

Sustainable Ester Reduction by Aqueous SmI₂/Amine: A Bimetallic Proton-Coupled Electron Transfer Mechanism from Density Functional Theory Calculations

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Received: 31 August 2026; **Revised:** 17 September 2026; **Accepted:** 22 September 2026; **Published:** 24 September 2026

Citation: Zhao, X.; Huang, M.; Maron, L. Sustainable Ester Reduction by Aqueous SmI₂/Amine: A Bimetallic Proton-Coupled Electron Transfer Mechanism from Density Functional Theory Calculations. *Sustain. Sci. Innov.* **2026**, *1*, 106154. <https://doi.org/10.54963/ssi.106154>

Abstract: The mechanisms by which cyclic and acyclic aliphatic esters are reduced into their corresponding diols by SmI₂ in water or water/amine solutions have been investigated computationally using density functional theory (DFT). Based on the calculations, the reduction is proposed to be initiated by a two-electron, two-metal reduction of the substrate, resulting in the formation of a bimetallic Sm(III)(substrate²⁻)Sm(III) complex. The reaction pathway then involves the protonation of the oxygen atom of the doubly reduced ketyl intermediate. For activated ester-lactone reduction, the lowest-energy pathway reveals the important role of a specific first-hydration-shell water molecule, which acts as the proton source and facilitates the overall transformation. For aliphatic esters in binary water/amine solution, the amine enables a proton cascade required to fulfill the reduction. As a consequence, the role played by the amine towards the reduction of aliphatic esters is attributed primarily to a specific relay in a proton cascade, in addition to, rather than instead of, any concurrent effect on the reduction potential of SmI₂. The results establish a unified bimetallic proton-coupled electron transfer (PCET) mechanism for SmI₂-mediated ester reduction in aqueous and water/amine media, which may extend to other divalent lanthanides, broadening the range of aqueous-compatible single-electron reductants for green synthesis.

Keywords: skeletal editing; single-carbon insertion; polarized σ -bonds; carbene chemistry; atom economy; step economy

1. Introduction

Since its introduction to the synthetic community in 1977 by Kagan,^{1,2} samarium(II) diiodide (SmI₂) has emerged as one of the most reductive powerful electron transfer reagents available for synthesis.^{3–7} The chemoselective reduction of common functional groups has been pivotal to organic synthesis. Several major developments in the functional group transformation mediated by SmI₂ have been reported in the past decades.⁴ The unactivated carboxylic acid derivatives had long been thought to lie outside the reducing scope of SmI₂. Until recently, significant progress has been made in the reductions of esters and amides by SmI₂, thus expanding the scope of applicability and broadening the versatility of SmI₂ as a reducing agent.⁸

This has been enabled by the use of appropriate additives, which either bind to the substrate or, more frequently, to

SmI₂.^{9–12} Water is a critical additive used to activate SmI₂ toward bond-cleaving and bond-forming reactions. In this condition, the addition of amine as a second co-solvent has a profound impact on the reactivity and selectivity of samarium(II) based reagents.^{13–17} Several groups have studied reactions initiated by SmI₂/H₂O/amine and have uncovered a complex mechanistic role for the additives.^{18–20} For example, Flowers showed that H₂O has a high affinity for Sm and displaces iodides and organic solvents such as THF from the inner coordination sphere. This modification of the coordination sphere of Sm(II) reagent proved to raise its reduction potential.^{21–25} The addition of amine further increases the reduction potential of SmI₂-H₂O.²⁵ Flowers's work on H₂O and amine activated SmI₂ reagents suggested that H₂O coordinates to and stabilizes the samarium-bound radical anions formed by elec-

tron transfer, thus promoting reduction.^{26–29} The first electron transfer is facilitated by Brønsted base-assisted deprotonation of water in the transition state.^{18,19} Conversely, researchers discovered that the most probable mechanistic role for amine in the mixture of water/amine/ SmI_2 is to deprotonate a water molecule complexed to Sm after the electron transfer step.²⁰ This deprotonation reduces the rate of back electron transfer and allows the reaction to progress. Alongside these experimental studies, we have previously investigated theoretically the role of H_2O in the electron transfer activated substrates using the SmI_2 reagent.^{18–20} Specifically, we found that ketyl radicals from ketone, lactone and ester are stabilized by hydrogen bonding of H_2O . More recently, additional computational and electrochemical studies have refined this picture, clarifying the role of spin–orbit coupling and Lewis-base additives on the Sm(III)/Sm(II) couple,³⁰ achieving catalytic and electrocatalytic turnover of Sm(II),^{30–33} and opening photochemical routes to divalent lanthanide reductants,^{34–37} further motivating the detailed mechanistic picture developed in this work.

