Fast Halogen Abstractions from Alkyl Halides by Alkyl Radicals. Quantitation of the Processes Occurring in and a Caveat for Studies Employing Alkyl Halide Mechanistic Probes
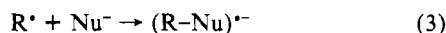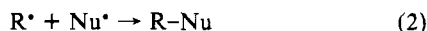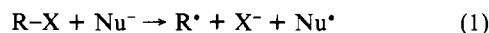
Martin Newcomb,* Robert M. Sanchez, and Jere Kaplan

Contribution from the Department of Chemistry, Texas A&M University, College Station, Texas 77843. Received April 24, 1986

Abstract: Second-order rate constants for halogen atom transfer (k_{RX}) in benzene at 50 °C were determined for reactions of octyl radical with *tert*-butyl, isopropyl, and cyclohexyl iodides and bromides and with ethyl iodide, *n*-butyl bromide, *tert*-butyl chloride, and carbon tetrachloride using two methods. In method A, an alkyl iodide and tributylstannane were allowed to compete for octyl radical in radical-chain reactions; in method B, an alkyl halide competed with 1-(1-oxononoxy)-2(1*H*)-pyridinethione (**1**) for octyl radical. The values for k_{RX} were calculated from the product distributions, the reactant ratios, and the known rate constants for reaction of tributylstannane or **1** with octyl radical. The possibility that rearranged products can be formed in reactions of alkyl halide mechanistic probes with nucleophiles via a sequence involving radical-chain isomerization that converts the probe halide into a rearranged halide followed by nucleophilic attack on the isomerized halide is discussed as are possible chain-terminating reactions. The conclusion is reached that the percentage of rearranged substitution products formed in reactions of alkyl halide mechanistic probes with nucleophiles can give misleading information about the number of radical-initiating events.

Recently there has been a considerable amount of attention directed at the possibility that alkyl halides can react with strong bases and nucleophiles via an initial electron-transfer process (Scheme I); such an initial reaction would produce an alkyl radical

Scheme I

$$R-X + Nu^- \rightarrow R^{\bullet} + X^- + Nu^{\bullet} \qquad (1)$$

$$R^{\bullet} + Nu^{\bullet} \rightarrow R-Nu \qquad (2)$$

$$R^{\bullet} + Nu^- \rightarrow (R-Nu)^{\bullet-} \qquad (3)$$

$$(R-Nu)^{\bullet-} + R-X \rightarrow R-Nu + R^{\bullet} + X^- \qquad (4)$$

and halide ion, and it has typically been presumed that the radical thus formed could eventually lead to substitution products either by radical couplings (eq 2) or radical–nucleophile coupling followed by oxidation (eq 3 and 4). Mechanistic probes, alkyl halides which if reduced in an electron-transfer step yield radicals that undergo isomerizations (usually skeletal rearrangements), have been broadly applied in attempts to study these reactions.[1] In a typical probe study one allows, for example, 6-iodo-1-hexene to react with a nucleophile and searches for the cyclopentylmethyl substitution product. Detection of the rearranged substitution product implicates a radical intermediate and by inference an electron-transfer pathway in the reaction of the nucleophile with the probe. In this paper we discuss another route to rearranged

Scheme II
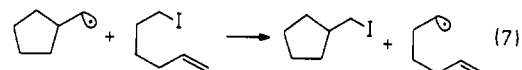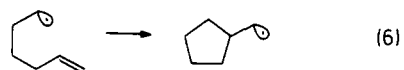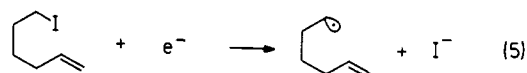
substitution products which incorporates a radical-chain isomerization sequence and does not necessarily require electron transfer from the nucleophile. Qualitative evidence that such a process is possible was reported nearly 20 years ago[2] and recently.[1h,j]

In Scheme II we exemplify a radical-chain isomerization sequence, using the common probe 6-iodo-1-hexene, which could produce cyclopentylmethyl substitution products in a probe study. Initiation (eq 5) could occur by a true electron-transfer process from nucleophile, from an anion formed by halogen metal exchange, or from adventitious impurities. Radical-chain propagation (eq 6 and 7) involves rearrangement and halogen atom exchange between the rearranged radical and the probe halide. Conventional nucleophilic attack (S_N2) on the rearranged halide would produce rearranged substitution products (eq 8).

For the radical-chain isomerization pathway to be competitive with conventional S_N2 attack on the *unrearranged* probe, the propagation steps in eq 6 and 7 must be fast relative to S_N2 attack since it might be assumed that few chains are initiated. Radical rearrangements of most probes are very fast; the 5-hexenyl cyclization ($k_r = 2.2 \times 10^5 \text{ s}^{-1}$ at 25 °C[3]) is one of the slowest probe rearrangements commonly employed. Similarly, iodine and bromine atom transfer reactions from alkyl halides to simple carbon radicals were expected to be fast.[4,8]

