JOC Article

# Mechanisms of Reaction of Aminoxyl (Nitroxide), Iminoxyl, and Imidoxyl Radicals with Alkenes and Evidence that in the Presence of Lead Tetraacetate, *N*-Hydroxyphthalimide Reacts with Alkenes by Both Radical and Nonradical Mechanisms

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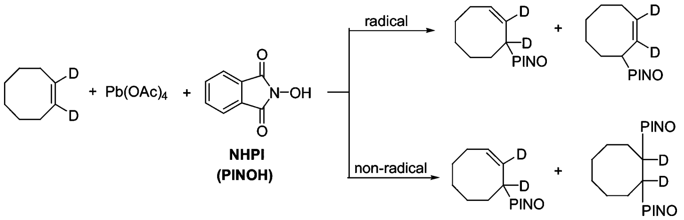
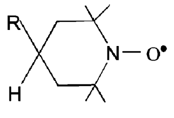


1,2-Dideuterio-cyclohexene, 1,2-dideuterio-cyclooctene, and *trans*-3,4-dideuterio-hex-3-ene were reacted with three $>NO^\bullet$ radicals: 4-hydroxyTempo, di-*tert*-butyliminoxyl, both used as the actual radicals, and phthalimide-*N*-oxyl (**PINO**) generated from *N*-hydroxyphthalimide (**NHPI**) by its reaction with *tert*-alkoxyl radicals ($t$-RO$^\bullet$) and with lead tetraacetate. In all cases, except the **NHPI**/$Pb(OAc)_4$ system, only mono $>NO$-substituted alkenes were produced. The $^2H$ NMR spectra imply that 88−92% of monoadducts were formed by the initial abstraction of an allylic H-atom, followed by capture of the allylic radical by a second $>NO^\bullet$, while the remaining 12−8% appear to be formed by an initial addition of $>NO^\bullet$ to the double bond followed by H-atom abstraction by a second $>NO^\bullet$. A substantial and sometimes the major product formed with the **NHPI**/$Pb(OAc)_4$ system has two **PINO** moieties added across the double bond. Since such diadducts are not formed with the **NHPI**/$t$-RO$^\bullet$ system, a heterolytic mechanism is proposed, analogous to that known for the $Pb(OAc)_4$-induced acetoxylation of alkenes. A detailed analysis of the **NHPI**/$Pb(OAc)_4$/alkene products indicates that monosubstitution occurs by both homolytic and heterolytic processes.

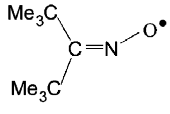
## Introduction

In recent years, there has been an upsurge in research directed toward improving the rates of oxidation of organic compounds and improving product selectivities. One promising approach uses radicals bearing the $>NO^\bullet$ moiety. Persistent $>NO^\bullet$ radicals have often been employed as neat, stoichiometric oxidants. Both persistent and transient $>NO^\bullet$ have been even more frequently employed in catalytic quantities in radical chain reactions in the presence of oxygen and, frequently, also in the presence of a transition metal ion as a cocatalyst. The $>NO^\bullet$ radicals used include aminoxyls (nitroxides) such as Tempo (**1a**) and related species,[1,2] iminoxyl radicals, particularly di-*tert*-butyliminoxyl (**2**)[3,4] and imidoxyls such as phthalimide-*N*-oxyl, **PINO** (**3**),[2,5−7] and related radicals.[8]

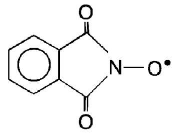


**1a** R = H

**1b** R = OH



**2**



**PINO (3)**

These radicals have been used to oxidize hydrocarbons, alcohols, and aldehydes at higher rates and with better

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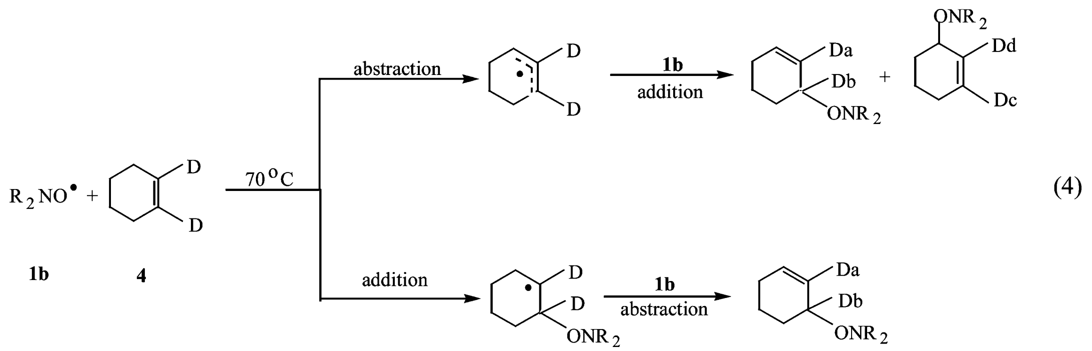
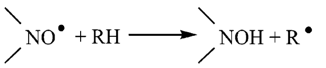
(1) Reviews: (a) Sheldon, R. A.; Arends, I. W. C. E.; Brink, G.-J. T.; Dijksman, A. *Acc. Chem. Res.* **2002**, *35*, 774−781. (b) Minisci, F.; Recupero, F.; Pedulli, G. F.; Lucarini, M. *J. Mol. Catal. A: Chem.* **2003**, *204−205*, 63−90. (c) Sheldon, R. A.; Arends, I. W. C. E. *Adv. Synth. Catal.* **2004**, *346*, 1051−1071.

10.1021/jo0504060 CCC: $30.25

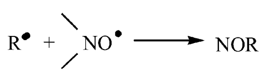
**SCHEME 1**



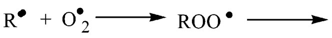
selectivities than can be achieved using oxygen alone. Generally, there is no mechanistic ambiguity: the $>NO^{\bullet}$-abstracts a hydrogen atom from the substrate, RH, and the derived carbon-centered radical may react with a second $>NO^{\bullet}$, or with dioxygen, depending on the conditions:



$$>NO^{\bullet} + RH \longrightarrow >NOH + R^{\bullet} \qquad (1)$$



$$R^{\bullet} + >NO^{\bullet} \longrightarrow NOR \qquad (2)$$

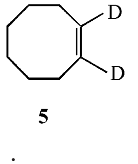


$$R^{\bullet} + O_2^{\bullet} \longrightarrow ROO^{\bullet} \longrightarrow \qquad (3)$$

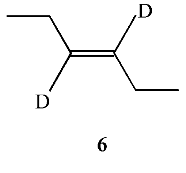
However, for some compounds, particularly the cycloalkenes, there is a mechanistic ambiguity. The common assumption[9] is that the $>NO^{\bullet}$ will abstract an allylic H-atom, thus forming an allylic radical that undergoes the further reactions. This assumption was recently challenged by Babiarz et al.[10] These workers suggested that the reaction of 4-hydroxyTempo, **1b**, with cyclohexene involved an initial addition of the radical to the double bond followed by H-atom abstraction from the $CH_2$ group adjacent to the new radical center. That is, Babiarz et al.[10] proposed that the monosubstitution product from **1b** and cyclohexene followed an addition−abstraction mechanism rather than an abstraction−addition mechanism as had normally been assumed. As we have noted previously,[11] the addition−abstraction mechanism was proposed "because the bond dissociation energy (enthalpies) for allylic and benzylic C−H bonds is expected to be nearly the same."[10] This mechanism was also claimed to be supported by semiempirical UHF/AM1 calculations.[10] Unfortunately, even if the enthalpic (thermochemical) arguments were correct,[12] entropic effects favoring H-abstraction from cyclohexene[13] had been ignored.

