Single Electron Transfer in Reactions of Alkyl Halides with Lithium Thiolates

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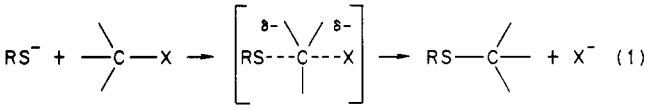
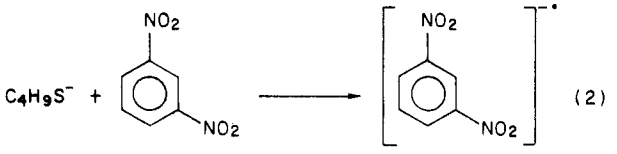
Single Electron Transfer (SET) in the reaction of lithium thiolates with trityl halides was studied in detail by (1) isolation and identification of all products, (2) studying the effects of the radical trap, dicyclohexylphosphine (DCPH), on product distribution, and (3) studying the effects of light and the presence of *p*-dinitrobenzene on the reaction rate. The reaction of lithium thiolates with the cyclizable alkyl iodide probe 2,2-dimethyl-1-iodo-5-hexene was also studied. Reactions carried out in the presence of the radical trap, DCPH, yielded up to 22% hydrocarbon products, suggesting a significant contribution of a SET pathway. Direct spectroscopic detection of radical intermediates was made for reactions of lithium thiolates with well-known one-electron acceptors, such as diaryl ketones, polynuclear hydrocarbons, trityl halides, and 9-bromofluorene.

The reaction of thiolate anions with organic substrates such as organic halides is well recognized as a fundamental reaction in organic chemistry. The mechanism of this reaction with alkyl halides was originally thought to be a S_N2 process primarily on the basis of kinetic and stereochemical studies, where the thiolate anion reacts as an excellent nucleophile (eq 1).[1] However, in 1963, Russell



(1)

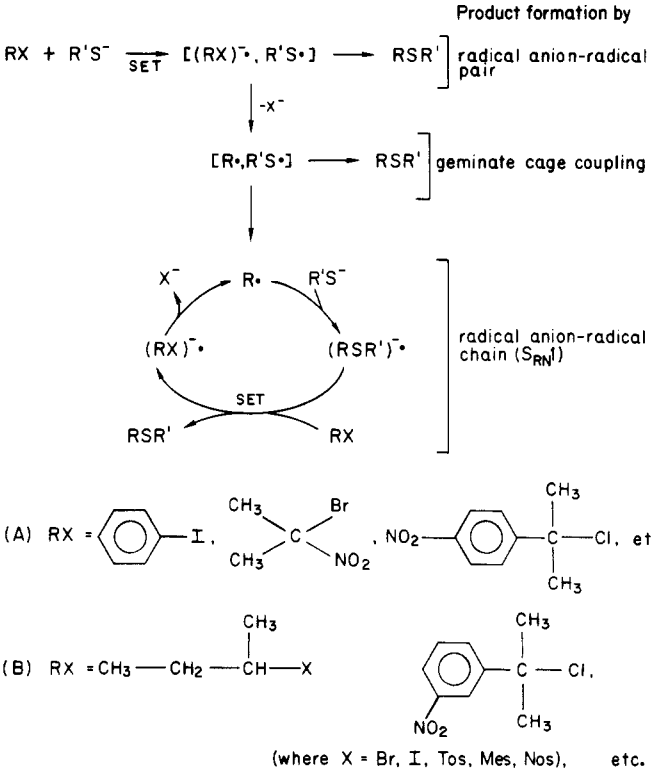
and his co-workers[2,3] showed that thiolates (derived from benzenethiol or *n*-butanethiol) on reaction with nitrobenzene or *m*-dinitrobenzene, exhibit the corresponding radical anion of the substrate as determined by EPR spectroscopy (eq 2).



(2)

Recently this laboratory has been involved in the investigation of the degree of polar and radical character exhibited in reactions of nucleophiles such as metal alkyls,[4] metal hydrides,[5-9] alkoxides,[10] enolates,[11,12] and the trialkyltin anion[13] with organic substrates. Involvement of a SET pathway in these reactions was demonstrated by

Scheme I. Summary of Mechanistic Schemes for the Reaction of Thiolates with Organic Halides



spectroscopic (visible and EPR) studies as well as product studies using cyclizable probes. Similar methodology was used in the evaluation of thiolate anions as one-electron donors toward various organic substrates.

In this respect, it is worth noting a recent theoretical correlation diagram on S_N2 reactivity proposed by Shaik and Pross.[14] This model describes a S_N2 reaction as a transformation which involves SET taking place synchronously with bond reorganization. Using this correlation diagram model formulated by the valence bond approach, these workers were able to explain the reactivity pattern in S_N2 reactions, such as reactivity crossover, reactivity-selectivity crossover, and α- and β-carbon substituent effects. In summary, their view on S_N2 reactions is that a significant improvement on the donor–acceptor

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abilities of nucleophiles and alkyl halides is likely to lead to bona fide SET reactions.

A variety of studies have suggested the occurrence of electron transfer in reactions of thiolates with organic halides. Mechanistic suggestions evolved from these studies can be summarized (Scheme I) depending on the structures of the organic halide substrates. When RX was defined as those alkyl or aryl halides represented by A, then a $S_{RN}1$ type chain process was suggested to be in effect.[15-19] However, when RX was defined as those organic halides represented by B, the radical anion–radical pair or a geminate cage coupling process was suggested to operate.[15,20]

If the second radical combination step is slow compared to the electron-transfer step ($k_1 \gg k_2$) in the reaction of a nucleophile with an alkyl halide involving SET (eq 3), then the intermediate radical species could be detected by spectroscopic methods (EPR and UV). However, for a

$$\text{Nu:} + \text{RX} \xrightarrow[k_1]{\text{SET}} [\text{RX}^{-}\cdot + \text{Nu}\cdot] \xrightarrow[k_2]{} \text{RNu} + \text{X}^{-} \quad (3)$$

reaction system where the intermediate radical produced is not stable, the SET step is rate determining ($k_1 \ll k_2$) and other methods need to be used to detect the radical intermediate. Among those methods reported to detect unstable radical intermediates, the following have been most often encountered in the literature: (1) use of cyclizable probes,[21-24] (2) use of radical traps,[23-26] (3) use of spin trapping techniques,[27,28] and (4) use of a linear free-energy correlation between the rate constants of the reaction and the reduction potentials of the substrates depending on the nature of the leaving group.[29-31]

In the present study concerning the reactions of thiolates with alkyl halides we report the results of (1) the use of cyclizable probes to detect radical intermediates, (2) direct spectroscopic (EPR) observation of the trityl radical in reactions of thiolates with trityl halides, (3) product distribution studies in the reactions of thiolates with 2,2-dimethyl-1-iodo-5-hexene, (4) studies on the effect of DCPH as a radical trapping agent, and (5) evaluation of thiolate anions as one-electron donors toward various organic substrates such as diaryl ketones, polynuclear hydrocarbons, and 9-bromofluorene (all well-known one-electron acceptors).[32]

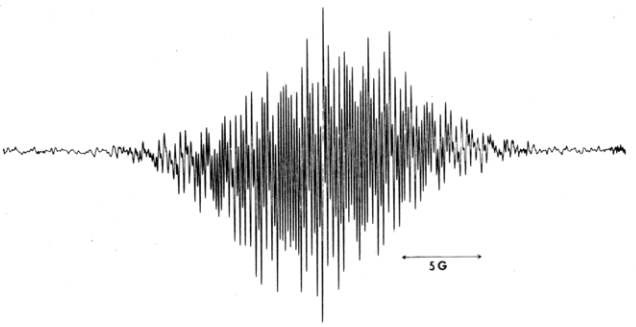

Figure 1. EPR spectrum of the radical intermediate formed on reaction of benzophenone with LiS-*n*-Bu in THF at room temperature.

Results and Discussion

Thiolate Ion as a One-Electron Donor. Reactions with Ketones. Recently we reported direct spectroscopic (EPR) evidence to support a radical pathway in the reactions of LiS-*n*-Bu and LiS-*i*-Pr with aromatic ketones [benzophenone and dimesityl ketone (DMK)] and polynuclear hydrocarbons (perylene, 2,3-benzanthracene, and benzo[*a*]pyrene).[33] The reaction of LiS-*n*-Bu with benzophenone in THF at room temperature slowly produced a blue colored solution which was found to be paramagnetic and exhibited a complex EPR spectrum (Figure 1). The EPR spectrum was found to be different from that of free lithium benzophenone ketyl, $Ph_2\dot{C}OLi$.[34] The intensity of the EPR spectrum increased slowly with time as the reaction proceeded, and the maximum concentration of the radical intermediate after 4 days was ca. 8% relative to the initial concentration of starting benzophenone. Slow formation of the reduction product, Ph_2CHOH, was observed during the course of the reaction. The reaction produced only ca. 3% of the reduction product after 4 days. Interestingly, a significant amount of the dimer byproduct, RSSR, is also formed during the course of the reaction.

