

# Radical Kinetics and the Quantitation of Alkyl Halide Mechanistic Probe Studies<sup>§</sup>

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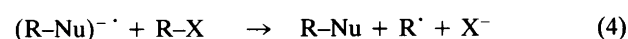
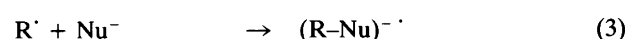
Newcomb, M., 1990. Radical Kinetics and the Quantitation of Alkyl Halide Mechanistic Probe Studies. – Acta Chem. Scand. 44: 299–310.

The rate constants for radical reactions that can occur in mechanistic probe studies designed to detect radical intermediates are collected. These include radical isomerizations, S<sub>H</sub>2 reactions, addition reactions and coupling reactions. It is shown that from this information and an estimate of the steady state concentration of radicals in a probe study, one can calculate the chain lengths of the radical chain isomerization reactions that complicate qualitative analyses based solely on the detection of rearranged products. Calculations based on reported results of alkyl iodide and bromide mechanistic probe studies of metal hydride reactions show that only small numbers of initiation events occur, much less than 1% of the substrate typically reacted in initiation reactions which sets a limit on the amount of electron transfer (ET) from the nucleophile to the halide. ET reactions cannot be excluded as the source of radical initiation, but the detection of rearranged products is not sufficient proof that ET reactions occur.

Over the past several years an increasing amount of attention has been directed towards the possibility that organic substitution reactions typically thought to occur by polar pathways might, instead, involve an electron transfer (ET) process. An inner-sphere ET reaction leading to substitution<sup>1</sup> or an outer-sphere ET process followed by combination within the solvent cage would be mechanistically equivalent to a polar S<sub>N</sub>2 transition state in terms of intermediates, but more commonly organic ET (or single electron transfer, SET) reactions have been envisioned as outer-sphere processes that produce distinct intermediates. For reactions of closed-shell species, such a process must form odd-electron species, radicals and/or radical ions. A significant number of qualitative studies have focused on reactions of nucleophiles with alkyl halides where the typical ET pathways for a nucleophilic substitution reaction have been envisioned according to the general paths shown in Scheme 1. Reaction of the nucleophile with the alkyl halide by ET [eqn. (1)] would give radicals from both the nucleophile and the alkyl halide because the one electron reduction of the alkyl halide would be a dissociative process. The substitution reaction would be consummated by radical–radical coupling [eqn. (2)] or by reaction of the alkyl radical with a molecule of nucleophile [eqn. (3)]. When eqn. (3) is included, the radical anion thus formed would be oxidized by R–X to give the substitution product [eqn. (4)]. Because the alkyl radical formed in Scheme 1 could have a finite lifetime as a free species outside a solvent cage, the concept of a mechanistic study employing

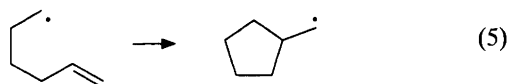
an alkyl halide ‘mechanistic probe’ as an indicator of ET reactions has gained popularity. In this context, the mechanistic probe is a species which would give a radical that can undergo a characteristic rearrangement such as cyclization of the hexenyl radical [eqn. (5)]. The detection of rearranged substitution products in the mechanistic probe study provides evidence that alkyl radicals were produced during the course of the reaction. From such evidence of a radical intermediate, one might infer that an ET process occurred. If the inference is correct, the mechanistic probe study would be a very easy method of detecting ET reactions since it only requires qualitative detection of rearranged products and more difficult kinetic studies could be avoided. The mechanistic probe is also appealing in that its use is conceptually simple to grasp in comparison with kinetic evaluations. Leading references are given for mechanistic probe studies of alkyl halide substitutions by enolates,<sup>2</sup> alkoxides,<sup>3</sup> cuprates,<sup>4</sup> thiolates,<sup>5</sup> alkyllithiums,<sup>6</sup> stannyl anionoids,<sup>7–9</sup> and metal hydrides.<sup>10–19</sup>

Researchers who have employed mechanistic probes have seldom critically evaluated the *assumption* that evi-

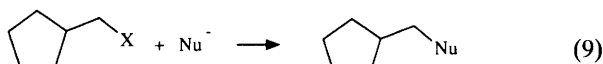
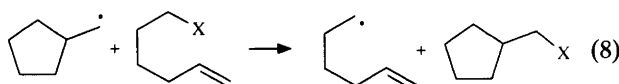
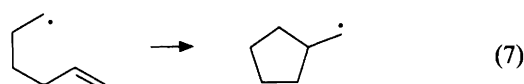
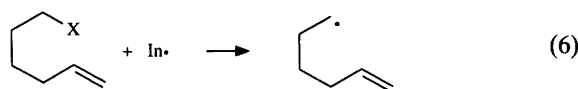


Scheme 1.

<sup>§</sup> Presented in part as a Main Section lecture at the 32nd IUPAC Congress in Stockholm, Sweden, August 2–7, 1989.



dence for radical intermediates provides proof of ET processes; rather it has been common to accept the inference as given. A few years ago, however, both Curran's and Newcomb's groups realized independently that the use of alkyl halide mechanistic probes as indicators of ET reactions was seriously flawed.<sup>20-22</sup> Alkyl halides, especially alkyl iodides, can isomerize by a radical chain process that is independent of the reaction of interest in the probe study. The chain-propagating steps of the isomerization involve radical rearrangement and halogen atom transfer. When these two steps are fast and the overall rate of nucleophilic substitution is slow, an alkyl halide probe can rearrange extensively before substitution occurs, and the rearranged alkyl halide can then be attacked by the nucleophile to give rearranged products. The overall sequence is outlined in Scheme 2. The effect of a rapid radical chain isomerization reaction is to amplify the amount of radical-initiation events that occur during the course of the experimental study. It was clear that even minute amounts of radical-initiation events (from any of a variety of sources) could lead to a sizeable percentage of rearranged products in the case of alkyl iodide probes from the kinetic studies of Newcomb *et al.*<sup>21</sup> Thus, it was apparent that a knowledge of the kinetics of radical reactions was required if one wished to draw meaningful conclusions from the results of mechanistic probe studies.<sup>22</sup> Ironically, the radical chain isomerization sequence had been known for over twenty years,<sup>23</sup> and it was apparent in the mechanistic probe studies of Ashby's group where rearranged alkyl iodides were detected.<sup>4,13-15</sup>



Scheme 2.