In a preliminary communication,[11] we reported a simple and convenient method for distinguishing between these two mechanisms and mixtures thereof. We employed the same reaction as Babiarz et al. except that cyclohexene was replaced by its 1,2-dideuterio isotopomer, **4**. This deuterium label was chosen because, for both mechanisms, there would be no primary deuterium kinetic isotope effect and hence little isotopic "biasing" of the results. Furthermore, $^2H$ NMR of the products would provide a clear marker of the reaction mechanism since one product would be unique to the abstraction−addition mechanism (see Scheme 1).

To our surprise, both mechanisms are operational in the **1b** + **4** reaction, the more important being abstraction−addition (see Scheme 1). We have carried this work forward with eight additional reactions, involving **4** and two new alkenes, 1,2-dideuterio-cyclooctene, **5**, and *trans*-3,4-dideuterio-hex-3-ene, **6**, using the $>NO^{\bullet}$ radicals **1b**, **2**, and **3**.



**5**



**6**

Both mechanisms are operative for all of the eight new reactions and, astonishingly, for both the nitroxide, **1b**, and the iminoxyl, **2**; the partitioning between the two

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(2) Minisci, F.; Recupero, F.; Cecchetto, A.; Gambarotti, C.; Punta, C.; Faletti, R.; Paganelli, R.; Pedulli, G. F. *Eur. J. Org. Chem.* **2004**, 109−119.

(3) Mendenhall, G. D.; Ingold, K. U. *J. Am. Chem. Soc.* **1973**, *95*, 2963−2971.

(4) (a) Lornejo, J. J.; Larson, K. D.; Mendenhall, G. D. *J. Org. Chem.* **1985**, *50*, 5382−5383. (b) Ngo, M.; Larson, K. R.; Mendenhall, G. D. *J. Org. Chem.* **1986**, *51*, 5390−5393. (c) Eisenhauer, B. M.; Wang, M.; Brown, R. E.; Labaziewicz, H.; Ngo, M.; Kettinger, K. W.; Mendenhall, G. D. *J. Phys. Org. Chem.* **1997**, *10*, 737−746. (d) Eisenhauer, B. M.; Wang, M.; Labaziewicz, H.; Ngo, M.; Mendenhall, G. D. *J. Org. Chem.* **1997**, *62*, 2050−2053.

(5) Reviews: (a) Ref 1b. (b) Ref 1c. (c) Ishi, Y.; Sakaguchi, S.; Iwahama, T. *Adv. Synth. Catal.* **2001**, *343*, 393−427.

(6) No *transition* metal ion cocatalyst; see e.g.: (a) Ueda, C.; Noyama, M.; Ohmori, H.; Masui, M. *Chem. Pharm. Bull.* **1987**, *35*, 1372−1377. (b) Amorati, R.; Lucarini, M.; Mugnaini, V.; Pedulli, G. F.; Minisci, F.; Recupero, F.; Fontana, F.; Astolfi, P.; Greci, L. *J. Org. Chem.* **2003**, *68*, 1747−1754. (c) Aoki, Y.; Sakaguchi, S.; Ishii, Y. *Adv. Synth. Catal.* **2004**, *346*, 199−202. (d) Koshino, N.; Saha, B.; Espenson, J. H. *J. Org. Chem.* **2003**, *68*, 9364−9370. (e) Koshino, N.; Cai, Y.; Espenson, J. H. *J. Phys. Chem. A* **2003**, *107*, 4262−4267. (f) Baciocchi, E.; Gerini, M. F.; Lanzalunga, O. *J. Org. Chem.* **2004**, *69*, 8963−8966.

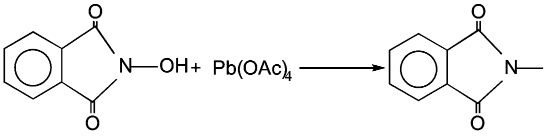
(7) With a transition metal ion cocatalyst; see e.g.: (a) Ishii, Y.; Iwahama, T.; Sakaguchi, S.; Nakayama, K.; Nishiyama, Y. *J. Org. Chem.* **1996**, *61*, 4520−4526. (b) Ishii, Y.; Sakaguchi, S. *Catal. Surv. Jpn.* **1999**, *3*, 27−35. (c) Minisci, F.; Punta, C.; Recupero, F.; Fontana, F.; Pedulli, G. F. *Chem. Commun.* **2002**, 688−689. (d) Figiel, P. J.; Sobczak, J. M.; Ziolkowski, J. J. *Chem. Commun.* **2004**, 244−245. (e) Minisci, F.; Porta, O.; Recupero, F.; Gambarotti, C.; Paganelli, R.; Pedulli, G. F.; Fontana, F. *Tetrahedron Lett.* **2004**, *45*, 1607−1609.

(8) (a) Annunziatini, C.; Gerini, M. F.; Lanzalunga, O.; Lucarini, M. *J. Org. Chem.* **2004**, *69*, 3431−3438. (b) Baucherel, X.; Gonsalvi, L.; Arends, I. W. C. E.; Ellwood, S.; Sheldon, R. A. *Adv. Synth. Catal.* **2004**, *346*, 286−296. (c) Cai, Y.; Koshino, N.; Saha, B.; Espenson, J. H. *J. Org. Chem.* **2005**, *70*, 238−243.

(9) See e.g.: Bottle, S. E.; Busfield, W. K.; Jenkins, I. D. *J. Chem. Soc., Perkins Trans. 2* **1992**, 2145−2150.

(10) Babiarz, J. E.; Cunkle, G. T.; DeBellis, A. D.; Eveland, D.; Pastor, S. D.; Shum, S. P. *J. Org. Chem.* **2002**, *67*, 6831−6834.

mechanisms for all three alkenes is roughly the same as that found for the **1b** + **4** reaction.[11] The same partitioning was also found for the imidoxyl, **PINO** (**3**), when this radical was generated by H-atom abstraction from *N*-hydroxyphthalimide, **NHPI** (**3H**), using *tert*-alkoxyl radicals, *t*-RO$^\bullet$. However, the same partitioning was not found when the alkenes were allowed to react with **NHPI** and lead tetracetate in benzene. This is a chemical system that was shown to form **PINO** radicals as early as 1964 by Lemaire and Rassat[15] using EPR spectroscopy (reaction 5). Furthermore, for the **NHPI**/Pb(OAc)$_4$ system, a significant, even major, product was a diadduct in which two **PINO** moieties had added across the double bond of the alkene.



(5)

**NHPI (3H)** **PINO (3)**

## Experimental Section

**Materials.** (i) *>NO$^\bullet$ Radicals **1**, **2**, and **3***. The stable nitroxide radical, **1b**, was purchased (Aldrich). Syntheses of the persistent iminoxyl radical, **2**, and its precursor, di-*tert*-butyl ketoxime, **2H**, have been described.[3] *N*-Hydroxyphthalimide, **NHPI** (**3H**, Aldrich), was used as the precursor for the nonpersistent **PINO** (**3**) radical.

(ii) *Dideuterio-alkenes **4**, **5**, and **6***. The synthesis of **4** has been described.[11] Alkenes **5** and **6** were synthesized by lithium aluminum deuteride reduction[16] of cyclooctyne[17] and 3-hexyne (Aldrich), respectively. For details, see Supporting Information.