Since the EPR spectrum of the intermediate radical species was found to be different from that of the free ketyl, it is possible that the spectrum is due to the formation of a radical anion–radical cation pair. The reduction of benzophenone to benzhydrol is probably occurring via an α-hydrogen atom transfer from LiS-*n*-Bu after benzophenone ketyl has diffused out of the solvent cage (eq 4–6). This pathway is supported by the fact that

$$Ph_2C{=}O + \text{LiS-}n\text{-Bu} \rightarrow [Ph_2CO^{-}\cdot, \cdot\text{S-}n\text{-Bu}, Li^{+}] \quad (4)$$

$$Ph_2CO^{-}\cdot \xrightarrow{\text{LiS-}n\text{-Bu}} Ph_2CHO^{-} \quad (5)$$

$$\cdot\text{S-}n\text{-Bu} + \cdot\text{S-}n\text{-Bu} \rightarrow n\text{-BuS–S-}n\text{-Bu} \quad (6)$$

when lithium benzophenone ketyl was treated with LiS-*n*-Bu, a slow formation of benzhydrol was observed during the course of the reaction at a rate approximating the formation of benzhydrol in the reaction of benzophenone with LiS-*n*-Bu. The dimer byproduct, RSSR, is probably formed via a dimerization of the thioalkoxide radicals (eq 6).

This process is similar to that of the Meerwein–Pondorf–Verly reduction of benzophenone by alkoxide reagents which we also found recently to possess radical character.[35] In addition, the intermediate radical species can possibly be produced from the diphenyl methoxide

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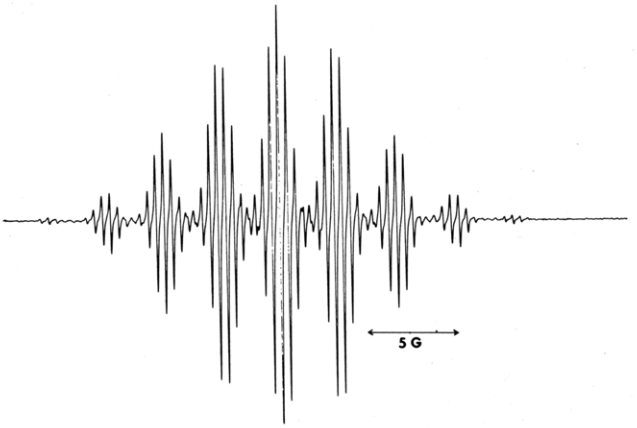

Figure 2. EPR spectrum of the radical intermediate formed in the reaction of perylene with LiS-*n*-Bu in THF at room temperature.

formed in the reaction. This alkoxide can either transfer an electron to benzophenone to form benzophenone ketyl (eq 7) or remove the protons from another molecule of alkoxide to form the dianion (eq 8), Ph_2CO^{-2}, which can then transfer an electron to benzophenone to form benzophenone ketyl (eq 9).[35] Formation of the reduction

$$Ph_2C{=}O + Ph_2CHO^- \rightarrow Ph_2C{=}O^-\cdot + Ph_2CHO\cdot \quad (7)$$

$$2Ph_2CHO^- \rightarrow Ph_2C^-{-}O^- + Ph_2CHOH \quad (8)$$

$$Ph_2C^-{-}O^- + Ph_2C{=}O \rightarrow 2Ph_2C{=}O^-\cdot \quad (9)$$

product via a hydrogen atom transfer process is further supported by the fact that when LiSPh was allowed to react with benzophenone, no reduction product was observed, although the formation of a radical intermediate was confirmed by EPR spectroscopy. Incidentally, the rate of the electron transfer in the reaction of LiSPh with benzophenone was found to be much slower compared to the reaction of LiS-*n*-Bu with benzophenone. The difference in reactivity between LiS-*n*-Bu and LiSPh can be related to the difference in basicities of the reagents.[36] Both of these reagents reacted with sterically hindered dimesityl ketone to give a radical intermediate; however, in both cases, no reduction product formed. The above results are not consistent with the formation of the ketyl via a redistribution of benzophenone with the dianion formed by deprotonation of the lithium salt of benzhydrol (eq 10–12).[37]

$$LiSCH(CH_3)_2 + Ph_2C{=}O \rightarrow Ph_2CHOLi + (CH_3)_2C{=}S \quad (10)$$

$$Ph_2CHOLi + LiSCH(CH_3)_2 \rightarrow [Ph_2COLi]^-Li^+ + (CH_3)_2CHSH \quad (11)$$

$$[Ph_2COLi]^-Li^+ + Ph_2C{=}O \rightleftharpoons 2[Ph_2C{=}O^-\cdot Li^+] \quad (12)$$

Reactions with Polynuclear Hydrocarbons. Electron transfer of LiS-*n*-Bu to polynuclear hydrocarbons possessing low reduction potentials[32] was also observed. When an excess of LiS-*n*-Bu ($\simeq$20-fold) was allowed to react with perylene, 2,3-benzanthracene, and benzo[*a*]pyrene in THF at room temperature, colored solutions formed that were EPR active. During the course of the reactions the EPR signal increased slowly in each case, and after a week the maximum radical concentrations measured were about 10–30% relative to the initial concentrations of polynuclear hydrocarbons used. The EPR spectrum of the radical intermediates (Figure 2) was found to be identical with that of the radical anions of the corresponding hydrocarbons, thus suggesting the dissociation of the radical pair into a solvent separated radical anion–radical cation, as shown (eq 13).

$$ArH + LiS\text{-}n\text{-}Bu \rightarrow (ArH)^-\cdot(LiS\text{-}n\text{-}Bu)^+\cdot \quad (13)$$

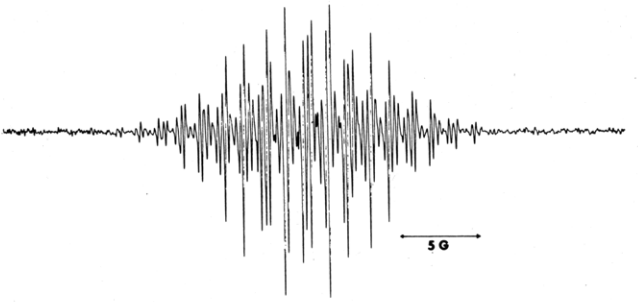

Figure 3. EPR spectrum of the trityl radical formed in the reactions of trityl halides with lithium thiolates in THF at room temperature.

Table I. Formation of the Trityl Radical in the Reaction of Trityl Halide with a Lithium Thiolate in THF at Room Temperature

expt	thiolates	trityl halides	maximum concentration of $Ph_3C\cdot$, %	time required to reach maximum $Ph_3C\cdot$, min
1	LiS-*n*-Bu	Ph_3CBr	10[a]	2
2	LiS-*n*-Bu	Ph_3CCl	2	40
3	LiS-*i*-Pr	Ph_3CBr	10[a]	2
4	LiS-*i*-Pr	Ph_3CCl	2	40
5	LiSPh	Ph_3CBr	2[a]	2
6	LiSPh	Ph_3CCl	0.2	20

[a] At the first measurement of the concentration, the concentration of trityl radical was already decreasing; therefore, the actual maximum concentration could be significantly higher than these values.

Reactions with Trityl Halides. LiS-*n*-Bu, LiS-*i*-Pr, and LiSPh were allowed to react with trityl halides (Ph_3CX; where X = Br or Cl) in THF at room temperature and the intermediate trityl radical ($Ph_3C\cdot$) was observed by EPR spectroscopy in all cases (Figure 3). As the reaction proceeded, the concentration of the radical increased rapidly with time and reached a maximum beyond which the radical concentration decreased slowly with the concurrent formation of products. The products of the reactions were formed throughout the entirety of the reactions, i.e., during the increase as well as the decrease of the radical concentration. Table I summarizes the maximum concentration of the trityl radical and the time required to reach this maximum concentration in the reactions of thiolates with trityl halides. The rate of formation of the intermediate trityl radical was faster in the case of trityl bromide than trityl chloride (compare experiments 1 vs. 2, 3 vs. 4, and 5 vs. 6). This is consistent with the larger negative reduction potential[32] of alkyl chlorides compared to bromides. The higher rate of intermediate trityl radical formation in the case of LiS-*n*-Bu and Li-*i*-Pr compared to that of LiSPh (compare experiments 1 and 3 vs. 5) is consistent with the relative reactivities of the thiolate reagents toward benzophenone and their relative basicities as discussed earlier.

