Registry No. (8a*S*)-(+)-1, 85337-23-1; (8a*S*)-(+)-**6**, 102934-57-6; (8a*S*)-(+)-**7**, 119326-97-5; **9a**, 94198-87-5; **9b**, 94198-84-2; (+)-**10**, 119365-57-0; **11a**, 119326-98-6; **11b**, 119365-59-2; **12**, 119326-99-7; **13**, 119327-00-3; **14**, 119327-01-4; **14** (ketone), 119327-12-7; (1*R*)-**15**, 119365-58-1; (1*S*)-**15**, 119327-02-5; **16**, 119327-03-6; **17**, 119327-04-7; **18**, 119327-05-8; **19**, 119327-06-9; **20**, 119327-07-0; **21**, 119327-08-1; **22**, 119327-09-2; *cis*-**23**, 119327-10-5; *trans*-**23**, 119327-13-8; *cis*-**24**, 119327-11-6; *trans*-**24**, 119327-14-9.

Rate Constants for Halogen Atom Transfer from Representative α-Halocarbonyl Compounds to Primary Alkyl Radicals

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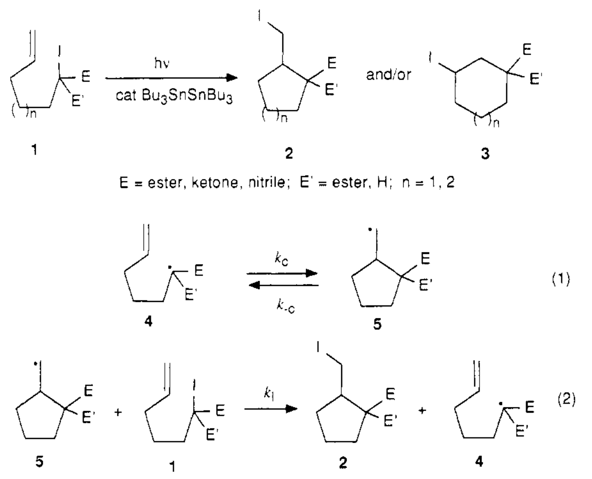
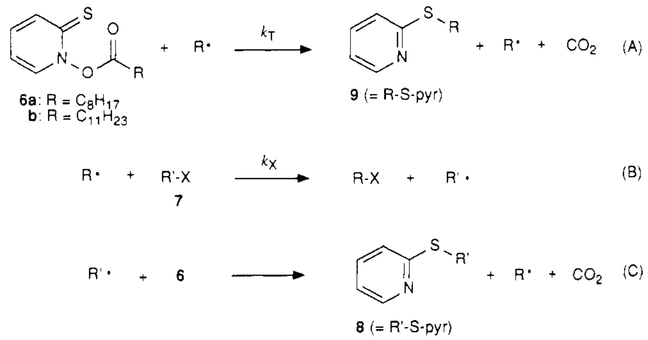
Rate constants for halogen atom transfer from diethyl methyliodomalonate (**7a**), iodoacetonitrile (**7b**), ethyl 2-methyl-2-iodopropanoate (**7c**), ethyl iodoacetate (**7d**), diethyl methylbromomalonate (**7e**), and ethyl bromoacetate (**7f**) to simple primary alkyl radicals have been studied by a variety of competition reactions. The Arrhenius functions for halogen atom transfer to the undecyl radical from halides **7d** and **7f** are log (k_I, M^{-1} s^{-1}) = 10.4 − 4.4/θ and log (k_{Br}, M^{-1} s^{-1}) = 10.4 − 8.2/θ, respectively. The rate constants for halogen atom transfer to a primary radical from the series of compounds **7a–f** at 50 °C are 1.8 × 10^9, 1.7 × 10^9, ca. 6 × 10^8, 2.6 × 10^7, 1.0 × 10^6, and 7.0 × 10^4 M^{-1} s^{-1}, respectively. The kinetic values are useful for the planning of synthetic methods that incorporate an atom transfer–cyclization process.

The cyclization of electrophilic radicals by the atom transfer method is emerging as a mild and powerful method for the formation of rings.[4] A generic example is shown in Scheme I. Irradiation of an α-iodo ester, ketone, malonate, or cyanomalonate (1) provides exo (2) and/or endo (3) cyclized products, depending upon the nature of the groups E and E′, the substituents on the alkene, and the chain length. The propagation steps (Scheme I) for this chain reaction are cyclization (step 1) and atom transfer (step 2). To establish that the products of such reactions were formed under kinetic control, we needed to determine whether or not atom transfer (step 2) was faster than ring opening of the cyclized product. Unfortunately, no absolute rate constants for reactions of the substrates or appropriate models required for an analysis of Scheme I were known, although control experiments with Bu$_3$SnH served to set upper limits for k_{-c}.[4b] We now report measurements of k_I, the halogen atom transfer step of Scheme I, for some representative α-halo esters, nitriles, and malonates. The results confirm that kinetic cyclization products are formed in the atom transfer cyclization sequence.[4b] Furthermore, the rate constants obtained will be valuable for synthetic planning of halogen atom transfer reactions.

Scheme I



Scheme II



Products from Halogen Atom Transfer Reactions. Rate constants for halogen atom transfer from alkyl halides can be measured by a kinetic adaptation[5] of the Barton thiohydroxamate ester decomposition reactions.[6] As summarized in Scheme II, a radical chain reaction (following initiation by visible-light irradiation) of an alkyl thiohydroxamate ester **6** in the absence of added reagents (step A) gives a decarboxylated alkyl pyridyl sulfide **9** by addition of the alkyl radical (R$^\bullet$) to its own precursor. The rate constant for this self-trapping reaction, k_T, has been measured for the case where R is octyl[7] or undecyl.[8]

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[4] (a) Curran, D. P.; Chang, C.-T. *Tetrahedron Lett.* **1987**, *28*, 2477. (b) Curran, D. P.; Chang, C.-T. *J. Org. Chem.*, in press.