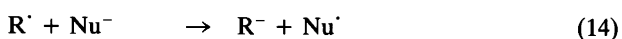
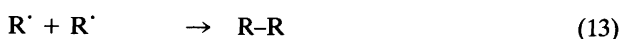
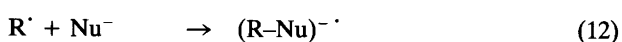
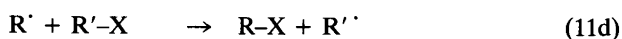
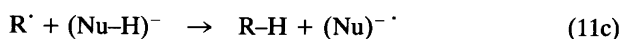
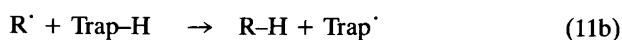
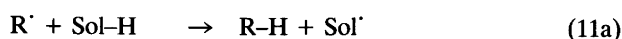
The ET schemes presented in many papers involve a large number of radical reactions including radical rearrangements, hydrogen atom abstraction from solvents, hy-

drogen atom abstractions from nucleophiles such as  $\text{LiAlH}_4$ , halogen atom abstractions, radical-radical couplings and radical-nucleophile couplings. Unfortunately, kinetic information about these reactions has seldom been employed even when rate constants for excellent model reactions were available. In this review, the kinetics of a variety of radical reactions important for mechanistic studies employing alkyl halide probes are collected and compared. From this information, it is possible to estimate the chain lengths of radical chain isomerization processes that occurred in several mechanistic probe studies, and one can determine the number of radical-initiation events that occurred in selected studies. Such calculations are demonstrated using reported results. It is shown that the amount of radical initiation required to account for the extent of isomerized products formed in alkyl iodide mechanistic probe studies can be so small that one cannot determine the origin of the initiation events with certainty. ET reactions cannot be excluded as the processes that initiated chain reactions, but the mechanistic probe studies do not provide definitive proof that ET reactions occurred. Even if ET processes are assumed to be the radical initiation events, the amount of alkyl halide consumed in these reactions is very small, usually much less than 1% of the total reacted halide.

#### Rate constants for radical reactions

The radical reactions proposed in various mechanistic probe studies can be divided into several groups as follows (Scheme 3): unimolecular radical rearrangements [eqn. (10)], bimolecular radical substitution reactions ( $S_{\text{H}2}$  reactions) of radicals with solvents [eqn. (11a)], trapping agents [eqn. (11b)], nucleophiles [eqn. (11c)] and alkyl halides [eqn. (11d)], bimolecular addition reactions of radicals with nucleophiles [eqn. (12)], and bimolecular radical-radical coupling reactions [eqn. (13)]. Another type of reaction, reduction of an alkyl radical by the nucleophile [eqn. (14)], also might be important although it has seldom been considered. For the  $S_{\text{H}2}$  reactions, reactions with solvents and trapping agents inevitably involve hydrogen atom transfer, a radical chain transfer process. The  $S_{\text{H}2}$  reactions of radicals with nucleophiles that have been proposed generally also involve hydrogen atom transfer from metal hydride nucleophiles such as  $\text{LiAlH}_4$ . The addition of radicals to nucleophiles [eqn. (12)] is one step in the radical chain  $S_{\text{RN}}1$  substitution pathway; it is typically followed by ET from the resulting radical anion species to an alkyl halide [eqn. (4) in Scheme 1].

Rate constants for most of the reactions in Scheme 3 are available at least for some representative cases. In many specific cases where the rate constants are not available, estimates of the limits of these values can be made. Thus, when the concentrations of reagents are known, the velocities of most of the reactions in Scheme 3 (or more correctly, the first-order and pseudo-first-order rate constants for reactions of the radicals) can be calculated or estimated.



*Scheme 3.*

The notable exceptions to this generalization involve the radical-radical coupling reactions [eqn. (13)] and the reductions of radicals by nucleophiles [eqn. (14)]. Although radical-radical couplings of simple radicals occur with diffusion-limited rate constants, the pseudo-first-order rate constant for consumption of one radical by reaction with another cannot be calculated without a knowledge of the radical concentration. Fortunately, however, such concentrations can often be estimated for a specific study. The rate constants for reduction of radicals by nucleophiles could be calculated by the Marcus theory if one knew the potentials for the radicals and nucleophiles and the reorganizational energies of the ET reactions; while some estimations of  $k_{\text{ET}}$  are possible, these values are typically the least secure of the group in Scheme 3.

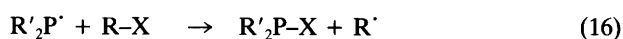
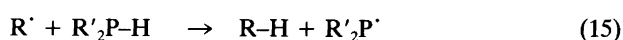
Radical rearrangement rate constants are the most secure values. For some rearrangements, very precise rate constants have been reported, and these first order reactions are usually considered to be relatively insensitive to solvent because little if any charge development is expected in the transition states. In general, the slowest rearranging probe that has been employed in mechanistic studies has been the 5-hexenyl radical which cyclizes to the cyclopentylmethyl radical [eqn. (5)] with a rate constant  $2.2 \times 10^5 \text{ s}^{-1}$  at 25 °C.<sup>24</sup> Perhaps the fastest radical rearrangements that have been employed as probes involve cyclizations across the *endo* face of 5-substituted norbornenes; rate constants as great as  $1.1 \times 10^9 \text{ s}^{-1}$  at 55 °C have been reported.<sup>25</sup> Thus, radical rearrangements of probes that have been employed fall in the range  $2 \times 10^5$  to  $1 \times 10^9 \text{ s}^{-1}$  at 25 °C.

Hydrogen atom abstraction from solvents is an important class of reaction to consider for mechanistic probe studies. The detection of reduced product (R-H) as opposed to substitution product (R-Nu) in reactions of R-X with a nucleophile and of protium-substituted product (R-H) as opposed to deuterium-substituted product (R-D) in reactions of R-X with a deuteriated metal hydride such as  $\text{LiAlD}_4$  have been ascribed to such a solvent reaction. By

their nature, most mechanistic probe studies of nucleophile reactions with alkyl halides have been conducted in ethereal solvents, almost exclusively THF and diethyl ether. Although hydrogen atom abstraction from the solvent is a second-order reaction, the high concentration of the solvent permits one to treat the reaction as a pseudo-first-order process. For the solvents THF and ether, pseudo-first-order rate constants for reaction with the octyl radical have been determined by competition between the solvent trapping reaction and 'self-trapping' by the radical precursor, an *N*-hydroxypyridine-2-thione ester.<sup>26</sup> The pseudo-first-order rate constants at 22 °C are  $k_{\text{H}} = 6000 \text{ s}^{-1}$  for THF and  $k_{\text{H}} \approx 1000 \text{ s}^{-1}$  for ether.<sup>27</sup> Other simple ethers undoubtedly react with radicals with similar rate constants.

Trapping agents have been employed on occasion to intercept radicals often with the expectation that the trapping reaction would be faster than radical rearrangement. Two such agents that have been employed are dicyclohexylphosphine (DCPH), first introduced as a trapping agent in mechanistic studies by Huivila,<sup>28</sup> and 1,4-cyclohexadiene (CHD). The rate constants for hydrogen atom transfer from these two agents to simple alkyl radicals have been measured; at 25 °C they are ca.  $1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$  for DCPH<sup>29</sup> and  $1\text{--}10 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$  for CHD.<sup>29,30</sup> Obviously, CHD reacts much too slowly to intercept a significant proportion of the alkyl radicals before rearrangements; at CHD concentrations of about 0.1 M, even the relatively slow rearrangement of the 5-hexenyl radical would be 20 times faster than trapping. DCPH will trap radicals more efficiently than CHD (at 0.1 M, DCPH will trap 5-hexenyl radical with about 30 % efficiency), but the use of such a trapping agent adds another complication to mechanistic probe studies. Specifically, the DCPH trapping reaction [eqn. (15) in Scheme 4] gives the dicyclohexylphosphine radical, and this radical might react with an alkyl halide. Indeed, Ashby has suggested that this radical reacts with an alkyl iodide by abstracting the halogen atom [eqn. (16) in Scheme 4]<sup>2,4,13,15</sup> providing yet another complicating chain sequence. At comparable concentrations of DCPH and RI, DCPH will trap a radical nearly an order or magnitude faster than the iodine atom transfer reaction. If the postulated reaction in Scheme 4 [eqn. (16)] were to occur, a radical chain sequence involving radical cyclization, reaction of the rearranged radical with DCPH, and abstraction of halogen from R-X by the phosphine radical would result. This would lead to the same amplification of radical initiation as the simple radical chain isomerization in Scheme 2.

