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Competition H(D) Kinetic Isotope Effects in the Autoxidation of Hydrocarbons

Hubert Muchalski,[†] Alexander J. Levonyak,[†] Libin Xu,[†] Keith U. Ingold,[‡] and Ned A. Porter*[,†]

[†]Department of Chemistry and Vanderbilt Institute of Chemical Biology, Vanderbilt University, Nashville, Tennessee 37235, United States

[‡]National Research Council of Canada, 100 Sussex Drive, Ottawa, Ontario K1A 0R6, Canada

Supporting Information

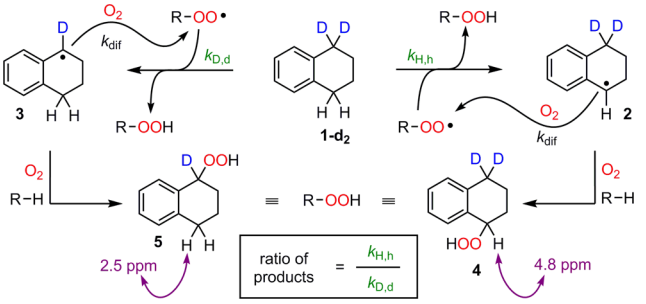
ABSTRACT: Hydrogen atom transfer is central to many important radical chain sequences. We report here a method for determination of both the primary and secondary isotope effects for symmetrical substrates by the use of NMR. Intramolecular competition reactions were carried out on substrates having an increasing number of deuterium atoms at symmetry-related sites. Products that arise from peroxyl radical abstraction at each position of the various substrates reflect the competition rates for H(D) abstraction. The primary KIE for autoxidation of tetralin was determined to be 15.9 ± 1.4, a value that exceeds the maximum predicted by differences in H(D) zero-point energies (~7) and strongly suggests that H atom abstraction by the peroxyl radical occurs with substantial quantum mechanical tunneling.

The determination of rate constants for important transformations has been central to advances in free radical chemistry. The measurement of absolute rate constants for reactions such as radical addition to olefins and atom transfer reactions has provided a basic framework for understanding radical chain processes.[1] Methods based on competition kinetics have expanded the set of free radical rate constants so that successful planning of chain sequences can be made based upon available kinetic data.[2] Radical clocks are among the competition methods that have been used to good advantage and the "clock" method is based upon setting up competing transformations, one of which has a known rate constant.[2b,3]

Hydrogen atom transfer is central to many important radical chain sequences. The rate-determining step in the autoxidation of hydrocarbons, for example, is an H atom transfer from carbon to a propagating peroxyl radical. Rate constants for this important process have been determined by both absolute[4] and competition methods,[5] and factors that influence the reaction are reasonably well understood. There is less agreement about the experimental H(D) kinetic isotope effect for radical H atom transfers with reports for the primary H(D) isotope effect of carbon to peroxyl radical transfer covering a wide range.[4c,e,6] Because of the importance of autoxidation (or peroxidation) in industry and biology,[7] we explored the use of competition methods to measure kinetic isotope effects in hydrocarbon autoxidation. We report here an NMR-based,[8] intramolecular competition method for determining the H(D) kinetic isotope effect for hydrogen/deuterium atom transfer from carbon to peroxyl radicals.

For symmetric oxidizable hydrocarbons like tetralin, an intramolecular competition reaction is possible when one of the two benzylic positions is substituted with deuterium. In such a case, products that arise from autoxidation at each position, although inseparable by chromatography, give a different ^{1}H NMR signal pattern that can be used to establish competition rates of H(D) abstraction. Scheme 1 describes the approach

Scheme 1. Chain Propagation in Autoxidation of Tetralin-d_2



using a pseudo C_{2v}-symmetric 1,2,3,4-tetrahydronaphthalene-1,1-d_2 (tetralin-d_2, **1-d_2**) as an example. According to the general autoxidation mechanism a carbon-centered radical is generated by abstraction of hydrogen (at rate $k_{H,h}$) or deuterium (at rate $k_{D,d}$), where H or D is the primary abstracted atom on the reactive carbon and h or d is the secondary atom on that center. The resulting carbon radicals **2** or **3** add oxygen at diffusion-controlled rates to give the corresponding peroxyl radicals (R–OO•) that propagate the chain reaction. Upon hydrogen atom abstraction, hydroperoxide products **4** or **5** form, and at early reaction times, the relative amounts of these products reflect the relative rate of hydrogen/deuterium atom abstraction at respective benzylic positions, namely, $k_{H,h}/k_{D,d}$.