[5] Newcomb, M.; Sanchez, R. M.; Kaplan, J. *J. Am. Chem. Soc.* **1987**, *109*, 1195.

[6] Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.

[7] Newcomb, M.; Kaplan, J. *Tetrahedron Lett.* **1987**, *28*, 1615.

[8] Kaplan, J., unpublished results; the Arrhenius function for the self-trapping reaction of undecyl radical by **6b** measured against reaction of undecyl radical with Bu$_3$SnH is log (k_T, M^{-1} s^{-1}) = 9.8 − 5.4/θ.

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Table I. Reactions of Halides with Thiohydroxamates 6 in Benzene

reagents	([**7**]/[**6**])[a]	method[b]	temp,[c] °C	% yield (R-X + **9**)	 **8**	product ratio[d]
6a,7a	1.07	NMR	50	97	90	>100
6a,7b	1.25		50	97	89	>60
6a,7c	1.12		50	100	52	10
6a,7d	1.18		50	99	90	20
6a,7e	1.22		50	81	80	1.25
6b,7f	6.2	GC	10	72		0.22
	5.9		20	100		0.20
	5.0		20	75		0.20
	7.5		20	95		0.32
	8.4		40	72		0.46
	5.0		40	72		0.27
6a,7f	9.5		20	85		0.20
	9.5		20	95		0.21
	11.3		20	86		0.20
	11.0[e]		50	90		0.245

[a] Initial ratio of reagents **7** and **6**. [b] See Experimental Section for details. [c] ±2 °C. [d] Product ratio of **8** to **9** for the NMR method and R-Br to **9** for the GC method. [e] This reaction was conducted in solvent THF, the yield includes octane from reaction of octyl radical with the solvent.

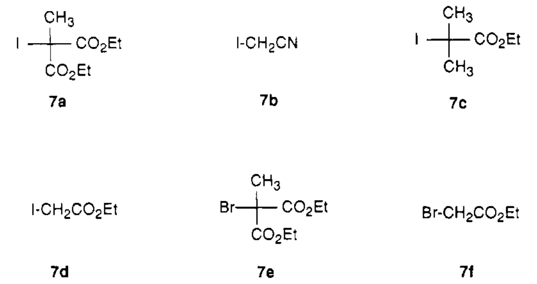

Figure 1. Substrates used in kinetic studies.

Table II. Competition Reactions with Thiohydroxamate 6a in Benzene at 50 ± 2 °C

entry	halides[a]	product ratios[b]
1	**7a** (1.33), **7b** (1.21)	1.1
2	**7a** (1.18), **7c** (1.27)	5
3	**7a** (1.18), **7d** (1.09)	42
4	**7b** (1.14), **7d** (1.11)	37
5	**7c** (1.01), **7d** (1.06)	11
6	**7e** (1.21), **7d** (1.24)	0.05

[a] The molar ratio of the halides with respect to **6a** is given in parentheses. [b] Ratio of products (see text); the rato is for the amount of product formed from the first halide divided by the amount of product formed from the second halide.

Addition of a reagent R′-X (**7**) that competes for the alkyl radical provides a second product, R-X, and another radical intermediate, R′• (step B). Provided that R′• continues the chain reaction by adding to the thiohydroxamate precursor to give adduct **8** (step C), the rate constant k_X can be obtained simply from the ratio of products R′-S-pyr:R-S-pyr (or R-X:R-S-pyr), the effective ratio of the reagents over the course of the reaction, and the known value for k_T. The rate constants for reactions of alkyl radicals with simple alkyl halides that had been measured by this method have already been useful in the quantitative analysis of "cyclizable probe" experiments.[9]

Substrates **7a–e** (Figure 1) were chosen for initial investigation. A benzene-d_6 solution (ca. 0.05 M) of the thiohydroxamate ester of nonanoic acid (**6a**) and a slight excess of halide (ca. 1.15 equiv) was irradiated for 1–2 min. Dissipation of the characteristic yellow color of the thiohydroxamate ester indicated that the reaction was complete. The amounts of products oct-I (or oct-Br), oct-S-pyr, and R′-S-pyr were then determined by ^{1}H NMR integration against two internal standards (see Experimental Section). Ethyl bromoacetate (**7f**) is substantially less reactive than the other halides we studied in this work; for this halide we allowed the thiohydroxamate ester of lauric acid (**6b**) to compete with an excess of **7f** in benzene and determined the product yields from reactions at several temperatures by GC. Data for these experiments are collected in Table I.

