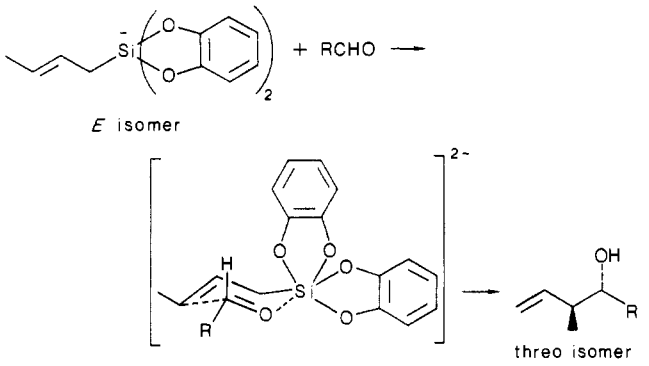
Scheme IV



methyl)-3-((trimethylsilyl)methyl)-1,3-butadiene[54] have been used as a synthetic equivalent of a 2,2′-biallyl zwitterionic species. 4-Alkoxy-substituted isoprenylsilanes are more active and regioselective for the cycloaddition and give the corresponding cycloadducts without catalyst. Cycloadditions of this reagent to carbonyl compounds give precursors of deoxy sugar derivatives.

Allylsilanes containing a leaving group at the δ position become a synthetic equivalent of 1,3-dienes by conjugate 1,4-elimination.[55]

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Concluding Remarks

Allylsilanes, stable in air and moisture, storable, and easy to handle, can be readily functionalized. Synthetic methods using these allylsilanes have developed rapidly, and allylsilanes are now having a strong impact upon the field of organic synthesis. Much more remains to be discovered in the area of allylsilanes as reagents in organic synthesis.

It is a pleasure to acknowledge the fine efforts of members of both the Sandai and Nagasaki groups, many of whose names appear in the references related to our work. Special thanks go to Professors Sakurai and Traylor for their valuable encouragement throughout this work. Financial support for our programs is provided by the Ministry of Education, Science and Culture (Grants-in-Aid for Scientific Research), the Houan-sha, the Research Foundation for Pharmaceutical Sciences, the Yamada Science Foundation, the Takeda Science Foundation, the Mitsubishi Foundation, Pfizer-Taito Inc., and Mitsubishi Chemical Industry Co. Ltd. We thank Toray Silicone Co. Ltd. and Shin-Etsu Chemical Industry Co. Ltd. for gifts of chlorosilanes.

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A Critical Evaluation of Studies Employing Alkenyl Halide "Mechanistic Probes" as Indicators of Single-Electron-Transfer Processes

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Chemical reactions come about through the reorganization of valence electrons. The notion that organic reactions proceed via either polar or single-electron-transfer (SET) processes is widespread in organic chemistry. If one considers an associative polar process versus an outer-sphere electron-transfer process that gives a radical species, then the two pathways are quite different. However, the distinction need not be so dramatic; for example, there is only a subtle difference between an inner-sphere SET process resulting in a substitution reaction and a polar S_N2 reaction.[1] For organic reactions, there has been some lack of appreciation of the details of outer-sphere (nonbonding) and inner-sphere (bonding) electron-transfer reactions, and most qualitative studies searching for SET pathways have sought evidence of radical or radical anion products. In other words, whether stated or not, these studies have been directed at uncovering outer-sphere

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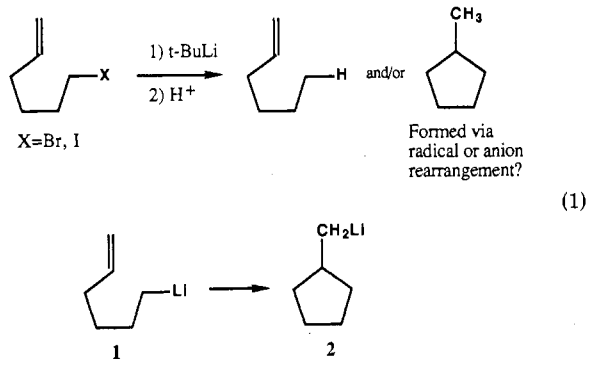
processes. In this type of study, an SET mechanism can be confirmed if the existence of an odd-electron intermediate can be demonstrated *and* a correlation between this intermediate and the final product can be established. Good evidence exists that a variety of important organic reactions proceed via single-electron-transfer mechanisms.[2]

Recently, it has been suggested that many organic reactions traditionally classed as polar may proceed via outer-sphere single-electron-transfer mechanisms.[3-6] Evidence for these conclusions has been based on the detection of radical intermediates in a reaction or on the isolation of products derived from radicals. Commonly, the presence of free radical intermediates has been inferred from the well-known intramolecular rearrangement of a variety of unsaturated radical clocks[7] generated from alkenyl halides: so-called "mechanistic (or cyclizable) probes".[8] It has usually been *assumed* that these intermediates are on the *direct* pathway between starting materials and products.

Several interfering reactions can compromise the use of alkenyl halide mechanistic probes. The possibility of rearrangement of the probe via a nonradical pathway has been recognized. For example, hexenyl bromide and iodide probes have been used to investigate the mechanism of halogen–lithium exchange, as shown in eq 1.[6] While the anionic cyclization (1 → 2) is much



(1)

slower than its radical counterpart, it can lead to significant amounts of rearranged products under certain reaction conditions.[9,10] With appropriate control experiments, the possibility of rearrangement of the probe by a nonradical pathway can be investigated.

A more insidious problem has surfaced recently. This Account will demonstrate that, while alkenyl halide cyclizable probes may indeed rearrange through radical intermediates, these intermediates may not always be on the direct pathway between reactants and products. As such, the observation of rearranged products in a cyclizable probe experiment does not provide conclusive evidence for a single-electron-transfer pathway in the reaction under study. Quantitative evidence supporting this conclusion will be presented. This evidence suggests that past interpretations of some cyclizable probe studies should be reevaluated. It will be demonstrated that alkenyl halide "mechanistic probes" should be used only with great care to obtain evidence for the existence of single-electron-transfer pathways. Guidelines for the use and interpretation of these experiments will be provided.