(iii) *Other*. Di-*tert*-butyl hyponitrite and dicumyl hyponitrite were synthesized by standard methods.[18]

**>NO$^\bullet$ + Dideuterio-alkene Reactions.** The alkene was always used in large excess over the >NO$^\bullet$ radical to minimize any further reactions of the initial products. In all cases, the radical/alkene adducts were placed under a high vacuum overnight to remove any traces of the alkenes. If present, these alkenes could, of course, confound appropriate analyses by $^2$H NMR of the products and, hence, the determination of the reaction mechanism. All $^2$H NMR spectra were obtained in CHCl$_3$. The $T_1$ relaxation times of the $^2$H signals were ~100 ms, and the delay time between pulses was therefore chosen to be 2s ($\gg 5 \times T_1$) to ensure accurate integration of these signals.

(i) **1b**. Each of the three neat alkenes was reacted with ca. 10 mol % of the neat nitroxide under nitrogen at the temperatures and for the times indicated: **4**, 70 °C, 72 h; **5**, 88 °C, 48 h; **6**, ~64 °C (reflux), 72 h. The workup of the **1b** (mono)-substituted dideuterio-alkene products for $^2$H NMR spectroscopic analysis was the same as that described previously for the **1b**/**4** reaction.[11] For both the abstraction−addition and addition−abstraction mechanisms, half of **1b** abstracts a hydrogen atom to form **1bH**. Thus, the maximum yield of the adducts is 50% on the basis of **1b**. The actual yields were 15.5% (**4**), 18% (**5**), and 20% (**6**). These yields would presumably have been doubled if the reactions had been carried out in the presence of an oxidizing agent (such as silver oxide), which would convert the **1bH** product back to **1b**. Even higher yields would have been obtained if the reactions had been run for longer times or at higher temperatures, since the $^2$H NMR showed no sign of other products (see Supporting Information). Higher yields were not, however, required for our purposes.

(ii) **2**. The three neat alkenes were mixed under nitrogen with the neat iminoxyl radical (molar ratio ca. 2.2:1.0) and allowed to stand (still under nitrogen) at room temperature. The blue color of the radical slowly faded, and crystals of di-*tert*-butyl ketoxime, **2H**, were formed. After 90 min, a roughly equal volume (0.5 mL) of pentane was added, and the mixture was cooled to −60 °C for 1 h. The supernatant was removed and passed through a short column of basic alumina to remove the remaining **2H**. The eluate and pentane washings were concentrated to give the *O*-(dideuterio-alkenyl) oxime products. Again, the maximum yield of the adducts is 50% on the basis of **2**. The actual yields were 28% (**4**, the isolation and characterization of the allylic substitution product of **2** + nondeuterated **4** have been described elsewhere[4d]), 30% (**5**), and 31% (**6**). These yields could also, presumably, have been doubled if the reaction had been carried out in the presence of an oxidizing agent to regenerate **2** from **2H** and could have been further improved by a longer reaction time and/or a higher reaction temperature.

(iiia) **3**. In our first investigation of the mechanism of reaction of this imidoxyl radical with our three alkenes, we oxidized **NHPI** (**3H**) with lead tetraacetate in the presence of dideuterio-alkenes at room temperature in deoxygenated acetonitrile, a solvent chosen to provide both reasonable solubilities for **NHPI** and Pb(OAc)$_4$ and easy product workup. The alkene, **NHPI**, and Pb(OAc)$_4$ were always reacted together at molar ratios of 10:2:1. The alkene (49 mM **4**, 76 mM **5**, and 83 mM **6**) and **NHPI** in 5 mL of acetonitrile were added to 5 mL of acetonitrile solutions of Pb(OAc)$_4$. Directly after mixing, the acetonitrile and excess alkene were removed under reduced pressure. The mono- and di-**PINO** alkene adducts were separated and purified by preparative TLC using hexane/ethyl acetate (2:1, v/v) as an eluent. Product yields based on **NHPI** were **4-PINO** 17%, **4**-(**PINO**)$_2$ 1% (**NHPI** reacted = 17 + 2 × 1 = 19%); **5-PINO** 9%, **5**-(**PINO**)$_2$ 16% (**NHPI** reacted = 41%); and **6-PINO** 9%, **6**-(**PINO**)$_2$ 10% (**NHPI** reacted = 29%). In the case of cyclooctene, the normal $^2$H NMR analyses were supplemented by $^1$H and $^{13}$C NMR and X-ray crystallography on the products formed from nondeuterated cyclooctene (see Supporting Information).

In view of the unusual pattern of products (see Results) and the well-known fact that Pb(OAc)$_4$ can, itself, oxidize alkenes,[19] including, e.g., cyclohexene,[20] we turned next to a system in which free **PINO** radicals would be the unquestioned product of a one-electron oxidation of **NHPI**.

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(11) Coseri, S.; Ingold, K. U. *Org. Lett.* **2004**, *6*, 1641−1643.

(12) Allylic C−H bonds may actually by slightly weaker than comparable benzylic bonds; e.g., for primary C−H, the bond dissociation enthalpies (kcal/mol) are 88.8 ± 0.4 for propylene and 89.7 ± 0.6 for toluene. See Table 2 in: Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255−263.

(13) H-abstraction from ethylbenzene requires the free rotation about the Ph−C bond to be "frozen out" in the transition state for PhC$^\bullet$-HCH$_3$ radical formation. There are no such restrictions on cyclohexene. Moreover, two of the allylic C−H bonds in cyclohexene are perpendicular to the CCH=CHC plane and are therefore well positioned for C−H bond rupture with full allylic stabilization. In contrast, the two benzylic C−H bonds in ethylbenzene lie at an angle of 30° to the aromatic plane and are not well positioned for C−H rupture. These factors are manifest in the rate constants for H-abstraction by the corresponding peroxyl radicals at 30 °C, viz.,[14] cyclohexene 6.0 M$^{-1}$ s$^{-1}$, ethylbenzene 1.3 M$^{-1}$ s$^{-1}$, and 1,2,3,4-tetrahydronaphthalene (where addition−abstraction is not possible) 6.4 M$^{-1}$ s$^{-1}$.

(14) Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1967**, *45*, 793−802.

(15) Lemaire, E.; Rassat, A. *Tetrahedron. Lett.* **1964**, 2245−2248.

(16) Kroll, J. H.; Donahue, N. M.; Cee, V. J.; Demerjian, K. L.; Anderson, J. G. *J. Am. Chem. Soc.* **2002**, *124*, 8518−8519.

(17) Brandsma, L.; Verkruijsse, H. D. *Synthesis* **1978**, 290.

(18) (a) Kiefer, H.; Traylor, T. G. *Tetrahedron Lett.* **1966**, 6163−6168. (b) Dulog, L.; Klein, P. *Chem. Ber.* **1971**, *104*, 895−901. (c) Ogle, C. A.; Martin, S. W.; Dziobak, M. P.; Urban, M. W.; Mendenhall, G. D. *J. Org. Chem.* **1983**, *48*, 3728−3733. (d) Quinga, E. M. Y.; Bieker, T.; Dziobak, M. P.; Mendenhall, G. D. *J. Org. Chem.* **1989**, *54*, 2769−2771.

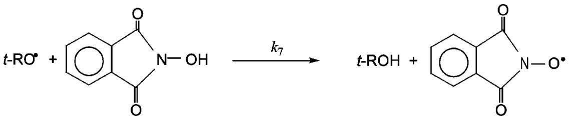
(19) Review: Moriarty, R. M. In *Selective Organic Transformations*; Thyagarajan, B. S., Ed.; Interscience: New York, 1972; pp 183−237.