Up to now, the reactivity of SmI_2 towards carboxylic derivatives has captured the attention of researchers, as many structural and mechanistic aspects remain unclear.^{15–17} As an illustration, the formation of dinuclear intermediates has been inferred,^{21–25} albeit no structural or thermodynamic data support this assertion; (i) the structure of the samarocene(II) dimer $[(\text{C}_5\text{Me}_5)_2\text{Sm}(\text{THF})_2]$ and its reactivity towards CO_2 has been reported;³⁸ (ii) a doubly reduced ketone sandwich complex between two Sm(III) centers has been suggested to enable the pinacol coupling mediated by SmI_2 in THF solution.³⁹

Despite the above groundbreaking studies,^{18–21} the mechanistic details of SmI_2 reagent mediated reduction of unactivated esters,^{22–26} including the coordination of amine to SmI_2 and the crucial role of H_2O and amine/ H_2O additives,^{27–29} remain poorly understood at the molecular level. Providing such information will bring insights for the development of new reductive processes and new subsequent C–C bond-forming reactions.

Therefore, herein we report a theoretical mechanistic investigation, at the DFT level, of the reduction of unactivated esters by the SmI_2 reducing reagent in aqueous or aqua/amine media. As a result of this study, we report three important features: (i) the two-electron reduction of unactivated esters by two metal centers is suggested; (ii) the reduction of lactone and aliphatic esters occurs through a proton-coupled electron transfer mechanism;⁴⁰ (iii) amine activates one molecule of water to facilitate proton shuttling from water to substrate. Overall, this study helps to uncover the mechanism of chemoselective electron transfer to esters using SmI_2 reagents and rationally design new reductive processes.

2. Computational details

All calculations were performed at the DFT level of theory using the Gaussian 09 suite of programs.⁴⁰ According to our pre-

vious contribution,³⁸ the equilibrium and transition structures were fully optimized using the M06 functional.⁴¹ To study the reactivity of SmI_2 mediated reduction from cyclic and acyclic esters, two types of Stuttgart-Dresden relativistic effective core potentials (RECPs) were used to describe samarium: small-core (SC) RECPs that include the 4th, 5th, and 6th valence shells and large-core (LC) RECPs that only explicitly consider the $5s^2$, $5p^6$, $5d^1$ and $6s^2$ electrons in the valence shell and thus implicitly account for the 4f core electrons. As a consequence, a large-core RECP is dedicated to each formal oxidation state of a metal center: 11 valence-electron LC-RECPs were used for Sm(III) and 10 valence-electron RECPs for Sm(II). Any step that does not involve oxidation of Sm was computed using LC-RECPs. SC-RECPs were used to study the single-electron transfer from the metal to the substrate. Iodine atoms were represented by means of Stuttgart-Dresden effective core potentials in association with their basis set, augmented by a *d*-polarization function ($\alpha = 0.730$).⁴² The augmented and polarized version of triple- ζ 6-311G basis set was used for oxygen,⁴³ the polarized double- ζ 6-31G basis set was used for nitrogen and the double- ζ 6-31G basis sets were used for carbon and hydrogen.^{44–46} To model solvent effects, optimizations were performed in an explicit water-amine droplet in conjunction with an implicit SMD model⁴⁷ to account for the bulk solvation effects of THF.