(1) Recent examples of the application of mechanistic probes in reactions with nucleophiles include the following: (a) Alnajjar, M. S.; Kuivila, H. G. *J. Am. Chem. Soc.* **1985**, *107*, 416–423. (b) Liotta, D.; Saindane, M.; Waykole, L. *Ibid.* **1983**, *105*, 2922–2923. (c) Ashby, E. C.; Su, W. Y.; Pham, T. N. *Organometallics* **1985**, *4*, 1493–1501. (d) Ashby, E. C.; DePriest, R. N.; Su, W. Y. *Ibid.* **1984**, *3*, 1718–1727. (e) Lee, K. W.; San Filippo, J., Jr. *Ibid.* **1983**, *2*, 906–908. (f) Ashby, E. C.; Argyropoulos, J. N. *J. Org. Chem.* **1985**, *50*, 3274–3283. (g) Russell, G. A.; Dedolph, D. F. *Ibid.* **1985**, *50*, 2498–2502. (h) Ashby, E. C.; Wenderoth, B.; Pham, T. N. *Ibid.* **1984**, *49*, 4505–4509. (i) Gibian, M. J.; Russo, S. *Ibid.* **1984**, *49*, 4304–4306. (j) Ashby, E. C.; DePriest, R. N.; Goel, A. B.; Wenderoth, B.; Pham, T. N. *Ibid.* **1984**, *49*, 3545–3556. (k) Bailey, W. F.; Gagnier, R. P.; Patricia, J. J. *Ibid.* **1984**, *49*, 2098–2107. (l) Alnajjar, M. S.; Smith, G. F.; Kuivila, H. G. *Ibid.* **1984**, *49*, 1271–1276. (m) Chung, S. K.; Dunn, L. B., Jr. *Ibid.* **1984**, *49*, 935–939. (n) Newcomb, M.; Williams, W. G.; Crumpacker, E. L. *Tetrahedron Lett.* **1985**, *26*, 1183–1184. (o) Ashby, E. C.; Bae, D. H.; Park, W. S.; DePriest, R. N.; Su, W. Y. *Ibid.* **1984**, *25*, 5107–5110. (p) Ashby, E. C.; Pham, T. N. *Ibid.* **1984**, *25*, 4333–4336. (q) Ashby, E. C.; Argyropoulos, J. N. *Ibid.* **1984**, *25*, 7–10. (r) Ashby, E. C.; DePriest, R. N.; Pham, T. N. *Ibid.* **1983**, *24*, 2825–2828.
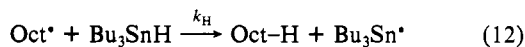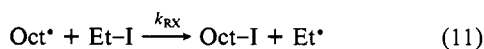
(2) Brace, N. O. *J. Org. Chem.* **1967**, *32*, 2711–2718.
(3) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739–7742.

Herein we report rate constants for halogen atom transfer from a variety of alkyl halides to octyl radical at 50 °C. We demonstrate that the rates of iodine and bromine atom transfer are fast enough to permit the radical-chain isomerization sequence to be the major pathway to rearranged products when typical alkyl iodide and bromide mechanistic probes are employed in reactions with nucleophiles, and we discuss possible radical-chain termination reactions.

Results

We determined rate constants for halogen atom transfer from alkyl halides to the octyl radical by two methods. In method A an alkyl halide competed directly with n-Bu$_3$SnH for octyl radical. The experiments were conducted by mixing, for example, iodoethane, 1-bromooctane, and tributyltin hydride in benzene at 50 °C; under these conditions the radical-chain reaction proceeded without the addition of initiators. The predominant reaction of the tin radicals was with iodoethane (eq 9), but a small amount of octyl radical (Oct$^\bullet$) was formed by reaction of tin radicals with 1-bromooctane (eq 10). The octyl radicals thus formed either reacted with iodoethane to give 1-iodooctane (eq 11) or with tributyltin hydride to give octane (eq 12). An excess of the halogen atom donor, iodoethane in this example, was used so that little of the 1-iodooctane formed would subsequently react with ethyl or tin radicals. The rate constants for halogen abstraction (k_{RX}) was calculated from the observed ratio of product 1-halooctane to octane, the effective ratio of the trapping agents, and the known rate constant for reaction of n-Bu$_3$SnH with a primary radical ($k_H = 3.92 \times 10^6$ M^{-1} s^{-1} at 50 °C)[11] according to eq 13 where ([Bu$_3$SnH]/[RX])$_{eff}$ is the effective concentration ratio of the reactants during the course of the reaction.

$$Bu_3Sn^\bullet + Et\text{-}I \rightarrow Bu_3SnI + Et^\bullet \qquad (9)$$

$$Bu_3Sn^\bullet + Oct\text{-}Br \rightarrow Bu_3SnBr + Oct^\bullet \qquad (10)$$

$$Oct^\bullet + Et\text{-}I \xrightarrow{k_{RX}} Oct\text{-}I + Et^\bullet \qquad (11)$$

$$Oct^\bullet + Bu_3SnH \xrightarrow{k_H} Oct\text{-}H + Bu_3Sn^\bullet \qquad (12)$$

$$k_{RX} = k_H(n\text{-}C_8H_{17}X/n\text{-}C_8H_{18})([Bu_3SnH]/[RX])_{eff} \qquad (13)$$

The rate constants for bromine atom transfer could be measured by method A by reversing the roles of the two halides. However,

(4) The activation energies for the halide transfer step have been estimated at 2–4, ~6, and ~10 kcal/mol for iodine, bromine, and chlorine atom transfer, respectively.[5a] Fast iodine and bromine atom transfer from the halides to carbon radicals are required to explain ESR and CIDNP results when alkyllithium reagents react with halides.[6] Fast equilibration between carbon radicals and alkyl iodides was essential in studies directed at measuring the ratios of the rate constants for radical recombinations and the heats of formation of radicals.[5,7]

(5) (a) Hiatt, R.; Benson, S. W. *J. Am. Chem. Soc.* **1972**, *94*, 25–29. (b) Hiatt, R.; Benson, S. W. *Int. J. Chem. Kinet.* **1972**, *4*, 151–157. (c) Hiatt, R.; Benson, S. W. *Ibid.* **1973**, *5*, 385–396.

