ORGANIC LETTERS

1999
Vol. 1, No. 2
327−329

^{13}C and ^{2}H Kinetic Isotope Effects and the Mechanism of Bromination of 1-Pentene under Synthetic Conditions

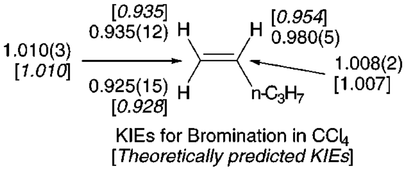
Steven R. Merrigan and Daniel A. Singleton*

Department of Chemistry, Texas A&M University, College Station, Texas 77843

singleton@mail.chem.tamu.edu

Received May 11, 1999

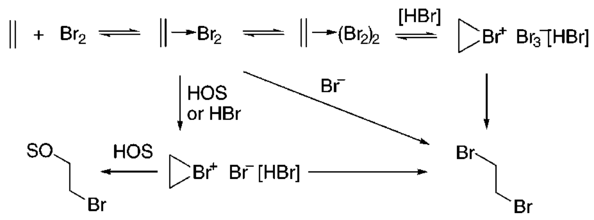
ABSTRACT



The ^{13}C and ^{2}H kinetic isotope effects for the bromination of 1-pentene with Br_2 in CCl_4 were determined and interpreted with the aid of calculationally predicted isotope effects. The isotope effects observed are consistent with rate-limiting bromonium ion formation and do not fit with either rate-limiting production of a π complex or reaction of a reversibly formed bromonium ion. This rules out some of the mechanistic complexities suggested for other brominations, though the identity of the brominating reagent(s) under these synthetic conditions remains uncertain.

The deceptively simple, undergraduate-textbook mechanism of bromination of alkenes via a bromonium ion gives way to a host of intricacies in reality. Complications include the involvement of bromocarbenium ions and alkene/Br_2 π complexes,[1] reversibility of bromonium ion formation,[2−4] the observation of second-order involvement of Br_2 or more complex kinetics,[5,6] catalysis by trace components,[7,8] and a variety of unique observations with hindered alkenes.[3,9] Scheme 1 illustrates some of the mechanistic possibilities. Considerable progress has been made in delimiting the possible mechanistic entanglements and understanding the bromination mechanism under many conditions, particularly in polar solvents.

Scheme 1



---

[1] (a) Bellucci, G.; Bianchini, R.; Ambrosetti, R. *J. Am. Chem. Soc.* **1985**, *107*, 2464.

[2] (a) Bellucci, G.; Bianchini, R.; Chiappe, C.; Brown, R. S.; Slebocka-Tilk, H. *J. Am. Chem. Soc.* **1991**, *113*, 8012. (b) Bellucci, G.; Chiappe, C.; Marioni, F. *J. Am. Chem. Soc.* **1987**, *109*, 515. (c) Brown, R. S.; Gedye, R.; Slebocka-Tilk, H.; Buschek, J. M.; Kopecky, K. R. *J. Am. Chem. Soc.* **1984**, *106*, 4515. (d) Zheng, C. Y.; Slebocka-Tilk, H.; Nagorski, R. W.; Alvarado, L.; Brown, R. S. *J. Org. Chem.* **1993**, *58*, 2122.

[3] (a) Brown, R. S.; Slebocka-Tilk, H.; Bennet, A. J.; Bellucci, G.; Bianchini, R.; Ambrosetti, R. *J. Am. Chem. Soc.* **1990**, *112*, 6310. (b) Bellucci, G.; Bianchini, R.; Chiappe, C.; Lenoir, D.; Attar, A. *J. Am. Chem. Soc.* **1995**, *117*, 6243.

[4] Slebocka-Tilk, H.; Zheng, C. Y.; Brown, R. S. *J. Am. Chem. Soc.* **1993**, *115*, 1347.

[5] Gebelein, C. G.; Frederick, G. D. *J. Org. Chem.* **1972**, *37*, 2211. Buckles, R. E.; Miller, J. L.; Thurmaier, R. J. *J. Org. Chem.* **1967**, *32*, 888. Sergeev, G. B.; Serguchev, Y. A.; Smirnov, V. V. *Russ. Chem. Rev.* (*Engl. Transl.*) **1973**, *42*, 697.

