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Contrasting Reactions of Ketones and Thioketones with Alkyllithiums: A Coordinated Experimental and Computational Investigation

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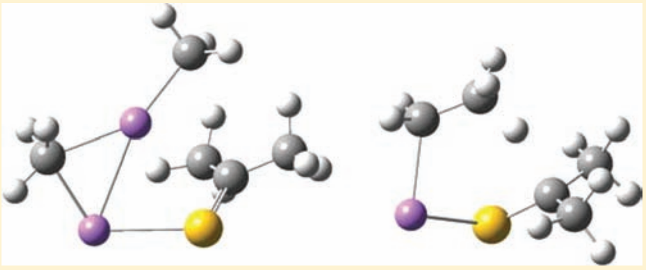
Supporting Information



ABSTRACT: The reaction of ketones with organolithium reagents generally proceeds by addition of the organometallic to the electrophilic carbon of the C═O group to give the lithium salt of a tertiary alcohol. The seemingly analogous reaction of thioketones with organolithiums is a fundamentally different process: such reactions typically afford a variety of products, and addition of the organolithium to carbon of the C═S group to give a thiol is a relatively unimportant component. Reactions of the stable thioketone, adamantanethione (**1**), with several alkyllithiums (MeLi, *n*-BuLi and *t*-BuLi) in a variety of solvents have been studied in the first comprehensive investigation of the reactions of organolithiums with a representative alkyl-substituted thione. Reactions of **1** with *n*-BuLi or *t*-BuLi afforded 2-adamantanethiol (**2**) as the major product. In an effort to explain the marked difference in behavior of ketones and thioketones in reactions with organolithiums, transition states for both the addition and reduction reactions have been located at the B3LYP/6-311+G* level using acetone and thioacetone as model substrates. The transition states for the addition of dimeric MeLi to the C═O and C═S carbons of acetone and thioacetone were significantly different as a result of the small bond angles preferred by divalent sulfur, and this accounts for the much slower addition to a C═S carbon vis-à-vis a C═O group. Transition states for reduction of acetone and thioacetone by EtLi were similar, but the greater exothermicity of the reduction of the thioketone results in an earlier transition state and lower activation energy for this process than that for the reduction of a ketone. The possible role of radical-mediated processes in this chemistry is also discussed.

INTRODUCTION

The addition of a main-group organometallic compound, such as a Grignard reagent or an organolithium, to a carbonyl group is arguably the most important method for formation of a carbon−carbon bond.[1] This fundamental reaction involves addition of the organometallic to the electrophilic carbon of the C═O group[2] which, in the case of an aldehyde or ketone, allows for the ready synthesis of secondary or tertiary alcohols. In striking contrast to the reactions of main-group organometallics with a carbonyl group, the seemingly analogous reaction of these reagents with a thioketone does not lead to a thiol by addition of the organometallic to the carbon of the C═S group; rather, the reaction of organolithiums or alkylmagnesium compounds with thioketones usually proceeds either by thiophilic addition to the sulfur atom of the C═S unit to give a sulfide or by reduction of the C═S group to give a thiol.[3]

The addition of main-group organometallics to aliphatic ketones has been investigated in detail.[1] Such reactions are generally considered to be ionic processes although radical intermediates, generated via SET, have been implicated in reactions involving some aromatic ketones. Somewhat surprisingly, the origin of the disparate behavior of thioketones when treated with a main-group organometallic remains poorly understood. Indeed, there are remarkably few reports of investigations of the reactions of main-group organometallics with thioketones.[4−11] This state of affairs is attributable largely to the fact that aliphatic thioketones are prone to fairly rapid oligomerization,[12] and those bearing α-hydrogens readily form the corresponding thioenols.[13] Consequently, the majority of the few mechanistic studies of the reaction of main-group organometallics with thioketones involved investigations of the behavior of aromatic substrates such as thiobenzophenone and related species.[5,9,11]

Several mechanistic scenarios, ranging from nucleophilic addition to the sulfur atom of a C═S group[5] to various free-radical mediated processes,[9,11] have been proposed to account for the outcome of the reactions of organolithiums or alkylmagnesium compounds with thioketones. Nonetheless, there is no consensus as to the etiology of the contrasting behavior of ketones and thioketones in their reactions with

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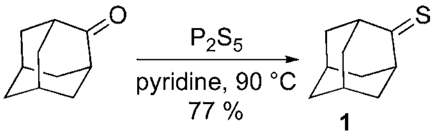
main-group organometallics. In an effort to more fully understand the strikingly different behavior of ketones, which add organolithiums to give tertiary alcohols, and thioketones, which are either reduced by organolithiums to afford secondary thiols or undergo thiophilic addition to deliver sulfides, we have investigated the reactions of a representative aliphatic thioketone, adamantanethione (**1**), with a selection of organolithiums and have explored both the addition reactions and the reduction reactions using computational methods.[14]

■ RESULTS AND DISCUSSION

Reactions of Adamantanethione with Organolithiums. Adamantantanethione (**1**) was readily prepared, as shown below, by treatment of adamantanone with phosphorus pentasulfide in pyridine as a solvent following the method of Greidanus.[15] This solid, orange, nonenolizable aliphatic thioketone is relatively stable but, as is the case with all thiones,[16] it is oxidized by molecular oxygen to the ketone. Precautions, such as storing **1** under an inert atmosphere and away from light, were taken to avoid such oxidation. However, a small amount (≤3%) of adamantanone was present in samples of **1** that were used in the studies described below. We were unaware of the rapidity of the oxidation at the inception of this study; consequently, the adamantanethione (**1**) used in initial studies contained more of the ketone (~3%) than did samples used in later studies (<~2%).



