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**Coordination-Induced O-H Bond Weakening in Sm(II)-
Water Complexes**

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C.O. Bartulovich,^a R.A. Flowers II^{*,a}

The combination of Sm(II)-based reductants with water provides reagent systems that promote a range of reductions and bond-forming reactions that are endergonic based on known redox potentials. Despite the utility of these reagent systems, little work has been done to elucidate the basis for this unusual reactivity. Herein we present recent work designed to explore the underlying mechanistic basis for the unexpected reactivity of the Sm(II)-water reducing system and demonstrate that O-H bond weakening induced by coordination of water to low valent samarium enables proton coupled electron transfer to substrates. We also demonstrate that coordination-induced bond weakening can be exploited and used to create extremely powerful reductants capable of reducing functional groups typically recalcitrant to reduction through single electron transfer alone.

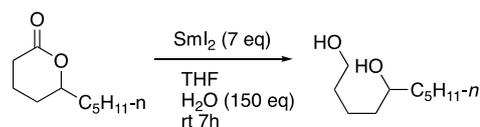
Introduction

Samarium diiodide (SmI₂) was first introduced to the synthetic community by Kagan and coworkers over 40 years ago and has been shown to be an extremely versatile single electron reductant capable of reducing a wide range of functional groups under mild reaction conditions.¹⁻³ Reactions using SmI₂ can be performed in several solvents but THF is typically the solvent of choice due to its limited solubility in other solvents. These reactions generally proceed rapidly at room temperature. Several classes of additives including Lewis bases, transition metal salts, and proton donors have been combined with SmI₂ and they effectively promote the reduction or reductive coupling of a wide range of functional groups including aldehydes, ketones, alkyl halides, alkenes, arenes, and carboxylic acid derivatives.⁴⁻⁸

Lewis bases including hexamethylphosphoramide (HMPA) and bis(trimethylsilyl)amide have been employed to accelerate reactions with Sm(II)-based reductants.^{9,10} In this class of reactions, Lewis bases act as ligands for Sm(II) and increase the rate of the electron transfer process by creating a stronger reductant and stabilizing the Sm(III) oxidation state.¹¹⁻¹³ Catalytic amounts of transition metal salts, most commonly those based on Ni(II) have been shown to increase the reactivity of Sm(II) mediated reactions and have been employed to accelerate the coupling of ketones and alkyl iodides. Recently however, it has been demonstrated that SmI₂ reduces Ni(II) to Ni(0), which is the active coupling reagent in solution.⁹ Proton donors are the most commonly used additives in Sm(II) chemistry with examples including alcohols, glycols, and water and have been shown to increase both the reactivity and selectivity when used in conjunction with Sm(II).^{6,14-20} The impact of proton donors are distinguished by those that form ground state complexes with Sm(II)

(glycols, water, methanol) and those that do not (*i*-propanol, *t*-butanol, trifluoroethanol).^{4,18,21-22}

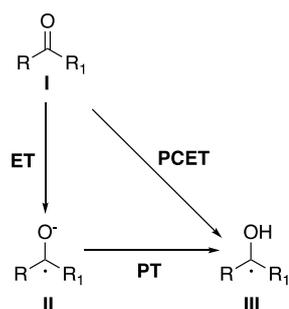
Among proton donors that coordinate to Sm(II), water is unique. One feature of this system that plays a role in its unusual reactivity is its unexpected stability. Strong reductants reduce water to hydrogen gas rapidly, yet in the case of SmI₂-H₂O this process occurs rather slowly. The combination of water and Sm(II)-based reagents enables highly selective reductions and reductive coupling reactions to be carried out with high efficiency.^{15,23-25} Another unique feature of the Sm(II)-water reagent combination is that it is capable of reducing substrates that are typically recalcitrant to reduction through electron transfer (ET). As an example, Scheme 1 shows the reduction of a lactone by SmI₂ in THF containing moderate amounts of water.²⁶ Since some reductions are significantly endergonic based on redox potentials, it raises the question: What is the mechanism of substrate reduction by Sm(II)-water?