Two problems arose in the study of the reactions of the iodides with **6a**. First, several of the iodides were so reactive that it was difficult to integrate accurately the small quantity of oct-S-pyr that was formed. This precluded the estimation of an accurate k_I for reagents **7a** and **7b** by this method. On the positive side, iodomalonate **7a** and iodoacetonitrile (**7b**) are such good iodine atom donors that octyl iodide was produced in virtually quantitative yield (>95%). Thus, these and related iodides should be considered as useful reagents for decarboxylative iodination by Barton's "radical Hunsdieker" reaction.[10]

The second problem involved iodide **7c**. The ratio of R′-S-pyr:oct-S-pyr in Table I appeared to indicate that a primary iodide, ethyl iodoacetate (**7d**), was a better iodine donor than the tertiary iodide, ethyl iodobutyrate (**7c**). This is very unlikely. Inspection of the mass balance of the thiopyridyl isobutyrate **8c** (only 52% yield) revealed the source of this contradiction. The highly stabilized tertiary radical does not add quantitatively to the thiohydroxamate **6a** in the chain propagation step.[11] Consistent with this was the observation that the reaction with the tertiary iodide **7c** required the longest irradiation time (ca. 2.5 min), which suggests that at least one radical chain propagation step was inefficient. Also, vinylic protons corresponding to those of ethyl methacrylate were observed in the ^{1}H NMR spectrum of the product mixture from **7c**; apparently, disproportionation of the tertiary radical is

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(9) (a) Newcomb, M.; Curran, D. P. *Acc. Chem. Res.* **1988**, *21*, 206. (b) Newcomb, M.; Kaplan, J.; Curran, D. P. *Tetrahedron Lett.* **1988**, *29*, 3451.

(10) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron Lett.* **1983**, *24*, 4979.

(11) The problem may be kinetic or thermodynamic. Either slow or reversible addition of the radical to the precursor **6a** would result in an accumulation of radicals and the onset of radical–radical reactions in competition with the desired radical–molecule reactions. The onset of radical–radical reactions has been observed by Barton's group when the stabilized radical was diphenylmethyl.[12] Similar results can be observed for more reactive primary alkyl radicals when the temperature of the reaction is lowered and the irradiation flux is increased.[13]

(12) Barton, D. H. R.; Bridon, D.; Fernandez-Picot, I.; Zard, S. Z. *Tetrahedron* **1987**, *43*, 2733.

(13) Kaplan, J., unpublished results.

Scheme III

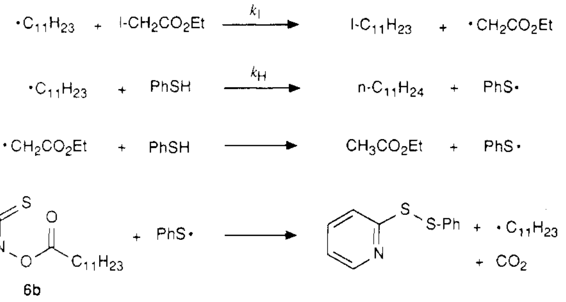

Table III. Reactions of Undecyl Radical with 7d and PhSH in Benzene

[6b][a]	[7d][a]	[PhSH][a]	temp,[b] °C	runs	product ratio[c]
0.01	0.128	0.052	10	1	0.332
0.01	0.088	0.029	20	2	0.65 (0.17)
0.01	0.128	0.052	40	2	0.51 (0.03)
0.01	0.088	0.028	50	3	0.83 (0.2)

[a] Initial molar concentrations. [b] ±2 °C. [c] Average ratio of 1-iodoundecane to undecane; for multiple runs, the range of measurements is given in parentheses.

competitive with chain propagation (step 2 of Scheme I). Thus, the observed ratio of R′–S–pyr:oct–S–pyr is not representative of the ratio k_I:k_T for **7c**.

The problems arising from the relatively slow self-trapping reaction in comparison to the iodine atom transfer reaction were circumvented by a combination of two methods. In one, a series of overlapping competition experiments was conducted with appropriate cross checks to ensure internal consistency. Thiohydroxamate **6a** was allowed to react in the presence of two halides (ca. 1.1 equiv each[14]); thus, the halides competed for limiting octyl radical. Where possible, the ratio of the two thiopyridyl products was measured by ^{1}H NMR spectroscopy, and this ratio was taken as a measure of the relative reactivity of the halides. For the reactions involving the tertiary iodide **7c**, the relative reactivity was based on the relative amounts of the starting iodides that were consumed. The experimental results are collected in Table II. As expected (entry 5), the tertiary iodide **7c** was significantly more reactive than **7d**.

Next, in order to anchor the relative reactivities of the iodides more firmly on an absolute scale, the reaction of ethyl iodoacetate (**7d**) with the undecyl radical was studied in some detail by another method. Rather than using the self-trapping reaction of undecyl radical with its precursor **6b** as the competition for iodine atom transfer, we allowed **6b** to react in the presence of ethyl iodoacetate and thiophenol. In this approach (Scheme III), iodine atom transfer competes with hydrogen atom transfer from PhSH, the rate constants for which have recently been measured.[15,16] The hydrogen atom transfer reaction from PhSH is 2 orders of magnitude faster than the self-trapping reaction with precursor **6b**, and comparable yields of undecane and undecyl iodide were formed as determined by GC. The results of reactions run from 10 to 50 °C are collected in Table III.

Table IV. Rate Constants for Halogen Atom Transfer from Halides 7 to Primary Alkyl Radicals in Benzene at 50 °C

halide	rate constant, M^{-1} s^{-1}	Origin	recommended *k*, M^{-1} s^{-1}
7a	1.8×10^9	competition against **7d** (entry 3)[a]	1.8×10^9
7b	1.7×10^9	competition against **7d** (entry 4)	
	1.8×10^9	competition against **7a** (entry 1)	1.7×10^9
7c	5.6×10^8	competition against **7d** (entry 5)	
	2.2×10^8	competition against **7a** (entry 2)	ca. 6×10^8
7d	2.6×10^7	competition against PhSH[b]	
	2.7×10^7	competition against **6a**	2.6×10^7
7e	1.3×10^6	competition against **6a**	
	0.75×10^6	competition against **7d** (entry 6)	1.0×10^6
7f	7.0×10^4	competition against **6b**[c]	
	2.7×10^4	competition against **6a** (in THF)	7.0×10^4

[a] Entry numbers refer to Table II. [b] From eq 3. [c] From eq 4.

