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# The Interplay between Substrate and Proton Donor Coordination in Reductions of Carbonyls by SmI<sub>2</sub>-Water Through Proton-Coupled Electron-Transfer

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Supporting Information Placeholder

**ABSTRACT:** The reduction of a carbonyl by SmI<sub>2</sub>-water is the first step in a range of reactions of synthetic importance. Although the reduction is often proposed to proceed through an initial stepwise electron transfer-proton transfer (ET-PT), recent work has shown that carbonyls and related functional groups are likely reduced though proton-coupled electron-transfer (PCET). In the present work, the reduction of an activated ester, aldehyde, a linear and cyclic ketone and related sterically demanding carbonyls by SmI<sub>2</sub>-H<sub>2</sub>O was examined through a series of mechanistic experiments. Kinetic studies demonstrate that all substrates exhibit significant increases in the rate of reduction by SmI<sub>2</sub> as [H<sub>2</sub>O] is increased. Under identical conditions, ketones and an aldehyde containing a methyl adjacent to the carbonyl are reduced slower than an unsubstituted variant by an order of magnitude, demonstrating the importance of substrate coordination. In the case of unactivated substrates, rates of reduction show excellent correlation with the calculated BDFE of the O-H bond of the intermediate ketyl and the calculated free energy of intermediate ketyl radical anions derived from unhindered substrates; findings consistent with concerted PCET. Activated esters derived from methylbenzoate are likely reduced through stepwise or asynchronous PCET. Overall, this work demonstrates that the combination of the coordination of substrate and water to Sm(II) provides a configuration uniquely suited to a coupled electron and proton transfer process.

#### Introduction

Not long after Kagan introduced samarium diiodide (SmI2) to the synthetic community in the late 1970s<sup>1</sup>, the versatility of this unique reagent expanded considerably to provide a variety of reactions important in synthesis.<sup>2-6</sup> One means by which this is accomplished is through the addition of proton donors such as water and alcohols. Proton donors are the most widely-utilized additive class and enable the reduction of a wide array of functional groups<sup>2,3,7,8</sup> and mediate a range of carbon-carbon bond-forming reactions and reductive cyclizations, providing a useful tool for many total syntheses.<sup>9,10</sup> The rate, selectivity, and product distribution of many reactions can be effectively tuned by altering both the concentration and identity of the proton donor employed.<sup>11-15</sup> Understanding the underlying mechanisms that provide the basis for the tunable reactivity of SmI<sub>2</sub> containing different proton donors has presented a number of challenges, in part due to difficulties associated with direct observation of lanthanide-ligand interactions in solution. Because Sm<sup>II</sup> has a large coordination sphere and is highly reactive, it is difficult to directly characterize the interactions of additive, substrate, and solvent molecules coordinated to the metal. Although a highly useful synthetic reagent combination, the unique reactivity produced by SmI<sub>2</sub>-water has been particularly challenging to study, especially with regard to substrates containing coordinating functional groups like carbonyls.

Over the past thirty years, significant clues about the SmI<sub>2</sub>water reagent system have been revealed through synthetic and mechanistic studies. Kagan was the first to show that 2octanone could be effectively reduced to 2-octanol through the addition of water whereas methanol was ineffective as a proton source, suggesting a unique reactivity for the combination of SmI<sub>2</sub> and water.<sup>16</sup> More than a decade later, Curran showed that the addition of water to SmI2 accelerated the reduction of multiple functional groups, including the reduction of a ketone.<sup>7</sup> The versatility of functional group reductions by SmI<sub>2</sub>-water was further expanded by Kamochi to include aromatic carboxylic acids, esters, amides, nitriles, ketones, and nitro compounds.8 Since then, the scope of SmI<sub>2</sub>water reductions has grown significantly through the seminal work of Procter and Szostak to include lactones, Meldrum's acid, and carboxylic acid derivatives.<sup>17,18</sup> In fact, synthetic pathways have emerged that capitalize on the importance of Sm-carbonyl coordination to drive targeted reactivity by stabilizing intermediates<sup>19</sup> or to provide significant rate enhancements through coordination or chelation.<sup>20,21</sup>

An early kinetic study by our group focused on the reduction of acetophenone with varying proton donors and showed a substantial difference in rate enhancement from the addition of alcohols versus water at constant concentrations of proton donor. For alcohols, the difference in rate correlated well with  $pK_a$ , but water deviated significantly from this observed trend. Rate data combined with the observed shift in the visible absorption spectrum of SmI<sub>2</sub> upon addition of water was consistent with water having a high affinity for Sm(II).<sup>22</sup> A later study employing cyclic voltammetry revealed that coordination of water at high concentrations provides a thermodynamically more powerful reductant.<sup>23</sup> Despite the boost in redox potential that results from the addition of water, the reduction of unactivated ketones by SmI<sub>2</sub> is a significantly endergonic process by 40-50 kcal/mol.<sup>24,25</sup>

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To study the driving force for ketone reduction by  $SmI_2$  in the absence of proton donors, Hoz examined the reduction of a ctivated ketones. By measuring the rate of reduction of a series of *p*-substituted benzophenone derivatives, a linear Hammett correlation was observed. Even though electrochemical data demonstrated the endergonicity of the reactions, they occurred readily. Based on these findings, Hoz proposed that a strong Coulombic interaction between the ketyl radical anion and Sm(III) aids the reduction through an inner sphere electron transfer mechanism that contributes to the driving force of the reaction by up to 25 kcal/mol.<sup>26</sup>