3. Results and discussion

3.1. Two-electron reduction of δ -valerolactone by SmI_2 - H_2O

In a previous study, single-electron reduction of lactones by the SmI_2 - H_2O complex was investigated computationally.^{18–20} Lactones are cyclic, ring-activated esters whose reactivity towards single-electron transfer parallels that of aromatic esters, both benefiting from partial charge delocalisation that lowers the electron-transfer barrier. It was shown that the 6-membered lactone 1 is activated by coordination to the SmI_2 - H_2O complex enabling single-electron transfer (SET) from Sm(II) to form the ketyl radical anion IM2. The associated reaction energy is 2.2 kcal mol^{–1}, which is in agreement with Procter's suggestions that 6-membered lactones are surprisingly receptive to electron transfer from SmI_2 - H_2O .^{18,19} However, although this SET is favorable, the SmI_2 -ketyl radical is not reactive enough to undergo further reactions. For instance, Procter proposed that the ketyl radical anion is protonated by water prior to a second reduction that would ultimately yield the alcohol (red pathway in Figure 1).⁴³ This hypothesis was computationally evaluated, and the formation of the protonated radical IM3a was found to be 35.4 kcal mol^{–1}, which thermodynamically prevents this mechanism (Figure 1). Interestingly, however, the coordination of a second SmI_2 complex to this alcohol radical, followed by a subsequent proton transfer, is computed to be highly exothermic by 56.1 kcal mol^{–1} relative to IM3a. These

results indicate that a proton is not a strong enough Lewis acid to stabilize the formed radical, and that another Sm(II) center is required. Consequently, an alternative mechanism may exist

(blue pathway in Figure 1), in which the coordination of a second samarium center would occur prior to, or simultaneously with, the proton transfer.

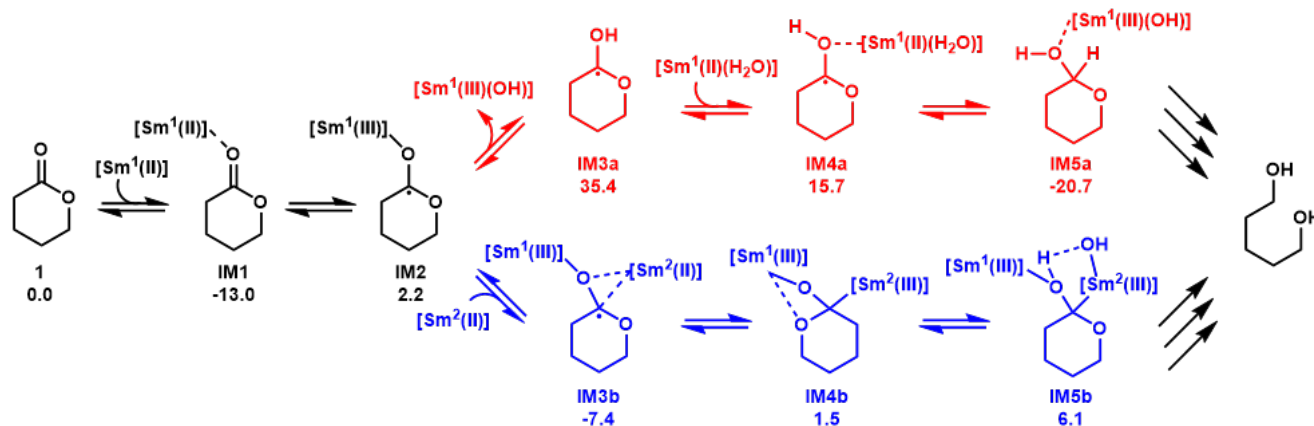


Figure 1. Mechanism pathways suggested for the reduction of lactone using $\text{SmI}_2\text{-H}_2\text{O}$. For the sake of simplicity, $[\text{Sm}^1\text{II}(\text{H}_2\text{O})_{24}]$ is labelled as $[\text{Sm}^1(\text{II})]$, $[\text{Sm}^1\text{II}(\text{H}_2\text{O})_{16}]$ is as $[\text{Sm}^2(\text{II})]$, $[\text{Sm}^2\text{III}(\text{H}_2\text{O})_{24}]$ is labelled as $[\text{Sm}^2(\text{III})]$, $[\text{Sm}^2\text{III}(\text{H}_2\text{O})_{16}]$ is as $[\text{Sm}^2(\text{III})]$.