Rate Constants of Halogen Atom Transfers. All of the reactions investigated here involve two competing second-order processes, and in most of the reactions the concentrations of both of the reagents changed dramatically over the course of the reaction. One method for treating the kinetics in such a situation is to calculate the effective ratio of the reagents over the course of the reaction and then calculate the relative rate constants from a pseudo-first-order approach. If one knows the initial and final concentrations of the reagents and makes the reasonable assumption that the concentrations change smoothly over the course of the reaction, then the ratio of the reagents can be calculated at any point in the reaction and averaged for the entire reaction to give the effective ratio during the reaction.[5] The effective ratio varies little from the ratio of the average concentrations which would have been adequate for this work.

We first consider the ethyl haloacetates. Ethyl iodoacetate (**7d**) competed with PhSH for the undecyl radical, and the rate constant for iodine atom transfer (k_I) is given by eq 1 where k_H is the rate constant for hydrogen atom

$$k_I = k_H([\text{PhSH}]/[\mathbf{7d}])_{\text{eff}}(\text{R–I/R–H}) \qquad (1)$$

transfer from PhSH to a primary radical,[15] ([PhSH]/[**7d**])$_{\text{eff}}$ is the effective ratio of the reagents and R–I/R–H is the observed product ratio of undecyl iodide to undecane. In a series of reactions run at various temperatures, ethyl bromoacetate (**7f**) competed with thiohydroxamate **6b** for the undecyl radical, and the rate constant for bromine atom transfer is given by eq 2 where k_T is the rate

$$k_{Br} = k_T[(\mathbf{6b}]/[\mathbf{7b}])_{\text{eff}}(\text{R–Br/R–S–pyr}) \qquad (2)$$

constant for the self trapping reaction of **6b**.[8] The rate constants for reactions of the haloacetates at various temperatures gave the following Arrhenius functions:

$$(\text{for } \mathbf{7d}) \ \log(k_I, \text{M}^{-1}\ \text{s}^{-1}) = (10.4 \pm 0.6) - (4.4 \pm 0.9)/\theta \qquad (3)$$

$$(\text{for } \mathbf{7f}) \ \log(k_{Br}, \text{M}^{-1}\ \text{s}^{-1}) = (10.4 \pm 0.5) - (8.2 \pm 0.6)/\theta \qquad (4)$$

where $\theta = 2.3RT$ and the errors are 1σ for the fit of the function and do not contain an estimate of the errors in

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(14) Ideally, we should have used a larger excess of the iodides to provide pseudo-first-order conditions. This was not possible because we needed to measure accurately the amount of consumed iodide in reactions of **7c**.

(15) The Arrhenius function for reaction of PhSH with the butyl radical in solvent nonane is log (k_H, M^{-1} s^{-1}) = $9.41 - 1.74/\theta$.[16] We make the standard assumptions[17] that the rate constants for hydrogen atom transfer to all primary alkyl radicals by a given reactive hydrogen atom donor will be approximately equal and will be unaffected by modest solvent changes. The same assumptions are made in kinetic competition reactions studied by the tin hydride method.[18]

(16) Franz, J. A.; Bushaw, B. A.; Alnajjar, M. S. *J. Am. Chem. Soc.* **1989**, *111*, 268; we thank Dr. Franz for communicating this information prior to publication.

(17) For a discussion, see: Newcomb, M.; Glenn, A. G. *J. Am. Chem. Soc.* **1989**, *111*, 275.

(18) Johnson, L. J.; Lusztyk, J.; Wayner, D. D.; Abeywickreyma, A. N.; Beckwith, A. L. J.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 4594.

the basis reactions. For comparison to the other rate constants discussed below, the rate constants for halogen atom transfer for **7d** and **7f** at 50 °C were calculated from eq 3 and 4 and are listed in Table IV.

The values of the Arrhenius functions for **7d** and **7f** deserve comment. In any indirect kinetic measurement, there is a chance that errors in the basis reaction rate constants can be compounded with errors in the relative rate constants. Possibly more insidious, however, is a situation where the basis reaction rate constants contain errors, but precise *relative* rate constants suggest an unwarranted level of accuracy. For the reactions of **7d** and **7e**, we have used two completely unrelated basis reactions. The rate constants for hydrogen atom transfer from PhSH to alkyl radicals were measured directly by Franz et al.[16] and the self-trapping rate constants for **6b** were determined against the rate constants for hydrogen atom transfer from Bu_3SnH.[7] Thus, it is satisfying to find that the log *A* terms for the two halogen atom transfer reactions are not only reasonable for second-order reactions but are also essentially identical. Given the similarity in structure of the two haloacetates, one would expect the organization in the transition states for halogen atom transfer to be similar. Also as expected, the large differences in rates originate only in the differences in the C–X bond energies. This kind of agreement suggests that the methods are reasonably accurate.