Recent work in our group has focused on elucidating the role of water in SmI<sub>2</sub>-based reactions by examining the reduction of non-coordinating substrates, 1-iodododecane and anthracene. These substrates were chosen since 1iodododecane should be significantly easier to reduce through an electron transfer (ET) based on redox potentials. If the only role of water was to provide a more powerful reducing system, the rate of reduction of an iodoalkane by SmI<sub>2</sub>-water would be faster than anthracene. However, experiments demonstrated that anthracene was reduced significantly faster under identical conditions. Further thermochemical analysis revealed that SmI<sub>2</sub>-water led to appreciable weakening of the O-H bond as a consequence of coordination. Additionally, the work was consistent with a formal hydrogen atom transfer from SmI2water to anthracene through a proton coupled electron transfer (PCET).<sup>25</sup> Although the term PCET was originally defined to describe concerted transfer of an electron and proton, it has evolved to define both concerted and stepwise ET and PT processes.<sup>27</sup> Henceforth, we will use PCET as a general label and will use concerted proton-electron transfer (CPET) to define the transfer of an electron and proton in a concerted kinetic step.

39 In additional work, SmI<sub>2</sub>-mediated reductions of anthracene 40 and benzyl chloride were surveyed with a range of sterically-41 hindered and unhindered glycols and water. These studies 42 showed not only that proton donor coordination was a crucial prerequisite for reductions, but a significant amount of the 43 driving force was a consequence of coordination-induced 44 This activation process was further bond-weakening.<sup>28</sup> 45 demonstrated through the elegant work of Mayer who showed 46 that even electron-rich enamines can be efficiently reduced by 47 SmI<sub>2</sub>-water through CPET.<sup>29</sup> 48

With the importance of proton donor coordination established, 49 the reaction of SmI<sub>2</sub>-water with coordinating substrates was 50 examined. Reduction of a representative aldehyde, ketone, and 51 lactone revealed that reduction of coordinating substrates 52 proceeds through a rate-limiting formal hydrogen atom 53 transfer (HAT) from the SmI2-water complex. The data were 54 consistent with an asynchronous PCET mechanism for the initial step of the reduction of more easily-reduced carbonyl 55 substrates while the reduction of a lactone occurred through a 56 concerted PCET that bypasses the high-energy ketyl, 57

providing a pathway for reduction of the otherwise recalcitrant functional group. This subtle variation in the SmI<sub>2</sub>-waterinduced PCET mechanism in the reduction of model carbonyls suggests that there are nuances in the reactivity of SmI<sub>2</sub>-water, especially in the case of coordinating substrates.<sup>30</sup>

Despite progress made on our understanding of the foundations of SmI<sub>2</sub>-water reactivity with carbonyls, several fundamental questions remain. In the following study, the reductions of unactivated aldehyde and ketone substrates as well as activated esters were examined through kinetic and thermodynamic experiments with the goal of addressing the following questions: 1) What is the significance of carbonyl coordination to Sm(II) and how do steric factors impact reactivity? 2) Does the coordinate and promote reduction? 3) If substrate reduction occurs through PCET from SmI<sub>2</sub>-water, is the interaction between Sm(III) and ketyl intermediates important in subsequent steps?

#### Results and Discussion

#### I. Role of Coordinating Reaction Components

The relationship between substrate structure and coordination to SmI<sub>2</sub>-water was examined through kinetic experiments employing a range of substrates including a linear aldehyde (**A**), a sterically-hindered aldehyde (**B**), linear and sterically demanding ketones (**C** and **D**), and cyclic and 2-substituted cyclic ketones (**E** and **F**), a homobenzylic ketone (**G**), and a series of *p*-substituted methyl benzoates (**H**-X) as shown in Figure 1. The substrates chosen are representative of those that have synthetically relevant applications of the SmI<sub>2</sub>-water reagent system.<sup>7,8,18</sup>



Figure 1. Carbonyl-containing substrates examined in this work.

The first set of experiments were designed to examine the influence of increasing quantities of water over a large

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concentration range under identical conditions for all substrates. Rate studies on each substrate were carried out under pseudo first-order conditions with substrate in at least a ten-fold excess with respect to the concentration of SmI<sub>2</sub>. Water concentrations were examined over a range of 50 mM to 7 M. Figure 2 shows a comparison of the observed rates measured with increasing concentrations of water for substrates within a similar range (C, D, E, F, and G) with other substrates excluded for the sake of scaling (see Supporting Information, Figures S3, S17, and S50). Substrate **E** reduces significantly faster than the other ketone substrates examined. This is likely in part a consequence of the release of strain upon reduction.<sup>31</sup> Interestingly, the addition of a methyl group in the 2 position (F) significantly retards the rate of reduction, although it is still faster than the linear alkyl ketones. Comparisons of the water curves obtained for each substrate reveal a number of qualitative findings: 1) Despite differences in the concentration where the rate maxima are reached, all substrates showed saturation behavior. 2) For those substrates that demonstrate water saturation at lower concentrations such as C, an inverse order is observed for high concentrations of water, consistent with displacement of the proton donor being necessary for the substrate to coordinate to Sm. Overall, the collection of data demonstrates that in the absence of large differences in redox potential, steric factors play a significant role in the ease of substrate reduction.