Hydrogen atom abstraction from metal hydrides by simple radicals is a critically important reaction to consider because, in ET pathways proposed for reactions of metal

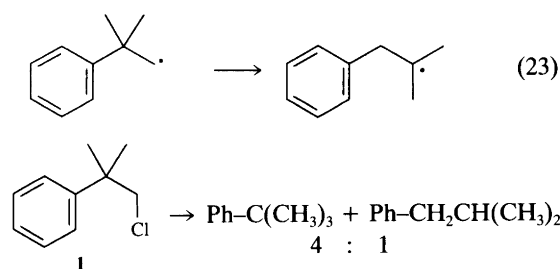
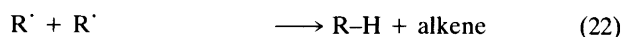
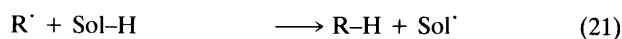
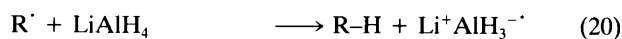
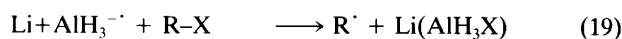
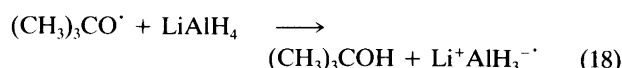
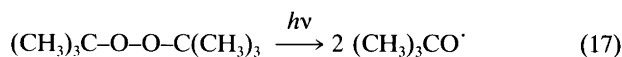


*Scheme 4.* R' = cyclohexyl.

hydrides (especially  $\text{LiAlH}_4$ ) with alkyl halides, the origin of reduced products (including unrearranged reduced products) has been ascribed to this process or to reaction of the radicals with the solvent.<sup>11-17</sup> Thus, if such reactions are not fast, a key element of these ET reaction schemes would be missing, and the entire scheme would break down. There is evidence that hydrogen atom abstraction from metal hydrides by alkyl radicals can occur,<sup>31,32</sup> but the assumption regarding the rates of such reactions is wrong. Two important studies show that the reactions of the archetypal metal hydride reagents,  $\text{LiAlH}_4$  and  $\text{NaBH}_4$ , with simple radicals are not at all fast in comparison with other radical reactions.

Beckwith and Goh<sup>31</sup> have reported that photolysis of a mixture of di-*tert*-butyl peroxide,  $\text{LiAlH}_4$  and alkyl halides in ether leads to reduction of the alkyl halides. The overall reaction sequence is shown in Scheme 5. Photolysis of the peroxide produces the *tert*-butoxyl radical [eqn. (17)] which is known from ESR studies<sup>33</sup> at low temperatures to react with  $\text{LiAlH}_4$  to give  $(\text{Li}^+\text{AlH}_3^-)$  [eqn. (18)]. This radical anion is known to abstract halogen from alkyl halides [eqn. (19)] in a remarkably fast reaction; at 205 K the radical reacted with propyl chloride before an ESR spectrum could be recorded.<sup>33</sup> The alkyl radical thus formed is reduced either by reaction with  $\text{LiAlH}_4$  [eqn. (20)], by reaction with the solvent ether [eqn. (21)] or by radical disproportionation [eqn. (22)]. Eqn. (20) in Scheme 5, of course, is the reaction invoked in the ET pathway for  $\text{LiAlH}_4$  reductions of alkyl halides. When Beckwith and Goh reduced neophyl chloride (**1**) by a photoinduced reaction at 25°C in the presence of 1 M  $\text{LiAlH}_4$ , they observed unrearranged and rearranged products in the ratio of about 4:1. The rate constant for rearrangement of the neophyl radical [eqn. (23)] at 25°C is known to be about  $750 \text{ s}^{-1}$ .<sup>34</sup> Therefore, even if the only source of R-H in the Beckwith and Goh study was from the reaction of radicals with  $\text{LiAlH}_4$ , the rate constant for this process would only be about  $3000 \text{ M}^{-1} \text{ s}^{-1}$ . This value can only be considered as an upper limit of the rate constant for the  $\text{LiAlH}_4$  hydrogen atom transfer for two reasons; the reaction of neophyl radical with ether ( $k \approx 1000 \text{ s}^{-1}$ ) must account for a portion of the trapping, and the high UV flux in the Beckwith and Goh study probably led to high radical concentrations and, accordingly, probably resulted in a substantial amount of radical-radical disproportionation reactions.

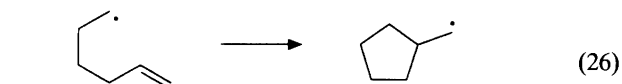
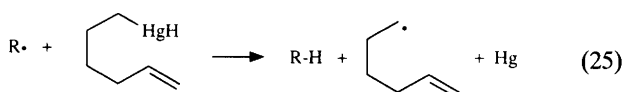
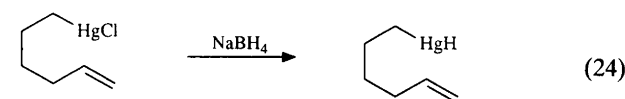
A limit for the rate constant for hydrogen atom transfer from  $\text{NaBH}_4$  to radicals was firmly established in a study reported by Russell and Guo<sup>32</sup> who investigated the reaction shown in Scheme 6. The reaction of alkylmercury halides with  $\text{NaBH}_4$  is well established and is an important source of radicals for synthetic conversions. In Scheme 6, 5-hexenylmercury chloride reacts with  $\text{NaBH}_4$  to give 5-hexenylmercury hydride [eqn. (24)]. The organomercury hydride then reacts with an alkyl radical to give R-H, 5-hexenyl radical and Hg [eqn. (25)]. Cyclization of 5-hexenyl radical to cyclopentylcarbinyl radical is possible [eqn. (26)] and would compete with reaction of the radical



Scheme 5.

with  $\text{RHgH}$  and  $\text{NaBH}_4$ .  $\text{RHgH}$  reacts very rapidly with alkyl radicals, but when the concentration of the  $\text{RHgCl}$  was kept constant (resulting in a constant concentration of  $\text{RHgH}$ ) and the concentration of  $\text{NaBH}_4$  was varied, Russell and Guo found no change in the methylcyclopentane to 1-hexene product ratio. Thus, there was no detectable reaction of hexenyl radical with  $\text{NaBH}_4$ . Accordingly, they<sup>32</sup> were able to set a limit on the rate constant for reduction of the 5-hexenyl radical by  $\text{NaBH}_4$ . The rate constant must be less than  $1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$  at 30°C and probably is less than  $1 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ .<sup>32</sup>

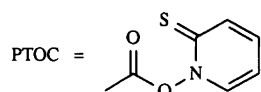
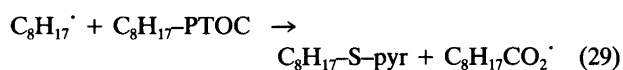
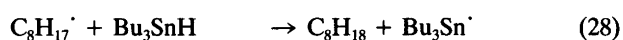
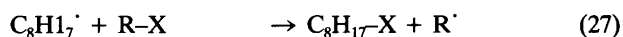
Thus, the archetypal metal hydride reducing agents  $\text{LiAlH}_4$  and  $\text{NaBH}_4$  react only slowly with alkyl radicals. Given the other fast reactions available to alkyl radicals, especially halogen atom transfer in the case of alkyl iodides (see below), these reactions are seen to be essentially irrelevant. Proposed ET pathways for reduction of alkyl halides by metal hydrides that postulate such a step as a major reaction pathway for consumption of alkyl radicals cannot be correct.