From the data in Table I, it is possible to calculate the rate constant for halogen atom transfer at 50 °C in competition with trapping by thiohydroxamate **6a** for **7d–f** by eq 5 where k_T, the rate constant for the self trapping reaction of **6a**, is equal to $2.3 \times 10^6\ M^{-1}\ s^{-1}$.[7] The rate

$$k_X = k_T([\mathbf{6a}]/[\mathbf{7}])_{eff}(R\text{-}X/R\text{-}S\text{-}pyr) \quad (5)$$

constants thus calculated are given in Table IV. The rate constant for reaction of **7d** compares quite favorably with that calculated from the PhSH results, and, again, this suggests good accuracy in the methods. The single value for the rate constant for reaction of **7f** with octyl radical at 50 °C in solvent THF based on trapping by **6a** (see Table IV) differs from the value calculated from eq 4 for by a factor of 2.6; this may reflect a small solvent effect. The average value for the reaction of **7f** based on **6a** trapping at 20 °C in benzene ($k_{Br} = 1.3 \times 10^4\ M^{-1}\ s^{-1}$) differs from that calculated from eq 4 by a factor of only 1.5.

The results of the competition experiments collected in Table II can now be considered. Iodides **7a–c** and bromide **7e** competed with **7d** for the octyl radical. Accepting that the rate constant for iodine atom transfer from **7d** to a primary radical at 50 °C is $2.6 \times 10^7\ M^{-1}\ s^{-1}$, the values for halogen atom transfer from **7a–c,e** were calculated by eq 6 where (product ratio) is the value from Table II. The

$$k_X,\ M^{-1}\ s^{-1} = (2.6 \times 10^7)([\mathbf{7d}]/[\mathbf{7x}])_{eff}(\text{product ratio}) \quad (6)$$

calculated rate constants are given in Table IV. For bromide **7e**, the one halide that was studied by both competition against **6a** and against **7d**, reasonable agreement between the rate constants from the two methods was found.

There is a possibility that the values for **7a** and **7b** contain substantial errors since the product ratios of ca. 40:1 were at the limits of accurate detection by the NMR technique. We can use the reaction in which **7a** competed with **7b** (Table II, entry 1) as a check on the rate constants derived from competition against **7d**. The **7a–b** competition reaction confirms that these reagents react with virtually identical rate constants, and we conclude that the kinetic values given in Table IV are reasonably accurate.

As discussed above, iodide **7c** was especially difficult to study since the tertiary radical derived from **7c** does not add efficiently to the thiohydroxamate. From the competition reaction between **7a** and **7c** (Table II, entry 2, adjusted for effective ratios), one would conclude that **7a** is 8 times as reactive as **7c**, but **7a** appears to be only 3 times as reactive as **7c** from the competitions against **7d** (Table II, entries 3 and 5). The persistence of the tertiary radical formed from **7c** (see discussion above) may be the source of the discrepancy since this radical may abstract iodine from other iodides. While it is more likely that the competition reaction of **7c** against the more reactive **7a** is in error from such an "iodine transfer equilibration" reaction, we caution that the value in Table IV for **7c** should be considered to be approximate.

In the final column of Table IV, we have given recommended values for the rate constants for halogen atom transfer at 50 °C. The Arrhenius functions (eq 3, 4) were considered reliable for **7d** and **7f**. For **7b** and **7c**, we believe the values from competition against **7d** are more useful, but the value for **7c** is questionable as noted above. For **7e**, both methods should be considered equally reliable, and we have taken the average value.

There is only limited kinetic data in the literature for halogen atom transfers related to those we have studied. For a crude comparison, the relative rate constants for bromine atom transfer to hexyl radical from bromoacetic acid and diethyl bromomalonate in competition with 1-iodobutane at 100 °C have been reported as 0.39 and 1.69, respectively.[19] If we assume that the relative reactivities are similar at 50 °C and use the value of $k_I = 3 \times 10^5\ M^{-1}\ s^{-1}$ for iodine atom transfer from a primary iodide to a primary radical at 50 °C,[5] then the bromine atom transfer at 50 °C would be ca. $1 \times 10^5\ M^{-1}\ s^{-1}$ for $BrCH_2CO_2H$ and ca. $5 \times 10^5\ M^{-1}\ s^{-1}$ for $BrCH(CO_2Et)_2$. These values are in reasonable agreement with our values of $7.0 \times 10^4\ M^{-1}\ s^{-1}$ and $1.0 \times 10^6\ M^{-1}\ s^{-1}$ for the reactions of $BrCH_2CO_2Et$ (**7f**) and $BrC(CH_3)(CO_2Et)_2$ (**7e**), respectively.[20]

Conclusion

Iodine atom abstraction from simple alkyl iodides by primary radicals is known to be quite fast[5,9b] even when the reactions are essentially thermoneutral. Thus, it is not surprising that the exothermic iodine atom transfers from substrates **7a–d** to primary radicals are very fast. The results of this study have been used to show that the intermediate radicals formed in the cyclization step of the atom transfer–cyclization protocol cannot equilibrate via ring opening; this has been discussed in detail elsewhere.[4b]

The kinetic values found in this work can be added to the growing list of radical rate constants available to the chemist and will be useful for planning synthetic conversions. For example, since iodine atom transfer from an α-iodocarbonyl compound to a simple alkyl radical is much faster than reaction of the alkyl radical with Bu_3SnH, radical chain isomerization will precede reductive deiodination in a tin hydride "reductive cyclization" of an α-iodo-ϵ-unsaturated carbonyl compound. Because radical reactions are relatively insensitive to solvent changes and because simple secondary and tertiary alkyl radicals generally react with rate constants similar to those of primary radicals, one can use the rate constants we have found for

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(19) Safronenko, E. D.; Afanas'ev, I. B. *Zh. Org. Khim.* **1968**, *4*, 2086.

