

The Role of Proton Donors in SmI₂-Mediated Ketone Reduction: New Mechanistic Insights

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Alcohols and water are commonly used as additives in numerous reductions and reductive coupling reactions of SmI₂.^{1–3} Typically, they are used as proton donor sources and have been shown to exert an influence on the regiochemical^{4,5} and stereochemical^{6,7} outcome of numerous Sm(II)-mediated reactions. Oftentimes changing the proton donor can have a profound impact on product distributions, yet the mechanistic details are poorly understood. To begin to understand the function of proton donors in Sm(II)-based reductions, a series of commonly utilized alcohols and water were examined to study their impact on the rate and mechanism of ketone reduction. The data described herein show two important features: (1) There is a direct correlation between the rate of ketone reduction and the pK_a of the alcohol proton source and (2) water has a higher affinity for SmI₂ than the alcohols examined in this study, and the onset of coordination leads to a change in the mechanism of ketone reduction.

Alcohols and water may coordinate to Sm(II) as well as donate a proton through heterolytic cleavage of the O–H bond. Since proton donors play an important role in many reactions of SmI₂, it is critical to determine the interplay between coordination and proton donor ability on the mechanism of reduction. The relationship between proton donation and complexation is poorly understood, and to date, only the seminal mechanistic analysis of Hoz has addressed this point.⁸ Curran found that water accelerated the rate of a number of SmI₂-mediated reductions and postulated that the reductant contained bound water.⁹ More recent work by Hilmersson has shown that coordinating alcohols enhanced the rate of ketone reduction substantially and the rate increase was proportional to the number of ethereal oxygens in the proton donor source.¹⁰

Examination of the literature shows that most SmI₂-based reductions and reductive couplings are carried out using between 2 and 25 equiv of proton source. Experiments described here were carried out at 25 equiv of proton source (based on SmI₂ concentration). Acetophenone was chosen as a model ketone substrate since its rate of reduction is in a convenient range for kinetic studies and its rate of reduction is well-established in the absence of proton sources.^{11,12} The reduction of acetophenone by SmI₂ in the presence of all proton sources was first-order in both substrate and reductant. Table 1 contains the observed rate constants and reaction order for each of the proton sources examined in this study.

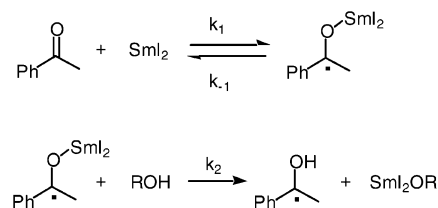
Both 2-propanol and 2-methyl-2-propanol had no effect on *k*_{obs} for the reduction of acetophenone by SmI₂. Subsequent studies designed to determine the reaction order of these proton sources showed no influence even at concentrations approaching 1 M. Conversely, methanol, ethanol, 2,2,2-trifluoroethanol, and phenol significantly accelerated the rate of reduction. Follow-up studies designed to determine the reaction order showed that these four

Table 1. Observed Rate Constant, Reactions Order, and *k*_H/*k*_D for the Reduction of Acetophenone by SmI₂ and Proton Donors

proton donor	<i>k</i> _{obs} (s ⁻¹) ^a	proton donor order	<i>k</i> _H / <i>k</i> _D
none	0.25 ± 0.02		
H ₂ O	7.6 ± 0.2	1.4 ± 0.1	1.8
CH ₃ OH	1.0 ± 0.1	0.9 ± 0.1	1.9
CH ₃ CH ₂ OH	0.9 ± 0.1	0.8 ± 0.1	1.8
(CH ₃) ₂ CHOH	0.33 ± 0.01	0	1.0
(CH ₃) ₃ COH	0.23 ± 0.01	0	1.0
CF ₃ CH ₂ OH	1.4 ± 0.1	0.9 ± 0.1	2.0
C ₆ H ₅ OH	1.7 ± 0.1	0.8 ± 0.1	1.9

^a Experimental conditions: [SmI₂] = 0.0025 M; [acetophenone] = 0.025 M; [proton donor] = 0.0625 M.

Scheme 1



proton donors have a rate order of 1 (within experimental error). Water provided the highest rate enhancement of the proton donors studied, and its reaction order was determined to be 1.4. Further studies of reactions showing rate enhancement in the presence of a proton source displayed a kinetic isotope effect *k*_H/*k*_D of approximately 2, indicating that the rate-limiting step in the reduction involved a proton transfer.

Scheme 1 shows the initial two steps for reduction of acetophenone by SmI₂ in the presence of an alcohol through a traditional House mechanism.^{9,13} Applying a steady-state approximation to the concentration of the ketyl radical, one derives the expression given in eq 1. When *k*₋₁ ≫ *k*₂,

$$\frac{d[\text{SmI}_2]}{dt} = \frac{k_1 k_2 [\text{sub}][\text{SmI}_2][\text{ROH}]}{k_2 [\text{ROH}] + k_{-1}} \quad (1)$$

the equation simplifies to that shown in eq 2:

$$\frac{d[\text{SmI}_2]}{dt} = \frac{k_1 k_2 [\text{sub}][\text{SmI}_2][\text{ROH}]}{k_{-1}} = k_{\text{obs}} [\text{sub}][\text{SmI}_2][\text{ROH}] \quad (2)$$

which predicts that the rate will exhibit a first-order dependence on [SmI₂], [substrate], and [ROH]. These conditions are met when methanol, ethanol, 2,2,2-trifluoroethanol, and phenol are used as proton sources.