Figure 2. Rates of reduction of ketones C-F in the presence of increasing [H<sub>2</sub>O]. Pseudo-1st order conditions with [H<sub>2</sub>O] (0 – 5 M) and constant [SmI<sub>2</sub>] (10 mM) and [substrate] (100 mM).  $\blacksquare$  = C,  $\blacklozenge$  = D,  $\blacklozenge$  = E,  $\blacktriangle$  = F,  $\blacktriangle$  = G.

The rate constants were determined for each of the substrates under identical conditions and are provided in Table 1. Rate constants were calculated up to a concentration of 1 M water since this is within the concentration range employed in the majority of carbonyl reductions by SmI<sub>2</sub>-water. The concentration of substrate was also fixed at 100 mM to ensure consistency between datasets. Each rate constant was determined thrice to examine reproducibility and is reported with the corresponding standard deviation.

While the rate orders described above for water are reported for conditions typically utilized in chemical reactions, there are cases where larger concentrations of water are used. Since the rate order of a coordinating component is dependent upon the concentration range being examined, great care should be taken in obtaining a rate order so that it accurately describes the synthetically-relevant conditions of the system under investigation. As is evident from Figure 2, the rate dependence

Table 1. Rate orders for substrate reduction by SmI<sub>2</sub>-water.

	Rate		Rate Orders		
Entry	Constant (M <sup>-3</sup> s <sup>-1</sup> ) <sup>a</sup>	k <sub>H</sub> /k <sub>D</sub> b	H <sub>2</sub> O <sup>c</sup>	Substrate <sup>d</sup>	SmI2 <sup>e</sup>
A	$4.2 \pm 0.3 \; x \; 10^4$	1.8	2	1.0	1
В	$5.6 \pm 0.4 \ x \ 10^3$	1.8	2	1.0	1
С	$28.5\pm4.3$	2.0	2	1.2	1
D	$8.47\pm0.9$	2.2	2	1.3	1
Е	$569\pm67$	2.3	2	1.4	1
F	$67.4\pm3.4$	2.0	2	1.4	1
G	$150\pm10$	1.8	2	1.5	1
н-н	$282\pm25$	1.7	2	0.9	1

<sup>a</sup> Computed from the rate law described by the reported integer orders in this table. <sup>b</sup>10 mM SmI<sub>2</sub>, 1 M H<sub>2</sub>O or D<sub>2</sub>O, and 100 mM **A-H-H** in THF. <sup>c</sup>Pseudo-1st order conditions with varying [H<sub>2</sub>O] (0 – 1 M) and constant [SmI<sub>2</sub>] (10 mM) and [substrate] (100mM).<sup>d</sup> Pseudo-1st order conditions computed for the order at 100 mM substrate from varying [substrate] (**A**: 100-160 mM, **B: 80-400 mM, C**: 80 mM-400 mM, **D**: 100 – 500 mM, **E**: 100-500 mM, **F**: 80-160 mM, **G**: 60-160 mM, **H-H**: 80-180 mM ) and constant [SmI<sub>2</sub>] (10 mM) and [H<sub>2</sub>O] (1 M). <sup>e</sup>Determined via fractional times method averaged over multiple trials.

of water decreases as the point of saturation is approached and the rate reaches an apex. Therefore, if the rates are measured over a range of concentrations and display nonlinear dependence, the rate order of the component (in this case water) can vary anywhere between two and zero and display fractional behavior between discrete integer order values. Typically, the rate order of a reaction component is found by plotting the log of the concentration versus the log of the observed rate over a range of concentrations with the slope of the resulting linear regression providing the rate order. In the present case however, this approach does not work and the order will vary depending on the concentration range chosen making it difficult to compare across data sets with different substrates.

To determine the order of a component of interest at a precise set of conditions that can be compared between datasets, the log-log plot of the data shown in Figure 2 can be fit to a second order polynomial equation. A second order polynomial fit is chosen for this system because the data shows two points of inflection and therefore this fit provides the greatest  $R^2$  with the minimum number of variables. For a linear log-log plot, the rate order is obtained from the slope of the line defined by the change in rate over the change in concentration. This same concept can be applied to a curved plot where the derivative of the polynomial equation provides an equation for the slope and thus can be used to obtain the rate order at a specific concentration of interest. Using this method, it is also possible to solve for the corresponding concentration where a reaction component provides an integer rate order as shown for the order of water in the reduction of E in Figure 3. Table 2 lists the concentrations where water is discretely second, first, and

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Figure 3. Rates of reduction of E in the presence of increasing  $[H_2O]$ . Pseudo-1st order conditions with  $[H_2O]$  (0 – 7 M) and constant  $[SmI_2]$  (10 mM) and [substrate] (100 mM).