Scheme 6.

Rate constants for halogen atom transfer from alkyl halides to alkyl radicals are known to be reasonably fast reactions based on the qualitative observations of radical chain isomerizations reported over two decades ago by Brace<sup>23</sup> (and more recently by Ashby<sup>4,13-15</sup>) and from CIDNP and ESR studies which required such fast halogen transfer steps to account for the observed effects.<sup>35-40</sup> Curran's group has exploited the radical chain isomerization sequence in synthetic applications, and during the course of development of their synthetic methods they realized the significance of radical chain isomerizations of simple alkyl halides as a interfering process in mechanistic probe studies.<sup>20</sup>

Our group also recognized the potential problem and reported rate constants for reactions of representative alkyl halides with the octyl radical (Scheme 7).<sup>21,27</sup> Rate constants were determined by competition between halogen atom transfer [eqn. (27)] and either reaction of octyl radical with Bu<sub>3</sub>SnH [eqn. (28)] or self trapping of the octyl radical by its *N*-hydroxypyridine-2-thione ester<sup>26</sup> precursor [eqn. (29)]. Rate constants for the last two reactions are known,<sup>24,41</sup> and the rate constants for halogen atom transfer could be calculated from the product distributions and reagent concentrations in the competition studies. Table 1 contains a list of rate constants for reactions of octyl radicals with a variety of simple alkyl halides.



Scheme 7.

Table 1. Rate constants for abstraction of halogen by octyl radical in benzene.

Halogen	<i>T</i> /°C <sup>a</sup>	<i>k<sub>RX</sub></i> /M <sup>-1</sup> s <sup>-1</sup> <sup>b</sup>	Ref.
(CH <sub>3</sub> ) <sub>3</sub> Cl	50	3 × 10 <sup>6</sup>	21
(CH <sub>3</sub> ) <sub>2</sub> CHI	50	8 × 10 <sup>5</sup>	21
<i>c</i> -C <sub>6</sub> H <sub>11</sub> I	22	2.6 × 10 <sup>5</sup>	27
	50	5 × 10 <sup>5</sup>	21
CH <sub>3</sub> CH <sub>2</sub> I	22	1.4 × 10 <sup>5</sup>	27
	50	2 × 10 <sup>5</sup>	21
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> I	22	1.1 × 10 <sup>5</sup>	27
(CH <sub>3</sub> ) <sub>3</sub> CBr	50	5 × 10 <sup>3</sup>	21
(CH <sub>3</sub> ) <sub>2</sub> CHBr	50	1 × 10 <sup>3</sup>	21
<i>c</i> -C <sub>6</sub> H <sub>11</sub> Br	50	1 × 10 <sup>3</sup>	21
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> Br	50	6 × 10 <sup>2</sup>	21
(CH <sub>3</sub> ) <sub>3</sub> CCl	50	6 × 10 <sup>2</sup>	21

<sup>a</sup> ± 2°C. <sup>b</sup> Second-order rate constant for formation of octyl halide.

Additions of radicals to nucleophiles have been invoked in several proposed ET reaction pathways. A typical such ET pathway is shown in Scheme 1. The radical is formed [eqn. (1)], it adds to the nucleophile [eqn. (3)] to give a radical anion, and the radical anion reacts with the alkyl halide [eqn. (4)]. Of course, eqns. (3) and (4) are the well known radical chain steps in the S<sub>RN</sub>1 reaction. However, there is a critically important difference between the reactions of localized anionic nucleophiles with simple alkyl radicals and true S<sub>RN</sub>1 reactions. Specifically, in all S<sub>RN</sub>1 reactions, either the radical or the nucleophile is delocalized. This delocalization is essential for the S<sub>RN</sub>1 pathway because the addition of the radical to the nucleophile produces a radical anion that contains an electron in an anti-bonding orbital. If a localized alkyl radical were to add to a localized anionic nucleophile, the resulting product would contain an electron in a σ\* orbital; such products are often energetically inaccessible. Consider, for example the proposed addition reaction of an alkyl radical to the localized anion Me<sub>3</sub>SnNa.<sup>9</sup> The product of this addition reaction would be the metal salt of a tetraalkyltin radical anion! It should be unstable with respect to dissociation and would be expected to form only slowly if at all.

Kinetic studies of alkyl radical additions to nucleophiles, mainly conducted by Russell's group, bear out the qualitative prediction given above. For example, the delocalized 2-nitro-2-propyl radical adds to delocalized nitronate anions and the localized (EtO)<sub>2</sub>PO<sup>-</sup> and (EtO<sub>2</sub>C)<sub>2</sub>CR<sup>-</sup> anions with comparable rates,<sup>42,43</sup> but localized alkyl radicals only add to the delocalized nitronate anions and do not add to localized anions such as (EtO)<sub>2</sub>PO<sup>-</sup> to any measurable extent.<sup>44</sup> Because *delocalized* radicals add to nucleophiles with rate constants of ca. 1 × 10<sup>4</sup> M<sup>-1</sup> s<sup>-1</sup> at 35°C,<sup>42,43</sup> one can predict with confidence that any addition of a simple alkyl radical to a localized anion will be much too slow to compete with other possible radical reactions.

Radical-radical coupling reactions have been proposed in many ET pathways. The basic reaction sequence is shown in Scheme 1 [eqn. (1), (2)]. Reaction between the nucleophile and an alkyl halide gives the radical from the nucleophile and an alkyl radical in addition to the salt MX [eqn. (1)]. Subsequent coupling of Nu' and R' gives the substitution product R-Nu [eqn. (2)]. Naturally, this sequence could occur within a solvent cage; if it were to do so, the products of the one electron pathway and the conventional two-electron polar pathway of an S<sub>N</sub>2 reaction would be indistinguishable. Attempts to differentiate between the two possibilities, i.e. and S<sub>N</sub>2 transition state and an ET sequence within a cage, have focused on the use of the Marcus theory to predict the rate constants for ET and comparisons of these values with the observed rate constants for substitution.<sup>45-47</sup> However, such cage reaction schemes are not the issue when mechanistic probes are found to lead to rearranged products. Reactions occurring within a solvent cage must be faster than the rate of diffusion or else the entities would simply diffuse apart. For typical solvents, the rate constant for diffusion at 25°C is

greater than  $1 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ . Thus, radical rearrangements are typically many orders of magnitude too slow to compete with cage couplings. Any radical rearrangement involving a bond-making or bond-breaking reaction requires the radical *not* to react in a cage immediately upon formation, and, because of this absolute requirement in probe studies, one can calculate the velocities of radical coupling processes.