In the reduction of acetophenone, 2-propanol and 2-methyl-2-propanol were not strong enough donors to protonate the ketyl radical anion of acetophenone. As a result, the first step of the

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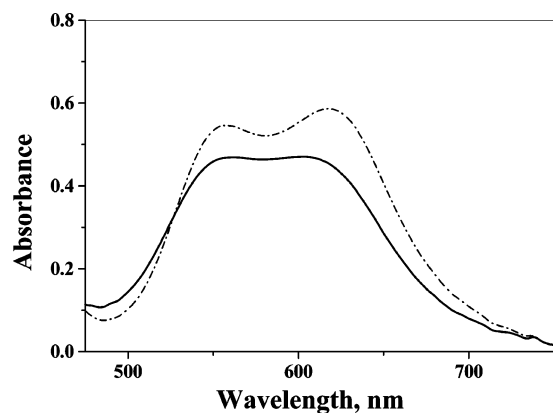


Figure 1. The UV-vis spectrum of SmI_2 (dash-dot line) and SmI_2 -water (1:25) mixture (solid line) in THF. The concentration of SmI_2 in both spectra is 5 mM.

reduction was the rate-limiting step. The presence of methanol, ethanol, 2,2,2-trifluoroethanol, and phenol influenced the rate, and the kinetic data were consistent with the second step being the rate-limiting step. For the second series of proton donors, a plot of $\text{p}K_a$ vs k_{obs} provided a correlation coefficient of 0.996, clearly indicating that the acidity of the proton donor dictated the rate of the reaction. While the mechanistic analysis above was consistent with the results obtained for the alcohols examined in this study, it did not explain the findings obtained for water. The rate constant for reduction under the conditions of this experiment showed no relation between the rate and $\text{p}K_a$ of water, and the rate order of 1.4 was inconsistent with the rate law in eq 2.

To study the system in more detail, UV-vis spectra of SmI_2 in the presence of increasing amounts of water were obtained. Clear differences in the spectrum of SmI_2 were apparent after the addition of as little as 10 equiv of water. Figure 1 contains the UV-vis spectrum of SmI_2 and SmI_2 containing 25 equiv of water. This analysis clearly showed that under the conditions of these experiments, the reductant contains bound water.¹⁴

Next, rate studies were carried out at both low and high concentrations of water to determine whether the fractional rate order of 1.4 could possibly be due to the superimposition of two mechanistic pathways. It was found that at concentrations less than 8 equiv, the reaction order of water was 0.9 ± 0.1 . Once the concentration of water reached 8 or more equivalents, the rate order was greater than 1. Subsequent experiments showed that at concentrations greater than 80 equiv, the rate order of water was 2.0 ± 0.2 . The rate order of 2 remained constant up to 130 equiv of water. At concentrations higher than this value, the rate was too fast to measure using stopped-flow spectrophotometric methods. At low concentrations of water (<8 equiv), the kinetic experiments showed that the rate law in eq 2 was obeyed. At higher concentrations of water (>80 equiv), coordination to SmI_2 produced a unique reductant that reduced acetophenone at an accelerated rate and the reaction was second order with respect to $[\text{H}_2\text{O}]$.

The same analysis was initiated to determine the effect of higher alcohol concentrations on the mechanism of acetophenone reduction. The UV-vis spectrum and rates of reduction by SmI_2 were examined over a proton donor range from 1 to 4 M. Addition of

1 M methanol to SmI_2 showed evidence of coordination, and examination of the observed rate over the concentration range showed a fractional rate order of 1.3 ± 0.1 . Although ethanol showed some evidence of coordination to SmI_2 at a concentration of 4 M, the rate law in eq 2 was obeyed through the entire concentration range. Phenol and 2,2,2-trifluoroethanol also obeyed the rate law in eq 2 over the whole concentration range.

Taken together, the mechanistic experiments described herein show the following: (1) There is a linear relationship between the acidity of the alcohol and the rate of acetophenone reduction. (2) The proton source must have sufficient acidity to protonate the intermediate formed upon initial reduction by SmI_2 . (3) Water has a much higher affinity for SmI_2 than the alcohols examined in this study. (4) Complexation between the proton donor and SmI_2 produces a reductant that reacts with acetophenone through a mechanistically distinct pathway.

From a practical point of view, these data suggest that the choice of proton donor can have a profound impact on the rate and mechanism of substrate reduction. As an example, a recent paper by Keck and co-workers describing the influence of proton sources on the diastereoselectivity of reduction of β -hydroxyketones by SmI_2 mirrors the mechanistic findings described herein.⁶ In their work, no reduction occurs in the presence of 2-methyl-2-propanol, and while reduction using 2 equiv of H_2O proceeds in high yield and diastereoselectivity, the use of 10 equiv of H_2O leads to a loss of diastereoselectivity (suggesting that coordination of H_2O to SmI_2 inhibits chelation to the β -hydroxyketone). Conversely, a range of methanol concentrations between 2 and 100 equiv provided high yields and stereoselectivities in the SmI_2 -mediated reductions. Further mechanistic studies on the role of proton donors in other functional group reductions and reductive coupling reactions are currently being pursued. The results of these studies will be reported in due course.

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Supporting Information Available: General experimental conditions, decay traces, absorption spectra, and plots of rate data (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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