Given this second Sm coordination, the existence of a singly reduced monometallic species becomes questionable. Indeed, previous experimental and theoretical studies on CO_2 reduction have underscored the critical role of dinuclear complex formation.⁴⁸ For instance, Labouille demonstrated that samarium complexes readily effect the double electron reduction of CO_2 , with the second electron transfer being barrierless and affording a highly stable dinuclear species.⁴⁹ Moreover, in a kinetic study, Procter also suggested that the rate order of two for the lactone probably results from the formation of a dimeric SmI_2 -lactone complex.^{18–20} To probe the formation of a bimetallic species computationally, we employed an iterative scheme in which $\text{Sm}(\text{II})\text{I}_2\text{-(H}_2\text{O)}_{16}$ coordinates to the ketyl complex IM2 (generated after the first reduction of the lactone by $[\text{Sm}(\text{II})\text{I}_2\text{-(H}_2\text{O)}_{24}]$).³⁸ The resulting bimetallic system is solvated by 40 water molecules, consistent with the established requirement that 20 water molecules are necessary for an accurate description of the reduction energetics. After the formation of a bimetallic lactone complex $[\text{Sm}^1(\text{III})]\text{-(lactone}^{\cdot-})\text{-}[\text{Sm}^2(\text{II})]$ IM3b, the $\text{Sm}^2(\text{II})$ center will oxidize to $\text{Sm}^2(\text{III})$, yielding a doubly reduced lactone in complex $[\text{Sm}^1(\text{III})]\text{-(lactone}^{2-})\text{-}[\text{Sm}^2(\text{III})]$ IM4b. Significantly, the second reduction is concomitant with the proton transfer from a coordinated water molecule, leading to the samarium(III) hydroxyl complex IM5b. Although Hoz recently reported a similar hydroxyl complex for a different substrate, they neither associated its formation with a bimetallic species nor noted its concurrence with the second reduction step.²⁹

The computed enthalpy energy profiles are shown in Figure 2. Reaction and activation energies are discussed as enthalpies (ΔH) throughout, since a rigorous harmonic estimate of the vibrational entropy of such large, explicitly solvated clusters (up to 40 water molecules per bimetallic complex) is not statistically meaningful. Because both the monometallic

and bimetallic association steps involve a comparable translational/rotational entropy cost, the entropic penalty typically associated with bimolecular association in solution (on the order of 10–15 kcal mol⁻¹ at 298 K) is far smaller than the 45–70 kcal mol⁻¹ enthalpic preference computed here for the bimetallic pathway, so that inclusion of ΔS is not expected to alter the mechanistic conclusions drawn from ΔH . The formation of the bimetallic species $[\text{Sm}^1(\text{III})]\text{-(lactone}^{\cdot-})\text{-}[\text{Sm}^2(\text{II})]$ IM3b is calculated to be exothermic by 9.6 kcal/mol relative to IM2 and the following second electron transfer reaction energy is almost athermic (1.5 kcal/mol), which is comparable to the first electron transfer (+2.2 kcal/mol). This is in line with recent suggestions that the electron transfer reduction of carboxylic acid derivatives is a reversible process.^{18–20} At this stage, one can then wonder if the sequential reduction process is real. Indeed, a concerted coordination-induced reduction of the lactone by the two Sm centers (a lactone sandwiched between two solvated SmI_2 species IM3c) would directly lead to complex IM4b. The formation of the $[\text{Sm}^1(\text{II})]\text{-(lactone}^{\cdot-})\text{-}[\text{Sm}^2(\text{II})]$ IM3c is thermodynamically favorable by 36.1 kcal/mol and provides a direct pathway to IM4b. This concerted route is the most favorable, rendering the formation of IM1 intermediate unlikely. Such a process has already been reported by Labouille for the reactivity of CO_2 with Cp^*Sm and appears to be operative here as well. Detailed geometric analysis of complex IM4b reveals a notable elongation of the $\text{O}^2\text{-H}$ bond (1.03 Å)⁵⁰ in the water molecule engaged in hydrogen bonding with the lactone (Figure 2). On this basis, we successfully located the proton-transfer transition state from a coordinated water molecule, characterized by cleavage of the $\text{O}^2\text{-H}$ bond and concomitant formation of the $\text{O}^1\text{-H}$ bond, as depicted in Figure 2. From IM4b the activation barrier of proton transfer is very low (2.9 kcal/mol), indicating that protonation of the ketyl

dianion by water is extremely facile and can be considered concomitant with the reduction steps. Therefore, the reaction is best described as a Proton Coupled Electron Transfer (PCET), in line with the report of Flowers, albeit occurring at a bimetallic species.²⁶ The formation of the protonated complex IM5b is

slightly endothermic (4.6 kcal/mol) relative to IM4b; however, this is largely overcome by the subsequent formation of IM6b, in which the $\text{Sm}^2(\text{III})$ center bound to the lactone carbon is replaced by a proton, driving the overall process by roughly -60 kcal/mol.