Scheme 1: Example reaction of the reduction of a six-membered lactone mediated by SmI₂-H₂O.²⁶

The thermodynamic square scheme shown below (Scheme 2) demonstrates the mechanistic possibilities for the initial step in the reduction of a carbonyl. Reductions of carbonyls by SmI₂-water have been proposed to occur through successive ET-PT steps. A viable alternative is reduction through proton-coupled electron-transfer (PCET). It is a common misconception that stepwise

^a Department of Chemistry
 Lehigh University, Bethlehem, PA 18015 (USA)
 E-mail: rof2@lehigh.edu



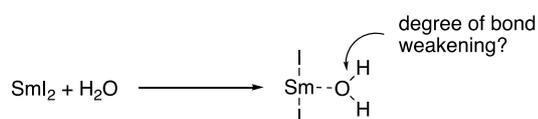
Scheme 2. Comparison of ET-PT vs. PCET.

transfers of an electron and proton are favored over PCET. Mayer has demonstrated that in many cases, the ΔG for PCET is lower than the ΔG for initial ET or PT.²⁷⁻²⁹ Another advantage of PCET from Sm(II)-water to carbonyls and other substrates is that it avoids the formation of high energy charge-separated intermediates such as ketyl radical anions. Herein, we present recent mechanistic work from our lab that demonstrates the generality of PCET from Sm(II)-water complexes and show that this formalism enables the design of reactions thought to be outside the range of Sm(II)-based reductions.

Discussion

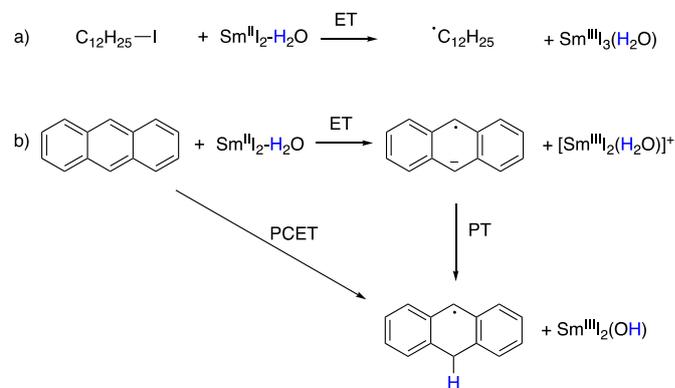
Curran and Hasegawa discovered that addition of water to SmI_2 accelerated the rate of functional group reduction and proposed that the effectiveness of the system was a consequence of water coordination to Sm(II).³⁰ This hypothesis was later confirmed through spectroscopic studies demonstrating a significant shift in the Sm(II) absorption in the UV-Vis spectrum upon the addition of water to a solution of SmI_2 in THF; a finding consistent with coordination. Initially, the basis for the increase in reactivity of SmI_2 -water was proposed to be a consequence of the creation of a stronger reductant.³¹ Although this supposition was supported by electrochemical experiments, work of Procter and others demonstrated the reduction of substrates by SmI_2 -water that are significantly endergonic based solely on initial ET.³² These findings raised the question: why does water coordination have such a large effect on reactions of SmI_2 and related reagents?

Weakening of the bonds of proton donors such as water and other ligands coordinated to low valent metals is referred to as coordination induced bond weakening and is a phenomenon that is well established in the literature. Bond weakening of O-H, N-H, and even C-H bonds have been observed with low valent metals such as titanium, zirconium, cobalt, nickel, and copper.³³⁻³⁹ Coordination of ligands to low valent metal complexes induces a weakening in proximal heteroatom-H and C-H bonds that enables formal hydrogen atom transfer through PCET. Based on the precedent from other systems, we sought to determine the degree of O-H bond-weakening upon coordination of water to Sm(II) and determine whether this phenomenon was responsible for the unique reactivity of the SmI_2 -water reagent system.



Scheme 3. O-H Bond Weakening upon water coordination to SmI_2 .