Reaction of Organic Halides with Nucleophiles

The belief that reactions of primary and secondary alkyl halides with most nucleophiles and reducing agents proceed by a polar (S_N2) pathway is supported by kinetic and stereochemical evidence. However, many reactions once classed as polar processes have now been reformulated as outer-sphere single-electron-transfer reactions. Such reactions include the reduction of primary and secondary alkyl halides[5] with lithium aluminum hydride, aluminum hydride, and lithium triethyl borohydride and the displacement of such halides with metal enolates,[4a,b] alkoxides,[4i] alkali stannanes,[4d-h] and organocopper species.[4c]

The single-electron-transfer mechanisms often proposed are outlined in Scheme I. Reaction of primary or secondary organic halide (RX) with a nucleophile (Nu^- or NuM) can result in electron transfer (step i) to give the alkyl halide radical anion and the corresponding radical of the nucleophile ($Nu^\bullet$ or $[NuM]^{\bullet+}$). Very rapid fragmentation of the radical anion to an alkyl radical ($R^\bullet$) and a halide ion (X^-) then ensues (step ii). It has been assumed[4,5] that the organic radicals ($R^\bullet$) would be transformed in subsequent steps to the formal products of substitution (RNu). Two paths that can lead to net substituion are radical–radical coupling (step iii) or radical–nucleophile coupling followed by electron transfer of the resulting complex to the starting halide (steps iv and v). The former pathway is a nonchain

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(5) (a) Ashby, E. C.; DePriest, R. N.; Pham, T. N. *Tetrahedron Lett.* **1983**, *24*, 2825. (b) Ashby, E. C.; DePriest, R. N.; Goel, A. B.; Wenderoth, B.; Pham, T. N. *J. Org. Chem.* **1984**, *49*, 3545. (c) Ashby, E. C.; Wenderoth, B.; Pham, T. N.; Park, W.-S. *J. Org. Chem.* **1984**, *49*, 4505. (d) Ashby, E. C.; Pham, T. N. *J. Org. Chem.* **1986**, *51*, 3598.

(6) (a) Bailey, W. F.; Gagnier, R. P.; Patricia, J. J. *J. Org. Chem.* **1984**, *49*, 2098. (b) Ashby, E. C.; Pham, T. N.; Park, B. *Tetrahedron Lett.* **1985**, *26*, 4691. (c) Ashby, E. C.; Pharm, T. N. *J. Org. Chem.* **1987**, *52*, 1291.

(7) General references to free radical clocks: (a) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; deMayo, P., Ed.; Academic: New York, 1980; Vol. 1, Essay 4. (b) Surzur, J. M. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum: New York, 1981; Vol. 2, Chapter 2. (c) Beckwith, A. L. J., In *Landolt-Börnstein, New Series*; Fischer, H., Ed.; Springer-Verlag: Berlin, 1984; Group II, Vol. 13a.

(8) We wish to draw a clear distinction between the use of intramolecular radical rearrangements as "free radical clocks" or as "mechanistic (or cyclizable) probes". The former provides quantitative information about the rate of a process known to proceed via a free radical intermediate by competition of this reaction with a rearrangement of known rate. The latter attempts to provide qualitative evidence that a mechanism under study proceeds via the intermediacy of a free radical.

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(10) For example, early results[6] showed the formation of cyclic products in the exchange reaction between *tert*-butyllithium and hexenyl iodide. Subsequently, Bailey[9a] was able to show that these products arose from the rearrangement of hexenyllithium rather than hexenyl radical. Both Bailey[9a] and Ashby[6c] now agree that this halogen–lithium exchange produces exclusively hexenyllithium.

process. Since the direct coupling of free radicals is unlikely to account for much product, cage processes have been proposed for step iii. The latter pathway is a chain process (S_{RN}) in which step i is an initiation step and steps ii, iv, and v comprise the propagation sequence.

Scheme I

$$R{-}X + Nu^- \rightarrow R{-}X^{\bullet -} \quad \text{(i)}$$

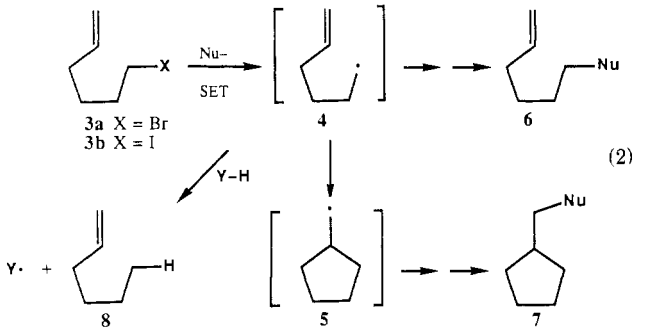
$$R{-}X^{\bullet -} \rightarrow R^\bullet + X^- \quad \text{(ii)}$$

$$R^\bullet + Nu^\bullet \rightarrow R{-}Nu \quad \text{(iii)}$$

$$R^\bullet + Nu^- \rightarrow (R{-}Nu)^{\bullet -} \quad \text{(iv)}$$

$$(R{-}Nu)^{\bullet -} + R{-}X \rightarrow R{-}Nu + R{-}X^{\bullet -} \quad \text{(v)}$$

The results of alkenyl halide cyclizable probe studies have been widely cited in support of mechanisms of the general type outlined in Scheme I.[4,5] An example of this analysis is outlined in eq 2. A hexenyl halide



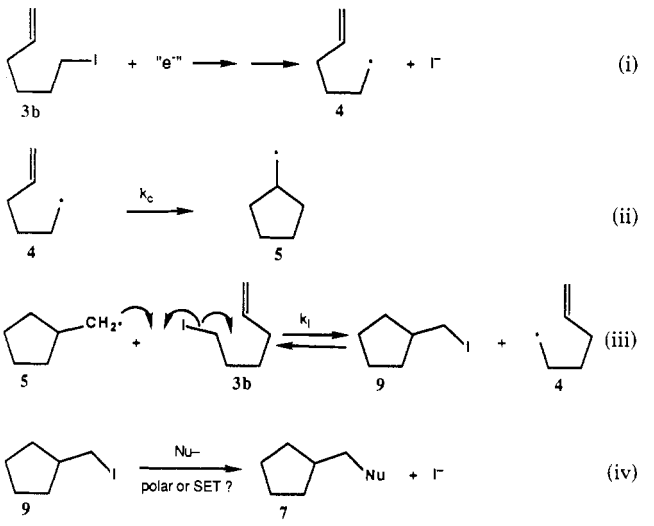
(2)

"cyclizable probe" (**3a**, **3b**, or a related molecule) is permitted to react with a nucleophile or reducing agent. The ratio of acyclic product **6** to cyclic product **7** is determined. It has been assumed that the observation of cyclic products in such an experiment provides prima facie evidence for the operation of an SET mechanism since the cyclic product **7** must result from the intermediate radical **5**. Furthermore, it has sometimes been assumed that the yield of **7** provides a direct measure of the *minimum* SET component in the reaction. Such a qualitative analysis is correct only if the intermediate radicals **4** and **5** are on the *direct* reaction path to the substitution products **6** and **7**.