The reactions of representative alkyllithiums (MeLi, *n*-BuLi, and *t*-BuLi) with **1** were conducted under an atmosphere of argon at −78 °C by dropwise addition of the alkyllithium to 0.1 M solutions of **1** in the appropriate solvent (Et_2O, THF, or *n*-pentane). During the course of the reactions, typically 10 min at −78 °C, the orange color of the thione solutions faded. Reaction mixtures were then quenched with oxygen-free MeOH, and the crude product mixtures were analyzed by both capillary GC and by GC-MS, affording baseline separation of the products.

The reactions of adamantanethione (**1**) with MeLi afforded small quantities of 2-adamantanethiol (**2**), identified by comparison of its GC retention time and mass spectrum to that of an authentic sample,[17] and a novel product, 2-adamantylthio-2-methylthioadamantane (**3**), along with recovered **1**. Significantly, no product attributable to attack at the carbon atom of the C═S group was detected in any of the reactions. The results of these experiments are summarized in Table 1.

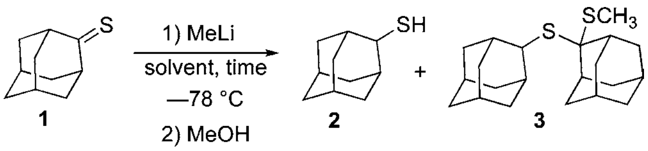
The major product of the reaction of **1** with MeLi in either Et_2O or THF as solvent was 2-adamantylthio-2-methylthioadamantane (**3**). Indeed, **3** was virtually the exclusive product of the reactions conducted in THF (Table 1, entries 3 and 4) and an analytical sample of **3** was prepared in this way. The reaction of MeLi with **1** in *n*-pentane was very slow; the majority of the reaction mixture consisted of unreacted starting material after a reaction time of 1 h (Table 1, entry 5). The formation of **3** is reminiscent of the generation of analogous compounds in the reactions of thiobenzophenone with main-group organometallics.[5] The mechanism illustrated in Scheme 1, analogous to one proposed by Beak and Worley in a similar context,[5] involving thiophilic addition of MeLi to the sulfur atom of the thione followed by a second addition of the same sort, nicely accounts for the generation of **3**.[18]

The presence of small quantities (2−4%) of 2-adamantanethiol (**2**) as a product of the reactions of **1** with MeLi was unexpected. Clearly, direct reduction of the thione by MeLi is implausible: the formation of **2** is likely due to reaction of **3** with MeLi. A separate experiment, involving addition of MeLi to a solution of **3** in Et_2O, revealed that MeLi reacts with **3**, albeit very slowly, to afford of **2**. A plausible mechanism that accounts for this reaction is illustrated in the Scheme 2.

The reactions of adamantanethione (**1**) with *n*-BuLi in Et_2O, THF, or *n*-pentane solution were also explored, and the results of these experiments are summarized in Table 2. Three products, 2-adamantanethiol (**2**), *n*-butyl-2-adamantyl sulfide (**4**), and 2-adamanthythio-2-butylthioadamantane (**5**), accounted for essentially the total material balance. Sulfide **4** was identified by comparison of its mass spectrum to that reported for this material[10,19] and the structure of **5** was assigned by analogy to that of compound **3** generated in the reaction of **1** with MeLi.

The reactions of **1** with *n*-BuLi in *n*-pentane as solvent (Table 2, entries 7 and 8) as well as those run in Et_2O solution (Table 2, entries 1−4) gave 2-adamantanethiol (**2**) as the major product along with smaller amounts of *n*-butyl-2-adamantyl

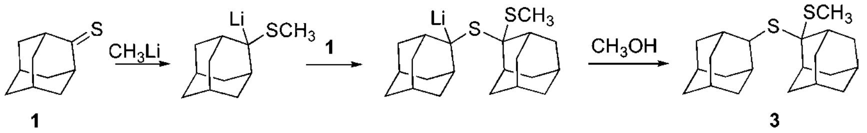
Table 1. Reactions of Adamantanethione (1) with MeLi



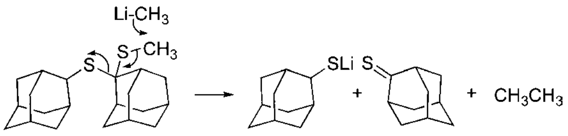
				products,[a,b] %		
entry	solvent	MeLi[c]	time (min)	1	2	3
1	Et_2O	1.1	10	21.5	3.0	75.5
2	Et_2O	1.5	60	10.3	3.2	86.5
3[d]	THF	1.1	10	5.3	1.5	92.3
4	THF	1.5	10	2.2	1.5	96.3
5[e]	$n\text{-}C_5H_{12}$	1.5	60	91.5	1.6	

[a] Yields were determined by capillary GC analysis of reaction mixtures. [b] A small quantity of adamantanone was detected due to inadvertent oxidation of unreacted **1** in the GC samples prior to analysis. [c] Molar equiv of MeLi. [d] The reaction mixture contained 0.6% and 0.3% of two unidentified compounds. [e] The reaction mixture contained 6.6% of an unidentified compound.