The reactions of LiS-*n*-Bu or LiS-*i*-Pr with trityl halides produced two different types of substitution products, namely, an α-substitution product [Ph_3CSR (**1**)] and a para-substitution product [*p*-$RSC_6H_4CHPh_2$ (**2**)] as well

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Table II. Reaction of Lithium Thiolates with Trityl Halides in THF at Room Temperature[a]

expt	substrate	additive	thiolate	time, h	yield, %[b] 1[c]	2[c]	3[d]	4[e]
1[f]	Ph_3CBr	none	LiS-*i*-Pr	1.0	22	35	20	23
2	Ph_3CBr	DCPH[g]	LiS-*i*-Pr	1.0	1	37	62	1
3	Ph_3CBr	*t*-BuOH[j]	LiS-*i*-Pr	1.0	23	37	19	21
4	Ph_3CCl	none	LiS-*i*-Pr	3.0	24	37	20	19
5	Ph_3CCl	DCPH[g]	LiS-*i*-Pr	3.0	3	30	65	2
6[h]	Ph_3CBr	none	LiSPh	3.0	65	35	*i*,*k*	*k*

[a] [LiSR]:[Ph_3CX] = 0.10:0.05 M. [b] Normalized percent. +80% mass balances. [c] Determined from weight of the mixture and the ratio of NMR integration of the sample separated from other components by column chromatography. [d] GLC analysis using an internal standard and response factor correction. [e] Determined by isolation. [f] 38% of 2-propyl disulfide (*i*-PrSS-*i*-Pr) was also detected by GLC analysis. [g] 5 equiv of dicyclohexylphosphine (DCPH) was used. [h] None of the phenyl disulfide was detected by GLC analysis. [i] In the presence of 5 equiv of DCPH, 30% Ph_3CH was detected by GLC analysis. [j] 10 equiv of *tert*-butyl alcohol was used. [k] Trace.

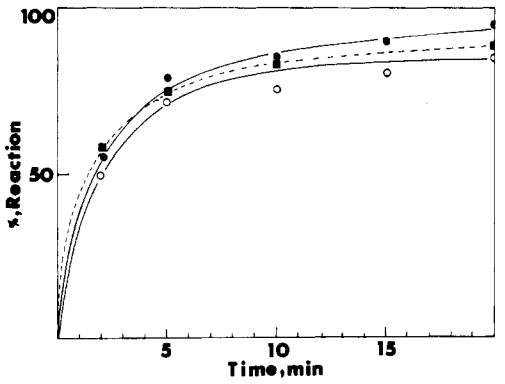


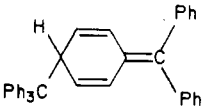
Figure 4. Effect of Light and the Presence of *p*-DNB on the rate of reaction of LiS-*i*-Pr with Ph_3CBr in THF at room temperature: (○) under laboratory light; (●) in the dark; (■) in the presence of 5% *p*-DNB.

as free-radical byproducts such as the reduction product [Ph_3CH (**3**)], the dimerization product of the trityl radical [*p*-$Ph_3CC_6H_4CHPh_2$ (**4**)], and the disulfide [RSSR (**5**)] (eq 14). Similar products were also reported by Meyers.[38]

$$\underset{}{LiSR} + Ph_3CX \rightarrow \underset{}{Ph_3CSR} + \underset{\mathbf{1}}{p\text{-}RSC_6H_4CHPh_2} + \underset{\mathbf{2}}{} \underset{\mathbf{3}}{Ph_3CH} + \underset{\mathbf{4}}{p\text{-}Ph_3CC_6H_4CHPh_2} + \underset{\mathbf{5}}{RSSR} \quad (14)$$

The results of these studies are summarized in Table II. Detection of the intermediate trityl radical by EPR spectroscopy and the formation of significant amounts of radical byproducts suggests strongly the involvement of a SET pathway in the reactions of thiolates with trityl halides. For the purpose of examining SET in the formation of substitution products, reactions of thiolates with trityl halides in the presence of the radical trap, DCPH, were also carried out and the results are included in Table II. Indeed in the presence of DCPH, the radical dimer product **4**, and the α-substitution product **1** were both diverted to the hydrogen abstraction product **3** (compare experiments 1 vs. 2 and 4 vs. 5).

The results suggest that **1** and **4** were both produced via a free trityl radical pathway. However, the formation of para-substitution product **2** was not affected by the presence of DCPH in the same reaction. Perhaps, RS· attacks the para position of the radical–anion pair, R·, X^-, in the solvent cage while the front side is still protected by the leaving group to form **2** exclusively. Once trityl radical diffuses out of the solvent cage, RS· attacks it exclusively from the front side to form **1**. In fact, it is known that the trityl radicals, generated by dissociation of 4-(triphenylmethyl-1-(diphenylmethylene)-2,5-cyclohexadiene, reacts with excess benzenethiol at room temperature to produce only Ph_3CH and Ph_3CSPh[39] (eq 15–17). Furthermore, in the presence of *tert*-butyl alcohol,



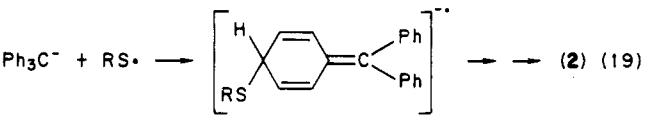
$$\rightleftharpoons 2Ph_3C\cdot \quad (15)$$

$$Ph_3C\cdot + PhSH \rightarrow Ph_3CH + PhS\cdot \quad (16)$$

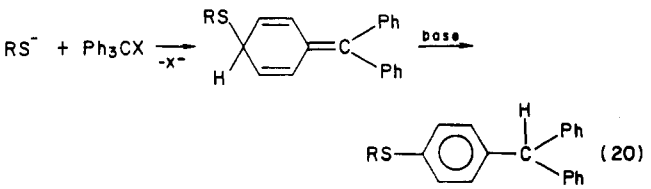
$$Ph_3C\cdot + PhS\cdot \longrightarrow Ph_3CSPh \quad (17)$$

a carbanion trap, the results are similar to those obtained in the absence of the trap (experiments 1 and 3). Thus we have no evidence for Ph_3C^- in a reaction in which perhaps RS· can add exclusively to Ph_3C^- by para attack (eq 18–19).[40] Of course it is possible that the formation

$$Ph_3CX + RS^- \longrightarrow Ph_3C^- + RSX \quad (18)$$



of **2** is due to para attack by thioalkoxide on the trityl halide via a polar process (eq 20). This pathway to **2**, as well as formation via a radical intermediate in the solvent cage, cannot be rigorously excluded. However, the reaction of LiSPh with trityl bromide (experiment 6, Table II) produced a strong EPR signal for the trityl radical and a significant increase in the formation of Ph_3CH (**3**) in the presence of DCPH (footnote *i*, Table II), thus further suggesting a SET pathway for this reaction.



