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Distinguishing between Abstraction and Addition as the First Step in the Reaction of a Nitroxyl Radical with Cyclohexene

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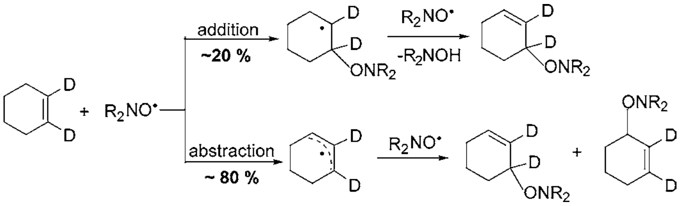
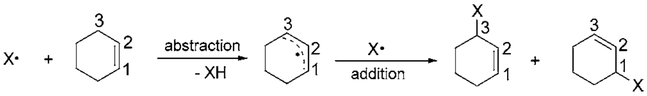
ABSTRACT



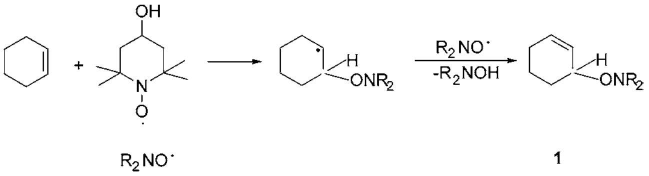
An unambiguous method for distinguishing between abstraction–addition and addition–abstraction mechanisms (and mixtures thereof) in the reaction of 4-hydroxy-2,2,6,6-tetramethylpiperidine-*N*-oxyl with a specifically deuterated cyclohexene, 1,2-dideuteriocyclohexene, is demonstrated.

It is commonly assumed that reactions between free radicals, X$^•$, and cycloalkenes that yield 3-X-substituted cycloalkenes occur by an initial H-atom abstraction to give an allylic radical to which a second X$^•$ adds, e.g., Scheme 1. For example, in 1992, Jenkins and co-workers[1] reported that in the reaction of the stable nitroxyl radical, 1,1,3,3-tetramethyl-2,3-dihydro-1*H*-isoindol-2-oxyl, with cyclohexene at 25 °C, "the hydrogen-abstraction product (3-(1,1,3,3-tetramethyl-2,3-dihydro-1*H*-isoindol-2-oxyl)cyclohexene) was cleanly produced." Ten years later, Barbiarz et al.[2] reported that another stable nitroxyl radical, 4-hydroxy-TEMPO (4-hydroxy-2,2,6,6-tetramethylpiperidine-*N*-oxyl, R$_2$NO$^•$) reacted with cyclohexene at temperatures ranging from room temperature to 70 °C to give the analogous 3-substituted cyclohexene, **1**. These workers[2] concluded that this reaction involved "addition of the nitroxyl radical to the double bond followed by H-atom abstraction from the intermediate by another equivalent of nitroxyl radical", Scheme 2.

Scheme 1



Scheme 2



This mechanism was based on the fact that ethylbenzene reacted with R$_2$NO$^•$ only at temperatures above 100 °C to

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[1] Bottle, S. E.; Busfield, W. K.; Jenkins, I. D. *J. Chem. Soc., Perkin Trans. 2* **1992**, 2145.

[2] Babiarz, J. E.; Cunkle, G. T.; DeBellis, A. D.; Eveland, D.; Pastor, S. D.; Shum, S. P. *J. Org. Chem.* **2002**, *67*, 6831.

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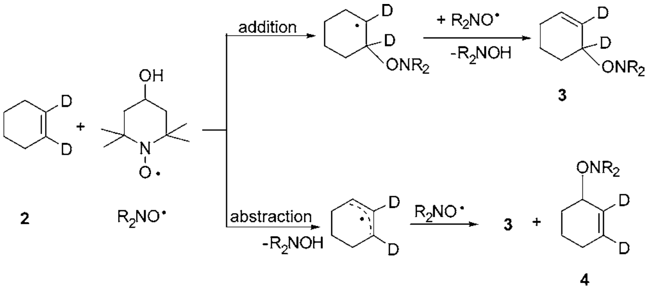
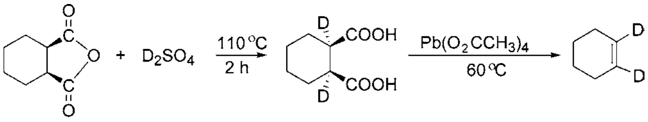
give $PhCH(ONR_2)CH_3$. This adduct could only be formed by abstraction−addition. The addition−abstraction mechanism for cyclohexene (Scheme 2) was proposed "because the bond dissociation energy (enthalpies) for allylic and benzylic C−H bonds is expected to be nearly the same." This mechanism was also claimed to be supported by semiempirical UHF/AM1 calculations.[2] Unfortunately, even if the enthalpic (thermochemical) arguments were correct,[3] entropic effects favoring H-abstraction from cyclohexene[4] had been ignored. Nevertheless, both mechanisms are certainly possible for this "simple" radical reaction and an unequivocal discrimination between them would require an isotopically labeled cyclohexene. 1,2-Dideuteriocyclohexene, **2**, was chosen because only minimal (i.e., secondary) deuterium kinetic isotope effects would be involved in either mechanism, see Scheme 3.