Scheme 1



Scheme 2



sulfide (**4**) and, in the case of reactions conducted in ether, some **5**. Compound **5**, presumably generated by initial attack of the organolithium on the sulfur atom of the C=S group followed by reaction of the sulfur-stabilized intermediate with **1** as found for the reactions of MeLi with the thione (Scheme 1), was the major product from reactions in THF (Table 2, entries 5 and 6). The reduction of **1** to thiol **2** almost certainly involves concomitant oxidation of *n*-BuLi to 1-butene via transfer of a *β*-hydrogen from the organometallic to the C=S group, a well characterized reaction,[9] but no effort was made to identify the 1-butene coproduct. The variation in the product ratios among reactions run in various solvents is likely related to the degree of aggregation of *n*-BuLi in the three solvents that were examined:[20] *n*-BuLi is a tetramer in Et_2O,[21] a temperature-dependent equilibrium of the dimer and tetramer in THF,[22] and a hexameric aggregate in hydrocarbons.[23] It should be noted that no product attributable to addition of *n*-BuLi to the carbon of the C=S unit was detected in any of these experiments.[24]

The outcome of reactions of adamantanethione (**1**) with *t*-BuLi, summarized in Table 3, were similar to those of *n*-BuLi. The major product observed under all reaction conditions studied was 2-adamantanethiol (**2**); the balance of the product mixtures consisted of sulfide **6** generated by thiophilic addition to the sulfur atom of the C=S group. The slight variation in product ratios is attributable to dfferences in the aggregation state of *t*-BuLi in the various solvents: *t*-BuLi exists predominantly as a dimer in Et_2O,[25] a monomer in THF,[22] and a tetramer in pentane.[26]

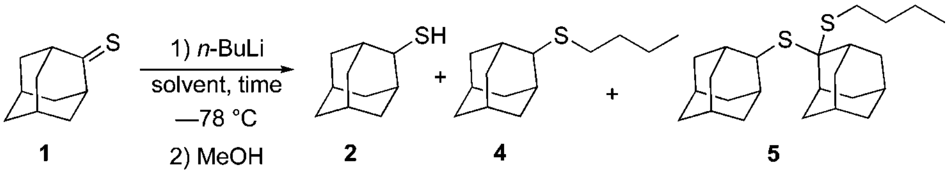
The results summarized above demonstrate that the reactions of organolithiums with ketones and thioketones proceed in fundamentally different ways. Whereas addition of the organolithium to the carbon of the C=O group is the major product in the reaction with ketones, reduction or thiophilic addition to the sulfur of the C=S group is the outcome of reactions with thiones. In an effort to understand these contrasting behaviors, the addition reactions and the reduction reactions were investigated using computational methods.

Computational Results. At the outset of the investigation, it was assumed that reactions of ketones and thioketones with organolithiums could be modeled as ionic processes. The possibility that reactions of thioketones are initiated by single-electron transfer is considered in the sequel.

Addition Reactions. The addition reactions were modeled using acetone and thioacetone as substrates and MeLi as the reagent. These reactions most likely involve alkyllithium aggregates.[27] Although it seems very unlikely that monomeric MeLi could participate in these processes, we studied its reactions in order to gain information on the relative reactivity of ketones and thioketones. In the gas phase, the reactions of polar molecules frequently involve formation of a prereaction complex that is stabilized by electrostatic effects. Therefore, the reactions were studied computationally in both the gas phase and in THF solution using the IEFPCM model in Gaussian.[28]

The intermediate complexes for the reaction of MeLi monomer with both acetone, to give the lithium salt of the tertiary alcohol, and thioacetone, to give the corresponding salt of the tertiary thiol, were readily located, and calculations were

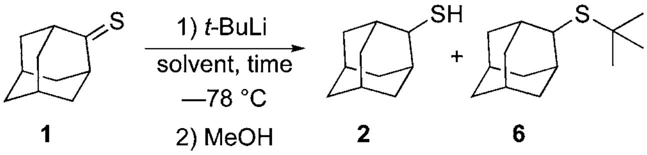
Table 2. Reactions of Adamantanethione (1) with *n*-BuLi



				products,[a,b] %			
entry	solvent	*n*-BuLi[c]	time (min)	1	2	4	5
1	Et_2O	1.1	10	7.7	70.8	17.5	4.0
2	Et_2O	1.5	10	3.3	70.0	13.0	13.7
3	Et_2O	1.5	20	4.2	80.9	11.9	3.0
4[d]	Et_2O	1.5	10	1.2	70.6	14.4	13.8
5	THF	1.1	10	5.1	33.4	13.7	47.8
6	THF	1.5	10	4.8	30.7	8.3	56.2
7	*n*-C_5H_{12}	1.1	10	2.7	88.5	8.8	
8	*n*-C_5H_{12}	1.5	10	1.3	90.8	7.9	

[a]Yields were determined by capillary GC analysis of reaction mixtures. [b]The reaction mixtures contained ~1.5% of 2-*n*-butyl-2-adamantanol generated by addition of *n*-BuLi to adamantanone present in the starting material. [c]Molar equiv of *n*-BuLi. [d]**1** was added to *n*-BuLi in Et_2O (reverse addition).

