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ATOM TRANSFER CYCLIZATION OF SIMPLE HEXENYL IODIDES. A CAUTION ON THE USE OF ALKENYL IODIDES AS PROBES FOR THE DETECTION OF SINGLE ELECTRON TRANSFER PROCESSES

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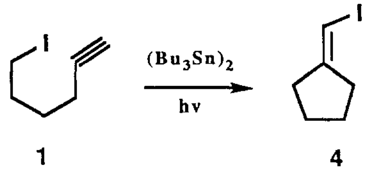
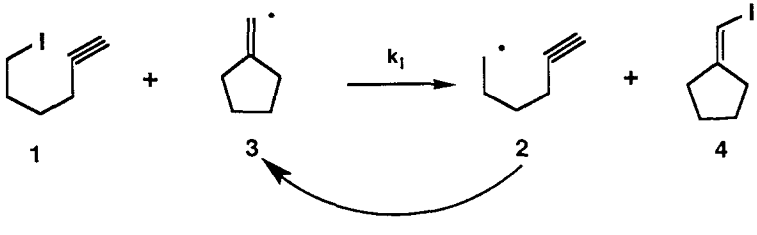
Abstract: The trialkyltin initiated isomerization of 1-iodo-5-hexene to (iodomethyl)cyclopentane is reported. Rapid and reversible iodine atom transfer between alkyl radicals is the key chain transfer step. The results suggest an important caution in the use of hexenyl iodides as SET probes: a good mechanism exists whereby the yield of rearranged products may be much greater than the amount of radicals produced by the reaction under study!

We have recently reported the development of a synthetically useful atom transfer cyclization reaction which involves the isomerization of an hexynyl iodide **1** to a cyclic vinyl iodide as summarized in equation 1.[2] After initiation to form the hexynyl radical **2**, standard cyclization generates the vinyl radical **3**. In the key chain transfer step, vinyl radical **3** abstracts an iodine atom from the starting iodide **1** to produce the cyclic vinyl iodide **4** and the hexynyl radical **2**. Note that the iodine atom transfer is effectively irreversible due to the nature of the radicals involved and we were readily able to estimate that k_I approaches the diffusion controlled limit. Since no good mechanism exists to recycle **4** to the radical pool, the yield of (iodomethylene)cyclopentane is very high. In effect, this sequence terminates a radical cyclization with an iodine atom transfer.

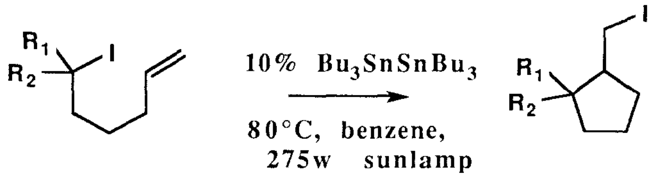


Eq. 1



Interest in this method as a possible alternative for commonly used trialkyltin hydride reagent in free radical cyclizations[3] lead us to consider the related isomerization of hexenyl iodides to (iodomethyl)-cyclopentanes. In this case, the key iodine atom transfer reaction will clearly be reversible. Nonetheless, if the rate for the exchange of alkyl radicals with alkyl iodides was sufficiently rapid,[4] useful results could be obtained. Indeed we found that one example of this reaction has already been reported. In 1966 in a study related to the polymerization of hexadienes, Brace reported the AIBN initiated isomerization of 2-iodo-6-heptene (**5b**) to the corresponding (iodomethyl)cyclopentane (**6b**).[5] We now report the cyclization of the other two iodides in the series (**5a** and **5c**) and conclude that: 1) the atom transfer cyclizations of alkenyl iodides can be useful synthetic procedures, and more importantly, 2) that such atom transfer cyclizations constitute a generally unrecognized mechanism for formation of rearranged products in the common tactic of employing alkenyl iodides as radical probes in the study of reactions which may proceed via electron transfer.