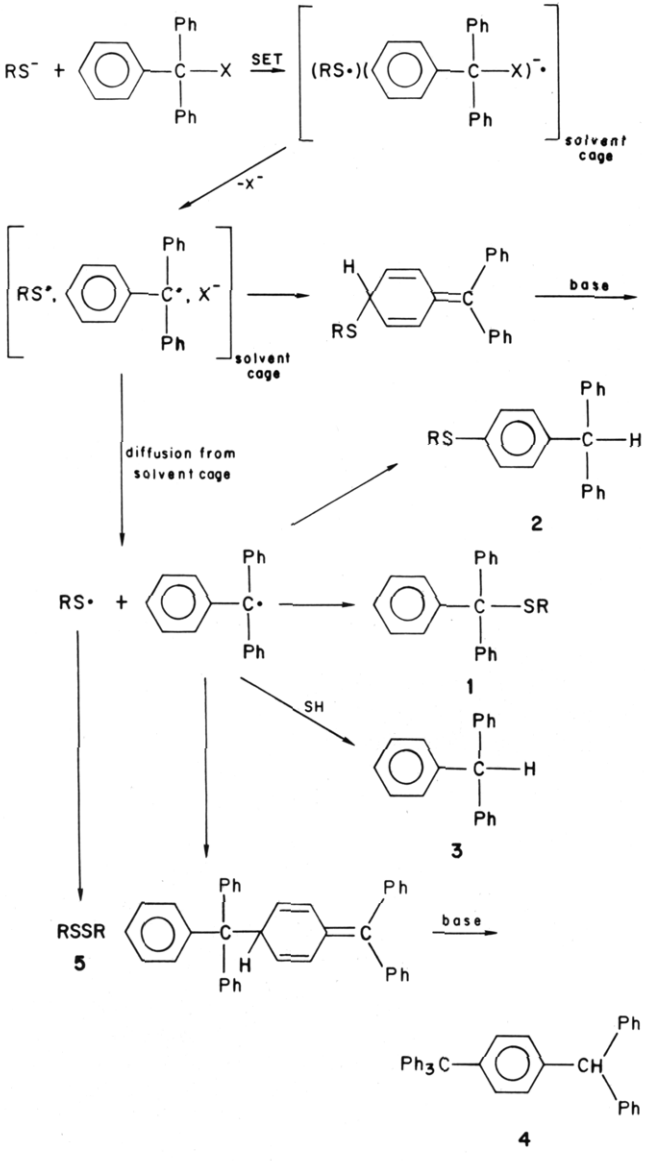
The exclusive formation of substitution products (Ph_3CSPh and *p*-$PhSC_6H_4CHPh_2$) in the reaction of LiSPh with Ph_3CBr without appreciable formation of free-radical byproducts such as Ph_3CH, *p*-$Ph_3CC_6H_4CHPh_2$, and PhSSPh (experiment 6, Table II), in contrast to the LiS-*i*-Pr case (experiment 1 in Table II), can be understood in terms of relative reactivities of alkyl disulfides vs. aryl disulfides toward the trityl free radical. The reaction of the trityl free radical with phenyl disulfide is known to produce Ph_3CSPh[41] (eq 21), whereas dialkyl

$$2Ph_3C\cdot + PhSSPh \rightarrow 2Ph_3CSPh \quad (21)$$

(38) Meyers, C. Y.; Hsu, M. L. "Abstracts of Papers", 170th National Meeting of Americal Chemical Society, 1975; American Chemical Society: Washington, DC, 1975; ORGN 45.

(39) Lewis, E. S.; Butler, N. M. *J. Org. Chem.* **1971**, *36*, 2582.
(40) Suggestion by referee.

Scheme II. Proposed Mechanism for the Reaction of Thiolates with Trityl Halides



disulfides are known to be substantially less reactive than aryl disulfides toward alkyl radicals.[22] Therefore in the reaction of LiSPh with trityl bromide, the free trityl radicals that diffuse from the solvent cage can react further with PhSSPh (which is an initial termination product of the PhS· radical) to form Ph_3CSR before the free trityl radical can undergo hydrogen atom abstraction or dimerization.

The Kornblum–Russell–Bunnett $S_{RN}1$-type radical–radical anion chain mechanism is not likely in the reaction of lithium thiolates with tritylhalides because the presence of a 5-fold excess of DCPH, which is known to be a good radical trap, did not show any significant retardation of the reaction rate. However, in order to examine this possibility further, experimental criteria established for the radical–radical anion chain mechanism were tested. The experiments carried out involve the determination of the rate enhancement of the reaction by light and the signficant retardation or complete inhibition of the reaction in the presence of 5 mol % *p*-dinitrobenzene (*p*-DNB). In this connection LiS-*i*-Pr was allowed to react with trityl bromide in THF. The effect on the rate of reaction carried

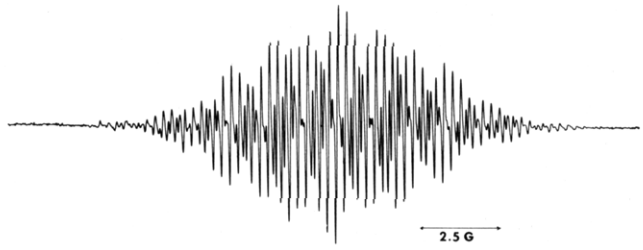
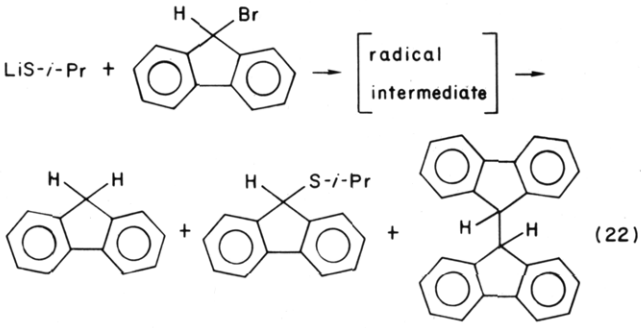


Figure 5. EPR spectrum of the radical intermediate formed in the reaction of LiS-*i*-Pr with 9-bromofluorene in THF at room temperature.

out in the absence of light or in the presence of the radical anion trapping agent, *p*-DNB (Figure 4), was insignificant. Therefore the involvement of a radical–radical anion chain mechanism in the reaction of lithium thiolates with trityl halides is unlikely.

On the basis of the above studies, a mechanistic scheme for the reaction of lithium thiolates with trityl halides is suggested (Scheme II).

Reactions with 9-Bromofluorene. Electron transfer from the thiolate anion to 9-bromofluorene was also observed. When LiS-*i*-Pr was allowed to react with 9-bromofluorene in THF, THF–HMPA (9:1), and THF–HMPA (1:1), a dark olive green color developed immediately, and the solution was EPR active[42] in all cases (Figure 5). The maximum radical concentration obtained was 0.2%, 2%, and 7%, respectively relative to the initial concentration of 9-bromofluorene. The reaction of LiS-*i*-Pr with 9-bromofluorene produced not only the normal substitution product, 9-fluorenyl 2-propyl sulfide, but also comparable amounts of fluorene and 9,9′-bifluorenyl (eq 22), which is consistent with the results expected for a free radical process.



(22)

So far we have shown that a thiolate ion behaves as a good one-electron donor to substrates such as diaryl ketones, polynuclear hydrocarbons, trityl halides, and 9-bromofluorene. These substrates are known to possess low reduction potentials[32] and the radical intermediates generated by one-electron transfer are relatively stable. Thus there was no difficulty in detecting the intermediate radical species generated in the reactions of these substrates with thiolates directly by EPR spectroscopy. However, in the reactions of thiolates with aliphatic alkyl halides, where the generated intermediate radicals are not stable, another method had to be used for the purpose of probing the intermediacy of a radical species. These methods include the use of cyclizable probe compounds and the use of radical traps.

Studies Using Cyclizable Alkyl Halide Probes. The reaction of LiS-*n*-Bu with 6-iodo-1-hexene, carried out at 8 °C for 72 h, yielded 5-hexenyl *n*-butyl sulfide as the only

(41) Lecher, H. *Ber. Dtsch. Chem. Ges.* **1915**, *48*, 524.

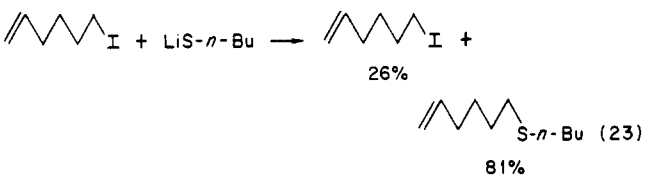
(42) Neugebauer, F. A.; Groh, W. R. *Tetrahderon Lett.* **1973**, *1005*.

Table III. Reaction of LiS-*i*-Pr with 6[a]

expt	LiS-*i*-Pr, mol equiv[b]	solv	additive (mol equiv)[b]	time, h	yield,[b] % 6	7	8	9
1	1	THF	none	96	30	65	0	0
2	1	THF	DCPH (10)	96	18	57	3	19
3	0.3	THF	DCPH (10)	96	73	17	1	8
4	0.3	THF	DCPH (10)	240	74	16	1	7
5	1	THF	*p*-DNB (0.1) DCPH (10)	96	34	62	<1	<1
6	1	DMF	none	1	2	95	0	0
7	1	DMF	DCPH (1)	1	0	98	<1	<1
8[c]	1	DMF	DCPH (5)	1	3	84	1	3
9[d]	1	DMF	DCPH (10)	1	23	60	2	7
10	1	HMPA	none	1	0	98	0	0
11	1	HMPA	DCPH (1)	1	0	96	0	<1
12	1	HMPA	DCPH (10)	1	0	97	0	1

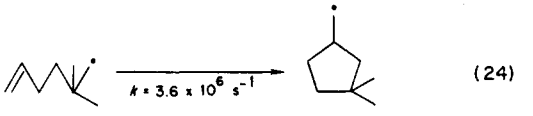
[a] Concentration of alkyl iodide is 0.10 M. [b] Based on alkyl iodide. [c] Concentration of alkyl iodide is 0.05 M, due to solubility limit of DCPH in DMF. [d] Concentration of alkyl iodide is 0.025 M, due to the same reason as in *c*.

product with no trace of the cyclic product, cyclopentylmethyl *n*-butyl sulfide (eq 23). Thus the reaction of



LiS-*n*-Bu with 6-iodo-1-hexene can be best described either as a classic S_N2 reaction or if radical intermediates are involved, then the radical combination step must be substantially faster than cyclization of the probe.