**Table 2.** Corresponding concentrations for integer rate order values computed for water with varying ketone.

	Rate Order H <sub>2</sub> O		
Ketone	Second Order	First Order	Zero Order
	( <b>M</b> )	( <b>M</b> )	( <b>M</b> )
С	0.7	2.0	6.0
D	1.2	2.5	5.0
E	0.8	2.0	5.2
F	1.2	2.5	5.2

Conditions: Concentrations corresponding to each rate order were solved by taking the derivative of the polynomial line of best fit of the ln-ln plot and solving for the concentration at each integer rate order value with 100 mM substrate and 10 mM  $SmI_2$ .

zero order for each of the ketones studied using the derivativebased method described vide supra. The data demonstrates that the rate orders of substrates and water vary according to both concentration and steric effects. Although all substrates experienced a significant rate enhancement as the concentration of water increased, the degree to which each was affected and the point of saturation varied according to substrate structure.<sup>25</sup> As found in previous studies, the rate order of SmI<sub>2</sub> was 1. The rate orders of the substrates determined at a concentration of 100mM using the derivative method were close to unity, but several provided fractional values greater than 1, with the highest (C) displaying a rate order of 1.5. This finding is consistent with previous reports, which have shown highly variable or fractional orders of > 1or < 1 for substrate or proton donor, with a dependence on the concentrations of all of the coordinating components present in the reaction.22,32-35

To examine the impact of substrate coordination on rate, the

influence of substrate concentration at a constant [H<sub>2</sub>O] on the rate of reduction was probed. Substrate rate dependence was more difficult to study over a large range of concentrations because for multiple cases, the upper limit of rate measurable by stopped-flow was reached. In an attempt to provide consistency for the range of carbonyls studied, all rate experiments were carried out over a range of concentrations that included 0.1 M, the standard concentration of substrate employed for all other experiments. The data shows that substrates that contain substitution on the carbon  $\alpha$ -carbon (**D** and **F** in Figures 4C and 4D) tend to display smaller slopes and therefore a smaller dependence on substrate concentration over the range studied. This trend is indicative of more sterically-hindered substrates reaching coordinative saturation at higher concentrations of substrate than their unhindered counterparts.

Figure 4D shows a comparison of the rate dependence of substrate concentration for cyclic ketones **E** and **F**, and demonstrates the large inhibitory effect of a methyl adjacent to the carbonyl on the rate of reduction by Sm(II) at a constant [H<sub>2</sub>O]. The resulting difference in rate constant is approximately an order of magnitude, despite a negligible difference in the redox potential. Overall, these studies show the high degree of substrate concentration dependence on rate order with coordinating substrates.

One potential concern in working at higher substrate concentrations is the possibility of perturbing the redox potential of Sm(II). Many additives and ligands that coordinate to Sm(II) through oxygen display a concentration dependent impact on the redox potential of Sm(II).36 To test whether the coordination of additional carbonyl moieties to Sm(II) act as electron-donating ligands, the rate of reduction of C was measured in the presence and absence of 3phenylpropionate, an ester that is not reduced by SmI<sub>2</sub>-water. When introduced as an additive in the reduction of **C** by premixing with SmI<sub>2</sub>-water, the resulting exponential decay traces in the presence and absence of 10 equiv. of 3phenylpropionate showed complete overlay (see Supporting Information, Figure S72). This suggests not only that the coordination of carbonyl-containing substrates does not further enhance the reactivity of Sm(II) beyond ensuring the advantage of an inner-sphere reaction, but also that performing experiments under pseudo first-order conditions with high concentrations of substrate likely does not provide erroneous information about the nature of the carbonyl-Sm interaction by activating the metal through additional substrate coordination. This indirectly demonstrates that saturation of the Sm(II) coordination sphere by substrate does not boost the redox potential of the SmI<sub>2</sub>-water complex by an appreciable amount.

To further examine the interplay between substrate and water coordination to Sm(II), the influence of water on the rates of reduction at two different concentrations of substrate was compared to determine whether the saturation behavior of water remained consistent independent of substrate concentration. Compound **D** was chosen since it could be examined



**Figure 4A.** Pseudo-1st order conditions with [A] (0.08-0.16 M) =  $\blacktriangle$  and [B] (0.08-0.4 M) =  $\blacklozenge$  and constant [SmI<sub>2</sub>] (10 mM), and [H<sub>2</sub>O] (1 M). **4B.** Pseudo-1st order conditions with [C] (0.08-0.4 M) and constant [SmI<sub>2</sub>] (10 mM), and [H<sub>2</sub>O] (1 M). **4C.** Pseudo-1st order conditions with [D] (0.1-0.5 M) and constant [SmI<sub>2</sub>] (10 mM), and [H<sub>2</sub>O] **4D.** Pseudo-1st order conditions with varying [substrate] (0-1 M) and constant [SmI<sub>2</sub>] (10 mM), and [H<sub>2</sub>O] (1 M) E =  $\blacklozenge$  and F =  $\bigstar$ .

over the greatest concentration range within the limit of the stopped-flow technique employed. Figure 5 reveals that even at a five times higher concentration of substrate **D**, the impact of [H<sub>2</sub>O] remained consistent and clearly showed that the [H<sub>2</sub>O] at which the rate maximum is reached does not appear to shift with substrate concentration. If high concentrations of substrate saturate the coordination sphere and displace water, one would expect a shift in the concentration at which H<sub>2</sub>O saturation occurs. However, the data in Figure 5 demonstrates that even at high concentrations of coordinating substrate, H<sub>2</sub>O has a high enough affinity to compete with substrate for access to Sm(II).