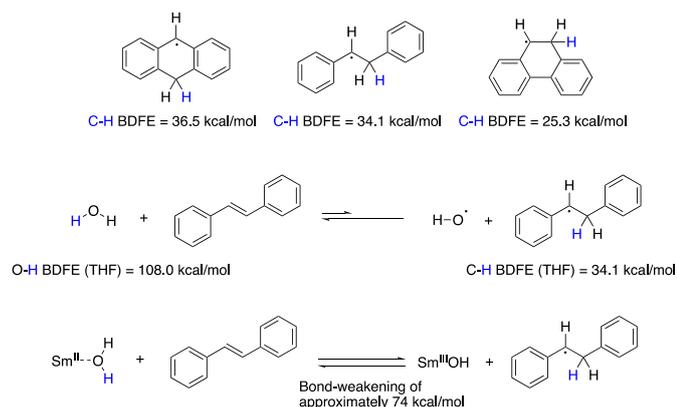
To fully examine the mechanism of SmI_2 -water reactions and determine the extent of coordination-induced bond weakening, the reduction of two non-coordinating substrates, 1-iodododecane and anthracene were examined (Scheme 4). Although both substrates



Scheme 4. Possible initial reduction steps in reactions of 1-iodododecane and anthracene with SmI_2 -water.

are reduced through outer-sphere ET, alkyl iodides are reduced through a rate-limiting dissociative ET whereas arenes can be reduced through a rate-limiting initial ET, or PT in the second step, or PCET. When the rate of reduction of both substrates was examined with SmI_2 in a series of experiments containing increasing amounts of water, anthracene was reduced substantially faster than 1-iodododecane.¹⁷ The reduction of anthracene through initial ET is a significantly more endergonic process than a primary iodoalkane based on standard redox potentials. As a consequence, this finding was inconsistent with rate-limiting reduction of the arene through initial ET. Further analysis of the system using D_2O to measure the deuterium isotope effect provided a $k_{\text{H}}/k_{\text{D}}$ of 1.7 consistent with PCET.¹⁷

With these studies establishing the likelihood of PCET, the next question addressed was the degree of O-H bond weakening upon coordination of water to SmI_2 . Thermochemical cycles are often used to estimate bond weakening. These estimates require the use of pKas and redox potentials that are often obtained in aqueous media. Since the majority of reactions of SmI_2 -water are carried out in THF, with water being a few percent of the milieu, we employed an alternative approach using a series of arenes that upon formal hydrogen atom transfer (HAT), form successively weaker C-H bonds in the resulting radical as shown below in Scheme 5.



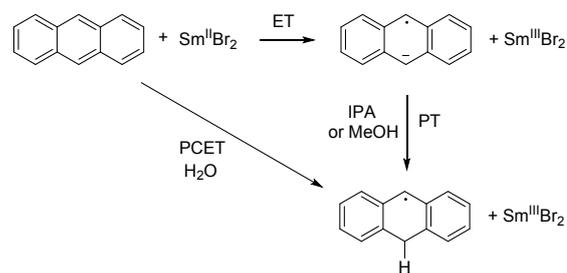
Scheme 5. Estimate of the Degree of O–H Bond-Weakening upon Coordination of Water to Sm^{II} in THF.

To test the limits of reduction, parent anthracene, *trans*-stilbene, and phenanthrene were reacted with SmI₂-water. Anthracene was completely reduced, *trans*-stilbene provided 50% reduced product, and phenanthrene was recovered unreacted.¹⁷ Using this approach enables *estimation* of the ability of SmI₂-water to function as a PCET donor and to determine the degree of O–H bond-weakening of water upon complexation to Sm. Concerted transfer of an electron and proton to substrate is thermodynamically equivalent to formal HAT between the same reactants. Using this formalism, the reaction can be regarded as one where water complexation to Sm(II) lowers the BDFE of the O–H of coordinated water enabling it to donate an H atom to the substrate. Subtraction of the O–H BDFE of *trans*-stilbene from that of water as shown in Scheme 5 provides a bond-weakening of approximately 74 kcal/mol rendering an estimated O–H BDFE for SmI₂-water of 34 kcal/mol.¹⁷ This estimate of bond-weakening is consistent with the value determined by Mayer and Kolmar employing thermochemical cycles but may be more relevant to synthetic systems in THF as opposed to values derived for an aqueous medium.¹⁴