In our hands, heating of hexenyl iodide **5a** with AIBN (benzene, 80°C) resulted in very low conversion to (iodomethyl)cyclopentane. However, treatment of **5a** with 10% hexabutylditin in benzene at 75-85°C with sunlamp initiation[2] resulted in smooth consumption of **5a** over about 30 minutes. The progress of the reaction was carefully monitored by capillary GC and the major product was **6a**. As the reaction neared completion, a significant amount of methyl cyclopentane was also observed.[6] As expected, a small amount of cyclohexyl iodide was also formed and the ratio of (iodomethyl)cyclopentane to cyclohexyl iodide was quite close to the known 50/1 kinetic partitioning of the 5-hexenyl radical between 5-exo and 6-endo modes of cyclization.[3] The yield of **6a** reached its maximum value (72%) at about 90% conversion and then began to slowly decrease.[6] Similar results were observed for the cyclization of **5c** to **6c** and the maximum yield of **6c** reached 75%.



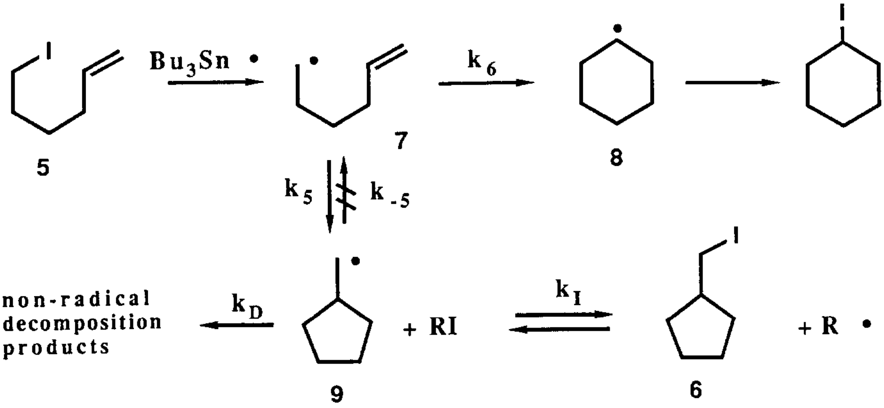
Eq. 2

5a $R_1=R_2=H$
5b $R_1=CH_3$, $R_2=H$
5c $R_1=R_2=CH_3$

6a
6b
6c

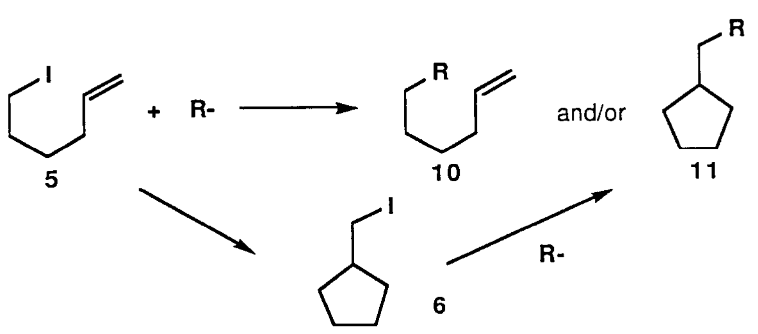
The mechanism for this atom transfer cyclization is outlined in Equation 3. Hexenyl radical **7**, generated in an initiation step, partitions between **8** and **9** with the expected 50/1 ratio. However, in contrast to the reaction outlined in Eq. 1, the key iodine atom transfer is not irreversible. Radical **9** now enters into an equilibration with the alkyl iodide pool. Exchange with **5** is a productive reaction while exchange with **6** is not. The results indicate that the equilibrium can indeed be established. The rate of iodine atom transfer must be greater than the rate of all possible decomposition reactions of **9** combined. In addition, the rate of these decomposition reactions must be greater than k_{-5} since an equilibrium between (iodomethyl)cyclopentane and cyclohexyl iodide is apparently not established. Indeed, the fact that alkyl iodides rapidly exchange iodine with alkyl radicals is known and this reaction has been used to great advantage in several important studies.[4]

Eq. 3



From the synthetic standpoint, the isomerization of hexenyl iodides to (iodomethyl)cyclopentanes is a potentially useful reaction. However, care must be taken to monitor the cyclization since yields can actually decrease toward the end of the reaction as the concentration of the starting iodide becomes quite low and radical decomposition intervenes.[6] In addition, consideration of the trends expected for k_I leads to the conclusion the isomerization of more highly substituted alkyl iodides to less substituted products may be more effective than the reverse process.[7]

