Solvent-Dependent Substrate Reduction by {Sm[N(SiMe$_3$)$_2$]$_2$(THF)$_2$}. An Alternative Approach for Accelerating the Rate of Substrate Reduction by Sm(II)

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S Supporting Information

ABSTRACT: The impact of solvent on electron transfer from Sm(II) to substrates was measured by determining the rate of reduction of 1-bromo-, 1-chlorododecane, and 3-pentanone in THF and hexanes using the highly soluble reductant {Sm[N(SiMe$_3$)$_2$]$_2$(THF)$_2$}. Rates were found to be 3 orders of magnitude faster in hexanes than THF, and reductions of alkyl halides were inverse first order in THF. These findings show the solvent milieu significantly impacts the rate of substrate reduction, a consideration that may prove useful in synthesis.

$k_{\text{(THF)}}$ = 0.35 M^{-1} s^{-1}
$k_{\text{(hexanes)}}$ = 540 M^{-1} s^{-1}
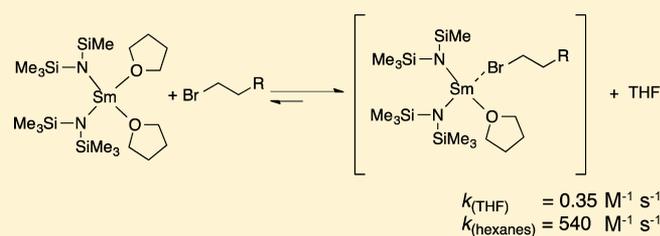
Samarium(II)-based reductants have become important reagents in organic synthesis due to their ability to initiate a wide variety of reductions and bond-forming reactions that proceed through radical and anionic intermediates.[1−5] The most commonly utilized Sm(II)-based reductant is samarium diiodide (SmI$_2$). In part, the utility of SmI$_2$ is a consequence of its straightforward preparation and storage in tetrahydrofuran (THF) under an inert atmosphere.[6,7] One important feature of reactions employing SmI$_2$ is the addition of oxygen-containing Lewis bases (predominantly HMPA) or proton donors (alcohols, glycols, and water) that compete with bound solvent (THF) for coordination to the oxophilic Sm(II) center, significantly altering the reactivity and selectivity of the reagent.[8,9] Although additives can impact the reactivity of the reagent through the production of a thermodynamically more powerful reductant[10−12] or through the stabilization of Sm(III),[13] the key feature in many of these processes is the displacement of THF or iodide ligands creating open sites for substrate coordination.[14] Given the oxophilicity of the reagent, and the importance of oxygen donor molecules in facilitating reactions of SmI$_2$, several questions come to mind: (1) Do coordinating oxygen-containing solvents inhibit substrate access to the metal? (2) Does dissolution of a Sm(II)-based reagent in a nondonor solvent facilitate electron transfer? (3) If so, can this be used as a means to accelerate substrate reduction without the use of additives? Herein, we describe initial studies designed to answer these questions and examine the role of donor solvents and alternative means of accelerating the rate of substrate reduction by Sm(II)-based reagents.

To effectively study the questions above, it is important to identify a reductant that is soluble in a range of solvents. Although SmI$_2$ is soluble in a small range of electron-donor solvents including THF, acetonitrile, and dimethoxyethane, it is not soluble in noncoordinating solvents.[15] After examining a number

of possible reagents, {Sm[N(SiMe$_3$)$_2$]$_2$(THF)$_2$} was chosen. The reagent, first introduced by Evans,[16] is well-characterized, has been used in a number of important synthetic transformations,[17−19] and most significantly, is soluble in a range of solvents from THF to hexanes. In addition, recent work by Hilmersson has shown that choice of solvent is important in the reductive cleavage of alkyl fluorides by {Sm[N(SiMe$_3$)$_2$]$_2$(THF)$_2$}, supporting an inhibitory role for THF.[20]