To complete these studies, the kinetic isotope effect was obtained by measuring the rate of reduction with D<sub>2</sub>O in place of H<sub>2</sub>O over a large concentration range. An example for substrate **A** is shown in Figure 6. The  $k_{\rm H}/k_{\rm D}$  values for each substrate are provided in Table 1. In all cases, the  $k_{\rm H}/k_{\rm D}$  value is very close to 2 and remains consistent for each substrate across a large concentration range.



**Figure 5.** Pseudo-1st order conditions with varying [H<sub>2</sub>O] (0-7 M) and constant [SmI<sub>2</sub>] (10 mM), and [**D**]  $\blacklozenge$  = 100 mM and **E** = 500 mM.

A  $k_{\rm H}/k_{\rm D}$  value above unity is typically indicative of a primary isotope effect and is consistent with previous studies of similar systems.<sup>30,37</sup>



**Figure 6.** Pseudo-1st order conditions with varying concentration of  $H_2O$  ( $\blacktriangle$ ) or  $D_2O$  ( $\blacksquare$ ) from 0.5-3 M and constant [SmI<sub>2</sub>] (10 mM), and [A] (100 mM).

Taken together, these results suggest that a complex equilibrium is at play between coordination of water and substrate as illustrated in the model shown in Scheme 1. It is important to note that this model is a simplification and omits the possibility of bridging clusters that can potentially occur in aqueous systems. In all cases, the rate order of water was 2 at lower concentrations (Region 1). This corresponds to the water concentration range where iodide is liberated from Sm(II).38 We posit that coordination of two molecules of water are required to displace iodide and facilitate substrate coordination in addition to facilitating formal HAT. Above a concentration of 1 M, water continues to displace coordinated THF and rate orders approaching unity suggest that only one water is involved in the rate limiting step as exemplified by Region 2 in Scheme 1. At very high concentrations of water, the rate orders are zero or inverse first order (Region 3).<sup>39</sup> The latter observation is attributed to coordinative saturation of Sm by water. Recent elegant work of Maron has shown that at high [H<sub>2</sub>O], there are likely 8-9 molecules of water coordinated to the inner-sphere of Sm(II).40 Kinetic isotope studies replacing water with D<sub>2</sub>O revealed  $k_{\rm H}/k_{\rm D}$  values of 2, a finding consistent with transfer of hydrogen from Sm-bound water in the rate-limiting step of the reaction. Additionally, steric crowding adjacent to the carbonyl significantly reduced the rate of the reaction; a finding likely a consequence of hindered coordination between substrate and Sm. Finally, these experiments show that even at high concentration of substrate, water coordination is not disrupted.

II. Thermochemical Analysis of Substrate Reduction

The studies presented in the previous section describe experiments designed to examine the effects of substrate and water concentration on reactivity (rate) providing a structurereactivity relationship based on kinetics. To supplement these experiments, thermochemical studies were performed to determine the relationship between the rates of reaction and the thermodynamics of the bond cleavage and forming reactions that occur upon carbonyl reduction by SmI<sub>2</sub>-water.



Region 1: 0-1 M H<sub>2</sub>C





Region 3: > 5 M H<sub>2</sub>C



Activation parameters were obtained to reveal information about the rate-limiting activated complex and the data are displayed in Table 3. Generally, the reduction of carbonylcontaining substrates proceeds through a relatively early and highly-ordered transition state. For most of the substrates, a negative  $\Delta H^{\ddagger}$  was observed, due to the observed rate of reaction slowing with increasing temperature. Negative enthalpies of activation are relatively rare, but several examples are known and ascribed to the presence of low concentrations of

Table 3. Activation parameters for reduction by SmI<sub>2</sub>-water.

	Activation Parameters				
Entre	$\Delta H^{\ddagger}$ $\Delta S^{\ddagger}$		$\Delta G^{\ddagger}$		
Епту	(kcal mol <sup>-1</sup> ) <sup>a</sup>	(cal mol <sup>-1</sup> K <sup>-1</sup> ) <sup>a</sup>	(kcal mol <sup>-1</sup> ) <sup>b</sup>		
А	-6.1 ± 0.2	-72 ± 1	$15.3\pm0.1$		
В	$-5.0\pm0.2$	$-72 \pm 1$	$16.4\pm0.1$		
С	$1.8 \pm 1$	$-60 \pm 1$	$20\pm0.1$		
D	$-0.7 \pm 1$	$-70 \pm 2$	$20\pm0.1$		
Е	$-1.7\pm0.3$	-65 ± 1	$17.8\pm0.1$		
F	-1 ± 1	$-66 \pm 2$	$19\pm0.1$		
G	$2 \pm 1$	-55 ± 3	$18\pm0.1$		
н-н	-3.4 ± 1	-72.6 ± 3	$18.3\pm0.1$		

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Pseudo-1<sup>st</sup> order conditions of 10 mM SmI<sub>2</sub>, 1 M H<sub>2</sub>O, and 100 mM A-H. The activation parameters are the average of 3 independent experiments from 293-323 °K and are reported as  $\pm \sigma$ . <sup>a</sup>Obtained from  $\ln(k_{obs}h/k_bT)$ - $\Delta H^{\ddagger}/RT + \Delta S^{\ddagger}/R$ . <sup>b</sup>Calculated from  $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$  at 25°C.