Table 3. Reactions of Adamantanethione (1) with *t*-BuLi



entry	solvent	*t*-BuLi[b]	time (min)	products,[a] %		
				1	2	6
1[c]	Et_2O	1.1	10	9.4	65.3	24.1
2	Et_2O	1.5	10	5.1	77.3	17.6
3	Et_2O	2.0	10	5.4	74.5	20.0
4	THF	1.1	10	16.0	63.8	20.2
5	THF	1.5	10	14.7	69.0	16.3
6[d]	n-C_5H_{12}	1.1	10	10.9	49.7	32.8
7[e]	n-C_5H_{12}	1.5	10	10.8	45.0	32.4

[a] Yields were determined by capillary GC analysis of reaction mixtures. [b] Molar equiv of *t*-BuLi. [c] The reaction mixture contained 1.3% of an unidentified compound. [d] The reaction mixture contained 6.4% of an unidentified compound. [e] The reaction mixture contained 3.9% and 7.8% of two unidentified compounds.

carried out at the B3LYP/6-311+G* level in which the distance between the CH_3 and the C═O or C═S carbon was reduced stepwise with optimization at each step. The highest energy species thus found were optimized to transition states both in the gas phase and in THF solution. The activation free energies were quite small ($\Delta G^{\ddagger}$ = 5.1 kcal/mol for acetone and $\Delta G^{\ddagger}$ = 4.1 kcal/mol for thioacetone; see Supporting Information) with thioacetone having the lower $\Delta G^{\ddagger}$. Because MeLi in solution reacted slowly with thioacetone and did not add to the carbon of the C═S (Table 1), the results of these calculations are not in accord with the experimental observations, showing that the reaction with monomeric MeLi is not a viable mode.

Given this result, the reactions of acetone and thioacetone with the dimer of MeLi were studied in a similar fashion starting with the initial complexes illustrated in Figure 1. The distance between one methyl group and the C═O or C═S carbon of the substrate was reduced in 0.1 Å steps with reoptimization at each step. It was found that the intermediate complexes unfolded, leading to the six-membered ring transition states that we previously found starting with a different initial premise.[14] These structures were optimized to the final transitions states, and they were found to have just one imaginary frequency. Using the frequency data determined at the B3LYP/6-311+G* level for all structures, the energies were corrected for the zero-point energies and for the changes in energy on going from 0 K to 298 K. The relative energies of the species involved in the reactions are summarized in Table 4; full data are available in the Supporting Information. In each case, the transition states were followed in the forward direction and were found to give the expected products.

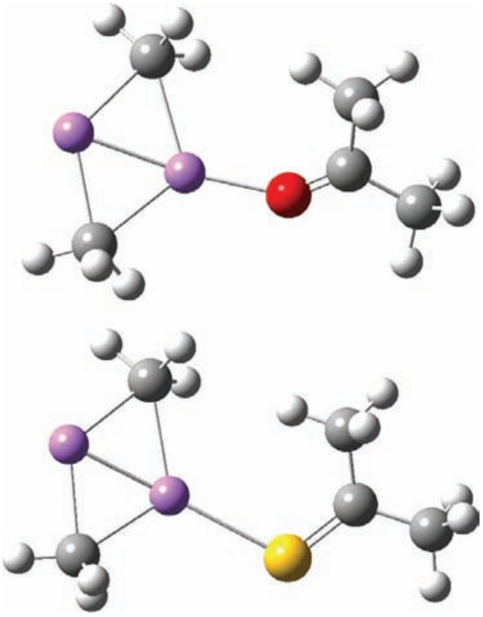


Figure 1. Initial complexes between dimeric MeLi and acetone (top structure) and thioacetone (bottom structure).

Table 4. B3LYP/6-311+G* Energies for the Addition of MeLi Dimer to Acetone and Thioacetone[a]

compound	gas phase		THF solution	
	ΔH	ΔG	ΔH	ΔG
acetone reactants	0.0	0.0	0.0	0.0
acetone initial complex	−13.2	−5.4	−4.7	5.5
acetone TS	−4.2	6.8	2.6	14.8
acetone products	−49.2	−36.8	−43.2	−29.7
thioacetone reactants	0.0	0.0	0.0	0.0
thioacetone initial complex	−7.7	1.2	−0.6	9.3
thioacetone TS	3.8	16.1	7.5	21.0
thioacetone products	−53.3	−41.0	−55.1	−39.2

[a] In kcal/mol; ΔH and ΔG values are corrected for both differences in ZPE and the change in enthalpy on going from 0 K (corresponding to the calculations) to 298 K.

The results of the calculations for the addition reactions of dimeric MeLi with both acetone and thioacetone are shown graphically in Figure 2. Addition to the carbonyl carbon of acetone involves a pronounced initial complex in the gas phase that disappears on going to THF solution; the initial complex in the analogous reaction with thioacetone has an energy near that of the reactants in the gas phase, but again, the energy increases on going to THF as the solvent.

Both of the addition reactions are found to be quite exothermic; $\Delta G°$ = −30 and −39 kcal/mol for the acetone and thioacetone reactions in THF, respectively: the computed