To study the reaction, {Sm[N(SiMe$_3$)$_2$]$_2$(THF)$_2$} was synthesized from SmI$_2$ and the sodium salt of N(SiMe$_3$)$_2$ in THF using the method developed by Evans.[16] The precipitated NaI was removed by dissolution of the reductant in hexanes and filtering. This procedure was repeated until no further precipitate was observed. Next, the UV−vis spectrum of {Sm[N(SiMe$_3$)$_2$]$_2$(THF)$_2$} was obtained in THF and hexanes to identify absorption bands appropriate for rate studies. Stopped-flow rate studies were carried out for the reduction of 1-bromododecane, 1-chlorododecane, and 3-pentanone in THF and hexanes. These substrates were chosen because these functional groups are employed in Sm(II)-based reductions, and in at least two cases, the rates of reaction in both solvents were within the window accessible for stopped-flow rate measurements. All reactions were approximately first order in reductant and alkyl halide, whereas reduction of 3-pentanone was second order in substrate. The results are consistent with rate-limiting cleavage of the carbon-halide bond in the reduction of alkyl halides[21] and the rate-limiting coupling of ketyls in pinacol formation from initial reduction of 3-pentanone.[22] Rate constants for the reduction in both solvents are displayed in Table 1.

Table 1. Rate Constants for the Reduction of 1-Bromododecane, 1-Chlorododecane, and 3-Pentanone in THF and Hexanes

substrate	rate constant (THF)[a] (M^{-1} s^{-1})	rate constant (hexanes)[b] (M^{-1} s^{-1})
1-bromododecane[c]	0.35 ± 0.03	540 ± 37
1-chlorododecane[c]	1.8 ± 0.4 × 10^{-3}	9.4 ± 0.2
3-pentanone[d]	26.0 ± 0.1	>10^4

[a]Determined by monitoring the decay of absorption at 400 nm. [b]Determined by monitoring the decay of absorption at 470 nm. [c]Reaction monitored at 15 °C. [d]Reaction monitored at 5 °C.

Examination of the rate constants shows that in the case of the alkyl halides, reductions in hexanes are 3 orders of magnitude faster than in THF. While the reduction of 3-pentanone in hexanes was too fast to measure since the majority of the reaction occurred in the mixing time of the stopped-flow experiment, the reaction was significantly faster in hexanes compared to THF. The fast rate of reduction of 3-pentanone is likely a consequence of the high affinity of the carbonyl oxygen for the oxophilic Sm. Overall, the most interesting finding is the large difference in rates of reduction between the coordinating THF, and the non-coordinating hexanes.

It is instructive to examine the rate enhancements for electron transfer from {Sm[N(SiMe$_3$)$_2$]$_2$(THF)$_2$} to substrates by changing from an electron donor solvent to a noncoordinating solvent and compare the impact of HMPA addition to SmI$_2$ in THF for similar substrates. Reductions of alkyl bromides and chlorides by SmI$_2$ and SmI$_2$−HMPA are too slow to measure by stopped-flow, but the impact of HMPA addition to SmI$_2$ on the rates of reduction of alkyl iodides are known.[23] Addition of HMPA to SmI$_2$ increases the rate of reduction of alkyl iodides by 3 orders of magnitude.[23] This rate increase is similar to that obtained for alkyl bromide or chloride reduction by {Sm[N(SiMe$_3$)$_2$]$_2$(THF)$_2$} upon changing solvent from THF to hexanes. Although the change in rate for the two systems is similar, the mechanistic basis must be different. In the SmI$_2$−HMPA system in THF, HMPA not only coordinates to Sm(II) altering its thermodynamic reducing ability, it also interacts with alkyl halide substrates to activate the carbon−halogen bond.[24] In an elegant study, Hoz found that the electrostatic attraction between ions generated by electron transfer from SmI$_2$ to a carbonyl was approximately 25 kcal/mol providing a significant part of the driving force for electron transfer.[25] If this phenomenon is operating in hexanes, this effect could be significantly larger due to diminished screening in the lower dielectric hexanes thus enhancing electron transfer relative to THF.