(20) Anderson, C. B.; Winstein, S. *J. Org. Chem.* **1963**, *28*, 605−606. Wiberg, K. B.; Nielsen, S. D. *J. Org. Chem.* **1964**, *29*, 3353−3361.

(iiib) **3**. **NHPI** was oxidized with *tert*-alkoxyl radicals generated by the thermal decomposition of di-*tert*-alkyl hyponitrites (reactions 6 and 7). Pedulli and co-workers[6b] have shown that reaction 7

$$t\text{-RON}{=}\text{NOR-}t \xrightarrow{\Delta} 2t\text{-RO}^{\bullet} + \text{N}_2$$
$$t\text{-R} = \text{Me}_3\text{C, PhMe}_2\text{C} \tag{6}$$

occurs because in the presence of **NHPI**, photochemically



NHPI (3H) PINO (3) (7)

generated $t$-RO$^\bullet$ radicals yield the characteristic **PINO** EPR spectrum. The hyponitrite/**NHPI**/alkene experiment must, of course, be designed to ensure that essentially the only radical to react with the alkene is **PINO**. This can only be done with a full knowledge of the rate constant for reaction 7 and the rate constants for reaction of $t$-RO$^\bullet$ radicals with the three alkenes (reaction 8), which includes both H-atom abstraction and addition to the double bond.

$$t\text{-RO}^{\bullet} + \text{alkene} \xrightarrow{k_8} \text{products} \tag{8}$$

There has been no measurement of $k_7$, while values of $k_8$ are available only for the reaction of *tert*-butoxyl with nondeuterated **4**[21] and **5**.[22] We therefore measured $k_7$ and $k_8$ for all three nondeuterated alkenes (see later).

Two sets of hyponitrite/**NHPI**/alkene experiments were carried out under oxygen-free conditions. In one, di-*tert*-butyl hyponitrite was employed in refluxing benzene (to reflect the temperatures of the **1b**/alkene reactions). Under these conditions the half-life of the hyponitrite will be about 5 min.[18a] In the other, dicumyl hyponitrite was employed in benzene at room temperature. The reaction was run in the dark for 14 days, which is sufficient for >99% of the hyponitrite to decompose[23] and reflects the temperatures used in the **NHPI**/Pb(OAc)$_4$ experiments and those used in the iminoxyl, **2**, experiments.

In refluxing benzene, the reactants were **NHPI**, 1.35 mmol; dideuterio-alkene, 1.35 mmol; and hyponitrite, 0.34 mmol (which will yield slightly less than 0.68 mmol of $t$-RO$^\bullet$ because of some in-cage coupling of the geminate radical pair).[24] The products of interest were again separated by preparative TLC as in the Pb(OAc)$_4$ experiments.

In room-temperature benzene, the reactants were **NHPI**, 0.4 mmol; dideuterio-alkene, 0.4 mmol; and hyponitrite, 0.125 mmol. The products were separated in the usual way.

**Measurement of the Rate Constants for Reactions 7 and 8.** The rate constants for the three reactions 8 were measured in benzene at room temperature by 308 nm laser flash photolysis (LFP) of dicumyl peroxide (0.13 M; at this concentration, the OD is ~0.3 at 308 nm). The LFP equipment and general procedure have been adequately described.[21,25] The decay of the cumyloxyl radical was monitored using its visible absorption band at ~485 nm[26] with at least five different concentrations of the three (nondeuterated) alkenes. Pseudo-first-order rate constants ($k_{\text{exptl}}$ (s$^{-1}$)) were determined using digitally averaged decay traces from 5−10 laser flashes. Second-order rate constants, $k_8$ (M$^{-1}$ s$^{-1}$) (see Results), were calculated from the slopes of the straight lines obtained by least-squares fitting of $k_{\text{exptl}}$ vs [alkene]; see Supporting Information.

**TABLE 1. Rate Constants for the Reactions of $t$-RO$^\bullet$ Radicals with NHPI at 30 °C and with Three Nondeuterated Alkenes at Ambient Temperatures**

| | $10^{-6}\,k$ (M$^{-1}$ s$^{-1}$) | | |
|---|---|---|---|
| substrate | this work | literature | ref |
| NHPI | 1050 | | |
| cyclohexene | 4.6 | 5.7 | 21 |
| cyclooctene | 2.3 | 2.6 | 22 |
| *trans*-3-hexene | 2.7 | | |

The LFP method could not be employed for reaction 7 because **NHPI** absorbed too strongly at the laser wavelength. This rate constant was therefore obtained by thermally decomposing dicumyl hyponitrite at 30 °C in benzene in the presence of five different concentrations of **NHPI** for 14 days (to ensure complete decomposition of the hyponitrite, vide supra). Under these conditions, reaction 7 (RO$^\bullet$ = cumyloxyl) and reaction 9 are in competition. The ratio of the yields

$$\text{PhCMe}_2\text{O}^{\bullet} \rightarrow \text{PhCOMe} + \text{Me}^{\bullet} \tag{9}$$

of the products of these two reactions, viz., [cumyl alcohol]/[acetophenone], when plotted against [**NHPI**] gave a straight line, the slope of which is $k_7/k_9 = 2760$ M$^{-1}$ (see Supporting Information). In benzene at this temperature, $k_9 = 3.8 \times 10^5$ s$^{-1}$,[27] and hence $k_7$ is readily obtained.

The LFP and competition kinetic data are presented in Table 1. For cyclohexene and cyclooctene, agreement with the literature is satisfactory. Even with the most reactive alkene, cyclohexene, the magnitudes of these rate constants ensure that with equimolar **NHPI** and alkene (vide supra), at least 99.5% of the alkoxyls generated will react with **NHPI** and form **PINO** (reaction 7) and only 0.5% will react with the alkene.

## Results

The $^2$H NMR spectra for 1,2-dideuterio-cyclohexene, **4**, and the products of its reaction with nitroxide **1b** have been presented previously.[11] Figure 1 shows the $^2$H NMR spectra for 1,2-dideuterio-cyclooctene, **5**, and the products of its reaction with **1b** and with the iminoxyl, **2**. The $^2$H NMR spectra for the products obtained when **NHPI** is oxidized by $t$-RO$^\bullet$ radicals and by Pb(OAc)$_4$ in the presence of **5** are shown in Figure 2. Additional $^2$H NMR spectra are available in Supporting Information. The relevant structures and $^2$H NMR chemical shifts are summarized in Table 2.

Even a cursory examination of Table 2 reveals that the two deuterium atoms labeled D$_a$ and D$_d$ for each pair of monoadducts have, as would be expected, identical

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[21] Paul, H.; Small, R. D., Jr.; Scaiano, J. C. *J. Am. Chem. Soc.* **1978**, *100*, 4520−4527.

[22] Encinas, M. V.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 6393−6397.

[23] Mendenhall, G. D.; Chen, H.-T. E. *J. Phys. Chem.* **1985**, *89*, 2849−2851. See also: Snelgrove, D. W.; Lusztyk, J.; Banks, J. T.; Mulder, P.; Ingold, K. U. *J. Am. Chem. Soc.* **2001**, *123*, 469−477.

[24] Kiefer, H.; Traylor, T. G. *J. Am. Chem. Soc.* **1967**, *89*, 6667−6671.