(6) Russell, G. A.; Lamson, D. W. *J. Am. Chem. Soc.* **1969**, *91*, 3967–3968. Fischer, H. *J. Phys. Chem.* **1969**, *73*, 3834–3838. Ward, H. R.; Lawler, R. G.; Cooper, R. A. *J. Am. Chem. Soc.* **1969**, *91*, 746–748. Lepley, A. R.; Landau, R. L. *Ibid.* **1969**, *91*, 748–749.

(7) Castelhano, A. L.; Marriott, P. R.; Griller, D. *J. Am. Chem. Soc.* **1981**, *103*, 4262–4263.

(8) Kinetic measurements of halogen abstractions from simple alkyl halides by alkyl radicals in solution have not been reported. Phenyl radical (which typically reacts about three orders of magnitude faster than primary alkyl radicals[9a]) abstracts iodine from simple alkyl iodides at rates approaching diffusion control[9b,c] and abstracts bromine from simple alkyl bromides with rate constants of 1–2 × 10^6 M^{-1} s^{-1}.[9d] Alkyl radicals react with CCl$_4$ in solution at 27 °C with rate constants in the range (0.5–6) × 10^4 M^{-1} s^{-1}.[10]

(9) (a) Johnston, L. J.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1984**, *106*, 4877–4881. (b) Danen, W. C.; Winter, R. L. *Ibid.* **1971**, *93*, 716–720. (c) Kryger, R. G.; Lorand, J. P.; Stevens, N. R.; Herron, N. R. *Ibid.* **1977**, *99*, 7589–7600. (d) Scaiano, J. C.; Stewart, L. C. *Ibid.* **1983**, *105*, 3609–3614.

(10) Hawari, J. A.; Davis, S.; Engel, P. S.; Gilbert, B. C.; Griller, D. *J. Am. Chem. Soc.* **1985**, *107*, 4721–4724.

(11) Johnston, 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*, 4594–4596.
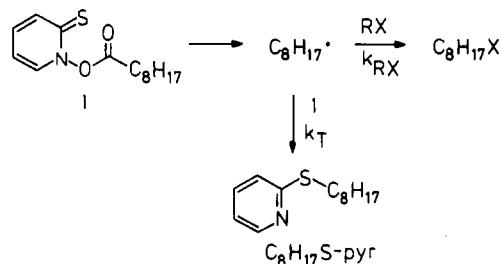
Table I. Rate Constants for Halogen Atom Transfer to Octyl Radical in Benzene at 50 ± 2 °C

| halogen donor | k_{RX} (M^{-1} s^{-1})[a] | | % octane[b] |
	method A	method B	
none			4.3–5.5
(CH$_3$)$_3$CI	(3 ● 2) × 10^6		
(CH$_3$)$_2$CHI	(5.6 ± 0.7) × 10^5	(9.5 ± 2.8) × 10^5	3.4–4.1
c-C$_6$H$_{11}$I	(5.1 ± 0.3) × 10^5	(5.4 ± 0.9) × 10^5	5.7–9.5
CH$_3$CH$_2$I	(1.7 ± 0.6) × 10^5	(3.4 ± 0.4) × 10^5	4.0–5.1
(CH$_3$)$_3$CBr		(4.6 ± 1.3) × 10^3	4.4–6.2
(CH$_3$)$_2$CHBr		(1.2 ± 0.5) × 10^3	5.1–6.9
c-C$_6$H$_{11}$Br		(0.8 ± 0.1) × 10^3	7.1–7.8
CH$_3$(CH$_2$)$_3$Br		(0.6 ± 0.1) × 10^3	8.2–8.6
(CH$_3$)$_3$CCl		(6 ± 2) × 10^2	5.1–5.4
CCl$_4$	(1.2 ± 1.0) × 10^5	(2.4 ± 0.3) × 10^5	2.6–3.7

[a] Averages of three runs; the error limit is 1 σ. [b] Percentage of octane relative to the sum of octane and octyl pyridyl sulfide found in method B studies.

since only small amounts of 1-bromooctane were formed in these studies, method A was used only to demonstrate that bromine atom transfer could occur. We believe that rate constants measured by this method were too imprecise for quantitative use.