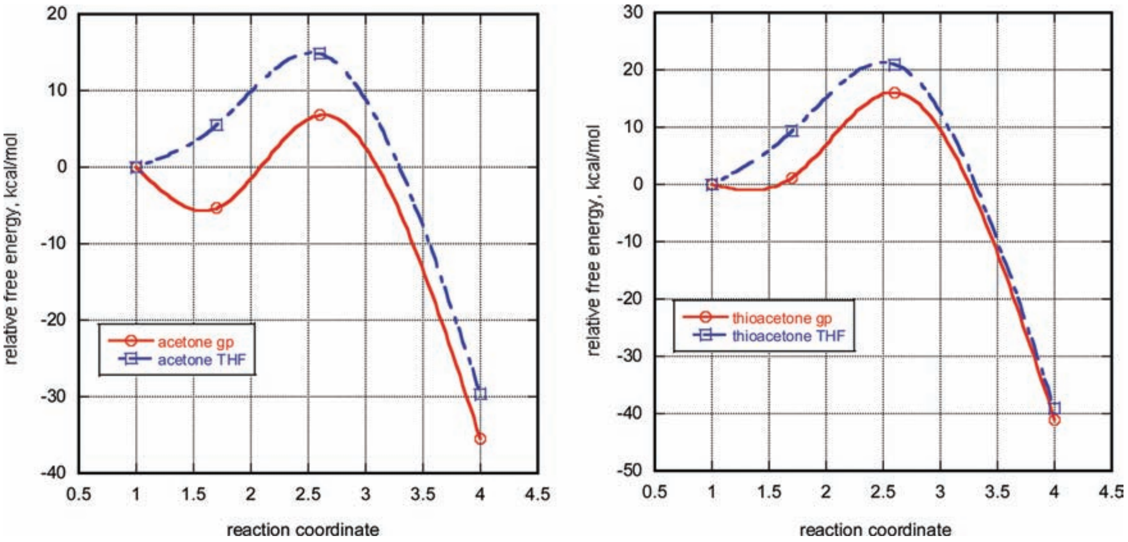


Figure 2. Comparison of the B3LYP/6-311+G* calculated free energy changes (ΔG) for reaction of dimeric MeLi with acetone (left graph) and thioacetone (right graph) in both the gas phase (gp) and in THF solution. The points on the plots are the relative free energies of the reactants, the initial complexes, and the products: the lines are drawn to connect these points and have no further significance. The intermediate complexes in THF were stationary points, and they must be preceded by a small transition state. This is of no consequence for the reaction and was not studied.

energy changes during the course of the reactions are illustrated in Figure 3. However, despite the fact that addition to thioacetone is a significantly more exothermic process than is the addition to acetone, the activation free energy ($\Delta G^{\ddagger}$) for the addition of dimeric MeLi in THF to acetone ($\Delta G^{\ddagger}$ = 15 kcal/mol) is some 6 kcal/mol lower than that for the analogous addition to the C═S compound ($\Delta G^{\ddagger}$ = 21 kcal/mol). This 6 kcal/mol difference in activation free energy (Figure 3) corresponds to a difference in relative rates for the additions of approximately 25 000 at room temperature. The computational result is consistent with the experimental observations presented above that, whereas addition of an organolithium to a ketone gives a high yield of the tertiary alcohol expected from addition to the carbonyl carbon, thioketones do not readily add main group organometallic reagents to the C═S carbon.

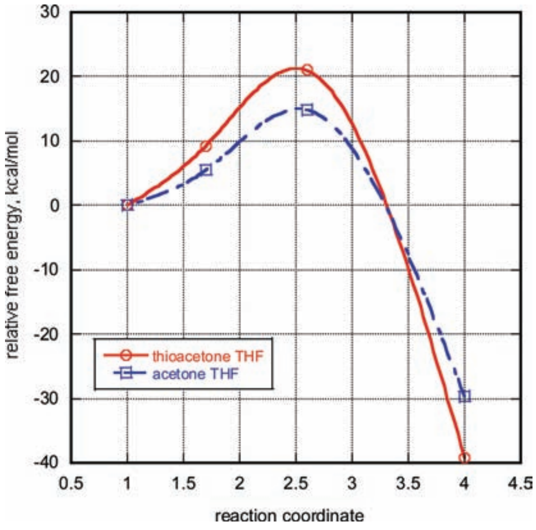


Figure 3. Comparison of the B3LYP/6-311+G* calculated free energy changes (ΔG) for reaction of dimeric MeLi with acetone (blue) and thioacetone (red) in THF solution. The points on the plots are the relative free energies of the reactants, the initial complexes, and the products: the lines are drawn to connect these points and have no further significance.

What then is the etiology of this effect? It has long been recognized that if two reactions proceed via a similar rate-determining step, the more exothermic reaction generally has the lower activation energy.[29] This is clearly not the situation for the reactions of MeLi with acetone and thioacetone (Figure 3): the more exothermic addition, that involving thioacetone, has the higher activation energy. The fact that the curves cross in Figure 3 suggests that there is some fundamental difference between the transition states for these two reactions; indeed, the calculations find just such a difference. An examination of the transition state structures for the additions to acetone and thioacetone, illustrated in Figure 4, demonstrates that the principal difference resides in the geometry about sulfur in the thioacetone transition state. The addition of dimeric MeLi to acetone leads to a transition state in which the carbonyl carbon of the acetone fragment is well aligned to accept the methyl group; the computed Li−O−C angle is 169.7°. However, in the transition state for addition to the C═S carbon of thioacetone, the analogous fragment is rotated, making it difficult to complete the transition; the Li−S−C angle is 110.2°. This result is, at least in part, a consequence of the well-known preference for divalent sulfur to favor relative small bond angles (e.g., the H−S−H angle in H_2S is 92°) whereas oxygen prefers larger angles (e.g., the H−O−H angle in H_2O is 105°).