intermediates that are enthalpically favored.<sup>41–44</sup> Within this study, most substrates display negative values for  $\Delta H^{\ddagger}$  that roughly follow the ease of reduction as measured by their redox potentials and ability to coordinate to Sm (based on steric considerations). Overall the results are consistent with a previous finding suggesting that carbonyl reduction is a consequence of the Coulombic interaction between oxygen and Sm allowing for an inner-sphere pathway.<sup>26,30,41</sup>

To further probe the thermochemical basis for the reactions, bond dissociation free energies (BDFE's) for the O-H bond of ketyls formed from HAT to substrates were estimated using DFT methods (see Supporting Information).<sup>45</sup> The BDFE values in THF are displayed below in Table 4. While these differences are small, these values follow a *general* trend where steric hindrance adjacent to the carbonyl leads to a slightly weaker O-H bond in the ketyl. Additionally, the substrates that are easiest to reduce have the largest BDFE's. The question that remains is: Is the strength of the O-H bond formed upon formal HAT from SmI<sub>2</sub>-water to aldehydes and ketones related to the driving force for reduction?

To further examine this supposition, we examined the relationship between rates of carbonyl reduction by SmI<sub>2</sub>-water and the O-H BDFE's of the ketyl formed after formal HAT.

Table 4. Computed BDFE values for the O-H bond formed up	on
HAT from SmI <sub>2</sub> -water.	

O <sup>−H</sup> R <sup>−−</sup> R	О + Н.
Substrate	O-H BDFE in THF <sup>a</sup>
	(kcal/mol)
Α	19.9
В	19.0
С	16.1
D	16.9
Ε	18.0
F	17.5
G	17.0
Н	12.6

 $^{\rm a}Values$  calculated employing a UB3LYP/6-31G basis set and CPCM for THF in the Gaussian09 software package.  $^{45}$ 

The relationship between the rate of substrate reduction and the free energy of the bond formed through formal HAT is

known as the Evans-Polanyi correlation. This correlation is specific to a reaction class where a series of similar substrates proceed through a common mechanism, in this case PCET.46-<sup>48</sup> The log of the rate constants for substrate reduction by SmI<sub>2</sub>-water was plotted vs. the BDFE's of the intermediate ketyl in THF as shown in Figure 7. A clear correlation exists between the O-H bond dissociation energy for substrate class (hindered and unhindered) and the rate of reduction. Interestingly, substrates containing substitution of the  $\alpha$ carbon are reduced up to an order of magnitude slower than the unsubstituted carbonyl. Unhindered carbonyls (A, C, and E), and hindered carbonyls (B, D, and F) as separate classes show an excellent correlation between the rate of reduction and the stability of the resulting ketyl radical among the groups. Homobenzylic ketone G falls on the correlation of the unhindered carbonyls whereas the activated ester methylbenzoate (H) falls outside of both trend lines and is reduced much faster than expected based on the stability of the radical ketyl formed after formal HAT. With the exception of **H**, this finding is consistent with the stability of the resulting ketyl radical providing the driving force for reduction and consistent with reduction through CPET.<sup>30</sup> One question that arises is: Are the rate differences between substrates steric in origin, or thermodynamic? If the rate differences among hindered and unhindered carbonyls are thermodynamic in origin, we would expect the rate of reduction to trend with changes in the BDFE's of the ketyls. The fact that the O-H BDFE of hindered ketyl **D** is nearly a kcal/mol stronger than that of unhindered C, yet C is reduced several times faster than **D** by SmI<sub>2</sub>-water under the same conditions is consistent with steric hinderance to coordination playing an important role in the reduction. Furthermore, examination of relevant literature reveals that rate differences arising from steric interactions near the site of bond formation are consistent with CPET more so than in ET mechanisms, particularly when the formation of a highly-ordered precursor complex precedes transfer events, 49-52 findings consistent with the data presented vide supra.

To probe this supposition further, the log of the rate constants for reduction was plotted vs. the energies calculated for each radical anion in THF as shown in Figure 8. There is also excellent correlation between rates and the calculated free energies of the radical anions of unhindered and hindered substrates. Substrate **G** falls slightly off of the trend line for the hindered and unhindered substates, whereas substrate **H** does not follow the trend indicating that the reduction likely occurs through a different process.



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**Figure 7.** Evans-Polanyi relation for O-H BDFE and rate constant for aldehyde and ketone reduction by SmI<sub>2</sub>-water. Solid line (log k =0.828(BDFE)-11.9, R<sup>2</sup>=0.990) for unhindered while dashed (log k =1.33 (BDFE)-21.5, R<sup>2</sup>=0.999) is hindered linear fits.



**Figure 8.** Evans-Polanyi relation for the calculated free energies of the radical anions of substrates and rate constant for reduction by SmI<sub>2</sub>-water. Solid line (log  $k = -0.588\Delta$ G-14.6, R<sup>2</sup>= 0.999) is for unhindered while dashed line (log  $k = -0.511\Delta$ G-13.1, R<sup>2</sup>= 0.999) is for hindered linear fit.