In method B octyl radical was generated from the corresponding N-hydroxypyridine-2-thione ester[12] (1) (see Scheme III) in the presence of an alkyl halide, and the rate constant for halogen abstraction was calculated from the rate constant for trapping by precursor 1 (k_T), the observed product ratio, and the ratio of reagents according to eq 14. The value used for k_T at 50 °C in

$$k_{RX} = k_T(n\text{-}C_8H_{17}X/n\text{-}C_8H_{17}\text{-}S\text{-}pyr)([1]/[RX])_{eff} \qquad (14)$$

eq 14 was 2.1 × 10^6 M^{-1} s^{-1}; the value for the reaction of an alkyl radical with an N-hydroxypyridine-2-thione ester was estimated to be 2 × 10^6 M^{-1} s^{-1} by our group previously,[13a] and we have now measured k_T for the reaction of 1 with octyl radical directly.[13b]

Method A suffers from the potentially complicating reduction of the initially formed product 1-halooctane, and a further complication might arise because halogen atom transfer reactions are reversible. However, both effects were minimized by the design of the experiments wherein excesses of the initial donor alkyl halides were employed. Several control experiments confirmed that other potentially interfering reactions did not complicate the results. Thus, reaction of excess n-Bu$_3$SnH with an alkyl iodide followed by addition of excess 1-bromooctane did not give 1-iodooctane, demonstrating that n-Bu$_3$SnI was not a source of nucleophilic iodide. In fact, nucleophilic iodide in the form of tetraethylammonium iodide did not react with 1-bromooctane (benzene, 50 °C, 4 h) to give appreciable amounts (<0.1%) of 1-iodooctane. Further, 2-iodopropane and 1-bromooctane (benzene, 50 °C, 4 h) without n-Bu$_3$SnH did not give an appre-

(12) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901–3924.

(13) (a) Newcomb, M.; Park, S.-U. *J. Am. Chem. Soc.* **1986**, *108*, 4132–4134. We have also found that the widely used radical trapping agent dicyclohexylphosphine[14] reacts with radicals too slowly to prevent most radical rearrangements but fast enough to compete effectively with halogen atom transfer from an alkyl halide to a radical. (b) Newcomb, M.; Kaplan, J. submitted for publication.

(14) Smith, G. F.; Kuivila, H. G.; Simon, R.; Sultan, L. *J. Am. Chem. Soc.* **1981**, *103*, 833–839.

Alkyl Halide Mechanistic Probes with Nucleophiles

J. Am. Chem. Soc., Vol. 109, No. 4, 1987 1197

ciable amount of 1-iodooctane. Finally, the formation of 1-iodooctane from the reaction of 2-iodopropane and 1-bromooctane in the presence of n-Bu$_3$SnH was suppressed when *tert*-butyl mercaptan was used to intercept the radicals; *tert*-butyl mercaptan reacts with an alkyl radical faster than does n-Bu$_3$SnH,[13] and the resulting radical cannot propagate the radical-chain reduction of alkyl halides.

Method B would appear to be inherently more reliable than method A since the product 1-halooctane was effectively unreactive in the presence of excess donor RX. In addition, an internal check on each experimental run with method B was possible. In the radical-chain propagation steps in which ester **1** reacted, not only was octyl pyridyl sulfide formed when octyl radical reacted with **1** but also another alkyl pyridyl sulfide (R–S–pyr) was formed when radical "R•" reacted with **1**. Since the reaction between octyl radical and RX led to 1-halo-octane and "R•" in equal amounts, we were able to compare the amounts of 1-halooctane and R–S–pyr to check the accuracy of the 1-halooctene yield. Good agreement was found.

There are two other possible radical reactions which should be considered. Octyl radical might be reduced to octane by abstraction of a hydrogen atom, presumably a β-hydrogen atom, from the alkyl halide (e.g., eq 15)[5] or by addition of the radical

$$R• + CH_3-CH_2I \rightarrow R-H + •CH_2-CH_2I \quad (15)$$
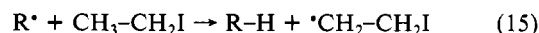
to solvent benzene[9a] followed by hydrogen atom donation from the octylcyclohexadienyl radical thus formed to a second octyl radical. Since in method B octane would only be formed by side reactions, we could determine the extent of these extraneous octyl reduction reactions. Although extraneous reduction reactions apparently occurred to a small extent, they did not preclude the use of either kinetic method (see below).

Table I contains rate constants for halogen atom transfer at 50 °C. The rate constants for iodine atom transfer found by method A were reproducible. The rate constants found by method B were reproducible, and those for iodine atom transfer agreed reasonably well with the method A results. The k_{RX} values appear to be accurate enough for the point of this paper. As expected,[4,8] these are fast reactions. Also as expected, the order of reactivity among a series of structurally analogous alkyl halides was RI > RBr > RCl, and the order of reactivity for the alkyl iodides and for the alkyl bromides was tertiary > secondary > primary. Primary and secondary alkyl chlorides reacted too slowly to be measured by our methods.

One substrate permitted a direct comparison between the rate constants found by our methods and a previously reported rate constant. When CCl$_4$ was used as the halogen donor, we obtained values for chlorine abstraction of $k_{RX} = 1.2 \times 10^5$ M^{-1} s^{-1} by method A and of $k_{RX} = 2.4 \times 10^5$ M^{-1} s^{-1} by method B. These values are in good agreement with the rate constant reported for the reaction of butyl with CCl$_4$ ($k_{RX} = 1.0 \times 10^5$ M^{-1} s^{-1} at 50 °C).[10]

Table I also reports the amount of octane formed by extraneous octyl reduction reactions in the method B studies. Given the small amount of octane found, we believed it was most reasonable to assume that the origin of octane was from pseudo-first-order processes. Thus, we have listed in Table I the percentage of octane relative to the total of octane plus octyl pyridyl sulfide. If the alkyl halide was a souce of hydrogen, then this percentage of octane would have been greater than that found when no alkyl halide was present. Typically, the percentage of octane was not increased by the presence of an alkyl halide; however, the cyclohexyl halides and butyl bromide appear to have been hydrogen atom sources. If these halides indeed were the source of hydrogen leading to the extra ca. 2% yield of octane, then one may use the amount of excess octane and the amount of octyl halide formed in these studies along with the calculated k_{RX} value for each halide to provide an estimate for k_H. The k_H values thus derived were 2–3 × 10^3 M^{-1} s^{-1}.