It should be noted that the KIE measured in autoxidation of **1-d_2** (Scheme 1) is a cumulative isotope effect from participating and spectator atoms. This posed an additional challenge of separating the primary and secondary isotope effect of the atom being removed by the peroxyl radical and the geminal spectator atom. To decouple both effects,[9] tetralins with increasing isotopic substitution were subjected to autoxidation as depicted

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in Figure 1. Tetralin with one benzylic hydrogen atom substituted with deuterium provided the secondary isotope

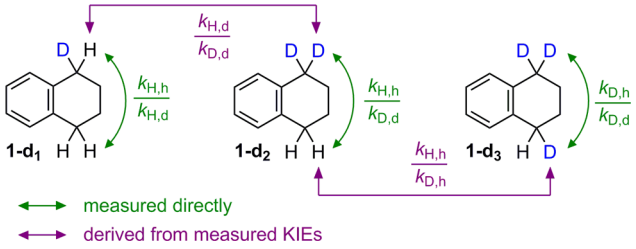

Figure 1. Experiment outline.

effect for the removal of hydrogen atom ($k_{H,h}/k_{H,d}$). Similarly, tetralin with three benzylic deuteriums and one hydrogen gave the secondary isotope effect for the removal of deuterium atom ($k_{D,h}/k_{D,d}$). The primary isotope effect for the removal of hydrogen atom ($k_{H,h}/k_{D,h}$) can be calculated by dividing the cumulative KIE obtained for tetralin-d_2 ($k_{H,h}/k_{D,d}$) by the rate ratio obtained for tetralin-d_3 ($k_{D,h}/k_{D,d}$).

Triplicate experiments were carried out on 3 M solutions of deuterium-labeled tetralins in oxygenated C_6D_6 initiated with AIBN (0.06 M) at 65 °C for 6 h. Analysis of these reaction mixtures showed approximately 10% of tetralin consumed with tetralin hydroperoxide being the dominant product formed with only trace amounts of the termination product (1-tetralone) found. The chain length calculated for the conversion of tetralin to tetralin hydroperoxide under these conditions was greater than 14.[10] The reaction mixture was immediately purified by preparative normal phase HPLC and then analyzed in C_6D_6 using high field NMR (600 MHz) with the delay time between pulses set to 20−30 s (at least 10× default value). During preliminary studies we noticed that the tetralin hydroperoxide slowly converts to tetralone on standing, which caused slight variations in measured KIE values. Therefore, KIE analyses were also carried out on products that were immediately treated with excess of Ph_3P with the KIE determined from ^{1}H NMR of the resulting alcohols.

Autoxidation of 1,2,3,4-tetrahydronaphthalene-1,1-d_2 (tetralin-d_2, **1-*d*$_2$**) produces two hydroperoxides, one with hydrogen on the α carbon and one with deuterium at that position (**4** and **5**, respectively, Figure 2). The integration of the benzylic methine resonance in **4** (4.81 ppm) reflects its relative amount in the product mixture. In hydroperoxide **5** resulting from abstraction of deuterium, the hydroperoxide methine deuterium is not observed in ^{1}H NMR but integration of the signal due to the benzylic geminal hydrogens $-CH_2$ at C−4 reflects the relative amount of **5** in the mixture (Figure 2). For the remaining peaks, either aromatic or aliphatic hydrogens serve as internal standards. We chose the resonance at 1.79 ppm because it is well separated and minimizes integration error caused by overlapping satellite peaks of neighboring resonances. The signal at 2.50 ppm corresponding to one of the hydrogens (presumably axial) at C−4 in **5** was selected as the most reliable measure of this product in the mixture.