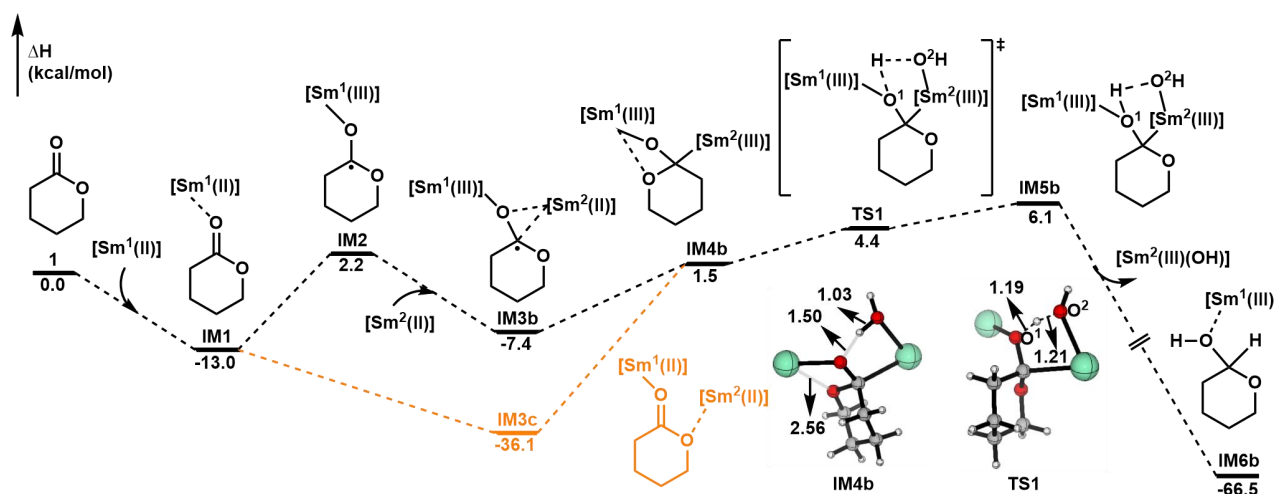


Figure 2. Enthalpy energy profiles of the two different pathways for the reduction of lactone with $\text{SmI}_2\text{-H}_2\text{O}$.

Based on the preceding discussion, the bimetallic two-electron reduction pathway is both kinetically preferred and thermodynamically highly favorable (-66.5 kcal/mol). This spontaneously drives proton transfer from a coordinated water molecule to the ketyl dianion. Accordingly, the mechanism is best described as a bimetallic proton-coupled electron transfer (PCET). To corroborate this mechanistic proposal, we extended our study to the reduction of aliphatic esters—a transformation that remains an experimental challenge.

3.2. Two-electron reduction of methylpropanoate by $\text{SmI}_2\text{-H}_2\text{O}$

In contrast to the lactone, the overall electron transfer reaction from $\text{SmI}_2\text{-H}_2\text{O}$ to aliphatic ester (yielding an acyl radical IM2') is strongly endothermic by 14 kcal/mol. This single-electron reduction is computed to be the most difficult one, in accordance with experimental observations.¹³ Recently, Procter proposed that an acyl radical anion could be generated via the reversible first SET and protonated reversibly by water in the presence of $\text{SmI}_2\text{-H}_2\text{O}$ and $\text{SmI}_2\text{-H}_2\text{O-NR}_3$.^{51,52} Analogous to the valerolactone, protonation of the acyl radical was computed to be highly endothermic by 22.8 kcal/mol (Supplementary Materials Figure S1). This unfavorable energetics prompted us to consider the alternative pathway involving a bimetallic species (Figure 3).