[6] (a) Schmid, G. H.; Toyanga, B. *J. Org. Chem.* **1984**, *49*, 761. (b) Fukuzumi, S.; Kochi, J. K. *J. Am. Chem. Soc.* **1982**, *104*, 7599.

[7] (a) Byrnell, C. J. A.; Coombes, R. G.; Hart, L. S.; Whiting, M. C. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1079. (b) Hart, L. S.; Whiting, M. C. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1087.

[8] (a) Smirnov, V. V.; Miroshnichenko, A. N.; Shilina, M. I. *Kinet. Catal.* **1990**, *31*482. (b) Smirnov, V. V.; Miroshnichenko, A. N.; Shilina, M. I. *Kinet. Catal.* **1990**, *31*486.

[9] Bellucci, G.; Bianchini, R.; Chiappe, C.; Gadjil, V. R.; Marchand, A. P. *J. Org. Chem.* **1993**, *58*, 3575.

10.1021/ol990659d CCC: $18.00 © 1999 American Chemical Society
Published on Web 06/25/1999

Interestingly, one of the least understood variations of the reaction is synthetically most common—the bromination of alkenes in CCl_4.[10] Kinetic results in CCl_4 are conflicting—rate laws which are first order in $[Br_2]$,[11] second order in $[Br_2]$,[5] a combination of the two,[6] and 1.5 order in $[Br_2]$[7] have all been observed. Induction periods and irreproducible rates have been noted, and substantially different rates have been reported by different workers.[7,8] Brominations in moderately polar solvents such as 1,2-dichloroethane are much more well behaved kinetically, but even very careful studies in very nonpolar solvents have led to conflicting results.[12]

The complexity of the bromination reaction in CCl_4 has long been suggested to result from catalysis by trace impurities, such as H_2O, HBr, or even the surface of the reaction vessel. Considerable light on these possibilities has been shed by the careful work of Whiting and co-workers.[7] In studies of the bromination of cyclohexene, they found that the presence of NBS as an HBr scavenger led to a slow reaction which was cleanly second order in $[Br_2]$ with a reproducible rate. After the initial NBS had all reacted, a faster bromination ensued of order 1.5 in $[Br_2]$. It thus appears that HBr is necessary to the catalysis of these reactions. Smirnov and co-workers have suggested that water is also essential—scrupulously dried additions to 1-heptene exhibited the uncatalyzed process second order in $[Br_2]$.[8] In the absence of additives but with no special purification of reagents, as would be typical of synthetic conditions, Whiting suggested that several modes of reaction are possible. These include reaction in an HBr/H_2O phase, through HBr_5 via the attack of $Br_3^+ \cdot HBr_2^-$ on alkene, through Br_6 or higher aggregates, and through HBr catalysis of bromonium ion formation from alkene−Br_2 π complexes.

We report here a study of the mechanism of bromination of 1-pentene in CCl_4 using ^2H and ^{13}C kinetic isotope effects (KIEs),[13,14] along with theoretical calculations to aid in the interpretation of these effects. The multifold mechanistic possibilities and complex kinetics in these reactions make many classical mechanistic probes inapplicable. However, kinetic isotope effects reflect a weighted average of the mechanistic pathways in a reaction and can thus provide basic information about the major mechanistic contributors, regardless of the complexities. The results implicate rate-limiting bromonium ion formation under synthetic conditions and exclude many of the mechanistic possibilities observed in specialized reactions.

Isotope effects for the bromination of 1-pentene in CCl_4 were determined combinatorially at natural abundance by recently reported methodology.[15] Br_2 was added to ≈2 M solutions of the alkene with vigorous stirring in a 25 °C water bath at such a rate that the concentration of $[Br_2]$ was maintained in a range of $\approx 1.5 \times 10^{-3}$ to 1×10^{-2} M (outside of the initial stage of the reaction[16]). Under these conditions the titrateable acid (presumably HBr) was $\approx 1 \times 10^{-3}$ M when determined both early and late in the reaction, and the reaction affords ≈95% of 1,2-dibromopentane along with trace amounts of bromopentenes and 1,2,3-tribromopentane. Unreacted 1-pentene from reactions taken to 88% (±1) and 95% (±0.5) was recovered by vacuum transfer followed by fractional distillation and then brominated in reactions taken to completion. The resulting 1,2-dibromopentane was purified by fractional distillation and analyzed by ^2H and ^{13}C NMR comparison to 1,2-dibromopentane obtained from the original 1-pentene. The changes in isotopic composition were calculated using the methyl group as an "internal standard" with the assumption that its isotopic composition does not change in the reaction. From the changes in isotopic composition, the KIEs and errors were calculated as previously described.[15]

The results of four measurements (each the average of three spectra) on two reactions are summarized in Figure 1.