Oxidations of tetralin-d_1 and tetralin-d_3 have more complex product profiles. The monodeuterated tetralin-d_1 (**1-*d*$_1$**) undergoes hydrogen atom abstraction at both benzylic positions, one having a geminal hydrogen and one with a geminal deuterium, while deuterium atom abstraction occurs from **1-*d*$_1$** at a carbon having a geminal hydrogen. The product mixture consists of

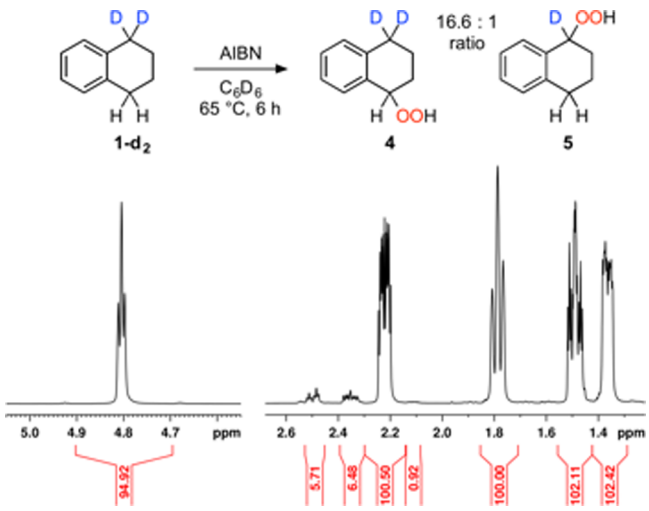

Figure 2. ^{1}H NMR of products from autoxidation of tetralin-d_2.

three hydroperoxides (**5**, **6**, and **7**, Figure 3A) with hydroperoxide **6** produced as a mixture of diastereomers. Compounds

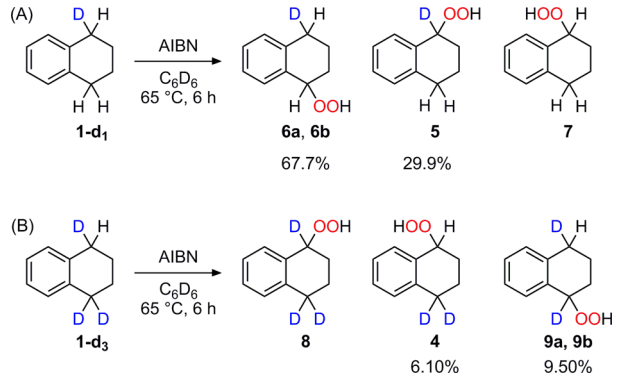

Figure 3. Products from oxidation of tetralin-d_1 and tetralin-d_3.

6a, **6b**, and **7** contribute to the resonance α to the hydroperoxide at 4.82 ppm, and compounds **5**, **6a**, and **7** contribute to the resonance at 2.52 ppm. With the signal at 1.82 ppm containing all compounds (**5**, **6a**, **6b**, and **7**) set as reference (100.00%), relative amounts of **5** and **6a** were calculated to be 29.92% and 33.86%, respectively (an equivalent amount of 33.9% of stereoisomer **6b** is formed). The ratio of **6a** to **5** reflects the secondary (h,d) isotope effect $k_{H,h}/k_{H,d}$ for hydrogen abstraction. Although it is possible to calculate the amount of product **7** that results from deuterium abstraction, it is a minor product and its concentration is close to the limit of detection.

To determine the $k_{D,h}/k_{D,d}$ rate ratio, we subjected tetralin-d_3 **1-*d*$_3$** to oxidation under the identical conditions as the other compounds. The diagnostic proton resonances α to the hydroperoxide at 4.8 ppm for the major product **8** are not present in the ^{1}H NMR, which greatly simplifies the analysis, and this absorbance can be used to assess the amount of **4** formed from deuterium atom abstraction at a carbon having a secondary spectator hydrogen. Since deuterium abstraction at C−1 produced two diastereomeric hydroperoxides (**9a** and **9b**), we used only half of the resonance at 2.48 for calculating the KIE.