Reduction Reactions. Reduction of the C═S group to give a thiol is the major outcome of reactions of adamantanethione (**1**) with either *n*-BuLi (Table 2) or *t*-BuLi (Table 3). In an effort to understand the origin of the facile reduction of thioketones, but not ketones, by main-group organometallics having a β-hydrogen, the reactions were modeled using acetone and thioacetone as substrates and monomeric EtLi as the reagent, which delivers a hydrogen to the C═O or C═S group with the formation of ethylene and the lithium salt of the alkoxide or thiol, in a fashion similar to that described above for the addition reactions. The EtLi was complexed to the heteroatom of the substrate, and the distance from the β-hydrogen of the reagent to the C═O or C═S

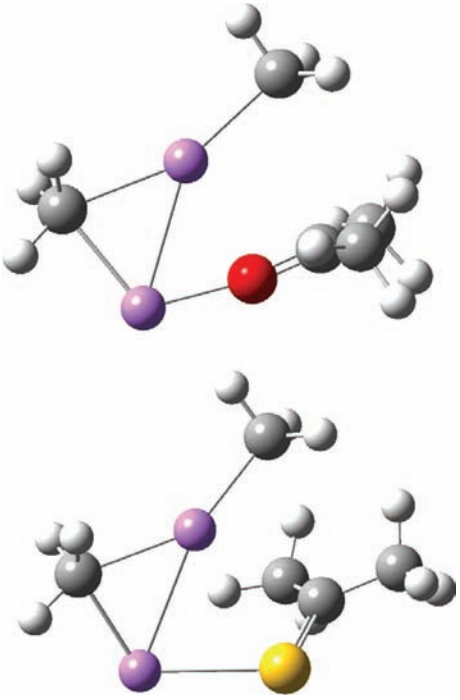


Figure 4. B3LYP/6-311+G*-calculated transition state structures for addition of dimeric MeLi to acetone (top structure) and thioacetone (bottom structure) in THF solution.

carbon of the substrate was reduced in 0.1 Å steps followed by geometry optimization at the HF/3-21G level. The highest energy structures were then optimized to a transition state at this level and in each case had one imaginary frequency. The resulting structures were reoptimized at the B3LYP/6-311+G* level in the gas phase and in THF as the solvent, frequencies were determined at this level, and free energies at 298 K were computed from these data. The calculated relative energies are summarized in Table 5, and the transition state structures are illustrated in Figure 5.

Table 5. B3LYP/6-311+G* Energies for the Reduction of Acetone and Thioacetone by Monomeric EtLi[a]

compound	gas phase		THF solution	
	ΔH	ΔG	ΔH	ΔG
acetone reactants	0.0	0.0	0.0	0.0
acetone initial complex	−18.9	−11.1	−5.0	3.2
acetone TS	−9.9	3.1	4.3	16.9
acetone products	−26.8	−24.8	−21.5	−22.9
thioacetone reactants	0.0	0.0	0.0	0.0
thioacetone initial complex	−13.7	−3.7	−1.3	7.5
thioacetone TS	−9.7	3.5	0.3	12.4
thioacetone products	−36.5	−34.0	−42.1	−40.6

[a] In kcal/mol; see footnote in Table 4.

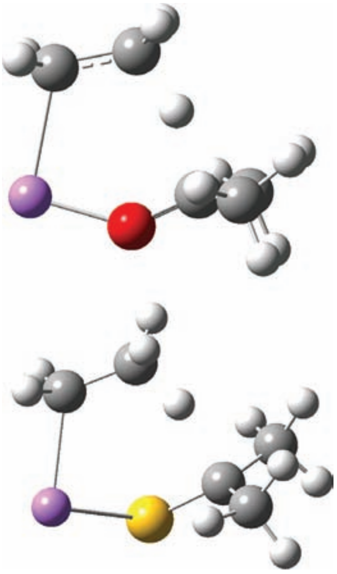


Figure 5. B3LYP/6-311+G*-calculated transition state structures for reduction of acetone (top structure) and thioacetone (bottom structure) by EtLi in THF solution.

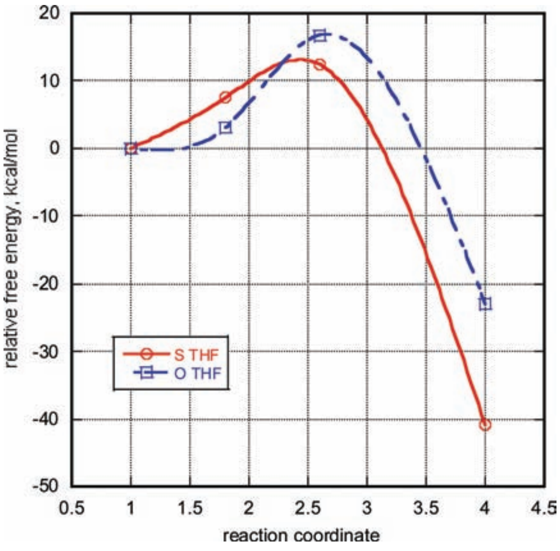


Figure 6. Comparison of the B3LYP/6-311+G*-calculated free energy changes (ΔG) for reduction of acetone (blue) and thioacetone (red) by EtLi in THF solution. The points on the plots are the relative free energies of the reactants, the initial complexes, and the products: the lines are drawn to connect these points and have no further significance.

The computed free energy changes during the course of the reductions in THF solution are shown graphically in Figure 6. Both reduction reactions are found to be exothermic; $\Delta G° =$ −23 and −41 kcal/mol for the acetone and thioacetone reactions, respectively. In contrast to the addition reactions discussed above, the reduction reactions conform to the Bell−Evans−Polanyi principle:[29] the more exothermic thioketone reduction has a lower activation energy ($\Delta G^{\ddagger} = 12.4$ kcal/mol) than does the less exothermic ketone reduction ($\Delta G^{\ddagger} \approx 17$ kcal/mol). This difference in activation free energy corresponds to a difference in relative rates for the reactions of approximately 2000 at room temperature favoring reduction of the thioketone, a result that is fully in harmony with the experimental observations.