(20) **Note Added in Proof.** Rate constants for iodine atom transfer reactions of the 2-hydroxy-2-methylpropyl radical with ICH_2CO_2H and ICH_2CN at 20 °C in water have been reported to be 1.3×10^7 and $2.0 \times 10^7\ M^{-1}\ s^{-1}$, respectively; cf. Gilbert, B. C.; Norman, R. O. C.; Sealy, R. C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1435.

halogen atom transfer to primary radicals as good approximations for the values of other nonstabilized alkyl radicals in a variety of solvents.

Experimental Section

General. All reactions were performed under an atmosphere of nitrogen in flame-dried glassware with dry solvents. 1-(1-Oxononoxy)-2(1*H*)-pyridinethione (**6a**) and 1-(1-oxododecoxy)-2(1*H*)-pyridinethione (**6b**) were prepared as previously described.[5] The bromo- and iodomalonates were prepared from diethyl methylmalonate (Aldrich) by the general procedure developed by Curran and Chang.[4] Ethyl iodoacetate and iodoacetonitrile were used as purchased (Aldrich) for the NMR studies. For the GC studies commercial (Aldrich) ethyl bromoacetate, ethyl iodoacetate, and thiophenol were distilled.

Diethyl Methyliodomalonate (7a). Sodium hydride was placed in a centrifuge tube (50 mL) and washed with hexane (3 × 10 mL). The flask containing the oil-free sodium hydride was then purged with nitrogen, and the sodium hydride was weighed (49 mg, 2 mmol). THF (10 mL) was added, and the suspension was cooled to 0 °C. A solution of diethyl methylmalonate (Aldrich) (173 mg, 1 mmol) in THF (10 mL) was then added dropwise to the stirred suspension. The solution was allowed to warm 25 °C over 1 h. The mixture was then centrifuged for 10 min, and the supernatant liquid was transferred to a dry flask (25 mL) and cooled to −78 °C. The flask was wrapped in aluminum foil, and all subsequent operations were performed in the dark. A solution of *N*-iodosuccinimide (Aldrich) (223 mg, 1 mmol) in THF (3 mL) was added dropwise to the stirred solution. After the mixture was warmed to 25 °C, the crude product was filtered through silica gel (5 g, 70–230 mesh) with diethyl ether (7 mL). Evaporation of the solvent *at room temperature* yielded **7a** (260 mg, 90.6%) as a pale orange oil: ^{1}H NMR (300 MHz) δ 3.88 (q, 4 H, J = 7.1 Hz), 2.24 (s, 3 H), 0.84 (t, 6 H, J = 7.1 Hz); IR (film) 2984, 2936, 1738, 1466, 1447, 1377, 1258, 1111, 1065, 1017 cm^{-1}; mass spectrum, m/e (relative intensity) 300 (M$^+$, 33), 255 (22), 200 (33), 173 (61), 145 (31), 43 (100); exact mass calcd for $C_8H_{13}IO_4$ m/e 299.9859, found m/e 299.9859.

Ethyl 2-Iodo-2-methylpropanoate (7c). Ethyl 2-bromo-2-methylpropanoate (Aldrich) (706 mg, 3.6 mmol) was added to a suspension of sodium iodide (2.7 g, 18 mmol) in acetone (10 mL), and the mixture was heated at reflux for 30 h. The mixture was cooled, diluted with water (30 mL), and extracted with diethyl ether (3 × 50 mL). The ether extract was washed with saturated aqueous sodium sulfite (20 mL), saturated sodium chloride solution (20 mL), and water (20 mL). Evaporation of the solvent followed by flash chromatography of the residue with hexane/ethyl acetate (15:1) as eluant yielded **7c** (0.84 g, 96%) as a pale orange oil: ^{1}H NMR (300 MHz) δ 3.90 (q, 2 H, J = 7.1 Hz), 1.86 (s, 6 H), 0.90 (t, 3 H, J = 7.1 Hz); IR (film) 2976, 2924, 1730, 1462, 1387, 1370, 1275, 1156, 1103, 1026 cm^{-1}; mass spectrum, m/e (relative intensity) 242 (M$^+$, 10), 169 (23), 115 (100); exact mass calcd for $C_6H_{11}IO_2$ m/e 241.9804, found m/e 241.9803.

Diethyl Methylbromomalonate (7e). The title compound (220 mg, 73%) was prepared according to the procedure described for the preparation of **7a** with the exception that *N*-bromosuccinimide (1 mmol) was used in place of *N*-iodosuccinimide: ^{1}H NMR (300 MHz) δ 3.88 (q, 4 H, J = 7.1 Hz), 2.05 (s, 3 H), 0.84 (t, 6 H, J = 7.1 Hz); IR (film) 2984, 2939, 1744 vs, 1466, 1447, 1377, 1368, 1264, 1119, 1071, 1019, 860 cm^{-1}; exact mass calcd for $C_6H_8O_3{}^{79}Br$ m/e 206.9657, found m/e 206.9657.

2-(1-Thia-2,2-dicarbethoxypropyl)pyridine (8a). Evaporation of the solvent from the crude reaction mixture followed by flash chromatography with hexane/ethyl acetate (9:1) as eluant yielded **8a** (71%) as a clear oil: ^{1}H NMR (300 MHz) δ 8.12 (m, 1 H), 6.84 (m, 1 H), 6.70 (m, 1 H), 6.32 (m, 1 H), 4.00 (q, 4 H, J = 7.1 Hz), 2.29 (s, 3 H), 0.88 (t, 6 H, J = 7.1 Hz); IR (film) 2984, 1732, 1578, 1455, 1416, 1256, 1105, 1019, 760 cm^{-1}; mass spectrum, m/e (relative intensity) 283 (M$^+$, 10), 238 (10), 210 (12), 111 (100); exact mass calcd for $C_{13}H_{17}NO_4S$ m/e 283.0878, found m/e 283.0878.