To obtain further insight into the reduction in both solvents, activation parameters were obtained in THF and hexanes for the reduction of 1-chlorododecane (Table 2). This substrate was chosen since data were readily attained over a range of temperatures in both solvents. Interestingly, there is a lower

Table 2. Summary of Activation Parameters[a] for the Reduction of 1-Chlorododecane in Hexanes and THF

solvent	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger b}$ (cal/mol*K)	$\Delta G^{\ddagger c}$ (kcal/mol)
hexanes	12.7 ± 0.5	−15 ± 2	17.3 ± 0.1
THF	6.7 ± 0.7	−51 ± 2	22.11 ± 0.01

[a]Activation parameters are the average of 3 independent experiments and are reported as ± σ. [b]Obtained from ln($k_{obs}h/kT$)= −$\Delta H^{\ddagger}$/RT + $\Delta S^{\ddagger}$/R. [c]Calculated from $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$.

degree of bond reorganization ($\Delta H^{\ddagger}$) and a higher degree of order ($\Delta S^{\ddagger}$) in the transition state for the reduction in THF compared to hexanes. Solvent polarity in conjunction with accessibility of substrate to the inner sphere of Sm(II) likely plays a role in the reduction. During cleavage of the alkyl chloride bond, charge is being created. In addition, solvent exchange in THF is likely to be rapid, whereas in hexanes, coordinated THF is likely to be more tightly bound to the oxophilic Sm.

The following question remains is: What is the basis for the deleterious effect of THF on the rate of substrate reduction? To probe the influence of THF on the reduction of an alkyl halide, a kinetic study was initiated to examine the role of THF concentration on the rate of reduction in hexanes. Figure 1
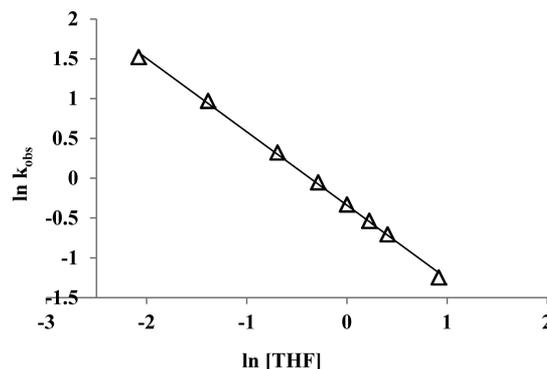
Figure 1. Plot of lnk_{obs} vs ln[THF] for the reduction of 1-bromododecane in hexanes by {Sm[N(SiMe$_3$)$_2$]$_2$(THF)$_2$} at 25 °C. [{Sm[N(SiMe$_3$)$_2$]$_2$(THF)$_2$}] = 5 mM, [1-bromododecane] = 50 mM, [THF] = 50−500 mM.

contains a plot of ln k_{obs} vs ln [THF] in hexanes for the reduction of 1-bromododecane. The rate decrease with increasing THF concentration is consistent with the involvement of THF in the rate-limiting step of reduction of 1-bromododecane. The rate order of −1.0 ± 0.1 obtained from the plot is consistent with 1 molecule of THF being displaced during substrate reduction. The mechanism for the reduction determined by varying the concentration of solvent, reductant, and substrate was found to be consistent with the rate law shown below in eq 1.

$$-d\{Sm[N(SiMe_3)_2]_2(THF)_2\}/dt$$
$$= k[\{Sm[N(SiMe_3)_2]_2(THF)_2\}][1\text{-bromododecane}]$$
$$[THF]^{-1} \qquad (1)$$
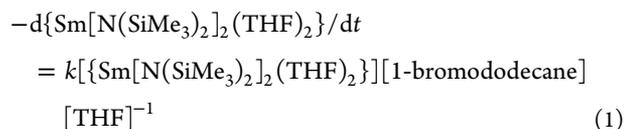
Since Sm is oxophilic, it is reasonable to expect THF to have a higher affinity for the metal than the alkyl bromide, thus impeding substrate access. This initial experiment shows that THF inhibits the reduction and is consistent with the mechanism shown in Scheme 1.