[25] Kazanis, S.; Azarani, A.; Johnston, L. J. *J. Phys. Chem.* **1991**, *95*, 4430−4435.

[26] Avila, D. V.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1992**, *114*, 6576−6577. Avila, D. V.; Ingold, K. U.; Di Nardo, A. A.; Zerbetto, F.; Zgierski, M. Z.; Lusztyk, J. *J. Am. Chem. Soc.* **1995**, *117*, 2711−2718.

[27] Avila, D. V.; Brown, C. E.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **1993**, *115*, 466−470.

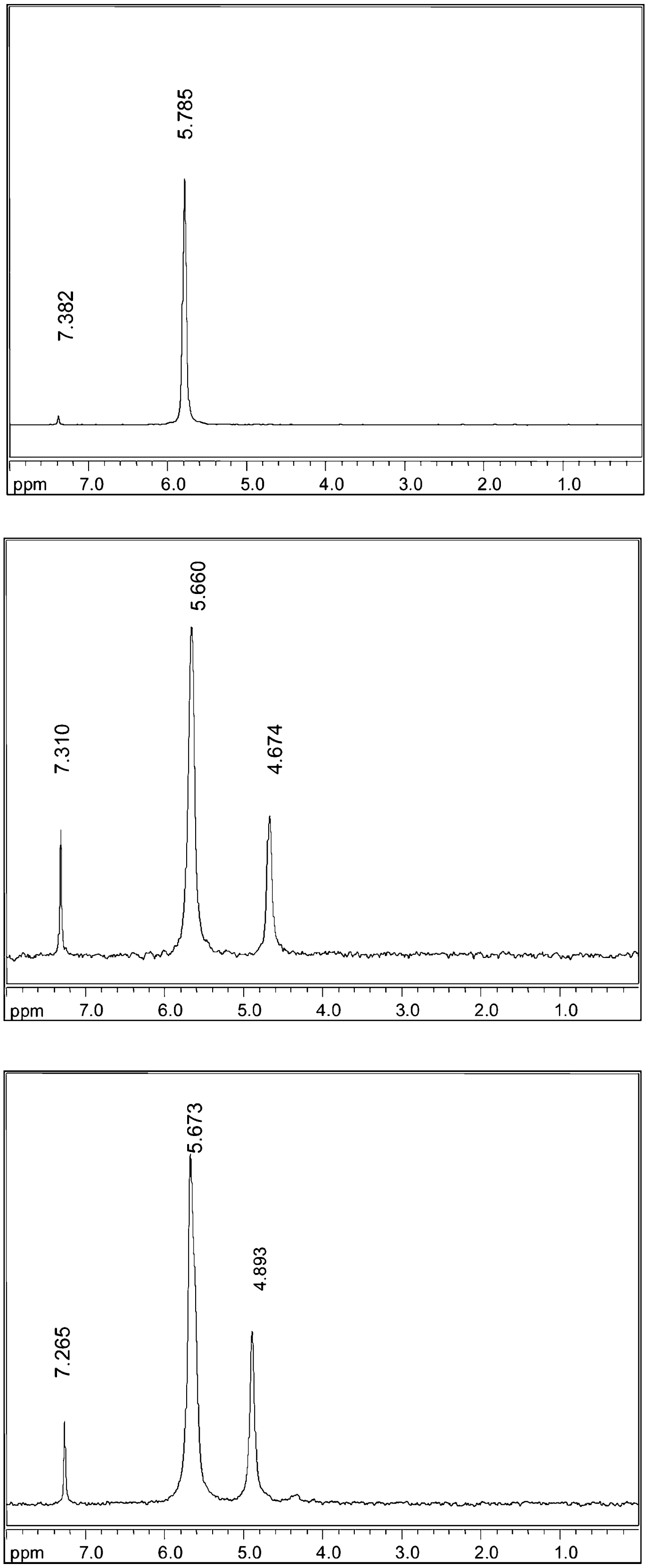


**FIGURE 1.** $^2$H NMR spectra for 1,2-dideuteriocyclooctene (neat, top) and for the products of its reaction with **1b** (middle) and **2** (bottom) in $CHCl_3$. The peaks at 7.382, 7.310, and 7.265 are due to natural abundance $CDCl_3$.

chemical shifts. The chemical shift for $D_c$ also overlaps those for $D_a$ and $D_d$ except for the **1/4** products.[11] However, the deuterium $D_b$, which is bonded to the sp$^3$-hybridized carbon bearing the radical moiety, **n**, always has a unique chemical shift. The product containing $D_b$ can be formed both by abstraction−addition and by addition−abstraction (see Scheme 1). Fortunately, the relative importance of the two mechanisms of formation of monoadducts can be determined by integration of the two signals, one arising from $D_a + D_c + D_d$ and another from $D_b$. Since $D_a = D_b$ (Scheme 1) we have:

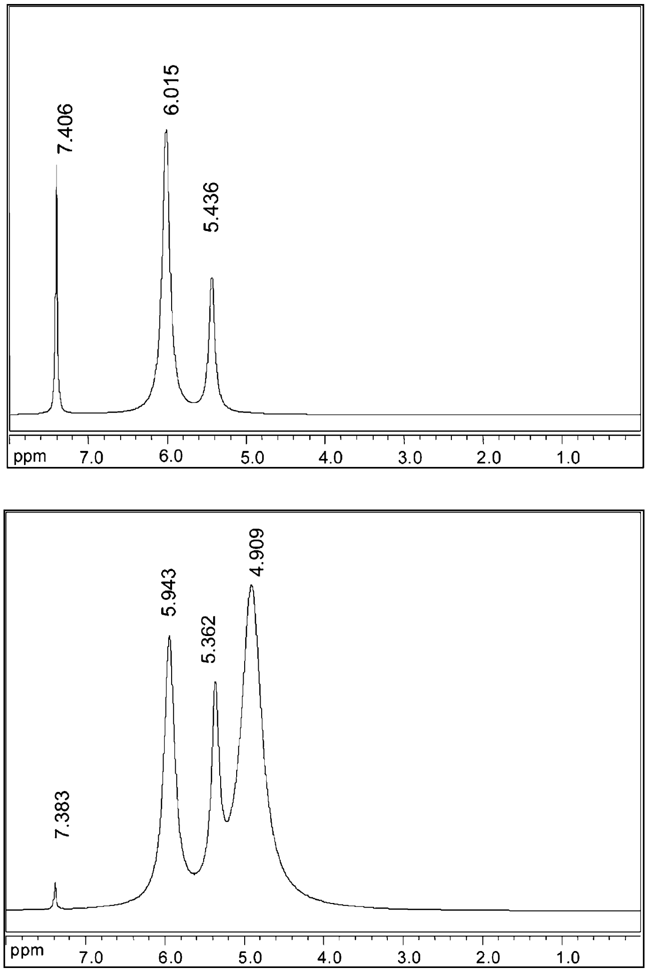


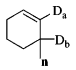
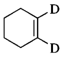
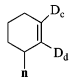
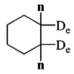
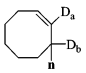
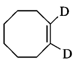
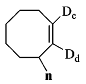
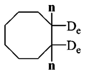
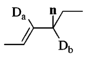
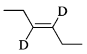
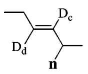
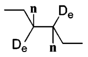
**FIGURE 2.** $^2$H NMR spectra for the products of 1,2-dideuteriocyclooctene reaction with **NHPI** oxidized with $t$-RO$^\bullet$ in benzene under reflux (top) and oxidized with lead tetraacetate (bottom). The peaks at 7.406 and 7.383 are due to natural abundance $CDCl_3$.