Similarly, the qualitative application of probe halides in the detection of SET processes would be fruitless if radical–molecule/ion reactions (cf. step iv) were fast relative to the rate of radical rearrangements. In such a case, large numbers of radicals could be formed but only small amounts of rearrangement products would be detected. Speculating that radical–molecule reactions were fast, the authors of some probe studies have concluded that electron transfer between a nucleophile and a class of alkyl halides was the major reaction pathway even when rearranged products were not observed in high yields.

In addition to the observation of cyclic products, reactions conducted in the presence of hydrogen atom donors (YH) have been cited as evidence for the intermediacy of radicals related to **4** and **5** and, by implication, evidence for the SET path. Here, it is assumed that the interception of unrearranged radicals

Scheme II



by the H atom donor (**4** → **8**) is competitive with rearrangement (**4** → **5**).

Whether the assumptions cited above, or the other steps demanded by the mechanisms outlined in Scheme I, are reasonable has not been carefully examined. In some cases, direct evidence to the contrary exists. There is now good reason to believe that free radical intermediates may be formed which are not on the direct pathway between reactants and products, that the reaction of certain hydride reducing agents with organic radicals (step iv, Scheme I) is not a facile reaction, and that certain widely employed hydrogen donors do not react sufficiently rapidly to quantitatively intercept even relatively slow alkenyl probe radicals before rearrangement.

Qualitative Considerations

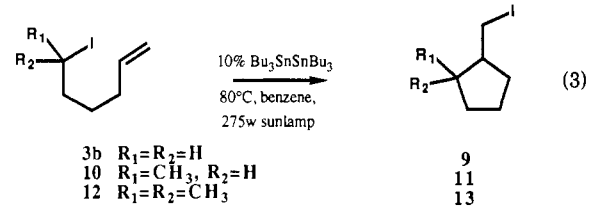
An alternative to the eq 2 mechanism for the formation of cyclic products is presented for hexenyl iodide (**3b**) in Scheme II. Radical **4** can be generated from **3b** (step i) by an electron-transfer step, followed by loss of iodide, as outlined in Scheme I. Irreversible hexenyl radical cyclization (step ii) generates **5**. Radical **5** can now abstract an iodine atom from *any* alkyl iodide present in the reaction mixture. The S_H2 iodine atom transfer from **3b** to **5** (step iii) is a productive event that transfers the chain, providing the cyclic iodide **9** and the starting radical **4**. Iodine atom transfer must be reversible since the C–I bond strengths and the stabilities of the radicals involved are essentially equal. Assuming that k_I is sufficiently rapid, so that all the alkyl iodides in the reaction are in equilibrium, the result is isomerization of **3b** to **9** by a chain process in which step i is only an initiation step. In a slower step, step iv, the cyclic iodide **9** may then react with the reagent under study to provide the cyclic product **7**.

While the cyclic product is formed via the intermediacy of a radical, a single-electron-transfer mechanism for the formation of **7** is not demanded. The electron-transfer reaction (step i) is only an initiation step in the chain. The yield of cyclic products may be only remotely related to the "SET component" of the reaction because the result of each single-electron-transfer step is multiplied many times by the ensuing propagation sequence (steps ii and iii). While the initiation may

result from SET from the reagent under study, the amount of initiator required could be so limited that trace contaminants of the reaction mixture might be responsible for initiation.[11]

For the proposal outlined in Scheme II to be operative, the rate of the isomerization of **3b** to **9** must be greater than the direct reaction of the nucleophile with the starting halide. While the rates of propagation steps in a radical sequence can usually be defined with reasonable accuracy, determination of the overall rate of a radical process requires a knowledge of the number and nature of initiation and termination events. Qualitative indications that the proposed chain reaction is indeed rapid were reported more than 20 years ago.

In 1966, Brace reported that the isomerization of 6-iodo-1-heptene (**10**) to 1-(iodomethyl)-2-methylcyclopentane **11** (eq 3) could be initiated by heating of



(3)

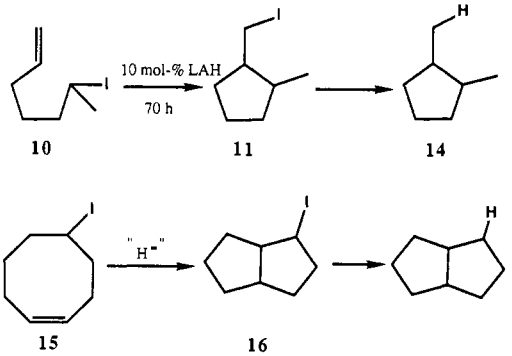
3b $R_1=R_2=H$ — 9
10 $R_1=CH_3$, $R_2=H$ — 11
12 $R_1=R_2=CH_3$ — 13

10 with a catalytic amount of AIBN.[12] Elegant experiments by Hiatt and Benson,[13] and later Castelhano and Griller,[14] relied on the equilibrium of alkyl radicals in the presence of alkyl iodides by means of a rapid iodine atom transfer.[15] In 1986, Curran and Kim reported on the potential synthetic utility of these iodine atom transfer reactions (eq 3).[16] While heating hexenyl iodide **3b** with AIBN according to the report of Brace resulted in the formation of only trace amounts of (iodomethyl)cyclopentane, irradiation of a solution of **3b** and 10% hexabutylditin resulted in the formation of significant amounts **9**. At 90% conversion, the GC yield of **9** reached a maximum of 72% before beginning to decline as the reaction neared completion. In addition, a 1.5% yield of cyclohexyl iodide was also indicated by GC. This is identical with the known 50/1 partitioning of the 5-hexenyl radical between 5-exo and 6-endo modes of cyclization. Similar results were obtained for the isomerization of the tertiary iodide **12** to **13**. Alkyl bromides cannot be isomerized successfully by this sequence due to the increased strength of the C–Br bond relative to the C–I bond.

The success of these reactions indicates that the alkyl iodide pool is continually equilibrated via iodine atom exchange between radicals and alkyl iodides as indicated in Scheme II. The abstraction of iodine atoms from alkyl iodides by alkyl radicals is a facile process that must be more rapid than other reactions such as hydrogen atom abstraction from the solvent (benzene) or the reactants or addition to the solvent. Considering the rate of a typical S_N2 reaction and the rates of the propagation steps in Scheme II, it can be estimated that a few initiation events could cause substantial isomerization of an alkenyl iodide to a cyclic iodide in a typical cyclizable probe study.

Common observations of the cyclizable probe experiments are readily interpreted by this atom-transfer mechanism. For example, maximum amounts of cyclic products are always formed with alkyl iodide probes. On occasion, alkyl bromides provide trace amounts of cyclic products but alkyl chlorides or alkanesulfonates never provide cyclic products. In the past, these observations have been interpreted in terms of reduction potentials. However, the controlling factor in the formation of cyclic products in Scheme II is the halogen atom donor capability of the starting halide; only alkyl iodides donate halogen rapidly enough to propagate the chain. As the direct reaction of the halide with the nucleophile or reducing agent is slowed, the isomerization competes more effectively. Thus unreactive halides (neopentyl, for example) are always found to give the most cyclic products.