Since it is possible that any 5-hexenyl radical formed in the reaction in eq 23 can be converted to products at a rate faster than that of probe cyclization, the reaction of thiolates with a sterically bulky probe compound, 1-iodo-2,2-dimethyl-5-hexene, was studied. If SET is taking place in the reaction of lithium thiolates with 2,2-dimethyl-1-iodo-5-hexene, the radical recombination step of the resulting bulky neopentyl-type radical, 2,2-dimethyl-5-hexene-1-yl, should be slower than that of the primary alkyl radical, and hence there should be a better opportunity for observing cyclization of the probe. Moreover Beckwith[43] and his co-workers recently reported that 2,2-dimethyl-5-hexene-1-yl radical undergoes cyclization at a rate about 15 times faster than that of the 5-hexene-1-yl radical (eq 24). In addition, the steric hindrance



(24)

of the alkyl halide substrate should raise the activation energy of a polar S_N2 process more than a SET process; thus, it is possible that a SET pathway is preferred because the S_N2 pathway is discouraged.[44]

The reaction of LiS-*i*-Pr with 2,2-dimethyl-1-iodo-5-hexane (**6**) was conducted in three different solvents (THF, DMF, and HMPA) and the results are given in Table III. An almost quantitative yield of the product 2,2-dimethyl-5-hexenyl isopropyl sulfide (**7**) was obtained and the formation of (3,3-dimethylcyclopentyl)methyl isopropyl sulfide was not observed in the reactions involving lithium thiolates in THF, DMF, or HMPA (experiments 1, 6, and 10) in the absence of a trapping agent. These results suggest that if SET is involved in the reaction of lithium thiolates with **6**, then the geminate coupling of the intermediate radical species to form product must be substantially faster than the cyclization of the probe.

Since the formation of cyclized substitution product was not observed in the reactions of thiolates with the alkyl iodide probe (**6**), radical trapping experiments were conducted. Kuivila[28] has shown that dicyclohexylphosphine (DCPH) can be utilized as a trapping agent for alkyl radicals. Therefore the reaction of LiS-*i*-Pr with **6** in the presence of varying amounts of DCPH was carried out and the results are also shown in Table III. Control experiments demonstrated that **6** was recovered quantitatively (by GLC) from a solution containing DCPH and that no reaction occurred between LiS-*i*-Pr and DCPH as determined by infrared spectroscopy (ν_{P-H} = 2260 cm^{-1}, ν_{C-S} = 680 cm^{-1}). The presence of DCPH indeed diverted the subtitution product (**7**) to hydrocarbon products, 5,5-dimethyl-1-hexene (**8**) and 1,1,3-trimethylcyclopentane (**9**), to varying extents depending on the nature of the solvents used (experiments 1 vs. 2, 6 vs. 9, and 10 vs, 12). The increasing amount of DCPH added in the reaction gave a increased amount of trapping as shown in the reactions carried out in DMF solvent (experiments 6–9). Hydrocarbon products **8** and **9** were observed in the reactions of 2-propanethiolate with the alkyl iodide **6** carried out in the presence of DCPH to an extent depending on the nature of the solvent used (1% in HMPA, 9% in DMF, and 22% in THF). This tendency is consistent with a solvent cage effect which should be a function of solvent viscosity[45] ($\eta_{THF}^{25\,°C}$ = 0.460, $\eta_{DMF}^{25\,°C}$ = 0.802, $\eta_{HMPA}^{20\,°C}$ = 3.47).[46] As the solvent becomes less viscous, the rate of escape from the solvent cage increases thus the intermediate radicals can be trapped more easily by the hydrogen atom donor, DCPH. Of course, this tendency is also consistent with the solvent cation chelating effect which should be a function of cation coordinating ability of the solvent. As the solvent becomes a better cation chelating solvent

(43) Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1983**, *36*, 545.
(44) Kochi, J. K. "Organometallic Mechanisms and Catalysis"; Academic Press: New York, 1978; pp 530–535.
(45) Wursthorn, K. R.; Kuivila, H. G.; Smith, G. F. *J. Am. Chem. Soc.* **1978**, *100*, 2779.
(46) Riddick, J. A.; Bunger, W. B. "Techniques of Chemistry"; Wiley-Interscience: New York 1970; Vol. II.

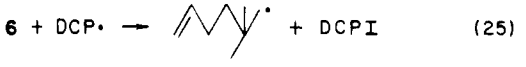
Table IV. Reactivity of Lithium Thiolate with 6 in THF[a]

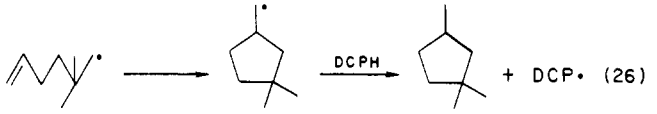
expt	thiolate	yield, % 6	yield, % SR
1	LiS-*i*-Pr	30	65
15	LiS-*n*-Bu	26	69
16	LiSPh	96	0

[a] All reactions were run for 96 h in ratio of 1:1 at a concentration of 0.10 M in each reactant.

(HMPA > DMF > THF), the reaction can proceed via a polar process to a higher extent.[47,48] Moreover, the formation of cyclized hydrocarbon **9** as well as straight chain hydrocarbon **8** indicates that cyclization of the straight chain radical is somewhat faster than hydrogen atom abstraction from DCPH.

It is interesting that DCPH does not just simply act as a hydrogen atom donor but also increases the amount of cyclized product. We have found that a significant amount of the byproduct, identified as $(C_6H_{11})_2P(O)S$-*i*-Pr, was formed in the reaction of LiS-*i*-Pr with **6** in the presence of DCPH and the yield of hydrocarbon products was decreased dramatically by the presence of the radical anion scavenger (*p*-DNB) (experiment 5, Table III). Control experiments showed that the reaction of LiS-*i*-Pr with **6** in the presence of DCPH did not proceed beyond the point corresponding to the amount of nucleophile used (experiments 3 and 4, Table III). It appears that the free-radical chain reaction involving DCP· as an initiator (eq 25 and 26) does not proceed. Thus, it further appears that a





radical intermeidate is formed in the reaction of LiS-*i*-Pr with **6** and an additional $S_{RN}1$ chain process is induced by the presence of DCPH.

The reactivity order of lithium thiolates toward the alkyl iodide probe **6** was found to be LiS-*n*-Bu ≈ LiS-*i*-Pr ≫ LiSPh in the reactions carried out in THF (Table IV). This trend is consistent with our earlier observation comparing the electron-transfer ability of lithium thiolates toward trityl halides and benzophenone. Incidentally, Bordwell[36,47] has suggested that SET, in the rate-limiting step of a reaction, gives rise to exceptional sensitivity of the reaction rate to the basicity of the nucleophile. His studies showed a correlation between electron-transfer abilities and basicities of the carbanions studied.

The reactivity order of LiS-*i*-Pr toward **6** as a function of solvent used is HMPA ≈ THF + HMPA (9:1) > DMF > THF + 12-crown-4 (2 equiv) ≫ THF (Table V). Apparently the presence of a dipolar aprotic solvent such as HMPA or DMF enhances the reactivity of LiS-*i*-Pr more than the reactivity enhancement demonstrated by a solvation effect of lithium cation using 2 equiv of 12-crown-4 which is known to be specific for the lithium cation.

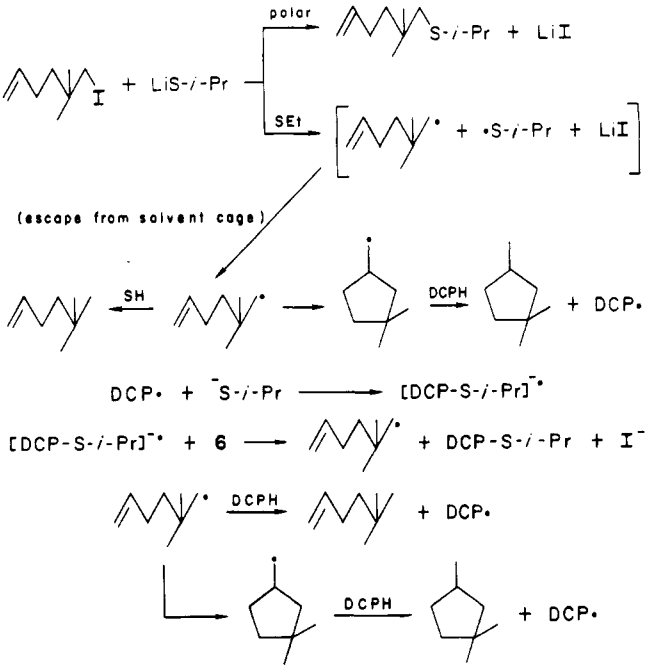
A mechanistic scheme which is consistent with all of the data obtained for the reaction of lithium thiolates with **6** is suggested in Scheme III. From the trapping experiments it appears that lithium thiolates react with **6** by a SET pathway, at least to some extent, producing the 2,2-dimethyl-5-hexene-1-yl radical intermediate.