Since many alkyl halide probe–nucleophile reactions are conducted in THF, a series of studies was performed in an attempt to deterine whether or not hydrogen atom transfer from THF to

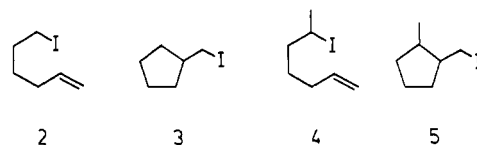**Table II.** Rearrangements of Iodide Probes in Benzene and in THF at 50 ± 2 °C

halide	solvent	mol % of **1**	% of rearrangement[a]	
			predicted	found
2	benzene	13	16	16
2	THF	12	17	10
4	benzene	14	54	43
4	THF	20	51	22

[a] Percent yield of cyclized iodide predicted by eq 17c and found by GC.

Scheme IV
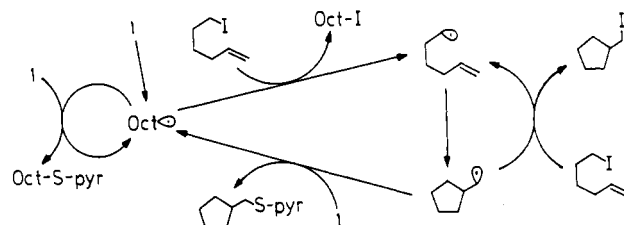
an alkyl radical will terminate the radical chain isomerization sequence or, more generally, whether or not THF will exhibit a significant solvent effect on the radical-chain sequence. Low-conversion radical-chain reactions of 6-iodo-1-hexene (**2**) to io-

domethylcyclopentane (**3**) and of 6-iodo-1-heptene (**4**) to *cis*- and *trans*-2-methyl-1-iodomethylcyclopentane (**5**) were conducted in both benzene and THF at 50 °C. Radical precursor **1** was used both as the radical source and the radical scavenger, and the reactions were run under comparable conditions. Table II contains the results; only a slight inhibition was observed in the THF reactions.

We were able to estimate the amount of rearranged product, **3** from **2** or **5** from **4**, expected in each analysis. Scheme IV shows the important reactions for this analysis when iodide **2** reacted with **1**. Decomposition of ester **1** produced octyl radicals that either reacted with **1** or abstracted iodine from RI to give a "probe" radical; we neglected hydrogen atom abstraction reactions. This ratio (D) of radicals that react with RI to those that are trapped is given by eq 16a. The mole fraction (X_0) of iodooctane and

$$D = (k_{RX}/k_T)([RI]/[1])_{eff} \quad (16a)$$

$$X_0 = [D/(D + 1)][1]_0/[RI]_0 \quad (16b)$$

$$X_n = [D/(D + 1)]X_{n-1} \quad (16c)$$

of "probe" radical formed is then given by eq 16b. At the concentrations we used, >90% of the "probe" radicals cyclized, and we assumed that cyclization was 100% efficient. The cyclized radicals then were trapped by **1** or reacted with RI to give rearranged alkyl iodide (R′I); for each successive cycle, the mole fraction of R′I and of "probe" radicals is approximated by eq 16c. Thus, the final concentrations of rearranged and unrearranged alkyl iodides are given by eq 17a and 17b, respectively, and the total percentage of rearranged alkyl halide formed is given by eq 17c. The summation in eq 17c was solved by evaluating X_n from

$$[R′I]_F = (\Sigma X_n)[RI]_0 \quad (17a)$$

$$[RI]_F = [RI]_0 - (X_0[RI]_0) - [R′I]_F \quad (17b)$$

$$\%R′I = 100\%[R′I]_F/([RI]_F + [R′I]_F) = 100\%\Sigma X_n/(1 - X_0) \quad (17c)$$

eq 16c until the mole fraction of "probe" radicals became less than

5×10^{-4}. For the rate constants in eq 16a, we used the values $k_T = 2.1 \times 10^6$ M^{-1} s^{-1},[13] $k_{RX} = 2.5 \times 10^5$ M^{-1} s^{-1}, and $k_{RX} = 6.4 \times 10^5$ M^{-1} s^{-1} for the rate constants for reaction of any radical of interest with **1**, **2**, and **4**, respectively. The results in Table II thus provided a crude check on the relative rate constants we found in this work for iodine atom transfer and the value we used for the rate constant for radical trapping by **1**. With one exception, the predicted and found amounts of rearrangement were in good agreement.