The mechanism for formation of cyclic products outlined in Scheme II permits clear-cut, verifiable predictions. It demands the accumulation of the cyclic iodide **9** in the reaction medium, provided that the starting iodide and the cyclic iodide are of comparable reactivity with the reagent under study.[17] This observation has already been reported by Ashby on several occasions (eq 4). For example, treatment of iodide **10**



10 11 14

15 16

(4)

with 10 mol % of LAH for 70 h resulted in conversion to **11** in 70% yield.[4b] The similarity of this result to the Brace report is striking. LAH apparently serves to initiate the isomerization. In a slower reaction, the cyclic iodide **11** can be reduced to 1,2-dimethylcyclopentane (**14**) if sufficient reducing agent is present. Clearly then, most of the final reduced product is produced via the intermediacy of **11**. Related observations have been made with cyclooctenyl iodide **15**, which was observed to isomerize to **16**.[4c,d]

Despite the observation of cyclic iodides in several probe experiments (and the postulation of the correct pathway for the formation of these iodides), Ashby and co-workers still concluded that an SET mechanism was operative in the conversion of cyclic iodide **11** to **14** based in part upon experiments conducted in the presence of hydrogen atom donors.[4b-d] The details of the conversion of **11** to **14** aside, it is now clear that the

(11) For example, with a chain length of 1000 and the observation of 10% rearrangement product in a study initially employing 0.1 M probe halide, only 1×10^{-5} mol of initiator per L is indicated. If the test reagent was also 0.1 M, then as little as 0.01 mol % of an impurity in the reagent acting as an initiator could account for all of the rearranged product.

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

(13) Hiatt, R.; Benson, S. W. *J. Am. Chem. Soc.* **1972**, *94*, 25.

(14) Castelhano, A. L.; Griller, D. *J. Am. Chem. Soc.* **1982**, *104*, 3655.

(15) Review of halogen atom transfers: Danen, W. C. In *Methods in Free Radical Chemistry*; Huyser, E. S., Ed.; Marcel Dekker: New York, 1974; Vol. 5, pp 1–100.

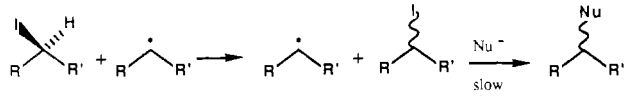
(16) Curran, D. P.; Kim, D. *Tetrahedron Lett.* **1986**, *27*, 5821.

(17) If the cyclic iodide is of greater polar reactivity than the starting iodide, it could conceivably be consumed as fast as it is produced. In such a case, the intermediate cyclic iodide, although an actual intermediate, could not be detected.

"cyclizable probe" is not effective in probing for an SET mechanism. While the heptenyl radical is undoubtedly involved in the conversion of **10** to **11**, it is not on the direct pathway to **14**, but is merely an intermediate in the "preequilibration" of the alkyl iodide pool.

We emphasize that *the ineffectiveness of a "cyclizable probe" in providing evidence for an SET mechanism is in no way proof that a polar mechanism is operating.* Whether the conversion of **11** to **14** occurs by a polar or SET process is an open question. We argue that the use of precursors such as **10** in these experiments provides quite limited information.[18] It actually complicates the interpretation of the experimental data. Despite claims to the contrary,[19] it is vital to know how much cyclic product **14** arises from the cyclic iodide **11**.

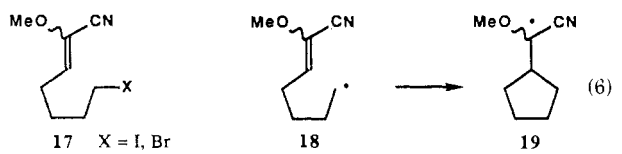
Other conclusions can be drawn from the mechanism in Scheme II. Since the generation of trace amounts of alkyl radicals should effect the equilibration of all alkyl iodides in the reaction (both cyclic and acyclic), it is conceivable that an optically active secondary iodide could racemize prior to nucleophilic substitution (eq 5). Thus, the use of optically active alkyl iodides as stereochemical probes should be avoided unless it can be demonstrated that the reaction under study is more rapid than the radical chain equilibration.



(5)

Finally, the facility of the atom-transfer step will be dramatically effected by the relative stability of the starting versus cyclic radicals. Thus, the atom-transfer step can be accelerated by designing systems in which the resonance energy of the product radical is *less* than that of the starting radical. Iodine atom transfer will be significantly exothermic and useful preparative procedures can result.[20] In the systems studied previously as SET probes, iodine atom transfer is (nearly) thermoneutral. Alternatively, if the product radical is *more* stable than the starting radical, iodine atom transfer will be endothermic and should be retarded.

Thus, if the mechanism outlined in Scheme II is correct, the incorporation of a radical stabilizing group into the "cyclizable probe" should actually reduce the amount of cyclic product formed (even if it accelerates the cyclization!) by not permitting the chain propagation by iodine atom transfer. This prediction has recently been confirmed by Newcomb, Chung, and Park[21] in the reaction of various hydride reducing agents with halides **17** (eq 6). Radical **18** cyclizes to **19** at a rate



(6)

17 X = I, Br 18 19

>100 times that of the parent 5-hexenyl radical.[22] Any radical **18** formed in the reduction of **17** should rapidly cyclize to **19**. However, since **19** is a captodative radical, it would not be expected to abstract a halogen atom from **17**. This effectively subverts the chain reaction of Scheme II for formation of cyclic product. Indeed, the reaction of **17** with various hydride reducing agents gave acyclic dehalogenated products but gave no products derived from **19**. It was concluded that SET from the hydride reagents to form intermediate free radical **18** must occur in less than 0.1% of the reactions.

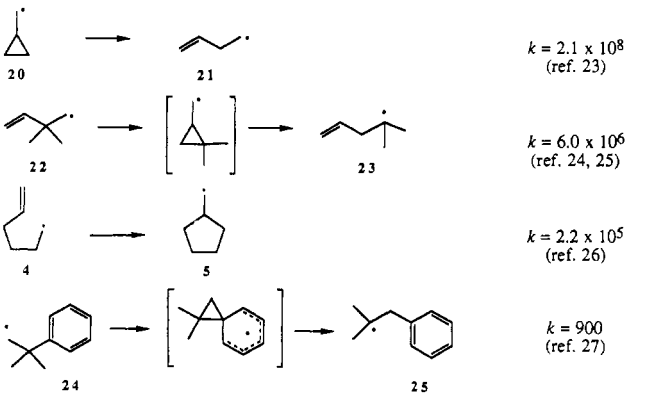


Figure 1. Radical rearrangements (s^{-1}) at 25 °C.