Delocalized and hindered radicals can have significant lifetimes in solution, but the simple alkyl radicals of interest here, lacking as they are in any special stabilizing groups, will react under diffusion control.<sup>48-50</sup> Because of spin statistical selection factors, one out of four radical-radical encounters can give singlet products and proceed to coupling and disproportionation products; the other three out of four encounters would give rise to energetically inaccessible triplet products and are unproductive.<sup>51</sup> Thus, one can calculate the rate constant for simple radical-radical termination reactions as  $k_{\text{term}} = 0.25k_{\text{D}}$  where  $k_{\text{D}}$  is the diffusion constant in the solvent of interest. Very accurate values of  $k_{\text{D}}$  can be calculated from sophisticated diffusion theories,<sup>48-50</sup> but for the purpose of this work such accuracy is not required. To a very good approximation, the value for  $k_{\text{D}}$  in a non-viscous and non-hydrogen bonding solvent is given by simple diffusion theory under the so-called 'slip' boundary conditions. Specifically,  $k_{\text{D}}$  is given by eqn. (30) where  $R$  is the gas constant in  $\text{J mol}^{-1} \text{ K}^{-1}$ ,  $T$  is the temperature in K, and  $\eta$  is the dynamic viscosity of the solvent in Pa s. Accordingly, the spin statistically corrected rate constant for radical-radical reactions ( $k_{\text{term}}$ ) is well approximated by eqn. (31). Thus, for the solvents THF and ether, the rate constants for radical-radical coupling reactions at 25°C are  $5 \times 10^9$  and  $1.0 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ , respectively. The velocity of radical-radical coupling reactions ( $v_{\text{term}}$ ) is given by eqn. (32), and the pseudo-first-order rate constant for reaction of one radical with a second radical ( $k'_{\text{term}}$ ) is given by eqn. (33).

$$k_{\text{D}} = 4000RT/\eta \quad (30)$$

$$k_{\text{term}} \approx 1000RT/\eta \quad (31)$$

$$v_{\text{term}} \approx 1000RT/\eta [\text{R}'^2] \quad (32)$$

$$k'_{\text{term}} \approx 1000RT/\eta [\text{R}'] \quad (33)$$

Unlike the case for rate constants considered previously, one must know the concentration of the radicals in the reaction in order to evaluate the significance of radical-radical coupling processes. The radical concentrations will be different in every study and must be evaluated individually. Fortunately, however, a steady state concentration of radicals can be assumed, and this concentration often can be calculated from other kinetic information. Consider, for example, a case where one employs an alkyl iodide mechanistic probe initially at 0.2 M concentration in THF and observes the half-life for rearrangement of the probe to be

1000 at 25°C. For the chain sequence involving rearrangement and iodine atom transfer, the iodine atom transfer will be the slower, rate controlling step. In the first half-life of the reaction, the velocity of the rearrangement reaction is 0.1 M per 1000 s or  $1 \times 10^{-4} \text{ M s}^{-1}$ . Over this period, the concentration of the initial RI substrate averages 0.15 M. Thus, if the rate constant for iodine atom transfer is  $2 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ , the average radical concentration can be solved from eqn. (34). In this example, the radical concentration would be about  $7 \times 10^{-9} \text{ M}$ . From this result, one can evaluate the pseudo-first-order rate constant for radical-radical coupling; it is  $35 \text{ s}^{-1}$  in this example, about three orders of magnitude lower than iodine atom transfer.

$$v = 1 \times 10^{-4} \text{ M s}^{-1} = (2 \times 10^5 \text{ M}^{-1} \text{ s}^{-1})[\text{RI}]_{\text{m}}[\text{R}'] \quad (34)$$

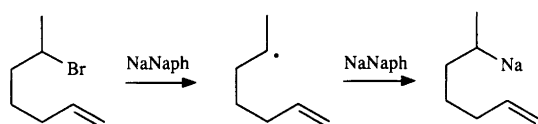
The above example illustrates an important feature of radical-radical reactions that has often been overlooked by authors who would fashion an ET mechanism by the simple pathway involving Scheme 1 [eqn. (1), (2)]. The extremely fast rate constant for radical-radical reactions is usually offset by the very low concentrations of radicals present during the course of the reaction. Hence, radical-radical coupling reactions are not the predominant reactions when there are reasonably fast alternative reaction pathways available for the radical. Indeed, on reflection one realizes that this is most often the case in radical chemistry; after all, a tremendous number of radical functionalization and polymerization reactions result in very high product yields and undetectable amounts of radical coupling products.

It is instructive to consider radical concentrations in more detail. Specifically, one might ask the question: what radical concentrations are required such that radical-radical coupling reactions can compete with another radical reaction such as iodine atom abstraction from an alkyl iodide? The velocity of the iodine atom abstraction reaction increases as a function of  $[\text{R}']$  whereas the velocity of radical-radical coupling increases as a function of  $[\text{R}']^2$ . For the case of a reaction in THF where  $k_{\text{RI}} = 2 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$  and  $[\text{RI}]$  is equal to 0.2 M, the two reactions will have essentially equal velocities when the radical concentration reaches  $1 \times 10^{-5} \text{ M}$ , and coupling will be an order of magnitude faster than halogen atom transfer when  $[\text{R}']$  is  $1 \times 10^{-4} \text{ M}$ . In this example, the total reaction velocity would be about  $1 \text{ M s}^{-1}$ , or, in other words, the reaction would be complete within 0.1 second of mixing which is typically many orders of magnitude faster than purported ET reactions of interest here have been observed to proceed. The high concentrations of radicals necessary for couplings to become significant has another ramification; in a carefully designed study at low temperatures, one would easily be able to detect the radical intermediate directly by ESR spectroscopy or indirectly by CIDNP if Scheme 1 [eqn. (1), (2)] were the correct reaction mechanism!

Reduction of radicals by nucleophiles is, as noted above, seldom considered by those proposing ET reactions of nucleophiles and alkyl halides. This is a serious shortcoming

in mechanistic logic because in many cases the radical formed from an alkyl halide will be a stronger oxidant than the alkyl halide itself. Further, as an open-shell species, the reorganizational energy of the radical is likely to be less than that of the halide as a general rule. Determinations of reduction potentials for simple alkyl radicals are current subjects of research,<sup>52,53</sup> and one should expect reliable values to emerge in the near future. Recent results from Savéant's laboratory<sup>53</sup> are important. They<sup>53</sup> found reduction potentials for *tert*-butyl and *sec*-butyl radicals of ca.  $-1.55$  and  $-1.45$  V vs. SCE, respectively, and estimated the reduction potential for *n*-butyl radical to be about  $-1.35$  V vs. SCE. They<sup>53</sup> also observed a single two-electron wave in cyclic voltammetry of *n*-butyl iodide (as well as *n*-butyl and *sec*-butyl bromide) reflecting the ease of reduction of the *n*-butyl radical. In addition, their estimate<sup>53</sup> for the intrinsic barriers for simple radical reductions (as high as 0.58 eV) is about half of the barrier Ebersson estimated for reduction of the alkyl halides.<sup>54</sup>

The lesson for those who would work with mechanistic probes in the future is the following: if the reducing agent under study is powerful enough to reduce an alkyl halide, it is also likely to be strong enough to reduce a primary (and possibly a secondary) alkyl radical very rapidly. One illustration will suffice. Garst observed the reaction sequence shown in Scheme 8; treatment of 2-bromo-6-heptene with sodium naphthalenide gave the 1-methyl-5-hexenyl radical, but further reduction of this radical to the corresponding anion occurred at least as fast as cyclization of the radical.<sup>55</sup>



Scheme 8.