2-(1-Thia-2-cyanoethyl)pyridine (8b). Evaporation of the solvent from the crude reaction mixture followed by flash chromatography with hexane/ethyl acetate (10:1) as eluant yielded **8b** (56%) as a clear oil: ^{1}H NMR (300 MHz) δ 8.09 (m, 1 H), 6.65 (m, 1 H), 6.54 (m, 1 H), 6.29 (m, 1 H), 3.15 (s, 2 H); IR (film) 2979, 2930, 2247, 1580, 1559, 1455, 1418, 1123, and 760 cm^{-1}; mass spectrum, m/e (relative intensity) 150 (M$^+$, 47), 123 (57), 78 (100); exact mass calcd for $C_7H_6N_2S$ m/e 150.0252, found m/e 150.0252.

2-(1-Thia-2-methyl-2-carbethoxypropyl)pyridine (8c). Evaporation of the solvent from the crude reaction mixture followed by flash chromatography with hexane/ethyl acetate (8:1) as eluant yielded **8c** (39%) as a clear oil: ^{1}H NMR (300 MHz) δ 8.15 (m, 1 H), 6.83 (m, 1 H), 6.73 (m, 1 H), 6.33 (m, 1 H), 4.04 (q, 2 H, J = 7.1 Hz), 1.74 (s, 6 H), 0.88 (t, 3 H, J = 7.1 Hz); IR (film) 2984, 2938, 1744, 1578, 1559, 1455, 1416, 1372, 1256, 1107, 1019, 764 cm^{-1}; mass spectrum, m/e (relative intensity), 225 (M$^+$, 9), 180 (4), 152 (60), 111 (100); exact mass calcd for $C_{11}H_{15}NO_2S$ m/e 225.0823, found m/e 225.0824.

2-(1-Thia-2-carbethoxyethyl)pyridine (8d). Evaporation of the solvent from the crude reaction mixture followed by flash chromatography with hexane/ethyl acetate (8:1) as eluant yielded **8d** (58%) as a clear oil: ^{1}H NMR (300 MHz) δ 8.16 (m, 1 H), 6.80 (m, 1 H), 6.70 (m, 1 H), 6.31 (m, 1 H), 3.90 (q, 2 H, OCH_2 and s, 2 H, SCH_2), 0.87 (t, 3 H, J = 7.1 Hz); mass spectrum, m/e (relative intensity), 197 (M$^+$, 14), 151 (20), 124 (100), 78 (43); exact mass calcd for $C_9H_{11}NO_2S$ m/e 197.0511, found m/e 197.0511.

NMR Procedure for Reactions with 6a. Individual solutions of each of the halides (about 1.15 equiv) and the thione **6a** in benzene-d_6 (0.01–0.2 M) were placed in a 5.0-mm NMR tube. Me_4Si and CH_2Cl_2 were added as internal standards, and the solution was diluted further with benzene-d_6 if necessary. The NMR tube was then sealed, and the spectrum was recorded. The tube was then submerged in an Erlenmeyer flask filled with water at 50 °C. (NOTE: *All operations up to this point were conducted with all solutions protected from the light.*) The reaction mixture was then irradiated with a 250-W sunlamp from a distance of 10 cm. The progress of the reaction was conveniently monitored by watching the color changes of the reaction mixture. The initial color of the reaction mixture was bright yellow, and on completion of the reaction the mixture was colorless. Prolonged irradiation led to the formation of free iodine and, consequently, a pink solution. Reaction time and temperature were monitored. An NMR spectrum was recorded, and the concentrations of each of the reactants and products were calculated relative to both of the internal standards. In all cases of reaction with a single halide, the crude product was chromatographed, and the pure *S*-pyridyl product **8** was fully characterized. Octyl iodide was purchased (Aldrich) for purposes of comparison.

GC Procedure for Reactions of 7f with 6. Solutions of weighed amounts of ethyl bromoacetate (**7f**) and of thiohydroxamate **6** and a hydrocarbon standard were prepared in dry, degassed benzene. Predetermined amounts of each of the above solutions were added via syringe to a 2-mL volumetric flask equipped with a magnetic stir bar, purged with N_2, and shielded from light, and dry benzene was added to bring the total volume to the mark. The reaction flask was placed in a controlled temperature bath, and the mixture was stirred via an electric stirring motor. After 1 min, the shield was removed, and the reaction mixture was irradiated with an uncoated 75-W tungsten filament bulb. The reaction progress was monitored by TLC. After the reaction was complete (<5 min), the products of the reaction were measured by GC on a 15-m, 0.5-mm i.d. fused silica column containing a bonded phase equivalent to OV-1 or OV-17. Products were identified by co-injections with authentic 1-bromooctane or 1-bromoundecane and by GC–mass spectrometry on an equivalent column. Yields were calculated with predetermined response factors. For calculations of k_{Br}, the final concentration of **7f** was determined by subtracting the amount of alkyl bromide formed in the reaction from the amount of starting material.