Kinetics of Radical Reactions

Despite the quantitative information inherently available from well-calibrated radical clocks, many mechanistic probe studies have employed these tools only in a qualitative sense. That is, the object of the studies was to observe products arising from radical rearrangements. Often this approach was justified because, although the rate constants for the radical rearrangement may have been known, the rate constants for a variety of radical–molecule reactions were not available. However, as we have noted, the qualitative application of probe halides can lead to confusing situations when radical chain reactions compete. If kinetic results had been available, such speculation would not have been necessary, and conclusions concerning the extent of electron transfer might have been made.

Over the past few years, several studies have provided kinetic information that is important in understanding the details of reactions occurring in radical probe experiments. In this section we have collected representative rate constants for several types of radical reactions. With these rate constants, one can determine whether mechanistic probe studies of potential SET reactions or other reactions involving radical intermediates would give meaningful results.

Radical Rearrangements. Among the reactions of interest for this Account, the radical rearrangements are the best studied. Compilations of radical rearrangement rate constants are available.[7] Representative rate constants are given in Figure 1. A widely used

(18) On the other hand, the absence of cyclic products is always informative. This proves that a *free* radical with a lifetime greater than the probe rearrangement rate is not formed.
(19) Ashby, E. C.; Pham, T. N. *Tetrahedron Lett.* **1987**, *28*, 3197.
(20) Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1986**, *108*, 2489.
(21) Park, S.-U.; Chung, S.-K.; Newcomb, M. *J. Org. Chem.* **1987**, *52*, 3275.
(22) Park, S.-U.; Chung, S.-K.; Newcomb, M. *J. Am. Chem. Soc.* **1986**, *108*, 240.
(23) Mathew, L.; Warkentin, J. *J. Am. Chem. Soc.* **1986**, *108*, 7981.
(24) Newcomb, M.; Williams, W. G. *Tetrahedron Lett.* **1985**, *26*, 1179; see ref 25.

Table I
Rate Constants for Halogen Atom Abstractions by Radicals

radical	alkyl halide	temp, °C	k, M^{-1} s^{-1}	ref
phenyl	$(CH_3)_2CHI$	45	1.1×10^9	33
phenyl	$CH_3CH_2CH(CH_3)Br$	25	2.3×10^6	34
octyl	$(CH_3)_3CI$	50	3×10^6	32
octyl	$(CH_3)_2CHI$	50	8×10^5	32
octyl	c-$C_6H_{11}I$	50	5×10^5	32
octyl	CH_3CH_2I	50	2×10^5	32
octyl	$(CH_3)_3CBr$	50	5×10^3	32
octyl	$(CH_3)_2CHBr$	50	1×10^3	32
octyl	c-$C_6H_{11}Br$	50	1×10^3	32
octyl	$CH_3(CH_2)_3Br$	50	6×10^2	32
octyl	$(CH_3)_3CCl$	50	6×10^2	32

radical rearrangement probe has been the 5-hexenyl cyclization; this reaction is also among the slowest radical rearrangements employed in probe studies.

Another common probe reaction has been the cyclopropylcarbinyl ring opening. Despite the fact that this reaction is among the fastest known radical skeletal rearrangements, cyclopropylcarbinyl halides probably should not be employed as qualitative mechanistic probes. These halides rearrange to butenyl products via processes that involve cationic,[28] anionic,[29] and radical intermediates. They can even give butenyl products via processes in which no free intermediates are formed.[30] Given the multitude of pathways available for conversion of a cyclopropylcarbinyl probe to a butenyl product, one should employ the radical ring opening only as a "clock"[8] in reactions known to proceed via radical intermediates.

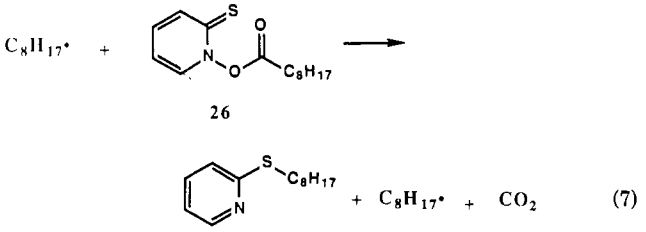
Rate Constants for Halogen Atom Transfer. As noted, qualitative evidence that iodine atom transfer from an alkyl iodide to an alkyl radical is a fast reaction was available in the literature.[12-16] Rate constants for reactions of phenyl radicals with alkyl iodides and bromides have been reported to be quite fast (see Table I), and generally phenyl radicals react only about 3 orders of magnitude faster than alkyl radicals with a variety of substrates.[31] Newcomb et al.[32] have recently studied the rates of reaction of octyl radicals with various alkyl halides at 50 °C. The results of these studies are also collected in Table I. The order of reactivities found was predictable; the alkyl halides reacted in the order RI > RBr > RCl and tertiary > secondary > primary.

Table II
Rate Constants for Hydrogen Atom Transfer Reactions

H atom donor	radical	temp, °C	k, M^{-1} s^{-1}	ref
$(CH_3)_3CSH$	**22**	32	1.1×10^7	36
$(c\text{-}C_6H_{11})_2PH$	**22**	27	1.0×10^6	36
	4	50	7×10^5	36
1,4-cyclohexadiene	ethyl	27	5.8×10^4	38
	tert-butyl	27	9.4×10^3	38
	22	50	4.8×10^5	36
	4	50	2.3×10^5	36
THF	**23**	50	2×10^3 (s^{-1})	36
	5	50	6×10^3 (s^{-1})	36
	octyl	22	6×10^3 (s^{-1})	39
	phenyl	25	4.8×10^6	34
diethyl ether	octyl	22	1×10^3 (s^{-1})	39

Rate Constants for S_H2 Hydrogen Atom Transfer. If alkyl radicals are formed as intermediates via SET reactions, then they could be reduced to alkanes by abstracting hydrogen atoms from solvent. Most "probe" studies of reactions of nucleophiles with an alkyl halide have been conducted in ethereal solvents such as THF. Since α-alkoxy radicals formed from ethers are relatively stable, it has been assumed that hydrogen atom abstraction from ethers was an important reaction in these studies. Alkyl radicals could also be reduced by hydrogen atom donation from a trapping agent intended to intercept these intermediates; dicyclohexylphosphine (DCPH)[35] and 1,4-cyclohexadiene (CHD) have been used.