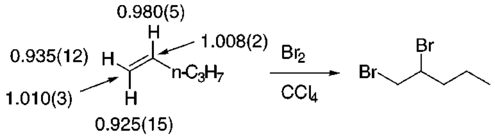


Figure 1. ^{13}C and ^2H KIEs for the bromination of 1-pentene in CCl_4. The results shown are the average of four measurements (with the standard deviation in parentheses) for two reactions.

The notable observations include substantially inverse ^2H KIEs for the hydrogens on the terminal carbon, a smaller inverse KIE for the hydrogen on the internal olefinic carbon, and relatively small but significant ^{13}C KIEs at both olefinic carbons.

Calculationally predicted isotope effects were used to aid in the interpretation of the experimental KIEs. The bromine−propene π complex (**1**), the bromonium ion (**2**), and the transition state for transfer of Br^+ from one molecule of propene to another (**3**) were located with Becke3LYP calculations using Alhrichs SVP basis set for the bromine atoms and a 6-31G* basis set for all other atoms. Equilibrium or kinetic isotope effects were then calculated by the method

---

[10] CCl_4 is the most common solvent used in *Organic Syntheses* brominations.

[11] Hanna, J. G.; Siggia, S. *Anal. Chem.* **1965**, *37*, 690. Garnier, F.; Dubois, J.-E. *Bull. Soc. Chem. Fr.* **1968**, 3797.

[12] See: Ruasse, M.-F.; Dubois, J.-E. *J. Am. Chem. Soc.* **1975**, *97*, 1977. Olah, G. A.; Hockswender, T. R., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 3574.

[13] For previous studies of substrate deuterium KIEs for brominations, see refs 3b, 4, and also: (a) Denney, D. B.; Tunkel, N. *Chem. Ind.* **1959**, 1383. (b) Koerner, T.; Brown, R. S.; Gainsforth, J. L.; Klobukowski, M. *J. Am. Chem. Soc.* **1998**, *120*, 5628. (c) Bellucci, G.; Chiappe, C.; Lo Moro, G. *J. Org. Chem.* **1997**, *62*, 3176. (d) Wilkins, C. L.; Regulski, T. W. *J. Am. Chem. Soc.* **1972**, *94*, 6016. (e) Slebocka-Tilk, H.; Motallebi, S.; Nagorski, R. W.; Turner, P.; Brown, R. S.; McDonald, R. *J. Am. Chem. Soc.* **1995**, *117*, 8769. (f) Slebocka-Tilk, H.; Neverov, A.; Motallebi, S.; Brown, R. S.; Donini, O.; Gainsforth, J. L.; Klobukoski, M. *J. Am. Chem. Soc.* **1998**, *120*, 2578.

[14] The only previous measurement of carbon KIEs from bromination gave results within experimental error of unity: Ropp, G. A.; Raaen, V. F.; Weinbergur, A. J. *J. Am. Chem. Soc.* **1953**, *75*, 3694.

[15] Singleton, D. A.; Thomas, A. A. *J. Am. Chem. Soc.* **1995**, *117*, 9357.

[16] If the reaction mechanism changes as the reaction proceeds, the KIE measurement by the technique employed is unevenly weighted toward the KIE operative near the end of the reaction. Small amounts of an alternative mechanisms or reactions at the beginning of a reaction will have minimal impact on the observed KIEs. The estimated $[Br_2]$ was judged visually by comparison with standard solutions.

of Bigeleisen and Mayer[17] from the scaled theoretical vibrational frequencies.[18] The results are summarized in Figure 2.