Scheme 3



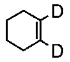
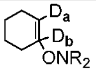
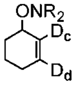
Compound **2** was prepared by a lead tetraacetate oxidative decarboxylation of 1,2-dideuteriocyclohexane-1,2-dicarboxylic acid,[6] which was itself synthesized by an α-proton−deuterium exchange of *cis*-cyclohexane-1,2-dicarboxylic anhydride with deuteriosulfuric acid,[7] Scheme 4, (see Supporting Information for synthetic details).

Scheme 4



Ignoring secondary isotope effects, Scheme 3 implies that initial H-abstraction should give equal yields of 1-*N*-[(1,2-dideuteriocyclohex-2-en-1-yl)oxyl]-4-hydroxy-2,2,6,6-tetramethylpiperidine (**3**) and 1-*N*-[(2,3-dideuteriocylohex-2-en-1-yl)oxyl]-4-hydroxy-2,2,6,6-tetramethylpiperidine (**4**), whereas initial addition will give only **3**. However, because the coupling of nitroxyl radicals with carbon-centered radicals occurs at close to the diffusion-controlled limit,[8] there is a potential mechanistic ambiguity. That is, in earlier nitroxyl/cyclohexene reactions,[1,2] the concentration of the nitroxyl was relatively high (e.g.,[2] 0.85 M). The hydroxylamine molecule formed in the initial H-abstraction could potentially shield that end of the allylic radical system for a time comparable to that required for the addition of an $R_2NO^•$ radical, which would, perforce, add to the other end of the allylic system. This would produce an excess of **3** over **4** so that even a "clean" abstraction mechanism could appear to contain a contribution from an addition pathway. The ^{2}H NMR spectral parameters for the products, **3** and **4**, are given in Table 1. The signal due to the deuteron labeled D_b is unique to **3**, and that labeled D_d is unique to **4**. The **3**/**4** product ratio is therefore given simply by the integrated peak intensity ratio, D_b/D_d. In the event, reaction of 0.83 M $R_2NO^•$ in neat **2**[9] gave $D_b/D_d = 1.22$ (see Figure 1B and Table 2, column D_b).

Table 1. Assignments of ^{2}H NMR Signals[a,b]

	compound	deuterium	δ, ppm
2		D	5.80
3		D_a D_b	6.02[c] 4.28
4		D_c D_d	6.02[c] 5.90

[a] Based on ACD Labs NMR Prediction Software. [b] ^{1}H NMR parameters for **3** and **4** are given in Supporting Information of ref 2. [c] Note that D_a (**3**) and D_c (**4**) are not resolved.

Since this result might have been due to the high concentration of $R_2NO^•$ (vide supra), the experiment was repeated using 0.0096 M $R_2NO^•$ and 0.099 M **2** in benzene, and the D_b/D_d ratio was found to be essentially unchanged,

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(3) 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.

(4) H-abstraction from ethylbenzene requires the free rotation about the Ph−C bond to be "frozen out" in the transition state for $PhC^•HCH_3$ 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.,[5] 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}.

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

(6) Bodot, H.; Lauricella, R.; Pizzala, L. *Bull. Soc. Chim. France* **1968**, *3*, 984.

(7) (a) Ingold, C. K.; Raisin, C. G.; Wilson, C. L. *J. Chem. Soc*. **1936**, 1637. (b) Otvos, J. W.; Stevenson, D. P.; Wagner, C. D.; Beek, O. *J. Am. Chem. Soc*. **1951**, *73*, 5741

(8) Chateauneuf, J.; Lusztyk, J.; Ingold, K. U. *J. Org. Chem.* **1988**, *53*, 1629.

(9) A sample containing **2** (0.4 g, 4.76 mmol) and $R_2NO^•$ (0.082 g, 0.476 mmol) under nitrogen was heated at 70 °C for 72 h, cooled to room temperature, and filtered to remove solid 1,4-dihydroxy-2,2,6,6-tetramethylpiperidine, R_2NOH. The rest of this product was removed by extracting the filtrate with 5 w/v % ascorbic acid (2 × 0.5 mL) and distilled water (2 × 0.5 mL). The organic phase was dried (Na_2SO_4), and volatiles (mainly **2**) were removed under vacuum. The residue was purified by chromatography (silica gel, eluent = ethyl acetate/hexane, 1:1 v/v) to give 0.0187 g (30.76% yield based on $R_2NO^•$) of a mixture of **3** and **4**. The same procedure was followed for the experiment with the much lower concentration of **2** and $R_2NO^•$ in benzene.