Despite the stability of the radicals formed by hydrogen abstraction from ethers or trapping agents, little was known about the kinetics of these reactions. In an attempt to provide quantitative information about these rate constants, Newcomb and Park measured the rate of reactions of two alkyl radicals, 5-hexenyl (**4**) and 2,2-dimethyl-3-butenyl (**22**), with various hydrogen atom donors using the radical clock method.[36] Some results are given in Table II. The rate constants for reactions of radicals with THF (pseudo first order in solvent THF) were estimated by competition between reduction of the radical by THF and addition of the radical to its precursor *N*-hydroxypyridine-2-thione ester; the rate constant for reaction of octyl radical with its parent ester **26** has recently been reported by Newcomb and Kaplan (eq 7).[37]



(7)

The results in Table II demonstrate that, regardless of the stability of the product radical, hydrogen atom abstraction reactions are sluggish. THF reacts so slowly with alkyl radicals that essentially all radical rearrangements used as probes to date are unaffected by THF. Thus, if a significant yield of a reduced, unre-

(25) The original values for these reactions were recalculated with the recently reported value for the reactions of neopentyl radical with *n*-Bu_3SnH as the model reaction. Cf.: Johnson, L. J.; Lusztyk, J.; Wayner, D. D. M.; Abeywickreyma, A. N.; Beckwith, A. L. J.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 4594.
(26) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739.
(27) Franz, J. A.; Barrows, R. D.; Camaioni, D. M. *J. Am. Chem. Soc.* **1984**, *106*, 3964; see ref 25.
(28) Wiberg, K. B.; Hess, B. A., Jr.; Ashe, A. J., III. In *Carbonium Ions*; Olah, G. A., Schleyer, P. v. R., Eds.; Wiley: New York, 1972; Vol. 3, Chapter 26.
(29) Hunter, D. H.; Stothers, J. B.; Warnhoff, E. W. In *Rearrangements in Ground and Excited States*; Mayo, P. D., Ed.; Academic: New York, 1980; Vol. 1, Essay 6.
(30) Alnajjar, M. S.; Smith, G. F.; Kuivila, H. G. *J. Org. Chem.* **1984**, *49*, 1271. Newcomb, M.; Smith, M. G. *J. Organomet. Chem.* **1982**, *228*, 61.
(31) Johnson, L. J.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1984**, *106*, 4877.
(32) Newcomb, M.; Sanchez, R. M.; Kaplan, J. *J. Am. Chem. Soc.* **1987**, *109*, 1195.
(33) Kryger, R. G.; Lorand, J. P.; Stevens, N. R.; Heron, N. R. *J. Am. Chem. Soc.* **1977**, *99*, 7589.
(34) Scaiano, J. C.; Stewart, L. C. *J. Am. Chem. Soc.* **1983**, *105*, 3609.
(35) Smith, G. F.; Kuivila, H. G.; Simon, R.; Sultan, L. *J. Am. Chem. Soc.* **1981**, *103*, 833.
(36) Newcomb, M.; Park, S.-U. *J. Am. Chem. Soc.* **1986**, *108*, 4132.
(37) Newcomb, M.; Kaplan, J. *Tetrahedron Lett.* **1987**, *28*, 1615.
(38) Hawari, J. A.; Engel, P. S.; Griller, D. *Int. J. Chem. Kinet.* **1985**, *17*, 1215.
(39) Newcomb, M.; Kaplan, J., unpublished results.

arranged product is formed from the reaction of a probe alkyl halide with a nucleophile in an ethereal solvent, this product did not arise from the reaction of radical intermediates with the solvent.

From the rate constants for reactions of the trapping agents DCPH and CHD one sees that these reagents donate hydrogen too slowly to prevent substantial skeletal rearrangements of probe radicals. When the probe rearrangement is the (relatively) slow cyclization of 5-hexenyl, DCPH at 1.0 M concentration is required to trap 50–60% of the radicals before rearrangement. DCPH reacts with a primary radical with about the same rate constant as does an alkyl iodide. At appropriately high concentrations, DCPH can intercept an alkyl radical and might effectively derail Scheme II. However, we do not know the fate of the phosphorus-centered radical thus formed; Ashby has suggested that this radical can react with another alkyl halide via halogen abstraction (eq 8).[5d] This would introduce another competing chain reaction into a given probe experiment.

$$(c\text{-}C_6H_{11})_2P^\bullet + RI \rightarrow (c\text{-}C_6H_{11})_2PI + R^\bullet \quad (8)$$

Rate Constants for S_H2 Reactions of Hydride Donors with Alkyl Radicals. Of the nucleophiles that have been investigated for potential SET reactions with alkyl halides, hydride donors are the best understood. For a simple alkyl radical reacting with a hydride donor, one can exclude an S_{RN} pathway (eq 9) since the

$$R^\bullet + M^+(G\text{–}H)^- \rightarrow M^+(R\text{–}G\text{–}H)^{\bullet-} \quad (9)$$

product $(R\text{–}G\text{–}H)^{\bullet-}$ would be a radical anion with an electron in a high-energy σ^* orbital. If hydride donors are to react in chain reactions with alkyl halides, the chain sequence must be that shown in Scheme III. Steps i and ii comprise the chain sequence when a neutral main-group metal hydride such as R_3SnH reduces an alkyl halide. The last step (step iii) shown in Scheme III is not required for the radical chain process and may or may not occur depending on the nature of the salt $M^+(G\text{–}X)^-$.

Scheme III

$$R^\bullet + M^+(G\text{–}H)^- \rightarrow R\text{–}H + M^+G^{\bullet-} \quad (i)$$

$$M^+G^{\bullet-}\ R\text{–}X \rightarrow M^+(G\text{–}X)^- + R^\bullet \quad (ii)$$

$$M^+(G\text{–}X)^- \rightarrow M^+X^- + G \quad (iii)$$

M = alkali metal

G = main group or transition metal

The mechanisms of reactions of alkyl halides with various anionic metal hydrides have been studied. Transition metal hydrides are quite reactive and can reduce alkyl halides by the pathway in Scheme III;[40-42] representative transition metal hydride anions react with alkyl radicals (Scheme III, step i) with $k > 1 \times 10^6$ M^{-1} s^{-1}.[43]

However, the situation with the more well investigated group III metal hydrides, $LiAlH_4$ and $NaBH_4$ and related reducing agents, is quite different. Several reports of SET in reactions of these reagents with alkyl halides based on the observation of probe-rearranged products have appeared,[5] but it would seem that in all cases the proposal of SET mechanism should be reconsidered. The important rate constants for reaching this conclusion are those for reactions of the archetypal reagents with alkyl radicals. Russell and Guo showed that $NaBH_4$ reacted with 5-hexenyl radical (**4**) too slowly to prevent cyclization ($k < 1 \times 10^4$ M^{-1} s^{-1} at 30 °C).[44] The rate constant for reaction of $LiAlH_4$ with an alkyl radical can be derived[21] from the results of a study by Beckwith and Goh wherein photoinitiated reductions of alkyl halides including neophyl chloride by $LiAlH_4$ were reported;[45] LAH reacts with the neophyl radical (**24**) slowly ($k \approx 4 \times 10^3$ M^{-1} s^{-1} at 30 °C).[21] Since the group III metal hydrides cannot intercept an alkyl radical faster than it will abstract iodine atom from an alkyl iodide and because the overall nucleophilic substitution rates for reactions of these hydrides with alkyl halides are slow,[46] radical chain isomerization of alkyl iodide probes via Scheme II can be extensive in these reactions. Subsequent conventional S_N2 reduction of the rearranged iodide gives rearranged hydrocarbon.