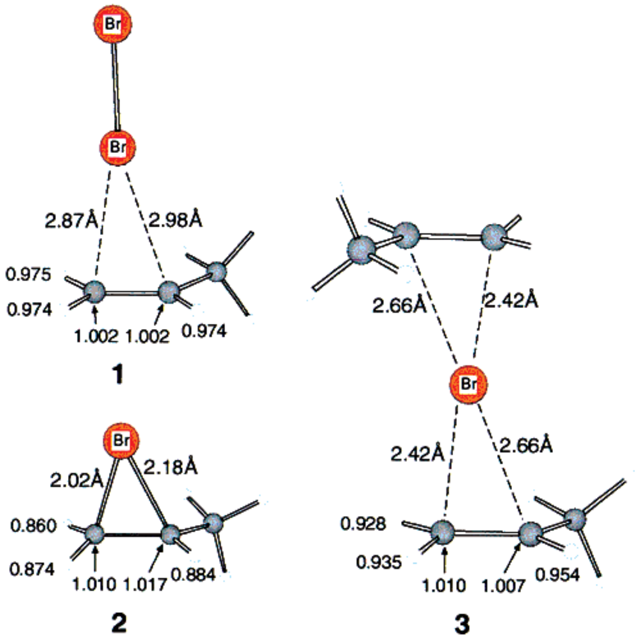
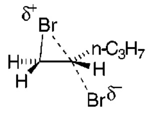


Figure 2. Calculated structures for the Br_2–propene π complex, the propene bromonium ion, and the transition structure for transfer of Br^+ between propene molecules (from Becke3LYP calculations), along with predicted equilibrium isotope effects (K_H/K_D and $K_{^{12}C}/K_{^{13}C}$) for formation of these structures from propene.

The predicted equilibrium isotope effects for formation of **1** support the intuitive idea that KIEs for formation of a π complex should be small. There is little rehybridization of the olefinic carbons—they remain nearly planar—and only modest inverse secondary ^{2}H isotope effects are expected. The larger experimental KIEs are not consistent with rate-limiting π complex formation. On the other hand, substantially inverse equilibrium ^{2}H isotope effects are predicted for the formation of **2**. On the basis of this prediction, any transition state occurring after bromonium ion formation would have more inverse deuterium isotope effects than those experimentally observed. Rate-limiting ring opening of **2**, as in a transition state that resembles **4**, for example, would be expected to exhibit more inverse KIEs for the terminal olefinic hydrogens than those observed, along with a more substantial ^{13}C KIE at the internal olefinic carbon.



4

Structure **3** was calculated as a model for transition states forming a bromonium ion. The difficulty of obtaining applicable gas-phase calculational predictions for the solution-phase polar bromination reaction has been previously discussed.[13b,f] The transfer of Br^+ from one molecule of propene to another was chosen as a model for the solution chemistry because the reaction is thermoneutral and does not involve the net development of charge. The isotope effects predicted for **3** match amazingly well with the experimental values, with four of the five predicted KIEs within error of experiment.

These results strongly support the interpretation of the experimental KIEs in terms of rate-limiting formation of a bromonium ion. The more inverse ^{2}H KIEs for the terminal hydrogens are suggestive of an asynchronous transition state with greater bond formation to the terminal carbon. The ^{13}C KIEs are consistent with this picture though they do not reflect as much asynchronous character. Greater bond formation to the terminal carbon at the transition state for bromonium ion formation would be expected due to the preference for buildup of a partial positive charge at the internal olefinic carbon.

It should be noted that if Br^+ transfer from alkene to alkene occurred rapidly, after some earlier rate-limiting step, the observed isotope effects in our competition reactions would not reflect the KIEs predicted for **3** but rather those for the product-determining step (e.g., **4**). The results here rule out any substantial importance for such Br^+ transfers among alkenes.

In summary, whatever the nature of the brominating species under synthetic conditions in CCl_4 (and this cannot be determined from isotope effects), the major mechanistic process involves rate-limiting bromonium ion formation. This indicates that some of the complications observed for other brominations are not important under these conditions.

Acknowledgment. We thank NIH (Grant GM-45617) and The Robert A. Welch Foundation for support of this research.

Supporting Information Available: Structures and energies of **1**–**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL990659D

---

[17] (a) Bigeleisen, J.; Mayer, M. G. *J. Chem. Phys.* **1947**, *15*, 261. (b) Wolfsberg, M. *Acc. Chem. Res.* **1972**, *5*, 225.

[18] The calculations used the program QUIVER (Saunders: M.; Laidig, K. E.; Wolfsberg, M. *J. Am. Chem. Soc.* **1989**, *111*, 8989) with Becke3LYP frequencies scaled by 0.9614. (Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502.)