Procedure for Reactions of 7d. Solutions of ethyl iodoacetate (**7d**) and dodecane and of thiophenol were prepared in dry, degassed benzene. A weighed amount of crystalline **6b** was placed in a 2-mL volumetric flask that was shielded from light and equipped with a magnetic stir bar. The reaction flask was sealed with a septum and flushed with dry N_2. Appropriate amounts of the two standard solutions were added to the reaction vessel via syringe, and benzene was added to bring the volume to the mark. The reaction was run as described above, and product yields were also determined by GC. Retention times and response factors for 1-iodoundecane and undecane were determined with authentic

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samples. Final concentrations of **7d** and thiophenol were determined by subtraction of the amount of product arising from each from the amount of starting materials.

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Registry No. **6a**, 111916-74-6; **6b**, 119368-34-2; **7a**, 119368-33-1; **7b**, 624-75-9; **7c**, 7425-55-0; **7d**, 623-48-3; **7e**, 29263-94-3; **7f**, 105-36-2; **8a**, 119391-50-3; **8b**, 7521-19-9; **8c**, 119368-35-3; **8d**, 28856-92-0; **9a**, 26891-70-3; **9b**, 119368-36-4; I_2, 7553-56-2; Br_2, 7726-95-6; $CH_3(CH_2)_9CH_2^{\bullet}$, 55101-35-4; $CH_3(CH_2)_6CH_2^{\bullet}$, 4606-96-6; octyl iodide, 629-27-6; octyl bromide, 111-83-1; undecyl bromide, 693-67-4; diethyl methylmalonate, 609-08-5; ethyl 2-bromo-2-methylpropanoate, 600-00-0.

Platinum Complex Catalyzed Carbonylation of Organic Iodides: Effective Carbonylation of Organic Iodides Having β-Hydrogens on Saturated sp^3 Carbons

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Dichlorobis(triphenylphosphine)platinum(II) is an effective catalyst precursor for the carbonylation of organic iodides having β-hydrogens on saturated sp^3 carbons. The carbonylation under carbon monoxide pressure in the presence of alcohol gives esters, and aldehydes are obtained by the reaction under carbon monoxide and hydrogen pressure. Thus, 1-iodohexane is carbonylated to methyl heptanoate in 79% yield in the presence of methanol at 120 °C under 70 kg cm^{-2} of initial carbon monoxide pressure. Heptanal is formed in 86% yield from 1-iodohexane at 120 °C under carbon monoxide (50 kg cm^{-2}) and hydrogen (50 kg cm^{-2}). Alkenyl and alkynyl iodides are also smoothly carbonylated in the presence of alcohol into the corresponding esters without reduction of unsaturated bonds.

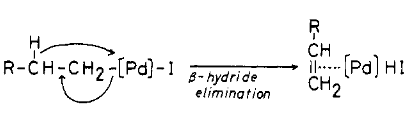
Table I. Activities of Several Catalyst Precursors and Effect of Bases on the Methoxycarbonylation of 1-Iodohexane[a]

run	catalyst	base	conv,[b] %	yield,[c] %
1	$PtCl_2(PPh_3)_2$	K_2CO_3	97	75
2	$PtCl_2(PPh_3)_2$	NaOAc	26	2
3	$PtCl_2(PPh_3)_2$	Na_2CO_3	49	13
4	$PtCl_2(PPh_3)_2$	$NaHCO_3$	29	4
5	$Pt(CO)_2(PPh_3)_2$	K_2CO_3	100	73
6	$Pt(PPh_3)_4$	K_2CO_3	97	52
7	$PtCl_2(AsPh_3)_2$	K_2CO_3	69	39
8[d]	$PtCl_2(PCy_3)_2$	K_2CO_3	99	58
9[d]	$Pd(PPh_3)_4$	K_2CO_3	100	21
10[d]	$PdCl_2(PPh_3)_2$	K_2CO_3	90	5

[a] 1-Iodohexane (10 mmol), catalyst (0.50 mmol), base (12 mmol), methanol (40 mmol), and dioxane (15 mL) at 120 °C for 9 h under CO (initial pressure 70 kg cm^{-2}). [b] Conversion of 1-iodohexane determined by GLC, i.e., 100 × (1 − starting material recovered/starting material charged). [c] Yield of methyl heptanoate determined by GLC, i.e., 100 × (product formed/starting material charged). [d] K_2CO_3 (6.0 mmol), MeOH (60 mmol).

Introduction

Transition-metal-catalyzed carbonylations of organic halides with carbon monoxide are valuable synthetic methods for the direct introduction of a carbonyl group into organic molecules and have been extensively studied.[1] Thus far, many transition-metal complexes such as iron,[2] cobalt,[3] nickel,[4] rhodium,[5] and palladium[6] are known to be active as catalysts. Among them, palladium complexes show high catalytic activity under mild reaction conditions and are very widely employed. Palladium complex catalyzed carbonylations of organic halides are extremely useful synthetic tools.[7] In the palladium-catalyzed reactions, however, there exists one major limitation. Applicable substrates are limited to organic halides such as aryl, alkenyl, benzyl, and allyl halides, since the intermediate (σ-organo)palladium species generated by oxidative addition of these halides to active metal centers do not undergo β-hydride elimination. On the other hand, in the case of organic halides having β-hydrogens on saturated sp^3 carbons, palladium catalysts do not afford carbonylated products effectively due to the β-hydride elimination of (σ-alkyl)palladium species (eq 1). Recently, Alper et al.



(1)

employed a palladium–rhodium binary catalyst system with metal alkoxides as alkoxylating reagents to overcome this limitation.[8] However, the catalytic activity was not satisfactory. Besides palladium-catalyzed reactions, cobalt-catalyzed carbonylation of organic halides having β-hydrogens on sp^3 carbons has been reported.[9] However, the catalytic activity was quite low and rearranged prod-

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