The combined KIE results for tetralin are presented in Table 1 (spectra and calculations are available in the Supporting Information). The cumulative KIE is 15.9 ± 1.4 and represents the ratio of rates for the fastest reaction ($k_{H,h}$) and the slowest

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Table 1. Kinetic Isotope Effects in Autoxidation of Deuterated Tetralins[a]

entry	KIE	OOH	OH
1	H,h/D,d	15.9 ± 1.4	16.1 ± 1.4
2	H,h/H,d	1.16 ± 0.04	1.10 ± 0.08
3	D,h/D,d	1.26 ± 0.06	1.13 ± 0.02
4	H,d/D,d	14.4	14.5
5	H,h/D,h	13.0	14.1

[a]Data from NMR analysis of hydroperoxides (OOH) and alcohols (OH).

reaction ($k_{D,d}$), Table 1, entry 1. The secondary effect of a deuterium substitution on the removal of a hydrogen atom is 1.16 ± 0.04 and is within values expected for this type of effect (Table 1, entry 2). Similar NMR analyses for calculating the KIE can be carried out with the mixture of tetralin alcohols that are isolated after reduction of the primary product mixture. However, the spectra are better resolved for tetralin hydroperoxides in C_6D_6 than for tetralin alcohols (examples available in Supporting Information). Nevertheless, the same trend in KIE values is observed for the KIEs obtained from analysis of the tetralin alcohols.

The competition KIE method can also be used for designed pseudosymmetric substrates such as those shown in Figure 4.

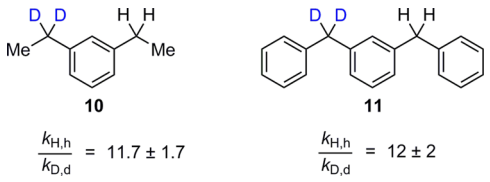

Figure 4. Other substrates evaluated.

Thus, the KIEs for the substrates 1,3-diethylbenzene-d_2 (**10**) were ($k_{H,h}/k_{D,d}$) 12.7 ± 1.0 and 10.8 ± 1.7, for analysis of hydroperoxide and alcohol products leading to the conclusion that the KIE for diethylbenzene is ∼11.7 ± 1.7. Autoxidation of dibenzylbenzene-d_2 (**11**) gives $k_{H,h}/k_{D,d}$ of 13.7 ± 2.0 and 11 ± 1.5 for analysis by the hydroperoxide and alcohol, respectively, suggesting that the H(D) KIE for diphenylmethane is ∼12 ± 2.

H(D) isotope effects substantially lower than the values reported here have been determined by measurement of peroxidation absolute rate constants for H and D substrates of diphenylmethane H(D)KIE = 5.1.[6] Attempts to measure H(D) KIEs for tetralin were considered unreliable by one of us[4c] because of questions about the quality of a commercial tetralin available at the time. It is of some interest, however, that an H(D) KIE of ∼18 was determined in *tert*-butyl-hydroperoxide tetralin co-oxidations.[4e]

The values for tetralin, ethylbenzene, and diphenylmethane are all greater than the H(D) KIE limit of ∼7 expected for the classical model based on H(D) differences in zero-point energies. Each of these H atom transfers is close to thermoneutral and each occur with rate constants substantially below the diffusion limit. H atom tunneling[11] must play a significant role in these atom transfers. Existing examples of tunneling have been reported for exothermic or thermoneutral transformations, in which the orientation of reactant C−H centers and the abstracting radical are constrained by an enzyme active site,[11i,j] a reaction in a glass, or an intramolecular geometry.[11m] The enzymatic transformations have been studied in great experimental detail and have also been the subject of extensive theoretical examination.[11i,j] The extent of tunneling that accompanies hydrogen atom transfer to peroxyls in solution has been the subject of less rigorous experimental and theoretical analyses. The high H(D) KIEs reported here for tetralin autoxidation calls for further examination of structure−reactivity patterns for hydrogen atom transfer from C−H bonds to peroxyl radicals in solution coupled with a theoretical analysis of such transformations.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all starting materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

n.porter@vanderbilt.edu

Notes

The authors declare no competing financial interest.

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This paper was published ASAP on December 31, 2014 with an incomplete Figure 2. The corrected version was reposted on January 2, 2015.

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