The theoretical pathways are summarized in Figure 3. Although the overall thermodynamic and kinetic trends for the reduction of valerolactone and aliphatic esters are broadly similar, distinct differences emerge. Specifically, the formation of the

bimetallic complex $[\text{Sm}^1(\text{III})]\text{-(ester)}^-\text{[Sm}^2(\text{II})]$ IM3a' is more exothermic than its lactone analogue (-24.7 kcal/mol vs. -9.6 kcal/mol). This thermodynamic difference stems from the fact that water molecules interact with both oxygens of the acyl radical anion upon formation of the bimetallic complex, whereas, in the lactone case, water binds only to the exocyclic oxygen, thereby reducing the overall stabilization of the ketyl radical anion. This is in line with our suggestion that water molecules stabilize the ketyl/acyl radical by hydrogen bonding.¹⁸⁻²⁰ Similarly, formation of $[\text{Sm}^1(\text{II})]\text{-(ester)}\text{[Sm}^2(\text{II})]$ IM3c' is the most favorable process (-32.1 kcal/mol), again supporting the direct formation of IM4a' via a concerted route, as proposed for the lactone. As in the lactone case, from complex IM4a', the protonation step occurs concurrently with the electron transfer but with a higher activation barrier (+8.0 kcal/mol) compared to the protonation of the lactone complex (+2.9 kcal/mol). This difference is attributed to variations in water coordination around the Sm center in the bimetallic species. For the lactone, coordination of water to $\text{Sm}^2(\text{III})$ increases the acidity of the O-H bond and facilitates proton transfer. In the aliphatic ester case, by contrast, this specific coordination is absent, as water molecules instead primarily stabilize the negative charges localized on the oxygen atoms. Overall, our theoretical results indicate that the bimetallic PCET mechanism is also preferred for the reduction of aliphatic esters by $\text{SmI}_2\text{-H}_2\text{O}$. Moreover, Procter demonstrated that amine additives are required to facilitate the reduction of aliphatic esters.²⁸ Accordingly, we have computationally investigated the influence of such additives on our proposed bimetallic pathway.

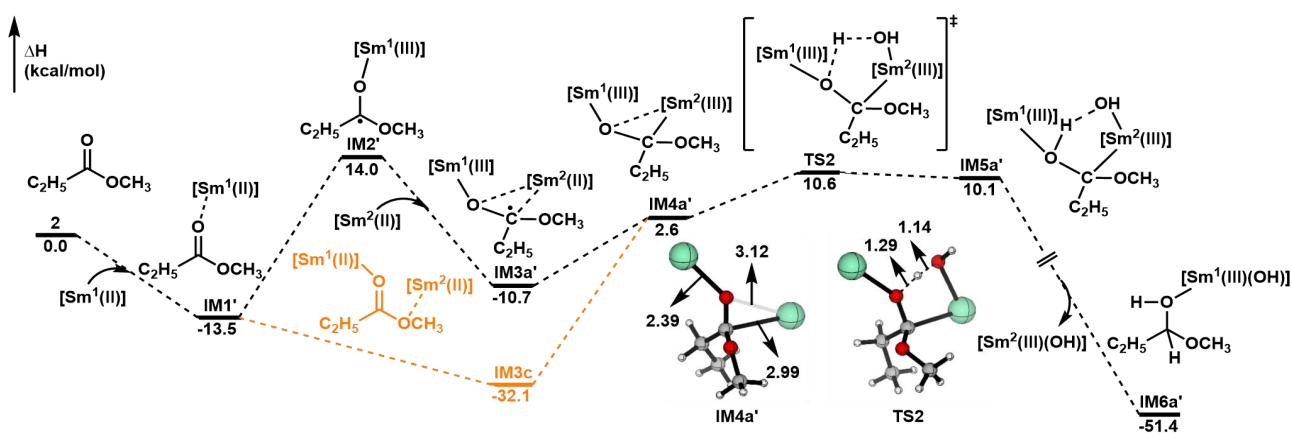


Figure 3. Enthalpy energy profiles of the two different pathways for the reduction of methylpropanoate with $\text{SmI}_2\text{-H}_2\text{O}$.