Upon initial examination, the fact that the O-H BDFE's and carbonyl reduction potentials trend together as displayed in Figures 7 and 8 may not be surprising since the  $pK_a$  values of the ketyl O-H bonds are similar across the series of substrates studied. It is our supposition that the correlation of rate with both the BDFE of the ketyl formed after hydrogen atom transfer, and the stability of the radical anion formed after electron transfer are consistent with CPET.<sup>53</sup> Similar correlations have been observed in catalytic olefin oxidations by iron-based pacman complexes.<sup>53</sup> An interesting feature of these oxidations are the relatively low isotope ( $k_H/k_D$ ) effects on the order of those described herein.<sup>54</sup>

As noted *vide supra* substrate **H** does not fit the trends displayed by the other carbonyls studied. Among the substrates examined, **H** has the weakest O-H BDFE for the

ketyl formed upon formal HAT from SmI<sub>2</sub>-water. As a consequence, it should be reduced more slowly if the driving force for reduction is comparable to the ketones and aldehydes examined. To further explore the difference between H and the substrates studied, the rate of reduction of several psubstituted methylbenzoate derivatives (-CF<sub>3</sub>, -CH<sub>3</sub>, -H, and -OCH<sub>3</sub>) were measured under identical conditons using 50 equivalents of water and 10 equivalents of substrate relative to [SmI<sub>2</sub>]. The Hammett plot in Figure 9 reveals a strong linear correlation with a steep slope providing a  $\rho$  value of 5.75. The large p value is consistent with a large degree of charge development in the transition state, but it is important to note that the magnitude of  $\rho$  is also dependent on solvation.<sup>55</sup> Since a direct comparison to the ionization of benzoic acid derivatives is not available in THF, it is instructive to compare against a similar study performed in the absence of proton donor.



Figure 9. Hammett plot for the reduction of methyl benzoate derivatives by  $SmI_2$ -H<sub>2</sub>O. Conditions: Pseudo-1st order conditions with constant [H<sub>2</sub>O] (0.5 M), [SmI<sub>2</sub>] (10 mM), and [H-X] (100 mM) X = - OMe, -Me, -CF<sub>3</sub>, and -H.

In a previous study from our group, the reductions of psubstituted acetophenone derivatives by SmI<sub>2</sub> alone were investigated. In the absence of a proton donor such as water, the coupling of acetophenone takes place through an electron transfer from samarium and subsequent coupling to yield a pinacol product. This work revealed a similar dependence on substrate electronics, although a Hammett plot was not generated.<sup>21</sup> Using the rate values obtained from the previous study on acetophenone derivatives provides a p value of 3.6 (see Supporting Information, Figure S73). Since no proton source was present in acetophenone study, the process certainly occurs through an ET where a radical anion is generated as an intermediate. This comparison demonstrates that reduction of the activated carbonyls by SmI<sub>2</sub> leads to a great deal of negative charge buildup in both the presence and absence of proton donors. Although caution must be exercised in comparing these two systems, the large positive  $\rho$  value obtained in both cases suggests that a very large degree of negative charge development in the transition state is a key aspect of the reactivity. The question remains, does the reduction of H occur through initial PCET or is the process different than that displayed by substrates A-G? In the absence of water, no reduction of H occurs and reaction only commences upon the addition of water. The addition of water up to 50 equiv based on [SmI<sub>2</sub>] does not have a measureable

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impact on the redox potential of Sm. As a consequence, the reduction of **H** is not a result of creating a more powerful Sm(II)-based reductant upon the addition of water. These findings indicate that in contrast to substrates **A-G**, the reduction of **H** by SmI<sub>2</sub>-water likely occurs through an asynchronous PCET or stepwise process.<sup>56</sup> A corollary of this hypothesis is the reduction of carbonyl-containing substrates occurs along a continuum between sequential and concerted pathways that are highly dependent on substrate structure and electronics.<sup>56</sup>

Putting aside the complexity of the interactions between 10 substrate, water, and Sm(II), considering the reduction of 11 carbonyls as a formal HAT occurring through CPET from 12 Sm(II)-water suggests that the  $\Delta G$  of the process can be 13 determined from the BDFE of the O-H bond broken and 14 formed during the reduction that produces the intermediate 15 ketyl radical. In addition, comparison with both the ET to 16 form an intermediate ketyl radical anion and PT to form an 17 intermediate protonated ketone enables comparison with the  $\Delta G$  required for the concerted formation of the ketyl. We note 18 that in the examples below simplified schemes are presented 19 to show PT, ET, or CPET and are not meant to convey 20 speciation. 21

Previous work of Mayer has demonstrated that the reduction of electron-rich enamines by SmI2-water occurs through a CPET since initial ET or PT are highly unlikely.<sup>29</sup> In the present study on carbonyl reduction, a similar argument can be made. In the case of unactivated ketone reduction, it is evident that both stepwise pathways lead to high energy intermediates. In considering proton transfer, it is unfortunate that pK<sub>a</sub> values in THF are sparse. Furthermore, it is difficult to model aqueous THF. While at high concentrations of water, aqueous values may be appropriate, most synthetic systems with water are performed at lower concentrations where water is only a few percent of the solvent milieu. While we are reticent to use thermochemical data obtained from aqueous systems in the present analysis, they are useful to demonstrate the relative magnitude of a proton transfer. Mayer has estimated that the  $pK_a$  of the Sm(II) agua complex is roughly 13.3<sup>29</sup> whereas the