Table V. Effect of Solvent on the Reaction of LiSR with 6 in Various Solvents[a]

expt	thiolate	solvent	time, h	yield, % 6	yield, % SR
1	LiS-*i*-Pr	THF	96	32	64
6	LiS-*i*-Pr	DMF	1.0	2	95
10	LiS-*i*-Pr	HMPA	1.0	0	98
13	LiS-*i*-Pr	THF + HMPA (9:1)	1.0	0	99
14	LiS-*i*-Pr	THF + 12-crown-4 (2 equiv)	1.0	67	34
16	LiSPh	THF	96	96	0
17	LiSPh	HMPA	1.0	0	96

[a] All reactions were carried out with the reactant ratio 1:1 and 0.10 M in each reactant.

Scheme III. Proposed Mechanism for the Reaction of Lithium Thiolates with 2,2-Dimethyl-1-iodo-5-hexene



Since it was possible to detect the occurrence of SET in the reaction of lithium 2-propanethiolate with **6** by trapping experiments using DCPH, similar trapping experiments were carried out using cyclizable alkyl bromide and tosylate probes with LiS-*i*-Pr in DMF (Table VI). Neither the formation of cyclic substitution product in reactions without any additive nor the formation of hydrocarbon products **8** and **9** in reactions carried out in the presence of 10 equiv of DCPH was observed for either substrate. Therefore, it appears that the reactions of LiS-*i*-Pr with alkyl bromides or alkyl tosylates in DMF are best described as proceeding by an S_N2 pathway. However, such results with the bromide all the more support a SET pathway for the corresponding iodide.

It is worth noting that the rate of reaction LiS-*i*-Pr with **6** in DMF as a function of leaving group is I ≫ Br > OTs. However, in HMPA the reaction of LiS-*i*-Pr with 2,2-dimethyl-1-halohexane showed the following order of reactivity: I ≳ Br ≫ OTS > Cl (Table VII). Therefore it is possible that a change of mechanism from SET to S_N2 is taking place between I and Br in DMF, whereas the same mechanistic change is taking place between Br and OTs in HMPA. Incidentally, Mosher and his co-workers[50]

(47) Hughes, D. L.; Bordwell, F. G. *J. Org. Chem.* **1981**, *46*, 3570.
(48) Ashby, E. C.; Su, W.-Y.; Pham, T. N. *Organometallics* **1985**, *4*, 1493.
(49) Alnajjar, M. S.; Kuivila, H. G. *J. Am. Chem. Soc.* **1985**, *107*, 416.

Table VI. Effect of Leaving Group on the Reaction of LiS-*i*-Pr with 2,2-Dimethyl-5-hexen-1-yl Halides in DMF[a]

expt	halide, X	additive (mol equiv)	time, h	yield, % starting material	7	8	9
6	I	none	1.0	2	95	0	0
7	I	DCPH (1)	1.0	0	98	<1	<1
9[b]	I	DCPH (10)	1.0	23	60	2	7
18[b]	Br	none	24.0	37	53	0	0
19[b]	Br	DCPH (10)	24.0	36	50	0	0
20[b]	OTs	none	72.0	81	14	0	0
21[b]	OTs	DCPH (10)	72.0	76	20	0	0

[a] All reactions were carried out at a reactant ratio of 1:1 and 0.10 M in each reactant if not stated otherwise. [b] Concentration of both reagents = 0.025 M, due to the solubility limit of DCPH in DMF solvent.

Table VII. Effect of Leaving Group in the Reaction of LiS-*i*-Pr with 2,2-Dimethyl-1-halohexane in HMPA at Room Temperature[a]

expt	halide, X	time, min	yield, % starting material	2,2-dimethylhexyl 2-propanethiolate
1	I	1.0	15	83
2	Br	1.0	17	82
3	OTs	60.0	18	81
4	Cl	60.0	50	45

[a] All reactions were carried out at a reactant ratio of 1:1 and 0.10 M in each reactant.

concluded that the reaction of neopentyl tosylate with HS^- in HMPA takes place via a S_N2 mechanism on the basis of the stereochemistry of the substitution product.

Conclusion

A variety of organic substrates possessing low reduction potentials and producing stable radical intermediates have been utilized in order to evaluate the one-electron transfer ability of lithium thiolates. Thus, direct spectroscopic detection of radical intermediates was made for reactions of lithium thiolates with diaryl ketones, polynuclear hydrocarbons, trityl halides, and 9-bromofluorene.

A mechanistic study concerning the reaction of lithium thiolates with trityl halides was conducted in more detail by (1) carrying out a complete identification of products, (2) studying the effect of the radical trap, DCPH, on product distribution, and (3) studying the effect of light and the presence of *p*-DNB on the reaction rate. Thus, reactions of lithium alkanethiolates with trityl halides produced α-substitution product (Ph_3CSR), and para-substitution product (p-$RSC_6H_4CHPh_2$), as well as radical byproducts such as reduction product (Ph_3CH), dimerization product of trityl radicals (p-$Ph_3CC_6H_4ChPh_2$), and dimerization product of thiyl radicals (RSSR), which suggests the occurrence of SET as the predominant pathway. The presence of DCPH in the reaction of alkanethiolates with trityl halides diverted the α-substitution product as well as radical byproducts to the formation of the reduction product (Ph_3CH), suggesting the formation of the α-substitution product as a result of nongeminate coupling of trityl and thiyl radicals. Carrying out the reaction of lithium 2-propanethiolate with trityl bromide in THF in the presence of light or absence of light or the presence of *p*-DNB did not affect the rate of reaction, thus suggesting the unlikelihood of a radical–radical anion chain process.

Studies concerning the reaction of lithium thiolates with the cyclizable alkyl iodide probe, 2,2-dimethyl-1-iodo-5-hexene, yielded straight chain substitution products quantitatively. However, the same reactions in the presence of the radical trap, DCPH, yielded up to 22% hydrocarbon products. These results are consistent with a SET pathway to describe this nucleophilic substitution reaction. No evidence supporting a SET pathway was observed for similar reactions involving alkyl bromides or tosylates.

Experimental Section

Materials and Apparatus. Solvent-grade pentane, hexane, benzene, and petroleum ether were stirred over concentrated H_2SO_4, washed with water, dried with anhydrous $MgSO_4$, and distilled from $NaAlH_4$ under nitrogen. Reagent-grade tetrahydrofuran (THF) was distilled under nitrogen from a deep purple solution of sodium benzophenone ketyl just prior to use. Hexamethylphosphoramide (HMPA) was distilled from sodium under reduced pressure. *N,N*-Dimethylformamide (DMF) was distilled from CaH_2 under nitrogen at reduced pressure. Samples of 1-heptene and *n*-decane were obtained with 99% purity from Aldrich and used without further purification. A 98% purity sample of 1,1,3-trimethylcyclopentane was purchase from Chemical Samples and used as received. Benzenethiol, *n*-butanethiol, and 2-propanethiol were obtained from Aldrich and distilled from CaH_2 under nitrogen. *n*-Butyllithium and methyllithium solutions were purchased from Foote Mineral Co. and used after standarization by Eastham–Watson titration.[51] Benzophenone was obtained from Aldrich and distilled under vacuum. Perylene, 2,3-benzanthracene, and benzo[*a*]pyrene were also obtained from Aldrich and used as received. Trityl bromide, trityl chloride, and 9-bromofluorene were obtained from Aldrich and recrystallized from a mixture of benzene–pentane. Phenyl disulfide and *n*-butyl disulfide were purchased from Aldrich and distilled under reduced pressure. 2-Propyl disulfide was prepared by the reaction of 2-propanethiolate with iodine.[52] 3-Carbamyl-2,2,5,5-tetramethylpyrrolidiene-1-oxyl was obtained from Alfa and used after purifiecation by vacuum sublimation.