### Comparison of rate constants for radical reactions

With the kinetic information discussed above, it is convenient to construct a list of relative radical rate constants. Such a list is presented in Table 2 where iodine atom transfer has been assigned a relative rate constant of unity. In order to compare first- and second-order reaction velocities in Table 2, the concentration of reagents have been assumed to be 0.2 M.

Probably the most important feature to note in Table 2 is that the rate of cyclization of any probe radical is by far the fastest reaction available to that radical. Consider, for example, a study conducted at 25 °C in which the 5-hexenyl radical might be formed. As noted above, this radical cyclizes slower than other probe radicals that have been used in the mechanistic studies of interest here. 5-Hexenyl radical, when formed in solvent THF, will cyclize with 97.5 % efficiency relative to trapping by the solvent, and in solvent ether 99.6 % of the radicals would cyclize. Further, reac-

Table 2. Relative rate constants for radical reactions at 25 °C.<sup>a</sup>

Reaction	$k_{rel}^b$
Iodine atom transfer	1
Bromine atom transfer	0.008
Rearrangement	4 to 20,000
Hydrogen abstraction from ether	0.02
Hydrogen abstraction from THF	0.12
Hydrogen abstraction from LiAlH <sub>4</sub>	<0.012
Hydrogen abstraction from NaBH <sub>4</sub>	<0.004
Hydrogen abstraction from DCPH <sup>c</sup>	4
Hydrogen abstraction from CHD <sup>d</sup>	0.2
Coupling with localized anions <sup>e</sup>	ca. 0
Radical coupling <sup>f</sup>	0.001
Radical coupling <sup>g</sup>	0.0001

<sup>a</sup>For reactions of simple alkyl radicals; first-order rate constants for unimolecular processes, pseudo-first-order rate constants for bimolecular processes assuming reagent concentrations of 0.2 M. <sup>b</sup>See the text for discussion and references. <sup>c</sup>DCPH = dicyclohexylphosphine. <sup>d</sup>CHD = 1,4-cyclohexadiene. <sup>e</sup>No limit can be established for these reactions which have not been observed. <sup>f</sup>For an experiment employing 0.2 M alkyl iodide probe in THF where the half-life for probe isomerization is ca. 15 min. <sup>g</sup>For an experiment employing 0.2 M alkyl iodide probe in THF where the half-life for probe isomerization is ca. 3 h.

tion of 5-hexenyl radical with LiAlH<sub>4</sub> or with a localized nucleophile is even slower than the pseudo-first-order reactions with the ethereal solvents. Finally, even if the reaction half-life is only 15 min, radical-radical coupling cannot possibly compete with cyclization. The resulting undeniable conclusion is that virtually all of the uncyclized products formed in a probe study employing 6-halo-1-hexene must have arisen from polar or equivalent cage reactions. Because other probes that have been employed would give radicals that cyclize faster than 5-hexenyl radical, the same conclusion is true in other cases studied to date. In other words, the amount of unrearranged products precisely limits the extent of radical formation (from all possible reactions). *When unrearranged products predominate, the major reaction pathways for substitution involve polar transition states or their mechanistically equivalent cage counterparts.* Purported ET pathways incorporating other radical trapping reactions to account for unrearranged products are not correct.

Another glaring feature of the kinetic comparisons in Table 2 is the efficiency of the iodine atom transfer reaction in comparison with other reaction channels available to a rearranged radical. Even at initial reagent concentrations as low as 0.1 M, the iodine atom transfer will by far be the major reaction available to rearranged radicals unless exceptionally fast radical traps are added. Thus, the radical chain isomerization sequence would always be efficient in a mechanistic probe study employing an alkyl iodide probe unless an extremely fast trapping agent was present. This means that the major pathway for formation of radicals in alkyl iodide probe studies was iodine atom transfer. Hence the qualitative conclusion can be made that *the percentage*

of rearranged products found in such studies represents a much smaller amount of radical initiation.

When the radical reaction rate constants are collected as in Table 2, one realizes that it is possible to predict the products that would be produced in some mechanistic probe studies with the assumption that any pathway exists for radical initiation events (be it ET, reactions of impurities, photolysis of R-X by room light or even solvent alkylation by R-X followed by reduction of the cation). Such a calculation has been reported<sup>56</sup> in which the results of studies of reductions of alkyl iodide mechanistic probes by LiAlD<sub>4</sub> in ethereal solvents<sup>17</sup> were analyzed. In these particular reactions, essentially all of the radicals formed from the iodide probes (R-I) would have cyclized, and the cyclized radicals thus formed would predominantly have abstracted iodine from the original probe to give R'-I and would have reacted with solvent to a lesser extent to give R'-H. One then needs only to assume that all R'-I thus formed will be converted into R'-D by nucleophilic substitution by LiAlD<sub>4</sub> to calculate the ratios R'-H to R'-D expected. Although the authors of the experimental paper did not report the concentrations of the reagents,<sup>17</sup> the calculated ratios R'-H to R'-D that resulted (assuming that the initial halide concentrations were 0.1–0.2 M)<sup>56</sup> were remarkably close to the experimental values.

#### Estimations of radical initiation rates and radical chain lengths

It is also possible to estimate the extent of radical initiation that occurs in mechanistic probe studies. Since an outer sphere ET reaction is one possible radical initiation reaction, such calculations provide *upper limits* of the extent of ET that occurs. Table 2 contains the rate constants necessary for evaluation of mechanistic probe studies of metal hydride reductions of alkyl iodides, and such reactions have received a considerable amount of attention.<sup>10–19</sup> Hence, we illustrate the quantitation of radical initiation for these

reactions in Table 3. The principles applied are general and can be used in other quantitative analyses.

Assuming that the only termination reaction is radical-radical coupling, one can calculate the velocity of termination and hence the velocity of radical initiation from the concentration of radicals and the diffusion-controlled rate constant. The concentration of radicals, in turn, can be calculated when the half-life for isomerization of the probe can be estimated. Table 3 contains examples taken from mechanistic probe studies reported by Ashby's group<sup>13–15</sup> where sufficient information was available to permit an estimation of the half-life for radical chain isomerization; these values are based on the percentages of unchanged halide, isomerized halide and their reduced counterparts, and, admittedly, some of them are quite crude. The half-lives were used to calculate the reaction velocities ( $v_{\text{isom}}$ ) for the first half of the isomerization reaction, and from these and the pseudo-first-order rate constants for halogen atom transfer, the concentration of radicals was calculated. Using the value  $k_{\text{term}} = 5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$  for diffusion-controlled termination in THF at 25 °C, the velocities of the termination reactions ( $v_{\text{term}}$ ) were then calculated. Division of  $v_{\text{isom}}$  by  $v_{\text{term}}$  gives the chain lengths for the radical isomerization sequence. As for all radical reactions, the velocity of termination must be equal to the velocity of initiation, and, therefore, a pseudo-first-order rate constant for radical initiation ( $k_{\text{in}}$ ) was calculated by dividing  $v_{\text{term}}$  by the initial halide concentration (0.1 M in each case considered here). Finally, from the percentage of isomerized materials observed at the end of the reactions and the chain lengths, one can calculate directly a limit for the amount of alkyl halide that could have reacted by ET; in Table 3 this is given as maximum percentages.