 $pK_a$  of a protonated ketone is approximately -7,<sup>57</sup> making initial proton transfer endergonic by approximately 28 kcal/mol. Estimates of the non-aqueous redox potentials makes initial proton transfer unlikely. Reduction of cyclohexanone by SmI<sub>2</sub>-



water through ET is endergonic by approximately 40 kcal/mol.<sup>25,58</sup> The thermochemical driving force for CPET can be estimated using the BDFE for the O-H bond of water bound to Sm(II) and the O-H bond of the ketyl formed upon formal HAT from reductant to substrate.<sup>58</sup> While the  $\Delta$ G of CPET is

estimated to be 16 kcal/mol, this pathway is significantly less

$$Sm(II)-O'_{H}$$
 +  $O_{\Delta G = 16 \text{ kcal/mol}} O'_{H}$  +  $O'_{H}$ 

endergonic than stepwise alternatives making it the most likely pathway. Additionally, the observed barrier to the reduction of cyclohexanone by SmI<sub>2</sub>-water (Table 3) is  $\Delta G^{\ddagger} = 18$ kcal/mol. Since this is significantly smaller than the  $\Delta G$  for initial PT or ET, stepwise pathways are unlikely based on ground state thermochemistry.<sup>59</sup> One caveat with this analysis is that the reverse PCET reaction to produce starting materials only provides a barrier of approximately +2 kcal/mol implying that the reaction could be reversible. Previous analysis of follow up steps in the reduction of intermediate ketvl radicals by SmI<sub>2</sub>-water shows that subsequent reduction steps are significantly exergonic (~50 kcal/mol) and likely have a lower barrier to reduction.<sup>60</sup> Thus in spite of the relatively low estimated activation barrier, these data support the reduction of unactivated aldehydes and ketones through a rate-limiting CPET.

#### Conclusion

The results presented above provide compelling evidence that the reduction of unactivated aldehyde and ketone substrates by SmI<sub>2</sub>-water proceeds through a CPET mechanism. Coordination between substrates and the water-coordinated metal center is sensitive to steric hindrance with even modest substitution by a methyl group adjacent to a carbonyl leading to a deceleration in the rate of reduction of up to an order of magnitude. Overall, the combination of the coordination of substrate and water to Sm(II) provides a configuration uniquely suited to a coupled electron and proton transfer process.

While these studies reveal the complexity of substrate reduction, they also raise important points worth considering. In all of the substrates examined herein, water is critical for reduction. In the absence of water, reductions are either exceedingly slow, or do not occur at all. Coordination of water to Sm is critical for reaction success and a wide [H<sub>2</sub>O] range successfully reduces substrates. One question that arises is: Do the energetics of the Sm(II)-water complex serving as a formal hydrogen atom donor vary as a function of the reaction conditions since the coordination around the metal changes? At low concentrations of water, rate orders above unity are likely a consequence of iodide displacement and as a source of proton required for reduction. As THF in the coordination sphere is displaced by water, reaction rates increase until substrate access to the inner sphere becomes more difficult. Studies of  $k_{\rm H}/k_{\rm D}$  throughout the entire concentration range show little variation. In addition, comparison of the impact of [H<sub>2</sub>O] on the reduction of substrates herein with that obtained for alkyl halides that are initially reduced through dissociative ET reveals that only a small portion of the driving force is a consequence of the redox potential of Sm(II) at concentrations of water used under typical synthetic conditions.<sup>28,39</sup> While it is possible that different regimes of water concentration could have different driving forces for reduction, the studies presented herein indicate that the same mechanism is operating at all concentrations of water.61

Another important point to consider is the following:

coordination of Sm(III) with a ketyl radical anion is used as the basis for describing the selectivity of a wide range of bond-forming reactions initiated by SmI<sub>2</sub>-water. Previous work has demonstrated that PCET from SmI<sub>2</sub>-water to a ketone to form an intermediate neutral ketyl is the ratelimiting step in the reduction of unactivated ketones.<sup>60</sup> The findings in the present work in concert with previous related studies<sup>28–30,60,62</sup> show that rate-limiting formation of a neutral ketyl radical upon substrate reduction by SmI<sub>2</sub>-water is inconsistent with a Sm(III)-ketyl radical anion as an intermediate in this class of reductions. As a consequence, many bond-forming reactions that are initiated through the reduction of a cyclic carbonyl followed by radical addition to a double bond *may* rely more on substrate control than previously recognized to achieve the observed selectivity.

Ideally, these principles can be applied to aid synthetic chemists in the optimal use of SmI2-water for the reduction of carbonyls and for the rational design of efficient reaction pathways that are especially important for multistep syntheses. We caution that the results presented herein apply specifically to unactivated carbonyl substrates and that reduction of activated substrates, such as H deviate from concerted PCET and likely occur through stepwise or asynchronous PCET. With an understanding of the factors affecting Sm-induced PCET reductions through coordination-induced bondweakening, the generation of novel systems capitalizing on these principles may be possible as demonstrated by the recent elegant work of Mayer.<sup>29</sup> It is also likely that this approach can be extended to other low-valent reductants enabling reduction of substrates recalcitrant to ET alone. We are currently examining these suppositions and experiments designed to test these hypotheses will be reported in due course.

# ASSOCIATED CONTENT

#### Supporting Information

General experimental methods, spectroscopic, rate, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The manuscript was written through contributions of all authors who have given approval to the final version of the manuscript.

## Notes

The authors declare no competing financial interests.

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# TOC Graphic