The transition state structures displayed in Figure 5 reflect the energy differences illustrated in Figure 6: the reduction of thioacetone displays a less advanced transition state than does the reduction of acetone. The developing π-bond in the EtLi fragment that transfers a hydrogen is significantly shorter in the transition state for reduction of acetone (1.438 Å) than is the same distance in the transition state for reduction of thioacetone (1.474 Å). Similarly, the distance between the hydrogen being transferred and the *β*-carbon of the EtLi fragment from which it departs is longer in the acetone reduction (1.238 Å) than it is in the thioacetone reaction (1.150 Å).

In the case of the addition reactions discussed above, it became apparent that the smallest MeLi aggregate participating in the reaction would be the dimer. In the case of reduction using via hydrogen atom transfer from the *β*-carbon of EtLi, there seems to be less of a structural requirement for a second EtLi in forming the transition state. In order to check this, we have carried out a similar study using the dimer of EtLi as the reactant. The transition states thus located (see Supporting Information) had the second EtLi appended in a nonfunctional manner to the transition states shown in Figure 4 for reduction via the EtLi monomer; thioacetone was again calculated to be more reactive than acetone.

In short, these computational results provide a reasonable explanation of the difference in the outcome of reaction of alkyllithiums with acetone and thioacetone, and by extension, they elucidate the origin of the disparate behavior of other ketones and thiones in reactions with main-group organometallics.

Radical-Mediated Reactions. Thus far, only ionic processes have been considered in the computational investigation of the reactions of ketones and thioketones with alkyllithiums. However, there is good evidence that the reactions of thiobenzophenone and related substrates with alkyllithiums involve radical intermediates generated via SET.[11] Could such a mechanism also be involved in reactions of alkyl-substituted ketones?

It is difficult to construct a complete model that might be investigated computationally for such an SET-initiated process. Presumably, a reaction of this sort is initiated by transfer of a lithium atom from an organolithium aggregate to the thione substrate to generate a lithium ketyl and an electron-deficient aggregate residue. In order to simplify calculation of the relative energy changes that might be involved in the generation of the lithium ketyl, we have modeled this initial step by examining the addition of a lithium atom to ketone and thioketone substrates. Nonetheless, it must be remembered that the removal of a lithium atom from an alkyllithium aggregate is an endothermic process. Notwithstanding this caveat, the energy required to remove the lithium atom from a given aggregate will be a constant because the aggregate less one lithium atom might reasonably be independent of the carbonyl or thiocarbonyl compound to which it is transferred. In short, the relative energy changes accompanying addition of a lithium atom to ketones or thioketones provide the information needed to evaluate the probability of SET-initiated reactions of such substrates.

The energy changes attending addition of a lithium atom to representative ketones and thioketones to give the lithium ketyl were calculated at two theoretical levels in order to ensure that the results are reliable. They include the model chemistry CBS-QB3 and B3LYP/6-311+G* level, giving the results summarized in Table 6. For the gas phase, the CBS-QB3 results should be the more reliable; in any case, the ΔH values from the CBS-QB3 and B3LYP calculations are linearly related. All of these reactions are found to be quite exothermic (Table 6).

Table 6. Energy Changes Attending Addition of a Lithium Atom to Ketones and Thioketones[a]

	B3LYP/6-311+G*		CBS-QB3	
compound	ΔH	ΔG	ΔH	ΔG
acetone	−18.4	−11.8	−16.2	−8.6
adamantanone	−16.0	−8.4	−10.4	−3.9
benzophenone	−34.7	−27.6	−35.7	−28.7
thioacetone	−30.0	−22.6	−30.3	−22.5
adamantanethione	−38.0	−30.3	−31.1	−23.8
thiobenzophenone	−46.3	−37.6	−45.2	−38.7

[a] In kcal/mol at 298 K.

Not surprisingly, addition of a lithium atom to thiobenzophenone is the most exothermic reaction among the thioketones, and the corresponding reaction with benzophenone is the most exothermic among the ketones. Undoubtedly, this result is a consequence of resonance stabilization of the diaryl ketyls produced in these reactions. The substantial difference between the exothermicity of the addition of a lithium atom to acetone or adamantanone vis-à-vis benzophenone makes it very reasonable to conclude that dialkyl ketones react with main-group organometallics via ionic mechanisms whereas benzophenone, and similar substrates, may react via SET-initiated processes. The distinction among the thioketones is not as obvious as is the case with the ketones. However, the CBS-QB3 results indicate that reaction of thiobenzophenone with a lithium atom is some 15−16 kcal/mol more exothermic than the analogous reactions with acetone or adamantanethione. This result is consistent with the observation that reaction of diaryl thiones with main-group organometallics may be initiated by SET while dialkyl substrates likely react via ionic mechanisms as suggested by the results presented above.

CONCLUSIONS

The outcome of the reactions of alkyllithium reagents with adamantanethione (**1**) in a variety of solvents, detailed in Tables 1−3, represents the first comprehensive investigation, of which we are aware, involving organolithiums and a representative alkyl-substituted thione. The results presented above clearly demonstrate that ketones and thioketones react with organolithiums in fundamentally different ways: sterically unencumbered alkyllithiums react rapidly with ketones via addition to the carbonyl group; thioketones, in contrast, are either reduced upon reaction with simple alkyllithiums or undergo thiophilic addition of the alkyl group to the sulfur atom of the C═S unit. Indeed, no products attributable to addition of an alkyllithium to the carbon atom of the C═S group in **1** was observed in any of the experiments.