When low-conversion radical-chain isomerizations of **4** were initiated by azobisisobutyronitrile (AIBN) in benzene and in THF, we found unusual results. In comparable reactions, 33% rearrangement of iodide **4** occurred in THF whereas only 0.8% rearrangement occurred in benzene. It is clear that this result does not support the hypothesis that hydrogen atom abstraction from THF can terminate the radical-chain isomerization sequence. A referee of an earlier draft suggested that these results indicate that the 1-cyano-1-methylethyl radical fails to attack a C–I in the benzene studies but abstracts H from THF to initiate the chain-reaction isomerizations.

Discussion

The iodine and bromine atom transfers are fast enough to lead to substantial radical-chain isomerization via Scheme II. Consider the slower bromine atom transfer; the rate-limiting step in the radical-chain isomerization process for most mechanistic probes will be halogen transfer. Second-order rate constants for S_N2 reactions of typical nucleophiles with primary alkyl bromides at 25–50 °C are 2×10^{-2} (LiAlH$_4$),[15] 2 (Me$_3$SnNa),[16] and 1×10^{-3} M^{-1} s^{-1} (RO$^-$).[17] If the probe bromide (for example, 6-bromo-1-hexene) and nucleophile (for example, LiAlH$_4$) in equal concentrations were allowed to react, a single propagation sequence of the radical-chain isomerization reaction would be greater than four orders of magnitude faster than nucleophilic substitution on the unrearranged alkyl halide. It would appear that the radical-chain isomerization sequence is so fast that, in principle, as little as 0.01 mol % radical initiation by adventitious sources could result in predominant formation of methylcyclopentane even if LiAlH$_4$ reduction occurred exclusively by a conventional S_N2 process. However, this prediction is inadequate because the extent of radical-chain isomerization will depend not only on the number of initiation events and the rates of the component steps, but also on the efficiency of termination processes. Thus, it is necessary to consider the rates of termination reactions.

One possible chain-terminating reaction involves hydrogen abstraction from the solvent. By their nature, mechanistic studies of reactions of nucleophiles with alkyl halides are usually conducted in ethereal solvents, and most commonly the solvent has been THF. We have previously shown that THF will react with a carbon radical with a pseudo-first-order rate constant of about 6×10^3 s^{-1} at 50 °C.[13] If a secondary alkyl iodide probe was being employed at 0.1 M concentration, radical attack on THF would be about 0.1 times as fast as halogen abstraction. But, based on the radical-chain isomerization reactions we conducted in THF, we concluded that the THF reaction does not terminate the radical-chain process for alkyl iodides successfully. We presume that the THF radical abstracts halogen from an alkyl halide in another chain-propagation step.

Another possible radical-chain terminating reaction in studies with an alkyl iodide probe would be hydrogen atom abstraction from the alkyl iodide. Abstraction of a β-hydrogen atom would be followed by homolytic cleavage to give an alkene and iodine atom.[5] This should be a chain-terminating event since the iodine atom is relatively unreactive. From the amount of octane we found in the method B studies with alkyl iodides, we would estimate that hydrogen atom transfer from alkyl iodides occurs with rate constants less than 3×10^3 M^{-1} s^{-1} and that radical isomerization

chain lengths with alkyl iodide probes must be greater than 100. For a bromide probe, a β-hydrogen atom transfer followed by elimination of a more reactive bromine atom probably would not be a chain-terminating event.

Other radical-chain terminating and chain-transfer events are possible in mechanistic probe studies depending on the nature of the nucleophile. These include addition of the radical to the nucleophile to give a radical anion which, of course, is one of the chain propagation steps in the $S_{RN}1$ mechanism. Clearly, in order to evaluate the results of mechanistic probe studies adequately, researchers must determine or set reasonable limits on the rate constants for reactions of radicals with nucleophiles.

It is instructive to consider the fate of probe studies if no chain-terminating radical–molecule reactions were to occur. In this case radical chains would be terminated only by radical–radical reactions, coupling and disproportionation. In virtually all radical-chain isomerizations the halogen atom transfer step will be rate limiting, and since the rate constants for these processes are now available, one may compare the velocities of these reactions with those of radical–radical reactions occurring with diffusion rate constants. For example, given an observed velocity of radical isomerization (in M s^{-1}) over a given time and a known concentration of alkyl halide, one can use the rate constant for halogen atom transfer to calculate the required average concentration of radicals. From the calculated concentration of radicals, one can then calculate the velocity of competing radical–radical reactions. As a general guideline, for reactions of alkyl iodide probes occurring at 25 °C in time frames of minutes or longer, the radical concentration will remain below 1×10^{-7} M, and radical-chain isomerization sequences will be faster than radical–radical reactions by two orders of magnitude or more. However, for alkyl bromide probes with slower rates of bromine atom transfer requiring higher concentrations of radicals to obtain necessary isomerization velocities, radical–radical termination will compete with halogen atom transfer unless reactions proceed over several hours or more. Alkyl chlorides would not be expected to exhibit radical-chain isomerizations because the chlorine atom abstraction reaction is simply too slow to compete effectively with radical–radical reactions. These guidelines are consistent with typical observations from probe studies where alkyl iodide probes are often found to give substantial amounts of isomerization, alkyl bromide probes small amounts of isomerization, and alkyl chloride probes no isomerization. Previously such behavior has been ascribed to increasing reduction potentials for alkyl iodides, bromides, and chlorides and, thus, to their probable susceptibility to "one-electron" reduction.