3.3. Proton shuttling within the $\text{SmI}_2/\text{H}_2\text{O}/\text{amine}$ system

As a first step, it is mandatory to validate our chemical model of the solvation of SmI_2 in the binary water/amine. This was achieved by scrutinizing the interactions between H_2O , amine and SmI_2 . Given the experimental steric and electronic influence of the amine,²⁸ pyrrolidine was selected as the model additive. Experimentally, the SmI_2 -water-amine reagent is prepared using an equimolar amount of amine and water—a combination commonly referred to as the “magic mixture”.^{27,28} Following the procedure developed for the water solution,³⁸ a stepwise construction of the computational model of SmI_2 in amine/water binary solution was carried out, with an equal number of amine and water molecules. Our calculations reveal that, upon increasing the number of pyrrolidine equivalents from 1 to 6, only two molecules remain directly coordinated to $\text{Sm}(\text{II})$; all others are readily displaced by water (Supplementary Materials Table S1). Consequently, water binding is favored over amine binding, and increasing the water molecules

leads to displacement of amine from the first solvation shell of samarium.

The mechanistic role of the amine, however, remains experimentally unclear and largely speculative. Procter initially proposed that the amine serves to deprotonate a water molecule bound to $\text{Sm}(\text{II})$, thereby raising the redox potential of the $\text{Sm}(\text{II})$ reductant and enabling reduction via a reversible first electron transfer step.^{27,28} To gain further insight, Hoz outlined three possible deprotonation scenarios: prior to electron transfer, following electron transfer (affording a hydroxide anion bound to $\text{Sm}(\text{III})$), or concomitantly with electron transfer—the latter representing a proton-coupled electron transfer (PCET) process, as computationally identified for both the lactone and the ineffective reduction of aliphatic esters in aqueous solution.^{29,39,53} Therefore, there is an alternative perspective on the role of amine is that one molecule of amine acts as a proton shuttle, facilitating deprotonation of H_2O and subsequent proton transfer. Herein, we present theoretical studies on the amine-assisted proton transfer pathway for aliphatic ester reduction (Figure 4).

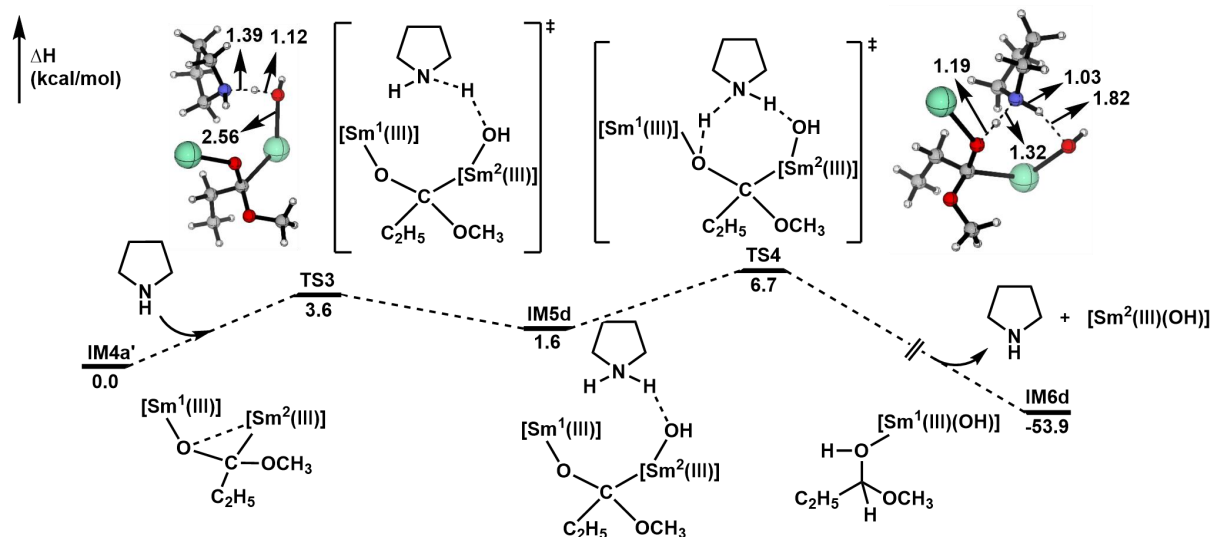


Figure 4. Enthalpy energy profiles of the two different pathways for the reduction of methylpropanoate with $\text{SmI}_2\text{-H}_2\text{O}$ -amine.