$$(D_a + D_c + D_d) - D_b = [D_c + D_d]$$

Because the >NO$^\bullet$ radical will add with equal probability to both ends of the allyl radicals, two of which are completely symmetric, the total amount of the abstraction−addition products is: $2[D_c + D_d]$. The percentage of the monoadduct products from abstraction−addition is therefore given by equation I:

$$\frac{2[D_c + D_d]}{(D_a + D_c + D_d) + D_b} \times 100 = \frac{2\{(D_a + D_c + D_d) - D_b\}}{(D_a + D_c + D_d) + D_b} \times 100 \quad \text{(I)}$$

**TABLE 2. Assignments[a] (and Relative Intensities[b] for Monoadducts, in Parentheses) of $^2$H NMR Signals in $CHCl_3$ of Radical (*n*)-Alkene Adducts, $\delta$ (ppm)[c]**

| Alkene | Product | Radical<br>**1b** | <br>**2** | <br>**3** ($t$-RO$^\bullet$)[d] | <br>**3** (Pb(OAc)$_4$) |
|---|---|---|---|---|---|
| |  | 6.04 (1.84)[e] | 5.97 (2.68) | 6.05 (2.57) | 6.04 (2.16) |
| | | 4.30 (1.00)[e] | 4.54 (1.00) | 4.83 (1.00) | 4.81 (1.00) |
|  5.80 |  | 5.92 (0.82)[e] | 5.97 | 6.05 | 6.04 |
| | | 6.04[e] | 5.97 | 6.05 | 6.04 |
| |  | nd[e,f] | nd[f] | nd[f] | 4.26 (3 %)[g] |
| |  | 5.69 (2.70) | 5.75 (2.68) | 5.95 (2.57) | 5.90 (1.96) |
| | | 4.70 (1.00) | 4.97 (1.00) | 5.37 (1.00) | 5.32 (1.00) |
|  5.74 |  | 5.69 | 5.75 | 5.95 | 5.90 |
| | | 5.69 | 5.75 | 5.95 | 5.90 |
| |  | nd[f] | nd[f] | nd[f] | 4.87 (61 %)[g] |
| |  | 5.65 (2.65) | 5.77 (2.70) | 5.83 (2.64) | 5.88 (1.65) |
| | | 4.00 (1.00) | 4.78 (1.00) | 4.63 (1.00) | 4.67 (1.00) |
|  5.56 |  | 5.65 | 5.77 | 5.83 | 5.88 |
| | | 5.65 | 5.77 | 5.83 | 5.88 |
| |  | nd[f] | nd[f] | nd[f] | 4.40 (27 %)[g] |

[a] Assignments are based on ACD Labs NMR Prediction Software. [b] For nonresolved $^2$H NMR peaks, the total relative intensity is given only once. [c] All $^2$H NMR peak positions are given in parts per million relative to the $^2$H NMR internal standard arising from the solvent's natural abundance $CDCl_3$, which has been set at $\delta$ 7.34 ppm. [d] These data were obtained in refluxing benzene. The results obtained at room temperature were essentially identical, see Supporting Information. [e] Data from ref 11. [f] Not detected. [g] Yield of the disubstituted alkenes as a percentage of the total product, i.e., 100 $D_e/(D_a + D_b + D_c + D_d + D_e)$.

**TABLE 3. Percentages of Monoadducts Formed by the Abstraction−Addition Mechanism and Percentage Yields of Diadducts as a Percentage of Total Adducts**

| radical | alkene | % abstraction−addition[a] | % diadduct |
|---|---|---|---|
| **1b** | 4 | 91 | 0 |
| **2** | 4 | 91 | 0 |
| **3** ($t$-RO$^\bullet$) | 4 | 88[b] | 0 |
| **3** (Pb(OAc)$_4$) | 4 | 73 | 3 |
| **1b** | 5 | 92 | 0 |
| **2** | 5 | 90 | 0 |
| **3** ($t$-RO$^\bullet$) | 5 | 89[b] | 0 |
| **3** (Pb(OAc)$_4$) | 5 | 65 | 61 |
| **1b** | 6 | 91 | 0 |
| **2** | 6 | 92 | 0 |
| **3** ($t$-RO$^\bullet$) | 6 | 90[b] | 0 |
| **3** (Pb(OAc)$_4$) | 6 | 50 | 27 |

[a] Random error < ±2.5%; see ref 29. [b] See footnote d to Table 2.

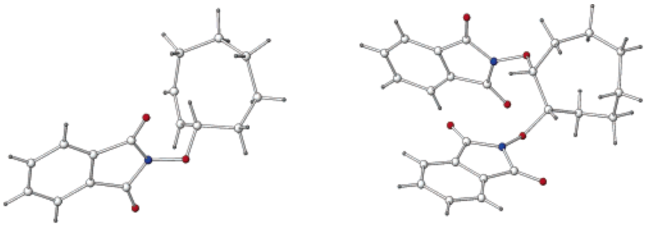


**FIGURE 3.** X-ray crystallographic structures for cyclooctene mono- (left) and diadduct (right) with the **PINO** moiety.

The results of these calculations are given in Table 3.[28] Table 3 also includes the yields of diadducts as a percentage of the total of all substitution products, i.e., equation II:

$$\text{diadduct \% yield} = 100\ D_e/(D_a + D_b + D_c + D_d + D_e) \tag{II}$$

That the diadducts are saturated[30] organic compounds is, of course, obvious from their $^2$H NMR spectra. Nevertheless, the structure of one of them was further confirmed by reacting **NHPI**, Pb(OAc)$_4$, and nondeuterated cyclooctene under the usual conditions, but on a larger scale. The mono- and diadducts were separated (TLC) in sufficient quantity to measure their $^1$H NMR and $^{13}$C NMR spectra (see Supporting Information) and to obtain X-ray crystallographic structures (Figure 3 and Supporting Information).

## Discussion

**Formation of Monoadducts.** The nitroxide, **1b**, the iminoxyl, **2**, and the imidoxyl, **PINO**, when generated from **NHPI** and $t$-RO$^\bullet$ radicals, react with the three alkenes mainly by an initial abstraction of an allylic H-atom. The allyl radical so formed then couples with a second >NO$^\bullet$ radical (see Scheme 1). In these nine reactions, 88−92% of the monoadducts are formed by this abstraction−addition mechanism (see Table 3), and the remaining 12−8% are formed by the addition−abstraction mechanism. Such a high (and constant) percentage of abstraction−addition raises the disturbing possibility that abstraction−addition is the only operative reaction mechanism. That is, the 88−92% value might be due to some artifact such as a systematic $^2$H NMR peak integration error or incorporation of the deuterium into more than just the two vinylic positions. The latter possibility can be discarded on the basis of the clean $^2$H NMR spectra of the starting alkenes (see, e.g., Figure 1 and Supporting Information). A systematic error in the $^2$H signal integrations (which were done both by machine and by hand)[29] appeared unlikely because the NMR pulse time (2 s) was much more than 5 times the $^2$H $T_1$ relaxation time[31] (~100 ms). However, to be "on the safe

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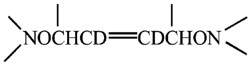
[28] Regretfully, this percentage was incorrectly calculated for the **1b**/**4** reaction in our original communication.[11]

[29] Repeated machine integration of the $D_a + D_c + D_d$ and $D_b$ peaks using different ranges of $\delta$ showed that random errors for the abstraction−addition percentages listed in Table 3 are less than 2.5%. In addition, integration by hand gave abstraction−addition percentages fully consistent with those listed in Table 3.