Certainly an excellent qualitative test for the intervention of a radical-chain isomerization sequence in a mechanistic probe study of a nucleophile–alkyl halide reaction would be simply to stop the reaction before completion and search for isomerized halide. For example, Ashby's group has detected formation of cyclic iodide **5** during reductions of probe **4** by LiAlH$_4$,[1j] AlH$_3$,[1j] and LiEt$_3$BH.[1h] Their detection of substantial amounts of rearranged iodide coupled with the kinetic information in this work shows that in the reactions of probe **4** with these reducing agents, the major reaction converting **4** to a radical was halogen abstraction and not electron transfer from the reducing agents.

Conclusion

Our kinetic results demonstrate that the use of alkyl halide probes as qualitative tests for electron-transfer processes in reactions of nucleophiles with alkyl halides is risky. In the case of alkyl iodide probes, the amount of rearranged product will probably be at least two orders of magnitude greater than the amount of radical initiation. One must consider the possibility that detection of isomerized products in a probe study reflects only minute amounts of radical-initiating impurities or side reactions which are unrelated to the nucleophilic substitution reaction under study. The ironic conclusion is that radical clocks may be excellent for quantitative evaluation of rate constants in known radical processes, but they are poor for qualitative evaluation of whether or not an electron-transfer process occurred in a reaction of a

(15) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1980**, *45*, 849–856.
(16) Kuivila, H. G.; Reeves, W. G. *Bull. Soc. Chim. Belg.* **1980**, *89*, 801–807.
(17) Charton, M. *J. Am. Chem. Soc.* **1975**, *97*, 3694–3697.

nucleophile with an alkyl halide.[18]

Experimental Section

General. Nitrogen gas was dried by passing it through a column of Drierite. Reactions of moisture and/or air-sensitive compounds were performed in flame-dried glassware under nitrogen using syringe transfer techniques. Benzene was distilled from LiAlH$_4$ under nitrogen. THF was distilled from potassium–benzophenone under nitrogen. All alkyl halides used in kinetic studies were purchased from Aldrich Chemical Co. and were distilled before use.

^{1}H NMR spectra were obtained on a Varian EM-390 (90 MHz) spectrometer with CDCl$_3$ solutions containing 1% Me$_4$Si as an internal standard; ^{13}C NMR spectra were obtained on a Varian XL-200E (50 MHz) spectrometer with CDCl$_3$ solutions containing 1% Me$_4$Si as an internal standard. Chemical shifts are reported in ppm downfield from Me$_4$Si. GC analyses were accomplished on a 25-m, 0.25-mm i.d., BP-10 capillary column (Scientific Glass Engineering), a 30-m, 0.75-mm i.d., SPB-5 wide-bore capillary column (Supelco), or a 15-m, 0.5-mm i.d. BP-1 wide-bore capillary column (J&W). GC–mass spectral analyses were performed on a HP 5790 GC equipped with a HP 5970-A mass selective detector using a 25-m, 0.25-mm i.d., BP-10 capillary column. Preparative GC separations were accomplished on a 2.5-m, 5-mm i.d., glass column packed with 10% OV-101 on 80/100 Chromosorb 750. Product identities were confirmed in most cases by analytical GC coelution of the product with a known sample and by comparison of the product's mass spectrum with that of a known sample.

1-(1-Oxononoxy)-2(1H)-pyridinethione (1) was prepared by the general method described by Barton.[12] Nonanoic acid chloride (2.00 g, 11.3 mmol) in 10 mL of benzene was added over 0.5 h to a stirred slurry of N-hydroxypyridine-2-thione sodium salt (Fluka, 1.70 g, 11.3 mmol) and p-dimethylaminopyridine (0.13 g, 1.13 mmol) in 10 mL of benzene in a vessel that was shielded from light and placed in an ice bath. The reaction mixture was stirred at 0 °C for 3 h and then warmed to ambient temperature. After 1 h, the mixture was extracted twice with a cold 10% NaHSO$_4$ aqueous solution and once with a saturated NaCl aqueous solution. The reaction mixture was dried (MgSO$_4$), and the solvent was distilled under high vacuum to yield a residual dark oil. Chromatography on silica gel (1:3 v:v, ethyl acetate–hexane elution) in a column shielded from light gave compound 1 as a yellow oil (1.84 g, 61%) which showed no impurity by TLC or ^{1}H NMR spectroscopy. Upon standing at −78 °C, the oil solidified: mp ca. 30 °C; IR (neat) 1800, 1605, 1525, 1460, 1450 cm^{-1}; ^{1}H NMR δ 0.75–1.8 (m, 15 H), 2.55 (t, 2 H), 6.5 (m, 1 H), 7.1 (m, 1 H), 7.4–7.5 (m, 2 H).

6-Iodo-1-hexene (2) was prepared from the corresponding bromide (Aldrich) by reaction with sodium iodide in acetone. Compound 2 was purified by preparative GC, and the sample thus obtained was >99% pure by analytical GC.

(Iodomethyl)cyclopentane (3) was prepared from the corresponding alcohol mesylate by reaction with sodium iodide in acetone. The product was purified by preparative GC, and the sample thus obtained was >99% pure by analytical GC.