Although SmI₂ is the most widely used reductant, other Sm(II) halides including SmBr₂ and SmCl₂ have been used in synthesis.^{40–42} The modest change of halide has a large impact on the reactivity of both reagents and the reductant that is formed *in situ*.⁴³ Water has been employed with SmBr₂ in a range of reductions including the reduction of amide-like carbonyls.⁴⁰ Given the unusual reactivity of the SmBr₂-water reagent, the system was characterized to determine whether reductions occurred through ET-PT or PCET.⁴³

To test and compare the limits of reduction, the arenes shown in Scheme 5 were reacted with the SmBr₂-water system. Anthracene was completely reduced, *trans*-stilbene provided 78% reduced product, and phenanthrene provided several percent of the reduced product.⁴³ Using the reduction of phenanthrene as the limit provides an estimated bond weakening of approximately 83 kcal/mol for the O–H bond of water complexed to SmBr₂. This is a substantial increase of 10 kcal/mol bond weakening compared to the SmI₂-water system. Further studies including conductance and Born-Oppenheimer molecular dynamics demonstrated that the difference in reactivity between the two complexes was a consequence of halide displacement.^{43–44} Addition of water to SmI₂ displaces the iodides to the outer sphere whereas bromide is less dissociated leading to a lower number of coordinated water molecules.^{43–45}

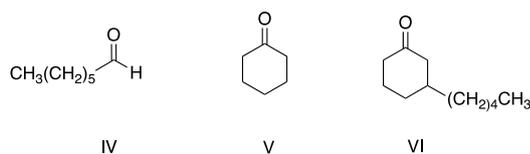
Since SmBr₂ is a stronger reductant, the increased bond weakening is unsurprising, but does not rule out sequential ET-PT as an energetically feasible pathway.^{7,46} To investigate this, the rates of reduction of anthracene by SmBr₂ using either water or two noncoordinating alcohols, ^{18,21} isopropanol (IPA) and methanol (MeOH) were compared. Both the SmBr₂-IPA and SmBr₂-MeOH systems were able to facilitate the reduction of anthracene. However kinetic studies showed that the reduction of anthracene by the SmBr₂-alcohol systems proceeded over two orders of magnitude slower than the reduction of anthracene by SmBr₂-water. The drastic difference in rates between strongly coordinating water and non-coordinating alcohols demonstrates the importance of coordination-induced bond weakening in substrate reduction through PCET. However, unlike the SmI₂-water system, this study demonstrated that SmBr₂ is a strong enough reductant to induce a sequential ET-PT in the presence of non-coordinating alcohols as shown in Scheme 6.



Scheme 6. Concerted and sequential pathways in the reduction of anthracene by SmBr₂ with both coordinating and noncoordinating additives.

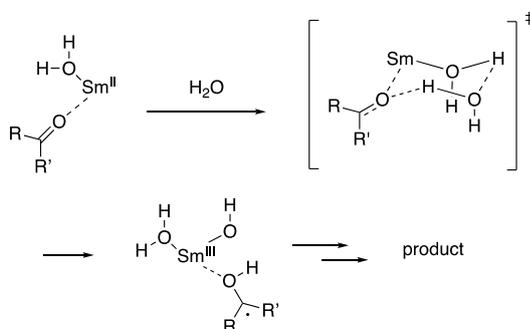
With these studies in hand, we next set out to examine the reduction of carbonyl containing substrates by SmI₂-water. Initial reduction of a carbonyl by SmI₂-water is the first step in a number of synthetic reactions and the mechanism is complicated by several factors. Although redox potentials demonstrate that the reductions of ketones by SmI₂ should be significantly endergonic, reductions proceed in some cases. Hoz has demonstrated that in the absence of proton donors, the reduction of activated benzophenone derivatives by SmI₂ is a consequence of strong Coulombic interaction between Sm(III) and the ketyl oxygen after ET.¹⁶ When water is employed, competitive coordination between carbonyl substrate and proton donor is likely to occur. Additionally, as increasing amounts of water are added to SmI₂ in THF, iodides are displaced to the outer sphere and as a result, the speciation is unclear.⁴⁵