Overall, these studies show that changes in solvent can have a profound effect on Sm(II)-mediated reductions with changes of up to 3 orders of magnitude. The observed change in rates upon carrying out reductions in THF and hexanes are on the same order of magnitude for that obtained by the addition of HMPA in reductions of alkyl halides by SmI$_2$ in THF. We are presently examining a variety of functional groups and substrate structural features as well as a range of solvents to determine if this approach can be used as an alternative to the use of additives in Sm(II)-mediated reductions and bond-forming reactions. The results of this study will be reported in due course.

Scheme 1
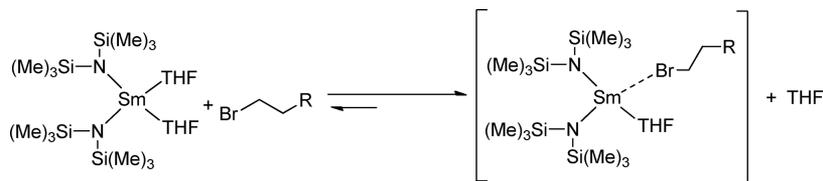
EXPERIMENTAL SECTION

Materials. The kinetic studies were carried out in dry hexanes and THF. Hexanes were prepared by distillation and stored over molecular sieves. THF was purified using an air-free solvent purification system. Samarium diiodide (SmI_2) was prepared by standard methods, and iodometric titration was employed to verify concentration prior to use.[6,7] $\{Sm[N(SiMe_3)_2]_2(THF)_2\}$ was prepared and purified by the method reported by Evans.[16] In all subsequent experiments KI-free $\{Sm[N-(SiMe_3)_2]_2(THF)_2\}$ was used as a free-flowing powder. Bromododecane and chlorododecane were purified using automated flash chromatography on prepacked silica gel columns with a gradient elution of ethyl acetate and hexanes. 3-Pentanone was used without further purification.

Kinetic Studies. Kinetic experiments were performed with a computer-controlled stopped-flow spectrophotometer. Substrates and $\{Sm[N(SiMe_3)_2]_2(THF)_2\}$ were taken separately in airtight syringes from a drybox and injected into the stopped-flow system. The cell box and the drive syringes of the stopped-flow reaction analyzer were flushed a minimum of five times with degassed solvents to make the system oxygen-free. The drive syringes were then primed with solvent and $\{Sm[N(SiMe_3)_2]_2(THF)_2\}$ (blank) to confirm the system was air-free and moisture-free and to verify the stability of $\{Sm[N(SiMe_3)_2]_2-(THF)_2\}$ under experimental conditions. 1-Bromododecane and 1-chlorododecane rate studies were performed at 15 °C, whereas 3-pentanone was performed at 5 °C. The concentrations of the substrates were kept high (50–300 mM) relative to $Sm(HMDS)_2THF_2$ concentrations to maintain pseudo-first-order conditions. Observed reaction rate constants were determined from exponential fitting of the decays of 5 mM $\{Sm[N(SiMe_3)_2]_2(THF)_2\}$ at 400 nm in THF and 470 nm in hexanes. Decays were obtained in the presence of increasing substrate concentrations to provide observed rate constants, which were then plotted against the substrate concentration, and the rate constant was determined from the slope of the plot. The rate order of $\{Sm[N(SiMe_3)_2]_2(THF)_2\}$ was determined using fractional times method. The THF addition study was performed by measuring reaction rates for reduction of 50 mM 1-bromododecane in solutions of increasing THF concentration (125 mM–2.5 M) Activation parameters were measured by varying the temperature from 5 to 30 °C with 75 mM 1-chlorododecane and 5 mM $\{Sm[N(SiMe_3)_2]_2(THF)_2\}$.