There is a caveat for the calculations in Table 3. The termination reaction velocity calculation was based on the assumption that alkyl radical coupling was the only termination reaction. Another termination sequence might exist. Specifically,  $\beta$ -hydrogen abstraction from an alkyl halide

Table 3. Quantitative analysis of mechanistic probe studies of metal hydride reductions.

Substrate <sup>a</sup>	Hydride	$t_{1/2}$ <sup>b</sup> /s	$v_{\text{isom}}/10^{-6} \text{ M s}^{-1}$	$[R^{\cdot}]/10^{-10} \text{ M}$	$v_{\text{term}}/10^{-10} \text{ M s}^{-1}$	Chain length	$k_{\text{in}}/10^{-8} \text{ s}^{-1}$	Maximum % ET	Ref.
12	LiAlH <sub>4</sub>	29000	1.7	1.9	1.9	9300	0.19	0.01	14
	AlH <sub>3</sub>	110000	0.5	0.5	0.13	35000	0.013	0.003	14
13	LiAlH <sub>4</sub>	900	55	37	680	800	70	0.1	14
	AlH <sub>3</sub>	1200	42	28	390	1100	40	0.09	14
14	Li(Et <sub>3</sub> BH)	12000	4.2	2.8	3.9	11000	0.8	0.0002	13
	LiAlH <sub>4</sub>	5400	9.3	9.3	43	2200	4.3	0.01	15
15	Li(Et <sub>3</sub> BH)	11000	4.6	4.6	11	4300	1	0.006	13
	LiAlH <sub>4</sub>	7200000	0.007	0.7	0.24	300	0.02	0.1	14
16	LiAlH <sub>4</sub>	1000000	0.05	5	12	40	1.2	0.05	14
17	LiAlH <sub>4</sub>	1400000	0.04	4	6	60	0.6	0.9	15
	Li(Et <sub>3</sub> BH)	2500000	0.02	2	2	100	0.2	0.4	13

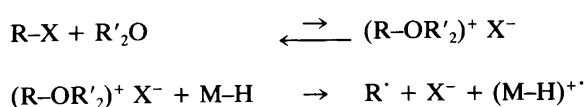
<sup>a</sup>The substrates are 6-iodo-5,5-dimethyl-1-hexene (12), 6-iodo-1-heptene (13), 5-iodocyclooctene (14), 6-bromo-5,5-dimethyl-1-hexene (15), 6-bromo-1-heptene (16), and 5-bromocyclooctene (17). <sup>b</sup>Half-life for substrate isomerization.



followed by elimination of halogen would give an alkene and a halogen atom. For alkyl iodides, the iodine atom thus formed might be so unreactive that it accumulates, and, as the concentration of iodine increases, the major termination reaction would be coupling between alkyl radicals and iodine. The radical elimination of HI from simple alkyl iodides such as ethyl iodide apparently is a reaction channel in the gas phase,<sup>35</sup> but in the kinetic studies of iodine atom transfer in solution, Newcomb *et al.* concluded that such reactions, if they occurred at all, were at least two orders of magnitude slower than iodine atom transfer.<sup>21</sup> Assuming the worst case, then, the elimination reaction would ultimately limit the chain lengths to about 100 which results in no substantial changes in the qualitative conclusions reached above. Further, the elimination reaction is not possible for the dimethyl-substituted halides which contain no  $\beta$ -hydrogen atoms; because the calculations in Table 3 for these cases are comparable to those for halides containing  $\beta$ -hydrogen atoms, we conclude that the elimination sequence as a termination event is unimportant.

The results in Table 3 are acceptably consistent given that the approximations required for the estimations of the isomerization half-lives could have led to errors as great as an order of magnitude. Despite these uncertainties, the calculations clearly show that only diminishingly small amounts of the halides could have reacted in radical initiation processes, most often much less than 1%. The small amounts of initiation might arise by ET from the metal hydrides to the halides, and, if they do, the values of  $k_{in}$  are the rate constants for the ET reactions expressed in pseudo-first-order terms. However, one must question whether or not reagent and solvent impurities and oxygen could have been avoided at the very low levels required to exclude completely extraneous reactions as radical initiation processes. Specifically, impurities at concentrations as low as about  $1 \times 10^{-5}$  M could account for the initiations in some cases. Given the ease with which alkyl iodides decompose, such levels of purity are doubtful.

Assuming that initiation was a result of reaction of the metal hydrides with the alkyl halides by ET, one can analyze the trends in  $k_{in}$  in Table 3. The values for the two secondary iodides **13** and **14** are larger than those for the primary iodide **12**, and this pattern appears to be present for the secondary bromides **16** and **17** in comparison with the primary bromide **15**. These orderings are consistent with the expected reduction potentials of the halides, but they are also consistent with the expected rates of ionization of the halides. Excepting the reaction of  $\text{Li}(\text{Et}_3\text{BH})$  with **13**, it appears to be possible that the initiation reac-

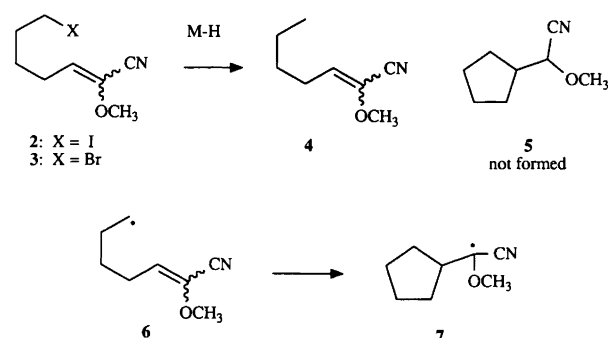


Scheme 9.

tions are independent of the metal hydride. This suggests a reaction sequence such as that shown in Scheme 9 where ionization of the alkyl halide in an ethereal solvent forms an oxonium ion (which would be a powerful oxidant) in very low equilibrium concentrations, and the oxonium ion is then reduced by the metal hydride in a diffusion-controlled reaction. We would encourage researchers to consider such a possibility and design experiments to test this hypothesis.

### Probes that avoid radical chain isomerization

The relative kinetic values in Table 2 show why the radical chain isomerization sequence has been a major source of confusion in mechanistic probe studies employing alkyl iodides; it ultimately leads to a tremendous amplification of radical initiation events. Accordingly, if one could suppress this isomerization sequence, the amount of isomerized material in a probe study would represent the amount of initiation. Such a study was designed by Park *et al.* (Scheme 10)<sup>57</sup> who employed the alkyl iodide **2** and bromide **3** as mechanistic probes in reactions with a variety of metal hydrides. The groups substituted on the olefin were expected to have virtually no effect on the reduction potentials of the remote halogens, however, these substituents lead to about a 400-fold rate acceleration in the cyclization of radical **6** to radical **7** in comparison with 5-hexenyl radical cyclization. More importantly, the captodative radical **7** would be expected to be much too stable to abstract iodine or bromine atoms rapidly from the precursor halides. Thus, with halogen atom transfer suppressed, the radical chain transfer reaction would not be possible. In reactions with a wide variety of metal hydrides [ $\text{LiBH}_4$ ,  $\text{NaBH}_4$ ,  $\text{KBH}_4$ ,  $\text{NaBH}_3\text{CN}$ ,  $\text{Li}(\text{Et}_3\text{BH})$  and  $\text{LiAlH}_4$ ], probes **2** and **3** were reduced to give the acyclic product **4**, but no detectable amounts (<0.1%) of cyclic product **5** were formed.<sup>57</sup> Because other radical reactions cannot compete successfully with the cyclization of radical **6**, the conclusion was that the amount of radical initiation in these reactions was diminishingly small; accordingly ET reactions were seen to be, at best, only very minor con-



Scheme 10.

tributors to the reactions of the metal hydrides with these primary halide probes.