Three classes of carbonyl-containing substrates shown below in Scheme 7 were initially examined. The rates of reduction of substrates **IV–VI** by SmI₂-water demonstrated that the reduction of these substrates occurred over a wide range of rates with **IV** reduced about two orders of magnitude faster than **V** and five orders of magnitude faster than **VI**. In spite of these large rate differences, the rate orders for Sm and substrate were near unity and water was approximately 2; findings consistent with identical mechanisms of reduction for each substrate.



Scheme 7. Model carbonyl substrates heptaldehyde (**IV**), cyclohexanone (**V**), and decanolide (**VI**).

Activation parameters determined for reduction of **IV-VI** by SmI_2 -water demonstrated that low enthalpies of activation were offset by substantial entropic costs in the transition state. Additionally, natural population analysis (NPA) of the charge on the carbonyl oxygen of **IV-VI** and the ketyl oxygen of the associated radical anions were determined. The change in charge upon ET determined by NPA demonstrated an excellent correlation with experimentally determined enthalpies of activation. This analysis is consistent with reduction occurring through a highly ordered transition state with the carbonyl and one or both waters coordinated to Sm as shown in Scheme 8.¹⁶



Scheme 8. Proposed transition state for carbonyl reduction.

Further studies on a series of aldehydes, ketones and structurally related variants containing a methyl group on the α -carbonyl of the carbonyl were examined. Rate studies on the reaction of substrates with SmI_2 -water showed that the rate of reaction increased as the concentration of water was increased until the coordination sphere of Sm(II) was saturated. Increasing the concentration of water beyond this point led to an inverse rate order for water. Carbonyl variants containing a methyl group adjacent to the carbonyl were reduced an order of magnitude slower than unsubstituted substrates. Furthermore, rates of reduction displayed an excellent correlation with the calculated bond dissociation free energies of the intermediate ketyl radicals. Taken together, these results established that the combination of water and substrate coordination to Sm(II) in THF provides an intermediate structure distinctively suited to PCET.⁵

Conclusions

In summary, the work described herein demonstrates that the reduction of both arenes,^{17,43} carbonyls,^{5,16} and related substrates¹⁴ by Sm(II)-water reagent systems occurs through PCET. Coordination of water to SmI_2 and SmBr_2 results in substantial weakening of the O-H bond of bound water by approximately 74 kcal/mol and 83 kcal/mol respectively.

Substrate reduction through PCET from Sm(II)-water bypasses the formation of high energy radical anions enabling the formation of extremely weak O-H and C-H bonds. It is our supposition that the concept of coordination induced bond weakening can be utilized to design extremely powerful reaction systems that facilitate PCET enabling the reduction of a variety of substrates that were thought to be outside the range of reduction by Sm(II)-reagents based on known redox potentials. In these cases the use of reagent and substrate redox potentials alone are not enough to predict the reducing power of Sm(II)- H_2O systems. The concept of coordination induced bond weakening is not limited to water. Secondary amides have been shown to exhibit significant N-H bond weakening upon coordination to Sm(II).⁴⁷ This finding demonstrates that this approach has the potential to be applied to a range of other ligands. A practical manifestation of this approach was recently used by Nishibayashi and coworkers who demonstrated that SmI_2 -water reduces nitrogen through molybdenum-catalyzed fixation.⁴⁸ Furthermore, these studies suggest that other Sm(II)-proton donor combinations should enable the reduction of substrates even more recalcitrant to reduction through SET alone. Several systems are currently being explored and the results will be reported in due course.

Conflicts of Interest

There are no conflicts to declare.

Acknowledgements

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Graphical Abstract

Coordination of water to low-valent Sm leads to O-H bond-weakening that enables PCET to substrates.