ASSOCIATED CONTENT

ⓢ Supporting Information

NMR spectra of products, UV–vis spectra of $\{Sm[N(SiMe_3)_2]_2-(THF)_2\}$ in THF and hexanes, decay traces, and plots of rate data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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DEDICATION

This work is dedicated to the memory of Dr. Masangu Shabangi (1965–2014), who provided seminal contributions on the mechanistic study of Sm(II) reagents.

REFERENCES

(1) Choquette, K. A.; Flowers, R. A. Sm and Yb Reagents. In *Comprehensive Organic Synthesis*, 2nd ed.; Molander, G. A., Knochel, P., Eds.; Elsevier: Oxford, 2014; Vol. *1*, pp 279–343.

(2) Szostak, M.; Fazakerley, N. J.; Parmar, D.; Procter, D. J. *Chem. Rev.* **2014**, *114*, 5959–6039.

(3) Szostak, M.; Spain, M.; Procter, D. J. *Chem. Soc. Rev.* **2013**, *42*, 9155–9183.

(4) Procter, D. J.; Flowers, R. A., I. I.; Skrydstrup, T. *Organic Synthesis using Samarium Diiodide: A Practical Guide*; RSC Publishing: Cambridge, 2010.

(5) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371–3404.

(6) Sadasivam, D. V.; Choquette, K. A.; Flowers, R. A., II. *J. Vis. Exp.* **2013**, *72*, e4323.

(7) Szostak, M.; Spain, M.; Procter, D. J. *J. Org. Chem.* **2012**, *77*, 3049–3059.

(8) Flowers, R. A., II. *Synlett* **2008**, 1427–1439.

(9) Dahlén, A.; Hilmersson, G. *Eur. J. Inorg. Chem.* **2004**, 3393–3403.

(10) Enemaerke, R. J.; Daasbjerg, K.; Skrydstrup, T. *Chem. Commun.* **1999**, 343–344.

(11) Shabangi, M.; Sealy, J. M.; Fuchs, J. R.; Flowers, R. A., II. *Tetrahedron Lett.* **1998**, *39*, 4429–4432.

(12) Shabangi, M.; Flowers, R. A., II. *Tetrahedron Lett.* **1997**, *38*, 1137–1140.

(13) Halder, S.; Hoz, S. *J. Org. Chem.* **2014**, *79*, 2682–2687.

(14) Prasad, E.; Knettle, B. W.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2004**, *126*, 6891–6894.

(15) Chopade, P.; Davis, T. A.; Prasad, E.; Flowers, R. A., II. *Org. Lett.* **2004**, *6*, 2685–2688.

(16) Evans, W. J.; Drummond, D. K.; Zhang, H.; Atwood, J. L. *Inorg. Chem.* **1988**, *27*, 575–579.

(17) Anker, T.; Fridén-Saxen, M.; Pemberton, N.; Seifert, T.; Grøtli, M.; Luthman, K.; Hilmersson, G. *Org. Lett.* **2010**, *12*, 2210–2213.

(18) Kim, M.; Knettle, B. W.; Dahlen, A.; Hilmersson, G.; Flowers, R. A., II. *Tetrahedron* **2003**, *59*, 10397–10402.

(19) Brady, E. D.; Clark, D. L.; Keogh, D. W.; Scott, B. L.; Watkin, J. G. *J. Am. Chem. Soc.* **2002**, *124*, 7007–7015.

(20) Janjetovic, M.; Träff, A. M.; Anker, T.; Wettergren, J.; Hilmersson, G. *Chem. Commun.* **2013**, *49*, 1826–1818.

(21) Miller, R. S.; Sealy, J. M.; Fuchs, J. R.; Shabangi, M.; Flowers, R. A., II *J. Am. Chem. Soc.* **2000**, *122*, 7718–7722.

(22) Farran, H.; Hoz, S. *Org. Lett.* **2008**, *10*, 865–867.

(23) Prasad, E.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2002**, *124*, 6895–6899.

(24) Choquette, K. A.; Sadasivam, D. V.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2010**, *132*, 17396–17398.

(25) Farran, H.; Hoz, S. *Org. Lett.* **2008**, *10*, 4875–4877.