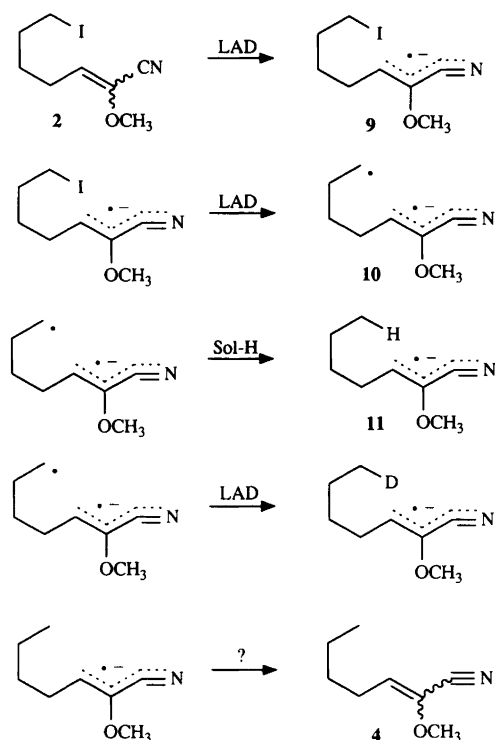
Subsequent to our report of the above experiments, Ashby has criticized the study, and we take this opportunity to answer the criticisms. Ashby's group has published two works describing reactions of iodide **2** with  $\text{LiAlH}_4$ , first in a review<sup>58</sup> and later in a communication.<sup>59</sup> Although not emphasized in the reports, Ashby's group found no detectable level of cyclized products in a large number of experimental runs thus confirming the results obtained by our group. Rather, focusing on two minor experimental details, they claimed that the results from probe **2** were meaningless. Specifically, they found that reduction of probe **2** with  $\text{LiAlD}_4$  led to acyclic product **4** with small amounts of protium incorporation and that the *E/Z* isomer ratio of the acyclic products **4** was not the same as that in probe **2**. The Ashby group also performed studies with probe **8** in which they did find cyclized products.

From these observations, they<sup>58,59</sup> formulated what can only be considered as a poorly conceived reaction sequence shown in Scheme 11. They state that their results show that the acrylonitrile portion of probe **2** was probably reduced to a radical anion (**9**);<sup>58</sup> this radical anion apparently is

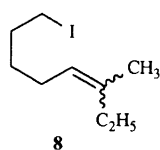
envisioned as being persistent throughout the course of the reaction because it is presented<sup>58,59</sup> as the entity that prevents a radical cyclization. Then, the alkyl iodide portion of **9** was reduced by ET to give a species (**10**) that must be both a radical and a radical anion. Somehow, this unprecedented radical-radical anion does not cyclize but rather reacts with solvent (the origin of the protium in the LAD studies) or with  $\text{LAH(D)}$  to give an acyclic intermediate (**11**). Finally, in an unspecified step, the dehalogenated acyclic radical anion **11** must somehow be oxidized to give the neutral product **4** which was detected at the end of the reaction. The change in the *E/Z* ratio was ascribed to the intervention of the radical anions which upon oxidation gave a new isomer ratio. Probe **8** was presented as equivalent to **2** because it formed a tertiary radical upon cyclization.

The above reasoning is inconsistent for numerous reasons including the following. (1) There is no evidence supporting the one-electron reduction of acrylonitriles by LAH. (2) If such a reaction were to occur, it should ultimately be consummated to give reduction overall, not simply isomerization. (3) The postulated persistent radical anions **9** and **11** should have been easily detected by a variety of methods. (4) There was no oxidant present to quench the purported radical anion **11** at the end of the reaction. (5) Given that radicals and radical anions typically couple in intermolecular reactions at nearly the diffusion-controlled rate constant,<sup>60,61</sup> the postulated radical-radical anion **10** should be expected to experience an *accelerated* cyclization in comparison with radical **6**. (6) The notion that a simple tertiary radical is as stable as the 'cpto-dative'<sup>62</sup> stabilized radical **7** is wrong as indicated literally by volumes of data.<sup>63</sup>

Ashby's results are easily explained. First, the small amount of protium found in the LAD reductions almost certainly arose from the protium in the LAD (the purity was not specified) coupled with an isotope effect favoring hydride transfer over deuteride transfer and experimental uncertainties. Second, the change in the isomer ratio in the products resulted because the two isomers of acycle **4** are destroyed by LAH with different rates. The latter effect has been observed in our laboratories by a simple control reaction in which **4** was added to a solution of LAH in THF and the slow destruction of **4** and concomitant change in the *E/Z* isomer ratio with time was followed.<sup>64</sup> Finally, the results with probe **8** have no bearing on those with **2**. Indeed, **8** reacts just as expected based on observations with other alkyl iodide probes; the radical chain isomerization sequence of **8** obviously was facile, and Ashby's group even detected the cyclic iodide product from isomerization of **8**.<sup>59</sup>



Scheme 11.



## Conclusions

Mechanistic probe studies have demonstrated that radicals can be formed in reactions of nucleophiles with alkyl halides, especially when alkyl iodides are employed and the

probes are designed such that the polar  $S_N2$  are slowed by steric effects. The qualitative observation of rearranged products in such a study, however, does not signal an outer-sphere electron transfer pathway as the major channel for reaction of the nucleophile with the halide. Kinetic analyses of radical reactions clearly show that virtually all radicals formed in a typical probe study must cyclize; thus, virtually all of the unrearranged products formed in the substitution reaction must arise from a polar  $S_N2$  reaction or a mechanistically equivalent cage process (or inner-sphere ET) and cannot arise by radical trapping reactions that compete with the rearrangements.

The kinetic evaluation also shows that when alkyl iodide and bromide probes are employed, radical chain isomerization sequences completely unrelated to the reactions of interest are the major pathways for radical formation. The isomerization sequences appear to have chain lengths in the thousands for alkyl iodides and tens to hundreds for alkyl bromides, and the chain isomerization leads to a tremendous amplification of the number of radical initiation events in the study. At best, outer sphere ET reactions giving radicals appear to account for much less than 1% of the reactions of alkyl iodides with metal hydrides, a group of nucleophiles which are among the most often studied by the mechanistic probe approach, and the amount of radical initiation necessary to explain the results in these reactions is so small that one must question whether or not reagent or solvent contamination or side reactions could account for radical initiation. The method applied for quantitative evaluation of reactions of metal hydrides with alkyl halides is general and can be applied in other cases where sufficient information is available to permit an estimation of the steady state concentration of radicals during the course of the reaction.

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