Addition of Radicals to Nucleophiles (S_{RN}). A radical can add to an anionic nucleophile to give a radical anion product (Scheme I, step iv). When alkyl halides are being studied, a subsequent one-electron oxidation of the radical anion (Scheme I, step v) could occur. These two steps comprise the chain sequence in an S_{RN} reaction mechanism. This sequence represents yet another potential problem in the qualitative application of alkyl halide probes; specifically, if an S_{RN} pathway exists for substitution, then *a small amount of initiation could lead to a substantial amount of radical formation if the chain reaction sequence has an appreciable length.* This possibility has seldom been addressed in qualitative studies of alkyl halide reactions with nucleophiles even when the addition of a radical to an anion (Scheme I, step iv) has been postulated.

The rates of addition of simple radicals to anions are not well understood, and progress in this area is required for quantitative treatments of potential SET reactions of alkyl halides. Important results in this area have come from Russell's laboratory, and some generalizations can be made. Low-lying antibonding orbitals must be available in the radical anion product of step iv (Scheme I) so that the reaction is energetically feasible. The initial delocalization can originate on the radical or the nucleophile. For example, simple alkyl radicals add to nitronate anions but not to $(EtO)_2PO^-$ or $(EtO_2C)_2CR^-$,[47] whereas 2-nitro-2-propyl radical adds to all of these nucleophiles with comparable rates.[48] The 5-hexenyl radical adds to $Me_2C{=}NO_2^-$ with $k \approx 1 \times 10^6$ M^{-1} s^{-1} at 40 °C,[44] and the *tert*-butyl radical adds to various delocalized anions $(PhC(O^-){=}C(CH_3)_2$,

(40) Kinney, R. J.; Jones, W. D.; Bergman, R. G. *J. Am. Chem. Soc.* **1978**, *100*, 7902.
(41) Kao, S. C.; Spillet, C. T.; Ash, C.; Lusk, R.; Park, Y. K.; Darensbourg, M. Y. *Organometallics* **1985**, *4*, 83.
(42) Ash, C. E.; Delord, T.; Simmons, D.; Darensbourg, M. Y. *Organometallics* **1986**, *5*, 17.
(43) Ash, C. E.; Hurd, P. W.; Darensbourg, M. Y.; Newcomb, M. *J. Am. Chem. Soc.* **1987**, *109*, 3313.
(44) Russell, G. A.; Guo, D. *Tetrahedron Lett.* **1984**, *25*, 5239.
(45) Beckwith, A. L. J.; Goh, S. H. *J. Chem. Soc., Chem. Commun.* **1983**, 907.
(46) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1980**, *45*, 849; **1982**, *47*, 276; **1983**, *48*, 3085.
(47) Russell, G. A.; Hershberger, J.; Owens, K. *J. Organomet. Chem.* **1982**, *225*, 43.
(48) Russell, G. A.; Ros, F.; Mudryk, B. *J. Am. Chem. Soc.* **1980**, *102*, 7601.

$PhCHCN^-$, and $PhC(CO_2Et)_2^-$) with rate constants of only ca. 4000–20 000 M^{-1} s^{-1} at 35 °C.[49,50] One can safely predict that the addition of an alkyl radical to a localized carbanion will be too slow to compete with other radical reactions.

Radical–Radical Reactions. If SET between a nucleophile and an alkyl halide were to occur, then one radical would result from the nucleophile (Nu•) and one from the alkyl halide (R•). In some mechanistic studies it has been stated or implied that substitution products could form by coupling of these radicals (Scheme I, step iii). There are two possible conditions for radical–radical coupling reactions: (1) reactions occurring in solvent cages and (2) reactions involving free radicals. In either case, substantial amounts of rearranged substitution products in probe studies are not expected to arise from radical–radical coupling.

Where radical couplings occur in solvent cages, it is necessary that coupling be faster than the rate of diffusion. Since skeletal rearrangements of radicals are substantially slower than diffusion, it is not possible for a mechanistic probe to give a rearranged product via radical coupling in the solvent cage. That is, mechanistic probe halides cannot give useful information about a reaction in which *free* radicals are not formed. The timing of inner-sphere one-electron versus two-electron processes in nucleophilic substitution reactions occurring within solvent cages remains an interesting problem; such reactions can be characterized by the application of Marcus theory and related approaches.[51]

When free radicals are formed and rearrangements can occur, the formation of product R–Nu (or R–H) via the coupling of two radicals (Scheme I, step iii) is not possible in many cases and highly improbable in most other cases. Often a rigorous kinetic evaluation can show that radical coupling is not possible.[52] Even when the kinetic information necessary for such an analysis is not available, the absence of other radical–radical products (R–R from coupling and disproportionation products) would demonstrate that the concentration of radicals was too small to permit coupling of R• and Nu•.[53]

Conclusions and Recommendations

This Account has surveyed the potential pitfalls that can be encountered in the interpretation of "mechanistic probe" experiments designed to provide evidence for an SET mechanism. While the negative evidence provided by the lack of rearranged products in a probe study is always meaningful,[18] the interpretation of the "positive" evidence provided by the observation of rearranged products is not straightforward. The simple observation of rearranged products does not justify the conclusion that an SET mechanism is operative.

As noted, the kinetic information now available permits some generalizations to be made regarding the use of alkyl halide probes in the studies of reactions with nucleophiles. Newcomb et al. concluded[32] that, due to the fast S_H2 iodine atom transfer rate, radical chain isomerizations of alkyl iodide probes could have chain lengths greater than 100. Thus, iodide probes cannot give useful results for SET studies unless the reaction of interest is fast enough (half-life 10 s or less), such that high concentrations of radicals will be generated, permitting (nonselective) radical couplings to occur. The kinetics of other radical–molecule reactions (i.e., S_H2 hydrogen atom transfer or S_{RN} reactions) can be studied conveniently with alkyl iodide probes when the velocity of the competing reaction is greater than that of iodine atom transfer.

