occurrence of low-energy pathways for the addition of hindered nitroxyl radicals to *unactivated* alkenes has previously been unrecognized when using nitroxyls as radical traps in mechanistic studies.¹³

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Supporting Information Available: Detailed descriptions of experimental procedures, compound characterization, and transition state structure coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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⁽¹²⁾ The conclusions of this study are further supported by studies on the rates of H-abstraction versus addition of hydrogen atoms to alkenes, see: (a) Tanner, D. D.; Zhang, L. J. Am. Chem. Soc. **1994**, *116*, 6683. (b) Tanner, D. D.; Zhang, L.; Kandanarachchi, P. J. Phys. Chem. **1997**, *101*, 9327.

^{(13) (}a) For the addition of perfluorinated nitroxyl radicals to olefins, see: Doba, T.; Ingold, K. U. *J. Am. Chem. Soc.* **1984**, *106*, 3958. (b) For addition to an activated olefin, see: Aldabbagh, F.; Busfield, W. K.; Jenkins, I. D.; Thang, S. H. *Tetrahedron Lett.* **2000**, *41*, 3673. (c) For addition to an alkyne, see: König, B.; Pitsch, W.; Klein, M.; Vasold, R.; Prall, M.; Schreiner, P. R. *J. Org. Chem.* **2001**, *66*, 1742. (d) For addition of sterically hindered nitroxyl radicals to styrene, see: (e) Ruban, L. B.; Buchachenko, A. L.; Neiman, M. B. *Vysokomol. Soedin., Ser. A* **1967**, *9*, 1559. (f) Reference 9b. (g) For the reaction of perfluorinated nitroxyl radicals with polyhalogenated alkenes, see: Makarov, S. P.; Englin, M. A.; Mel'nikova, A. V. *Zh. Obshch. Khim.* **1969**, *39*, 538.