Melting points were corrected. Proton NMR spectra were recorded with a Varian T-60 instrument or on a 300-MHz FT NMR with chemical shifts reported in δ units relative to tetramethylsilane. EPR spectra were recorded with a Varian E-109ES spectrometer. Mass spectral analyses were performed with a Varian MAT-112S spectrometer. Microanalyses of carbon and hydrogen were conducted by Atlantic Microlabs, Inc. of Atlanta, GA. Gas–liquid chromatographic (GLC) analyses were conducted on a Hewlett-Packard Model 700 instrument or on a Varian Model 3700 instrument equipped with an a automatic integrator and a flame ionization detector (FID) using packed columns. Preparative GLC separations were performed on a F&M Model 720 instrument equipped with a thermal conductivity detector (TCD).

Preparation of Lithium Thiolate Reagents. In general, lithium thiolate reagents were prepared by the slow addition of a solution of *n*-BuLi to a thiol solution (10% excess) in THF at 0 °C under nitrogen atmosphere. The mixture was allowed to react for 20 min with stirring and then allowed to warm to room temperature. After evaporation of all the volatile components under vacuum overnight, the resulting white solid material was stored in a glovebox equipped with a recirculating system using

(50) Stephenson, B.; Solladie, G.; Mosher, M. S. *J. Am. Chem. Soc.* **1972**, *94*, 4184.

(51) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, 165.

(52) Vogel, A. I. "Practical Organic Chemistry", 3rd ed.; 1952.

manganese oxide columns to remove oxygen and dry ice–acetone traps to remove solvent vapors. Lithium benzenthiolate was prepared by a similar procedure in hexane solvent and excess thiol was removed by washing with hexane. A small portion of lithium thiolate reagent dissolved in THF was tested with 2,2′-biquinoline (Eastham-Watson indicator)[51] to ensure the absence of *n*-BuLi in the reagent. Another small portion of lithium thiolate reagent was hydrolyzed, and the total base was determined by a standard acid–base titration to compare with the weight of the reagent. A solution of lithium thiolate reagent was prepared fresh before use by dissolving a weighed portion of the solid reagent, stored in a glovebox, in an appropriate solvent.

Preparation of Cyclizable Alkyl Halide Probes. The procedures for the preparation of 2,2-dimethyl-1-iodo-5-hexene, 1-bromo-2,2-dimethyl-5-hexene, 2,2-dimethyl-5-hexenyl tosylate 2,2-dimethyl-1-iodohexane, 1-bromo-2,2-dimethylhexane, 1-chloro-2,2-dimethylhexane, and 2,2-dimethyl-1-hexyltosylate have been described previously.[23]

General Procedures. All glassware and syringes were oven-dried at 150 °C for at least 2 h and cooled under a flow of nitrogen just prior to use.

Transfer of reagent solutions or solvents was performed with syringes equipped with stainless steel needles. A solution of reagent was prepared in a round-bottomed flask equipped with a T-bore stopcock attached to a 24/40 standard taper joint (allows nitrogen flush while reagents are being transferred through the stopcock by a syringe) and a Teflon-coated magnetic stirring bar. Reactions were conducted under a nitrogen atmosphere in Pyrex test tubes or round-bottomed flasks equipped with T-bore stopcocks. For an EPR study, a reaction was carried out in a quartz EPR tube equipped with a ground glass stopcock, a side arm for the purpose of nitrogen flush, and small reaction bulb attached to a side wall of the tube. The solution of a reagent and a substrate initially placed in a tube portion and a bulb portion, respectively, were combined just before the measurement of the EPR signal. The concentration of radical species was estimated by a comparison of the peak height of the first derivative EPR signal generated in the reaction being studied with the peak height of the signal obtained from a standard solution of 3-carbamyl-2,2,5,5-tetramethylpyrrolidine-1-oxyl.[53]

Reaction of Lithium 2-Propanethiolate with Trityl Halide (EPR Study). A solution of trityl chloride (0.1 M) and a solution of 2-propanethiolate (0.1 M) were prepared by dissolving a weighed amount of each compound into a calculated volume of THF. A 0.5-mL aliquot of the trityl chloride was syringed into an EPR tube and a corresponding aliquot of the thiolate was syringed into a side bulb of the EPR tube. After the EPR instrument was tuned, the reagents were mixed as quickly as possible, and the increase and decrease of the EPR signal was monitored at appropriate time intervals. A highly resolved EPR spectrum of the radical intermediate was also recorded. For the reaction of trityl bromide with lithium thiolate, an EPR tube was equipped with a side bulb and a 14/20 female taper joint equipped with a ground-glass stopcock. Because trityl bromide solution is unstable in a stainless steel needle of a syringe, instead of transferring solutions, a known amount of trityl bromide solid was placed in a side bulb and a solution of trityl bromide made directly inside of the EPR tube. The remaining procedure was the same as the case of trityl chloride.

Reaction of Lithium 2-Propanethiolate with Trityl Halide (Product Study). Trityl halide (2.0 mmol) was dissolved in 20 mL of THF in a 100-mL reaction flask, and then 20 mL of lithium 2-propanethiolate solution (0.1 mM) was added with stirring. After the reaction was complete, 20 mL of aqueous NH_4Cl solution was added, and the product mixture was worked up. An oily mixture was obtained by extraction with benzene followed by evaporation of the solvent. When the mixture was dissolved in cold petroleum ether, white crystals of *p*-$CPh_3C_6H_4CHPh_2$ separated and exhibited the following NMR spectrum after isolation: NMR (benzene-d_6) 5.55 (s, 1 H), 7.00–7.65 (m, 29 H); MS, *m/e* 486 (M^+); mp 227–228 °C (lit.[54] mp 226–227 °C). The solution in petroleum ether after filtration of *p*-$CPh_3C_6H_4CHPh_2$ was loaded on a 3 ft × 1 in. chromatographic column packed with neutral alumina (Brockman, activity I). A fractional elution with petroleum ether–benzene (2:1) solvent (each fraction was monitored by GLC using column A) yielded Ph_3CH: NMR ($CDCl_3$) 5.35 (s, 1 H), 7.00–7.40 (m, 15 H); ms, *m/e* 244 (M^+); mp, 92–93 °C (lit.[53] mp 93–94 °C). The next fractional elution with petroleum ether–benzene (1:2) solvent gave a partial separation of *p*-*i*-$PrSC_6H_4CHPh_2$ and Ph_3CS-*i*-Pr. Ph_2CS-*i*-Pr was isolated as a white crystalline solid by a repetitive elution of the fraction richer with Ph_3CS-*i*-Pr: NMR ($CDCl_3$) 0.97 (d, 6 H), 2.42 (heptet, 1 H), 7.00–7.60 (m, 15 H); ms, *m/e* 318 (M^+); mp 56.5–57.5 °C (lit.[55] mp 57–59 °C); all the properties agreed with those for Ph_3CS-*i*-Pr prepared independently by the reaction of 2-propanethiol with trityl chloride in refluxing pyridine.[55] An isomer, *p*-*i*-$PrSC_6H_4CHPh_2$, was also isolated but as a colorless oil by repetitive elution of the fractions richer with *p*-*i*-$PrSC_6H_4CHPh_2$: NMR ($CDCl_3$) 1.26 (d, 6 H), 3.22 (heptet, 1 H), 5.52 (s, 1 H), 7.00–7.60 (m, 15 H); MS, *m/e* 318 (M^+). Anal. Calcd for $C_{22}H_{22}S$: C, 82.97; H, 6.96. Found: C, 82.95; H, 6.93.

The yield of Ph_3CH was determined by GLC analysis using a 1 ft × $^1/_8$ in, 5% OV-101 column (column A) at 160 °C column temperature and 25 cm^3/min flow rate of nitrogen using dimesityl ketone as an internal standard. The mixture of Ph_3CS-*i*-Pr and *p*-*i*-$PrSC_6H_4CHPh_2$ was separated from other components by column chromatography as described above. From the weight of the mixture and the ratio of integration of each characteristic peak in the NMR spectrum of the mixture, the yield of each product was calculated. The yield of product, *p*-$CPh_3C_6H_4CHPh_2$ was determined by isolation.

The Effect of Light and the Presence of *p*-DNB on the Rate of Reaction of Lithium 2-Propanethiolate with Trityl Bromide. The study was performed by carrying out three sets of reactions. One set was carried out under normal laboratory light, another was carried out in a tube wrapped with aluminum foil, and the other was carried out in the presence of 5 mol % of *p*-DNB under laboratory light. Aliquots taken from each reaction at appropriate times were quenched with a mixture of MeOH + Et_3N, and the amount of unreacted trityl bromide was analyzed by GLC as trityl methyl ether using column A (135 °C column temperature, 10 cm^3/min flow rate). Mesityl phenyl ketone was used as an internal standard.