More importantly, the above observations suggest an obvious caveat in the use of hexenyl iodides as mechanistic probes for free radical intermediates. Equation 4 provides a generic example of this commonly employed technique.[8,9] Treatment of **5** (or any related derivative) with a nucleophile or reducing agent (R-) can produce mixtures of normal products **10** and rearranged products **11**. Based on the ratio of the products and the well known rate constants for radical cyclization, the importance of single electron transfer (SET) processes is assessed. Reactions assumed to proceed via a polar mechanism have been proposed to have a significant electron transfer component.[8] However, this deceptively simple analysis neglects the atom transfer cyclization. Generation of trace amounts of *any* radical can initiate the chain isomerization of **5** to **6**.[9] Simple ionic reaction of **6** with R- can then produce **11**. Thus, *while a radical intermediate is involved in the conversion of* **5** *to* **11***, the yield of* **11** *may in no direct way reflect the component of the reaction of R- with* **5** *which proceeds via a single electron transfer mechanism.*



Eq. 4

Clearly these observations are based on qualitative considerations and it would be inappropriate to conclude that all mechanistic studies using on this concept are invalid. Relevant quantitative studies will be required on a case-by-case basis to determine the importance of atom transfer cyclization in the formation of products related to **11**. Much more data is needed than is presently available and it is hoped that this work will stimulate such studies.[10] For the present, these considerations should serve as a red flag for those inclined to interpret the observation of rearranged products such as **11** as *prima facie* evidence for a significant radical component in an polar reaction.

Note Added in Proof. We have recently learned that quantitative studies including direct measurements of relative rate constants have been carried out by Prof. M. Newcomb. The studies fully support the conclusions drawn in this paper. Newcomb, M.; Sanchez, R. M.; Kaplan, J., submitted for publication. We are grateful to Prof. Newcomb for a preprint of this paper.

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References and Notes

1) Recipient of Dreyfus Teacher-Scholar Award (1986-91), and Sloan Foundation Fellow, (1985-87).

2) Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1986**, *108*, 2489.

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5) Brace, N. O. *J. Org. Chem.* **1967**, *32*, 2711; *Ibid.* **1966**, *31*, 2879.

6) The major new product formed at longer reaction times was methyl cyclopentane. This results from a hydrogen atom abstraction by radical **9**. Potential H-atom donors include any alkyl iodide or the tri-n-butyltin products. At longer reaction times (>30 min.), the total mass balance also began to decrease.

7) The iodine donor capability of alkyl radicals should follow the standard trend 3°>2°>1° (refs. 3 and 4). For an optimum isomerization, the starting material should be a better iodine atom donor than the product.

8) For some recent examples of this approach see: Ashby, E. C.; Argyropoulos, J. N. *J. Org. Chem.* **1985**, *50*, 3274, Alnajjar, M. S.; Kuivila, H. G. *J. Am. Chem. Soc.* **1985**, *107*, 416, Ashby, E. C.; Wenderoth, B.; Pham, T. N.; Park, W.-S. *J. Org. Chem.* **1984**, *49*, 4505.

9) Indeed, Ashby has shown that a catayltic amount of LAH can initiate the isomerization of 2,2-dimethyl-1-iodo-5-hexene to the corresponding (iodomethyl)cyclopentane. Ashby, E. C.; DePriest, R. N.; Wenderoth, B.; Pham, T.M. *J. Org. Chem.* **1984**, *49*, 3545.

10) To quantitatively access the importance of the atom transfer cyclization, rate constants for iodine atom abstractions need to be obtained and some knowledge of rates of initiation and termination is also required. Note also that our work is carried out in benzene while most mechanistic studies are conducted in ethereal solvents. It has been proposed that the rate constants for transfer of iodine from alkyl iodides to alkyl radicals are in the vicinity of 10^5 $M^{-1}s^{-1}$(ref 4c). Based on this and other relevant rate constants, it is easy to imagine that iodine atom transfer is more rapid than reaction of R- with a radical and that, even with a relatively small number of initiation events, atom transfer cyclization could be competitive with a typical ionic process such as S_N2 displacement. In this regard, see Note Added in Proof above.

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