The enthalpy energy profile for the bimetallic complex in the binary water/amine is depicted in Figure 4. The energy that is needed to reach the first transition state, TS3, is only 3.6 kcal/mol, indicating that amine further increases the acidity of the O–H bond of water, even though not interact with the samarium center. In this pathway, the proton is initially transferred from water to the lone pair on the amine nitrogen. Notably, the process proceeds via a two-step proton transfer. The second step involves transfer of a proton from the amine to the partially negatively charged oxygen bound to Sm¹(III), with an associated barrier of 5.1 kcal/mol relative to IM5d. Overall, the barrier for proton transfer is reduced by 2.9 kcal/mol compared with the barrier of 8.0 kcal/mol computed for the SmI₂–H₂O system, clearly demonstrating that the amine assists the proton transfer. The computational results indicate that in the reduction of aliphatic ester by SmI₂–amine–water, amine serves as a proton relay, overcoming the lack of water coordination to the Sm that would otherwise hinder proton transfer to the acyl dianion, in addition to any concurrent influence the amine may have on the overall reduction potential of the Sm(II) center. From a thermodynamic point of view, the proton transfer energy barrier that is needed to pass from the bimetallic complex is lower, pushing the reaction to completion.

4. Conclusion

In summary, theoretical investigations have been conducted to elucidate the mechanism of unactivated ester reduction by SmI₂-based reagents. These computational results provide a clear rationale for the reactivity of lactones and aliphatic esters with SmI₂ in both aqueous and binary water/amine solutions. Specifically, the reaction proceeds via a proton-coupled electron transfer (PCET) mechanism originating from a bimetallic Sm(II) complex. The efficiency of this process is governed by the activation of a water molecule, which occurs through two distinct pathways: (i) direct Lewis acid coordination and activation of a water molecule by the samarium center, or (ii) an amine-mediated proton relay that activates non-coordinated water molecules when direct metal–water interaction is absent. The latter pathway, consistent with previous proposals for organometallic samarium (II) systems, effectively lowers the proton-transfer barrier and ultimately drives the reduction to completion.

Looking beyond the present mechanistic picture, the proton-relay concept identified here for pyrrolidine offers a rational handle for future reagent design. Because the amine need not coordinate directly to samarium to be effective, replacing stoichiometric SmI₂ with catalytic, sub-stoichiometric samarium loadings regenerated in situ by a sacrificial reductant or by photo- or electrochemical means appears feasible whenever an efficient external proton shuttle is present, a strategy that would directly lower the cost and waste associated with Sm-

mediated reductions and would further align this chemistry with green-chemistry principles.^{54–57} The bimetallic PCET pathway and the associated proton-shuttle mechanism established here are, in principle, not unique to Sm(II): related divalent lanthanide reductants such as YbI₂, NdI₂ and DyI₂ possess comparable Lewis acidity and redox behavior, and the water/amine activation rules established here should extend to these systems, broadening the toolbox of aqueous-compatible single-electron reductants available for green synthetic protocols, including for pharmaceutical intermediate synthesis.³⁰ Finally, amides—which, like the aromatic esters they resemble in reactivity, undergo a competing deoxygenation pathway after single-electron reduction and have emerged as attractive substrates for Sm(II)–water chemistry^{17,58}—represent a natural extension of the present mechanistic framework, and computational studies addressing how the amine/water proton relay operates for these more challenging functional groups are a promising direction for future work.

Supplementary Materials

The supporting information can be downloaded at https://ssi.ukscip.com/uploads/7/asset-file/2026/09/asset-file_83393008d17b6d337c8b4534696c29fa.pdf.

Author Contributions

Conceptualization, X.Z. and L.M.; methodology, X.Z. and L.M.; software, X.Z.; validation, X.Z., M.H. and L.M.; formal analysis, X.Z. and M.H.; investigation, X.Z. and M.H.; resources, L.M.; data curation, X.Z.; writing—original draft preparation, X.Z.; writing—review and editing, X.Z., M.H. and L.M.; visualization, X.Z.; supervision, L.M.; project administration, L.M.; funding acquisition, L.M. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Data Availability Statement

The data supporting this article, including full optimized Cartesian coordinates, absolute and relative energies, and Table S1, have been included as part of the [Supplementary Materials](#). No new experimental data were generated in this study.

AI Use Statement

The authors declare that no artificial intelligence (AI) tools were used in the preparation of the scientific content, analysis, or conclusions of this manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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