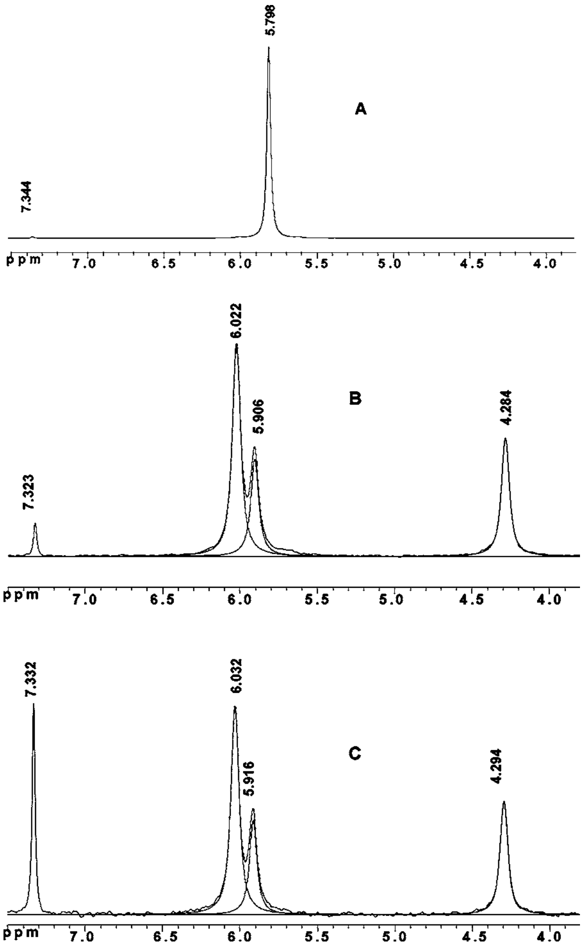

Figure 1. ^{2}H NMR spectra in $CHCl_3$. The signal at 7.3 ppm is due to the natural abundance of $CDCl_3$. **A**: 1,2-Dideuteriocyclohexene (**2**). **B**: Neat **2** + 0.83 M $R_2NO^\bullet$ at 70 °C for 72 h. **C**: 0.099 M **2** + 0.0096 M $R_2NO^\bullet$ in benzene at 70 °C for 360 h.

viz., 1.26 (see Figure 1C and Table 2). An internal check for consistency is provided by the sum of the integrated areas for $D_b + D_d$, which, in both experiments, is essentially equal to the integrated area for the common peak due to $D_a + D_c$ (see Table 2).

Table 2. Reaction Conditions,[9] Relative Integrated ^{2}H NMR Signals, and Percentage Abstraction in the Reaction of 1,2-Dideuteriocyclohexene, **2**, with 4-Hydroxy-2,2,6,6-tetramethylpiperidine-*N*-oxyl, $R_2NO^\bullet$, at 70 °C

conditions[9]			relative integrated areas			% abstraction[a]
[**2**] (M)	[$R_2NO^\bullet$] (M)	time (h)	$D_\mathbf{d}$	$D_\mathbf{b}$	$D_\mathbf{a} + D_\mathbf{c}$	100/$D_\mathbf{b}$
8.26[b]	0.83	72	(1)	1.22	2.25	82
0.099[c]	0.0096[c]	360	(1)	1.26	2.37	79

[a] This can be calculated in various ways, but the simplest is $100 \times D_d/(D_b - D_d) + D_d = 100/D_b/D_d$. [b] Neat. [c] In benzene.

In conclusion, the reaction of $R_2NO^\bullet$ (and presumably many other nitroxyls) with cyclohexene has been unambiguously demonstrated to occur mainly (~80%) by an initial hydrogen abstraction and to a lesser extent (~20%) by an initial addition to the double bond. This duality of mechanism has been previously reported only, so far as we are aware, for the reactions of peroxyl radicals with certain alkenes (not including cyclohexene).[10] It will be further explored using other deuterated alkenes and other radicals.

Acknowledgment. We thank Don Leek for valuable NMR advice. S.C. thanks the Natural Sciences and Engineering Research Council (NSERC) of Canada for receipt of a Visiting Fellowship.

Supporting Information Available: Experimental procedures for the synthesis of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Mayo, F. R. *Acc. Chem. Res.* **1968**, *1*, 193.