[30] Unsaturated diadducts containing the following structural element were not detected in any system:



$$\rangle\mathrm{NO}\overset{|}{\mathrm{C}}\mathrm{HCD}{=\!=}\mathrm{CD}\overset{|}{\mathrm{C}}\mathrm{HON}\langle$$

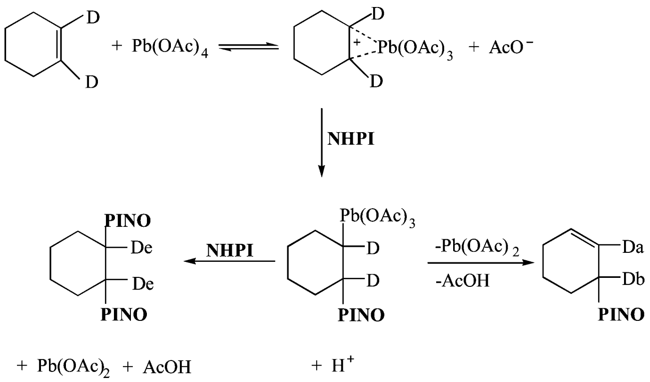
[31] Mantsch, H. H.; Saito, H.; Smith, I. C. P. *Progress in NMR Spectroscopy*; 1977, Vol. II, Part 4, pp 211−271.

side", the **PINO** radical was reacted with *trans*-3,4-dideuterio-hex-3-ene on a sufficient scale to isolate the diadduct. This compound was separately mixed with an equimolecular quantity of the dideuterioalkene in $CHCl_3$. The $^2H$ NMR integrations were fully consistent with the experimental 1:1 molarities of the adducts and alkene (see Supporting Information). We therefore conclude that in all the $>NO^\bullet$/alkene reactions under consideration, there is good evidence that ca. 8–12% of the (monoadduct) product is formed by the addition–abstraction mechanism, although it must be admitted that the absence of diadducts, particularly for the reactions involving **1b** and **2** at the relatively high radical concentrations employed, is a worry and may indicate that we are overlooking some aspect of the chemistry or of the $^2H$ NMR analytical procedure. However, in this connection, we note that other oxygen-centered radicals have been demonstrated to add to alkenes as well as to abstract allylic H-atoms. For example, there is 3.8% addition in the $t$-$RO^\bullet$ + cyclohexene reaction,[32] 4.4% addition in the $ROO^\bullet$ + cyclohexene reaction,[33] and an amazing 71% addition in the $ROO^\bullet$ + cyclooctene reaction.[33,34]

The relative rate constants for the reactions of different alkenes with a common radical are determined by the interplay of entropic and enthalpic effects. The former arise because in the reactions of alkenes there is either a partial "freeing" or a partial "freezing" of a bond rotation in the transition state. For this reason, entropic effects favor acyclic over cyclic alkenes for addition reactions but favor cyclic over acyclic alkenes for H-atom abstractions. Enthalpic effects on the rates of addition to, and H-atom abstraction from, cyclic alkenes are determined, in part, by changes in ring-strain in the transition states. Convoluted with "normal" ring-strain in these H-atom abstractions will be the extent to which the cyclic allyl radicals are, perforce, twisted away from their preferred planar geometry. Since only two cyclic and one acyclic alkene were examined and since the percentage yields of monoadducts formed by the abstraction–addition mechanism are essentially identical (88–92%) for reaction of the three alkenes with **1b**, **2**, and **PINO** generated from **NHPI** with $t$-$RO^\bullet$ radicals, it would seem that the entropic and enthalpic effects on the rates of the two processes are roughly in balance for these nine $>NO^\bullet$ + alkene reactions.

**Formation of Diadducts.** The alkene/**NHPI**/Pb(OAc)$_4$ system yields diadducts, which are not formed in the alkene/**NHPI**/$t$-$RO^\bullet$ system (see Tables 2 and 3). This raises the question, is diadduct formation specific to the experimental procedure? This involved mixing the alkene and **NHPI** in deoxygenated acetonitrile followed by the addition of $Pb(OAc)_4$ in deoxygenated acetonitrile and product workup (see Experimental Section). Using cyclooctene (because this gave the highest yields of diadduct) and deoxygenated acetonitrile as the solvent, we carried out reactions with different experimental protocols. In one set of three experiments, the **NHPI** and $Pb(OAc)_4$ were mixed together and allowed to stand for 1, 3, and 10 min prior to the addition of the cyclooctene, with product workup taking place 2 min after the addition of the alkene. In the second set of three experiments, the cyclooctene and $Pb(OAc)_4$ were mixed and allowed to stand for 1, 3, and 10 min prior to the addition of the **NHPI**, with product workup taking place 2 min later. Analyses of the products from these six reactions by CI-MS showed always the same monoadduct/diadduct ratio, and furthermore, this ratio was the same as that obtained with the original experiment protocol (see Supporting Information). In none of the experiments was there a CI-MS M + 1 peak corresponding to 2-acetoxycyclooctene or a peak for 1,2-diacetoxycyclooctane.

**SCHEME 2**



Our results prove that free **PINO** radicals cannot be involved in the formation of the diadducts in the alkene/**NHPI**/$Pb(OAc)_4$ system. We therefore suggest a mechanism based on that proposed for the lead tetraacetate oxidation of cyclohexene to *cis*- and *trans*-1,2-diacetoxycyclohexanes and 3-acetoxycyclohexene via a symmetric intermediate (see Scheme 2).[19,20,35,36]

This mechanism accounts both for the formation of **PINO** diadducts and for the reduced percentage of the abstraction–addition mechanism for the three alkene/**NHPI**/$Pb(OAc)_4$ reactions relative to all the other alkene–radical reactions (see Table 3). That is, the **PINO** monoadduct that is formed according to Scheme 2 gives rise to the $D_a$ and $D_b$ $^2H$ NMR signals. This is the product that is formed by both the abstraction–addition and the addition–abstraction mechanisms (see Scheme 1). The product that is unique to the addition–abstraction mechanism gives rise to the $D_c$ and $D_d$ $^2H$ NMR signals (Scheme 1). Formation of the $D_b$ product according to Scheme 2 will cause the calculated percentage of abstraction–addition to decrease (see eq I). Indeed, if all $D_b$ were formed according to Scheme 2, the calculated percentage of abstraction–addition would be zero (as it should be). That this percentage is not zero, implies that some of the monoadduct products must be formed by **PINO** radicals.

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[32] Walling, C.; Clark, R. T. *J. Am. Chem. Soc.* **1974**, *96*, 4530–4534.

[33] Van Sickle, D. E.; Mayo, F. R.; Arluck, R. M. *J. Am. Chem. Soc.* **1965**, *87*, 4824–4832.

[34] For a review of $ROO^\bullet$ + alkene addition and abstraction reactions, see: Mayo, F. R. *Acc. Chem. Res.* **1968**, *1*, 193–201.

[35] Separate experiments showed that **NHPI** did not replace the acetate group in acetoxycyclohexane.