The use of alkyl iodide probes solely to provide qualitative evidence (i.e., by the observation of a cyclic product) should be avoided. As a minimum requirement of evidence for SET, a series of probes should be studied to demonstrate that the product ratios correlate with the rates of rearrangement of the series.[54] In the competing atom transfer isomerization outlined in Scheme II, the ratio of unrearranged to rearranged

(49) Russell, G. A.; Khanna, R. K. *Tetrahedron* **1985**, *41*, 4133.

(50) These values were estimated from the relative rates in ref 49 and an assumption that 5-hexenyl and *tert*-butyl radicals react with $Me_2C{=}NO_2^-$ with similar rate constants.

(51) Eberson, L. *Adv. Phys. Org. Chem.* **1982**, *18*, 79–185. Eberson, L. *Acta Chem. Scand., Ser. B* **1984**, *B38*, 439. Eberson, L. *Electron Transfer Reactions in Organic Chemistry*; Springer-Verlag: Berlin, 1987. For a recent example, see: Lund, T.; Lund, H. *Acta Chem. Scand., Ser. B* **1986**, *B40*, 470.

(52) As a demonstration, radical coupling to form the product R–Nu is not possible in the following example. Assume that a primary alkyl iodide probe initially at 0.1 M is observed to react at 25 °C under pseudo-first-order conditions with a half-life of 1000 s. Then for the first half-life

$$(d[P]/dt)_{obsd} = 0.05M/1000\ s = 5 \times 10^{-5}\ M\ s^{-1} \quad (i)$$

Now assume further that rearranged iodide probe and rearranged substitution products comprise <10% relative yield of the products. If R• is the sole source of R–Nu, then the product-forming pseudo-first-order rate constant for the reaction of R•(k_{prod}) must be at least 10 times faster than iodine atom transfer from RI, the slow step in the radical chain isomerization. Thus

$$\begin{aligned} k_{prod} \times [R^\bullet] &> 10 \times k'_{RI} \times [R^\bullet] \\ &> 10 \times k_{RI} \times [RI]_m \times [R^\bullet] \\ &> 1.5 \times 10^5\ s^{-1} \times [R^\bullet] \end{aligned} \quad (ii)$$

where $[RI]_m$ is the mean concentration of RI in the first half-life (=0.075 M in this example) and the value for k_{RI} comes from Table I. But if coupling of R• is the sole source of R–Nu, then

$$(d[P]/dt)_{obsd} = k_{prod} \times [R^\bullet] \quad (iii)$$

Using the values from eq i and ii in eq iii gives

$$5 \times 10^{-5}\ M\ s^{-1} > 1.5 \times 10^5\ s^{-1} \times [R^\bullet]$$

$$[R^\bullet] < 3 \times 10^{-10}\ M$$

Stated in words, the maximum concentration of radical R• has been calculated based on the observed rate of product formation and the fact that the product-forming step must be faster than the radical chain isomerization. Now an untenable situation exists. In a nonchain radical coupling process like Scheme I, R• and Nu• are formed in equal amounts. Allowing that R• and Nu• react at a diffusion-controlled rate ($k_d = 2 \times 10^{10}$ M^{-1} s^{-1}), one can calculate a limit for the velocity of the radical coupling process

$$\begin{aligned} (d[P]/dt)_{coupling} &= k_d \times [R^\bullet] \times [Nu^\bullet] \\ &= 2 \times 10^{10}\ M^{-1}\ s^{-1} \times (<3 \times 10^{-10}\ M)^2 \\ &< 2 \times 10^{-9}\ M\ s^{-1} \end{aligned}$$

Because of small radical concentrations, the velocity of the radical–radical coupling reaction is more than 4 orders of magnitude *slower* than the observed velocity of the reaction! Radical–radical coupling cannot be an important source of products in the above example given the constraints of the observed velocity and the percent rearrangement. A slower overall velocity will lead to even lower concentrations of R• for the hypothetical radical coupling reaction. For radical–radical coupling to be an important source of products in the above example, the half-life of the reaction would have to be less than 10 s.

(53) The nonselective formation of radical coupling and disproportionation products assumes that all radical–radical reactions occur at a diffusion-controlled rate. Selectivity can occur if this condition is not met. See: Fischer, H. *J. Am. Chem. Soc.* **1986**, *108*, 3925.

(54) For an example of precisely this technique, see: Garst, J. F.; Deutch, J. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1986**, *108*, 2490.

products depends not on the rate of rearrangement (provided it is not unreasonably slow) but on the viability of the atom-transfer step. This can be controlled by the relative stability of the starting and final radicals. To suppress the atom transfer isomerization, probes should be employed in which the rearranged radical is significantly *more* stable than the starting radical.

S_H2 bromine atom transfer is slower than iodine atom transfer. Hence, the bromide probes are more useful. Radical isomerization chain lengths with bromides may be short. The formation of R–Nu could possibly be accounted for by radical coupling.[55] Of course, other radical–radical reactions will also compete. However, if the overall velocity of the reaction of interest is quite slow (half-life on the order of hours), then the alkyl bromide probes will also not be useful for SET studies because the radical concentration will again be too small to permit coupling in competition with simple chain-transfer reactions. Because of the slow rates of S_H2 chlorine atom transfer, an alkyl chloride would not be expected to give an appreciable amount of product by the pathway outlined in Scheme II.

In qualitative SET studies, we recommend the use of alkyl bromides and chlorides; alkyl iodide probes should be avoided in the absence of quantitative kinetic information. As noted above, it has not escaped our attention that there are cases where alkyl iodide probes give rearranged products in an SET probe study but alkyl bromides and chlorides give little or no rearrangement. We suggest in these cases that the evidence that SET processes represent a major pathway is not conclusive.

Reactions of nucleophiles with alkyl halides are typically conducted in ethereal solvents. S_H2 hydrogen atom transfer from THF (and, presumably, other ethers) to a radical is not expected to interfere with the use of alkyl halide mechanistic probes. This reaction is too slow to intercept most probe radicals before skeletal rearrangements occur. If a substantial amount of unrearranged product resulting from H atom abstraction is detected in a study, it is not appropriate to ascribe the origin of this product to the S_H2 reaction with THF. Although S_H2 reaction of a rearranged radical with THF can compete with S_H2 halogen atom transfer, that reaction apparently does not terminate chains.[32]

The use of mechanistic probes for the detection of SET processes can be accompanied by serious complications. Available evidence on the nature of these complications has been summarized, and guidelines for the use of probes have been presented in this Account. With this information, a researcher can avoid drawing erroneous conclusions from the results of past probe studies and can design discerning experiments.

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(55) For example, in the sample calculation in ref 52, if an alkyl bromide is substituted for an alkyl iodide, one concludes that [R·] could reach 1×10^{-7} M; if it does, then the velocity of the radical–radical coupling reaction would be similar to the observed velocity of product formation.