6-Iodo-1-heptene (4) was prepared by the method of Ashby.[1j] Final purification of the compound was accomplished by distillation, bp 68–71 °C (20 torr) [lit.[1j] bp 77–79 °C (25 torr)]. The compound was >99% pure by analytical GC.

cis- and trans-2-methyl-1-(iodomethyl)cyclopentane (5) were identified by their known GC elution order relative to 4[2] and by their mass spectral fragmentation patterns.

2-(1-Thianonyl)pyridine. A 50% dispersion of sodium hydride in mineral oil (0.2 g, 4 mmol) was washed with hexanes several times. Benzene (15 mL) was added, and to the resulting slurry was added 0.5 g (4.5 mmol) of 2-mercaptopyridine (Aldrich). The reaction mixture was heated at reflux for 4 h during which time the yellow color of the mercaptan was lost and a white salt precipitated. The reaction mixture was

cooled to room temperature, and the solvent was removed in vacuo. 1-Bromooctane (0.8 g, 4 mmol) in 20 mL of dry acetonitrile was added, and the mixture was stirred overnight. The reaction mixture was filtered, and solvent was removed from the filtrant in vacuo. The resulting residue was purified by silica gel chromatography (hexanes elution) to give a mixture of unreacted 1-bromooctane and the desired sulfide. Bulb-to-bulb distillation of the 1-bromooctane at high vacuum left the desired product as a residual oil (0.5 g, 2 mmol, 50%) which was >95% pure by analytical GC: ^{1}H NMR δ 0.9 (m, 3 H), 1.17–1.52 (m, 10 H), 1.7 (m, 2 H), 3.13 (t, 2 H), 6.94 (t, 1 H), 7.16 (d, 1 H), 7.47 (d of t, 1 H), 8.42 (d, 1 H); ^{13}C NMR δ 14.2, 22.7, 29.0, 29.1, 29.2, 29.4, 30.2, 31.9, 119.1, 122.1, 135.7, 149.3, 160.0.

Rate Constants for Halogen Atom Transfer Reactions. Method A. A typical procedure is described. To a 1-mL volumetric flask containing a small stir bar were added nonane (24.0 mg, internal standard), 1-bromooctane (45.2 mg, 0.23 mmol), and iodocyclohexane (110 mg, 0.53 mmol). The flask was purged with nitrogen, and benzene was added to the mark. Following three freeze–thaw cycles under ca. 30 torr pressure, the flask was placed in a constant-temperature bath at 50 ± 2 °C; stirring was commenced. After 0.25 h, neat n-Bu$_3$SnH (27 μL, 0.1 mmol) was added via syringe. (In some studies a catalytic amount of AIBN was added, but this initiator was found not to be necessary.) The mixture was stirred for 4 h and then analyzed by GC. Yields of octane and 1-iodooctane were determined by GC by comparison of these products' peak areas to that of nonane using predetermined response factors.

Method B. To a 2-mL volumetric flask were added a weighed amount of ester 1 (10–30 mg), a weighed amount of the halogen donor such that the concentration was at least five times that of 1, and a weighed amount of nonane (ca. 20 mg) as an internal standard. The flask was sealed with a septum and placed in a −78 °C bath; the mixture was degassed with an aspirator. The flask was removed from the bath, and degassed benzene was added to the mark. The flask was shielded from light and placed in a 50 °C bath. After a 1-min equilibration, the reaction mixture was checked by TLC to ensure that no reaction had occurred. The flask was then irradiated with a 150-W tungsten filament flood lamp. The reaction progress was checked by TLC; it was noted that completion of the reaction corresponded to bleaching of the yellow solution to give a water-white solution. After reaction completion, products were analyzed by GC on a wide-bore capillary column. Yields were calculated using predetermined response factors. The total yield of 1-halooctane, octyl pyridyl sulfide, and octane was 70–100%. For calculations of rate constants, the final concentration of halogen donor was obtained by subtracting the concentration of product 1-halooctane from the initial concentration of halogen donor.

Radical Reactions of 2 and 4 in Benzene and in THF. Samples of 2 and of 4 in benzene and in THF were mixed with ca. 15 mol % of ester 1. The mixtures were allowed to react at 50 °C with visible irradiation for ca. 5 h (2) or ca. 1 h (4), and products were determined by analytical GC.

Samples of 4 in benzene and in THF were mixed with ca. 18 mol % of AIBN. The mixtures were allowed to react at 50 °C for 18 h, and products were determined by analytical GC.

Effective Molar Ratios of Reagents. Since the reagents A and B (i.e., alkyl halide and n-Bu$_3$SnH in method A) were linked in a radical-chain process, they decreased in concentration with the same velocity as corrected by the stoichiometric ratio with which they were consumed. A simple computer summation program was used to calculate numerically the integral in eq 18. The effective molar ratio is given by eq 19

$$(A/(A + B))_{eff} = \int (A_0 - A_t)/((A_0 - A_t) + (B_0 - B_t)) \, dt \quad (18)$$

$$([A]/[B])_{eff} = (A/(A + B))_{eff}/(1 - (A/(A + B))_{eff}) \quad (19)$$

---

(18) Curran's group has recently demonstrated that radical-chain isomerizations of iodoalkynes can be synthetically useful (cf. Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1986**, *108*, 2489–2490). More recently this group presented a caveat concerning the use of alkyl iodide mechanistic probes identical with ours (Curran, D. P.; Kim, D. *Tetrahedron Lett.* in press). We thank Professor Curran for disclosing the latter before publication.