[36] We cannot rule out the possibility that the first steps in Scheme 2 involve the substitution of one or two acetate groups in the $Pb(OAc)_4$ by **PINO** moieties, reaction 10 and 11, followed by chemistry similar to that shown in Scheme 2.

$$\textbf{NHPI} + Pb(OAc)_4 \rightleftarrows \textbf{PINO}Pb(OAc)_3 + AcOH \qquad (10)$$

$$\textbf{NHPI} + \textbf{PINO}Pb(OAc)_3\ (\textbf{PINO})_2Pb(OAc)_2 + AcOH \qquad (11)$$

This is hardly surprising in view of the known[15] production of **PINO** radicals from **NHPI** and $Pb(OAc)_4$.

The relative importance of the radical (Scheme 1) and nonradical (Scheme 2) routes to **PINO** monoadducts can be readily estimated. For example, *trans*-hex-3-ene has the lowest calculated percentage of the abstraction–addition mechanism, viz., 50% (Table 3). Using eq I and taking $D_b = 1.00$, the calculated value of $(D_a + D_c + D_d) = 1.667$, and since $D_a = D_b$, the $(D_c + D_d)$ monoadduct = 0.667. This compound is probably formed solely via **PINO** radicals, and it will be formed in equal amounts to the $(D_a + D_b)$ monoadduct arising from the **PINO** radical reaction (Scheme 1). The **PINO** abstraction–addition reaction therefore forms $0.667/2 = 0.334\ D_b$. The remainder of the $D_b$ signal, i.e., $1.00-0.33 = 0.67$, must therefore arise mainly from the Pb(IV)-mediated reaction together with the small amount formed via the **PINO** radical addition–abstraction mechanism. From the *trans*-hex-3-ene/**NHPI**/*t*-RO$^\bullet$ data (Table 3), this small amount is ca. 10% of the amount of monoadduct formed by abstraction–addition. Thus, for this alkene, $\{0.67 - (0.1 \times 0.33)\} \times 100 = 64\%$ of the monoadduct is formed according to the nonradical Scheme 2, and the remaining 36% of the monoadduct is formed via **PINO** radicals according to Scheme 1.

Although iminoxyl radicals have been detected (EPR) in the reaction of $Pb(OAc)_4$ with a number of oximes,[15] neither mono- nor diadducts of the iminoxyl, **2** were formed from cyclooctene upon reaction of the ketoxime, **2H**, and $Pb(OAc)_4$ for 15 min. (The alkene/**NHPI**/$Pb(OAc)_4$ reactions yielded products in <1 min.) Similar negative results were obtained with cyclooctene and the hydroxylamine **1bH**. Thus, reaction via the mechanism in Scheme 2 (or analogous mechanisms) appears to be confined to **NHPI**. This we attribute to the much greater acidity ($pK_a$) of **NHPI** compared with **2H** and **1bH**.[37] The absence of radical products in the alkene/**2H**/$Pb(OAc)_4$ and alkene/**1bH**/$Pb(OAc)_4$ reactions we attribute to the combination of two factors. The first factor is the slow radical formation in these systems, which is probably due to the difficulty of replacing acetate in $Pb(OAc)_4$ with the much less acidic **2H** and **1bH**.[37] The second factor is that the radicals, **2** and **1b**, are considerably less reactive than **PINO**. Monoadducts of **2** and **1b** would presumably have been formed by radical processes (Scheme 1) if the reactions had been run for longer times and at higher temperatures.

The intervention of some form of Pb(IV) in the **NHPI**/alkene/$Pb(OAc)_4$ reaction introduces two quite different channels for product formation, viz., radical and nonradical reactions. A similar phenomenon may occur with other substrates and may provide an explanation for a puzzling kinetic anomaly in the literature. Thus, Minisci et al.[7c] reported that **NHPI** and a cobalt salt in aerated acetonitrile oxidized benzyl alcohol quantitatively to benzaldehyde without the formation of significant amounts of benzoic acid. However, Espenson and co-workers[6e] using the **NHPI**/$Pb(OAc)_4$ system later reported that the rate constant for reaction of **PINO** with benzyl alcohol ($5.65\ M^{-1}\ s^{-1}$) was *lower* than the rate constant for **PINO**'s reaction with benzaldehyde $10.6\ M^{-1}\ s^{-1}$, implying that a clean conversion of benzyl alcohol to benzaldehyde would not be possible. More recently, Pedulli and co-workers[6b] reported a much higher rate constant for the reaction of **PINO** with benzyl alcohol ($28.3\ M^{-1}s^{-1}$), which would be consistent with Minisci's observations.[7c,43] Clearly, the **NHPI**/$Pb(OAc)_4$ method for generating **PINO** radicals should be treated with caution until these (and other[43]) anomalies have been sorted out.

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**Supporting Information Available:** Experimental procedures for the syntheses of **5** and **6**; LFP and competitive kinetics results; $^1H$ NMR and $^{13}C$ NMR spectra for cyclooctene mono- and diadducts with the **PINO** moiety; $^2H$ NMR spectra for the **2/4**, **3/4**, **1b/6**, **2/6**, and **3/6** reaction products, an equimolecular mixture of the *trans*-3,4-dideuteriohex-3-ene and *trans*-3,4-dideuteriohex-3-ene-**PINO** di-adduct, and neat **6**; comparison of the CI-MS M + 1 peaks for the cyclooctene reaction with **NHPI** in the presence of lead tetraacetate using the two different protocols described in the text, and X-ray crystallographic data for the cyclooctene/**PINO** mono- and diadducts (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(37) **NHPI** (**3H**), $pK_a = 6.1$;[38,39] $Me_2NOH$, $pK_a = 8.80$;[40,41] $Me_2C{=}NOH$ and $Et_2C{=}NOH$, $pK_a = 12.4$ and 12.6, respectively,[42] where the last three compounds must be seen as surrogates for **1bH** and **2H**.

(38) Green, A. L.; Sainsbury, G. L.; Saville, B.; Stansfield, M. *J. Chem. Soc.* **1958**, 1583–1587.

(39) Some papers and databases give the $pK_a$ for **NHPI** as 7.0 without comment. However, this value was measured in $H_2O$/MeOH (1:1, v/v); see: Ames, D. E.; Grey, T. F. *J. Chem. Soc.* **1955**, 3518–3521.

(40) Bissot, T. C.; Parry, R. W.; Campbell, D. H. *J. Am. Chem. Soc.* **1957**, *79*, 796–800.

(41) The compound that was actually titrated with base was $Me_2NOH$. HCl and two pKs were found: 5.20 and 8.80.[40] Unfortunately, the first pK was listed as $pK_a$ and the second as $pK_b$. For this reason, the $pK_a$ of $Me_2NOH$ is often given as 5.20.

(42) King, C. V.; Marion, A. P. *J. Am. Chem. Soc.* **1944**, *66*, 977–980.

(43) Pedulli et al.[2,6b] used the **NHPI**/*t*-RO$^\bullet$ system to generate **PINO**, with *t*-RO$^\bullet$ being generated photochemically from the peroxide, *t*-ROOR-*t*. This allowed the measurement by kinetic EPR spectroscopy of the **PINO**/benzyl alcohol rate constant. However, it would probably not have been possible to measure the rate constant for **PINO**/benzaldehyde reaction because of benzaldehyde's strong UV absorbance. Interestingly, the rate constants for reaction of **PINO** with alkyl aromatics measured by Pedulli[6b] using **NHPI**/*t*-RO$^\bullet$ and by Espenson[6e] using **NHPI**/$Pb(OAc)_4$ are in fairly good agreement. However, Espenson and co-workers[8c] have very recently reported that the rate constants for H atom abstraction by **PINO** from *p*-xylene and toluene using **NHPI**/Co(III) were "slightly different" from those obtained using **NHPI**/Pb(IV).