Reaction of Lithium Thiolate with Benzophenone. The product was analyzed by GLC using a 2 ft × $^1/_4$ in 10% Carbowax 20M on chromosorb G column (column B) at 150 °C column temperature and 50 cm^3/min flow rate of nitrogen with Ph_3CH as an internal standard.

Reaction of Lithium 2-Propanethiolate with 9-Bromofluorene. Among the products, fluorene and 9-fluorenyl 2-propyl sulfide were separated by HPLC using a Partisil M9 column, hexane + benzene (2:1) solvent, 45 mL/h flow rate, and exhibited the following. Fluorene: NMR (CCl_4) 3.87 (s, 2 H), 7.20–7.80 (m, 8 H); MS, *m/e* 166 (M^+); mp 116–117 °C; same physical properties compared to an authentic sample. 9-Fluorenyl 2-propyl sulfide: NMR ($CDCl_3$) 0.82 (d, 6 H), 2.43 (m, 1 H), 5.93 (s, 1 H), 7.20–7.80 (m, 8 H); MS, *m/e* 240 (M^+). 9,9′-Bifluorenyl was separated by trituration of the product mixture with cold pentane followed by filtration. The product exhibited the following: NMR (C_6D_6)[56] 4.66 (s, 2 H), 6.84–7.60 (m, 16 H); MS, *m/e* 330 (M^+); mp 247–248 °C dec (lit.[57] mp 246 °C dec).

Reaction of Lithium 2-Propanethiolate with 2,2-Dimethyl-1-halo-5-hexene. 2,2-Dimethyl-1-iodo-5-hexene (47.6 mg, 0.2 mmol) was dissolved in 1.0 mL of DMF in a Pyrex reaction tube, and 1.0 mL of lithium 2-propanethiolate solution (0.2 M) was added and mixed by shaking the reaction tube. After 1.0 h the total mixture or an aliquot was hydrolyzed with aqueous NH_4Cl followed by addition of an appropriate amount of internal standard and an equal volume of pentane. The organic layer was separated and washed with an equal volume of water repeatedly until the solvents used for the reactions could be removed. The washed organic layer was analyzed by quantitative GLC analysis,

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which was conducted using a response factor correction of the relative peak areas using internal standards. A 4 ft × $^1/_8$ in. 8% Apiezon L on Chromosorb P column (column C) was used for the analyses of 2,2-dimethyl-1-iodo-5-hexene, 2,2-dimethyl-1-iodohexane, 1-bromo-2,2-dimethyl-5-hexene, 1-bromo-2,2-dimethylhexane, 2,2-dimethyl-5-hexenyl 2-propyl sulfide, 2,2-dimethylhexyl 2-propyl sulfide, and *n*-butyl 2,2-dimethyl-5-hexenyl sulfide with *n*-decane as an internal standard at 95 °C column temperature and 18 psi of nitrogen flow pressure. Column C was also used for the analysis of 1-chloro-2,2-dimethylhexane with *n*-decane as an internal standard at 90 °C column temperature and 18 psi of nitrogen flow pressure. 2,2-Dimethyl-5-hexenyl phenyl sulfide was analyzed with column C with the use of *n*-dodecane as an internal standard at 110 °C column temperature and 40 psi. A 1.5 ft × $^1/_8$ in., 10% SE-30 column (column D) at 115 °C and 18 psi was used for analysis of 2,2-dimethyl-5-hexenyl tosylate and 2,2-dimethylhexyl tosylate with *p*-chlorobenzophenone as an internal standard. A 20 ft. × $^1/_8$ in, 8% Apiezon L on Chromosorb P column (column E) was used for the analysis of 5,5-dimethyl-1-hexene and 1,1,3-trimethylcyclopentane with 1-hexene as an internal standard at a column temperature of 65 °C and 40 psi of nitrogen flow pressure.

The retention time of 2,2-dimethyl-5-hexenyl 2-propyl sulfide and 2,2-dimethylhexyl 2-propyl sulfide were established from spectral data of pure materials isolated by preparative GLC using a 6 ft × $^1/_4$ in, 10% Apiezon L column (column F) with a column temperature of 140 °C and 50 cm^3/min helium flow rate. 2,2-Dimethyl-5-hexenyl 2-propyl sulfide: NMR ($CDCl_3$) 0.91 (s, 6 H), 1.25 (d, 6 H), 1.52–1.85 (m, 4 H), 2.40 (s, 2 H), 2.77 (m, 1 H), 4.73–5.25 (m, 3 H); MS, *m/e* 186 (M^+). Anal. Calcd for $C_{11}H_{22}S$: C, 70.88; H, 11.92. Found: C, 70.96; H, 17.95. 2,2-Dimethylhexyl 2-propyl sulfide: NMR ($CDCl_3$) 0.95 (s, 6 H), 1.25 (d, 6 H), 1.50–2.00 (m, 9 H), 2.42 (s, 2 H); MS, *m/e* 188 (M^+). Anal. Calcd for $C_{11}H_{24}S$: C, 70.12; H, 12.87. Found: C, 70.13; H, 12.88. 2,2-Dimethyl-5-hexenyl phenyl sulfide and *n*-butyl 2,2-dimethyl-5-hexenyl sulfide were also isolated by preparative GLC using column F at 150 °C. 2,2-Dimethyl-5-hexenyl phenyl sulfide: NMR ($CDCl_3$) 0.97 (s, 6 H), 1.27–1.60 (m, 4 H), 2.82 (s, 2 H), 4.77–6.13 (m, 3 H), 7.00–7.50 (m, 5 H); MS, *m/e* 220 (M^+). *n*-Butyl 2,2-dimethyl-5-hexenyl sulfide: NMR ($CDCl_3$) 0.97 (s, 6 H), 0.90–2.60 (m, 13 H), 2.43 (s, 2 H), 4.80–6.00 (m, 3 H); MS, *m/e* 200 (M^+). The retention time of 5,5-dimethyl-1-hexene was established by an authentic sample obtained by preparative GLC of a hydrolyzed sample of the corresponding Grignard reagent: NMR (CCl_4) 0.88 (s, 9 H), 1.05–2.33 (m, 4 H), 4.83–6.25 (m, 3 H); MS, *m/e* 112 (M^+). A sample of 1,1,3-trimethylcyclopentane was purchased from Chemical Samples with 98% purity and used to determine its retention time.

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Reductive, Radical-Induced Cyclizations of 5-Hexenals as a Biomimetic Model of the Chemistry of Secologanin Formation

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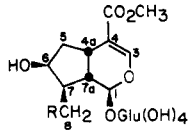
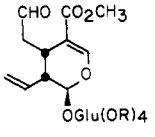
A model reaction for studying the mechanism of the biological conversion of the iridoid loganin (1) to the secoiridoid secologanin (2) is the reductive, radical-induced cyclization of secologanin tetraacetate (4) to loganin tetraacetate. Treatment of 4 with Mg and Me_3SiCl in THF at room temperature gives a mixture of the four possible C-6 and C-7 epimers of loganin tetraacetate in which the natural stereochemistry predominates. This result suggests that the biochemical event, which involves cleavage of the C-6 and C-7 bond of 1 in forming 2, may be a homolytic process that is initiated by formation of a carbon radical at C-8. The scope of the cyclization reaction, which formally occurred in a 5-hexenal moiety in 4, is defined by studies of the cyclization of six other δ,ε-unsaturated aldehydes. The results illustrate a new way for ring annulation through the reductive, radical-induced cyclization of δ,ε-unsaturated aldehydes.

The biosynthesis of many of the monoterpenoid indole alkaloids found in plants uses an amino acid and the cyclopentanomonoterpenoid ("iridoid"), loganin (1), in forming their principal structural framework.[1] Loganin first is converted to the secoiridoid secologanin (2), a key



1, R = H
3, R = OH



2, R = H
4, R = Ac

intermediate which then undergoes a biochemical Pictet–Spengler cyclization with an amino acid. Subsequent biochemical processing converts the secoiridoid moiety into a nine- or ten-carbon portion of the final alkaloid.

The mechanism of cleavage of the C-6/7 bond of 1 when it is converted to 2 is still obscure despite several studies of this process. It is known that cleavage occurs without loss of the hydrogen at positions 5, 6, and 7 of 1 in vivo.[2] This eliminates mechanisms involving oxidation of position 6 to a ketone or substitution at position 7. Battersby, Tietze, and their co-workers[3] have tested 8-hydroxyloganin (3), which was suggested by Battersby et al.[4] to be a likely

† In part.

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