The addition reactions and the reduction reactions of ketones vis-à-vis thioketones with alkylithiums were modeled computationally as ionic processes using acetone and thioacetone as substrates. The results of these studies, which are in full agreement with the experimental results, indicate the following: (1) the failure to observe addition of an alkyllithium to the carbon atom of the C═S group is likely the consequence of a relatively high $\Delta G^{\ddagger}$ for the process caused by a transition state geometry that makes it difficult to transfer the alkyl group to the thiocarbonyl carbon; (2) the reduction of thioketones on reaction with alkyllithiums bearing a *β*-hydrogen is more facile than is reduction of a carbonyl group, and a six-membered transition state accounts nicely for the difference in rate of reduction of ketones and thioketones; (3) calculations that modeled SET-initiated reactions by investigation of the reaction of a lithium atom with representative ketones and thioketones suggest that, whereas the reactions of thiobenzophenone and related substrates with an alkyllithium may be initiated by SET, the analogous reactions of dialkyl thiones, such as **1**, likely involve ionic processes.

■ EXPERIMENTAL SECTION

General Procedures. Reactions involving alkyllithiums were performed in flame-dried glassware under an atmosphere of argon. Alkene-free *n*-pentane was purified by repeated washings of commercial technical grade pentane with concentrated sulfuric acid until the acid layer remained colorless, followed by washing with water and saturated sodium bicarbonate, drying over magnesium sulfate, and distillation from sodium/benzophenone/tetraethylene glycol. Et_2O and THF were freshly distilled from sodium/benzophenone. Commercial alkyllithium solutions were titrated prior to use with a standard solution of *sec*-butanol in xylene using 1,10-phenanthroline as the indicator, as described by Watson and Eastham.[30] Literature procedures were followed for the preparation of adamantanethione (**1**)[15] and 2-adamantanethiol (**2**).[17]

Product mixtures (Tables 1-3) were analyzed by GC on a 15-m × 0.25-mm × 1 μm MXT-200 capillary column using temperature programming (35 °C for 10 min, increasing 5 °C/min to 240 °C for 25 min) and by GC-MS on a 25-m × 0.2-mm × 0.33-μm HP-5 capillary column using temperature programming (100 °C for 2 min, increasing 10 °C/min to 250 °C for 20 min).

General Procedure for the Reactions of Adamantanethione (1) with Organolithiums. Approximately 0.1 M solutions of adamantanethione (**1**) in the appropriate dry and oxygen-free solvent (Et_2O, THF, or *n*-pentane; Tables 1−3) were cooled to −78 °C under an atmosphere of argon, 1.1 or 1.5 molar equiv of an organolithium solution (MeLi in Et_2O, *n*-BuLi in hexanes or *t*-BuLi in *n*-pentane) was added dropwise, and the resulting solutions were stirred for a period of time at −78 °C (specific conditions are given in Tables 1−3), during which time the orange color of the thione faded. The reactions were then quenched with methanol, the cooling bath was removed, and the reaction mixtures were allowed to warm to room temperature. The resulting solutions were washed with water and brine, dried ($MgSO_4$), and analyzed by GC and by GC-MS. In most cases, the products were identified by comparison of their GC retention times and mass spectra to those of authentic samples or by comparison of their mass spectra to those reported in the literature.[10,19] The structure of **3** obtained in reactions of **1** with MeLi (Table 1) was assigned on the basis of the spectroscopic data obtained from an analytical sample prepared as described below; the structure of **5** generated in reactions of **1** with *n*-BuLi was assigned by analogy to that of **3**.

2-Adamantylthio-2-methylthioadamantane (3). A solution of 833 mg (5.01 mmol) of adamantanethione (**1**) in 50 mL of dry, oxygen-free Et_2O was cooled to −78 °C under an atmosphere of argon, and 5.78 mL of a 1.57 M solution of MeLi (9.07 mmol) in Et_2O was added dropwise. The solution was stirred for 4 h at −78 °C, during which time the orange color of the thione faded, and 1 mL of methanol was then added to quench the reaction. The cooling bath was removed, the reaction mixture was stirred for an additional 15 min and then washed with water, brine, and 5% aqueous NaOH solution. The organic layer was dried ($MgSO_4$) and concentrated to afford a white paste that was recrystallized from ethanol−water to yield 423 mg (48%) of the title compound as a white solid: mp 87−92 °C; ^1H NMR ($CDCl_3$, 400 MHz) 3.26 (broad s, 1 H), 2.54 (t, 4 H), 2.11 (broad s, 1 H), 2.08 (broad s, 1 H), 2.00 (s, 3 H), 1.89−1.84 (m, 14 H), 1.73 (broad s, 2 H), 1.70 (broad s, 2 H), 1.63 (broad s, 2 H), 1.60 (broad s, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 71.7, 51.2, 39.4, 39.2, 37.8, 36.1, 35.8, 33.9, 33.8 (two carbons), 27.9, 27.6 (two carbons), 27.4, 11.2; GC-MS *m*/*z* (% relative intensity) 348 (1, M^+), 301 (78, $M^+ - SCH_3$), 181 (100, $M^+ - SC_{10}H_{15}$), 167 (14, $SC_{10}H_{15}$), 135 (68, $C_{10}H_{15}$), 91 (30), 79 (34), 67 (30); HRMS-ESI (*m*/*z*): [$M - SCH_3$] calcd for $C_{20}H_{29}S$, 301.1990; found, 301.2005.

Calculations. All of the ab initio calculations were carried out using Gaussian-09.[28]

■ ASSOCIATED CONTENT

Supporting Information

Complete ref 28, a summary of the calculations, including computed energies, imaginary frequencies for transition states, free energies in THF solution, and computed atomic coordinates for transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.

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