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Reduction of 4-Styrylpyridine by SmI_2: An Inner Sphere Electron Tranfer Case Where the Binding Site Differs from the Reaction Center

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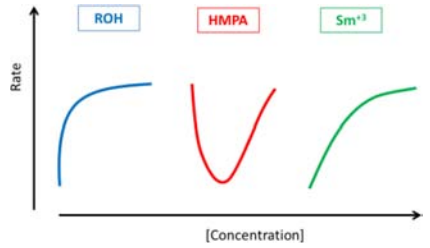
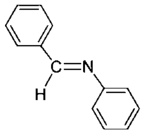
ABSTRACT

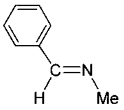


In the reduction of 4-styrylpyridine by SmI_2, the binding site for SmI_2 differs from the reaction center. MeOH and TFE exhibit an unprecedented behavior showing a sigmoidic effect on the reaction rate, which levels off around 0.5–1 M. The reactions display autocatalytic behavior and a U shape dependence of the reaction rate on the HMPA concentration. With high likelihood, the reactions involve a proton coupled electron transfer step.

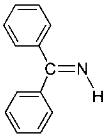
In a previous work we described the reduction of three systems **BAI**, **BMI**, and **BPI** by SmI_2.[1,2] All these nitrogen containing substrates exhibit autocatalytic kinetics (reaction rates do not decrease but rather increase as the reaction progresses), and the catalyst is the Sm^{3+} generated in the course of the reaction.



BAI

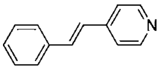


BMI



BPI

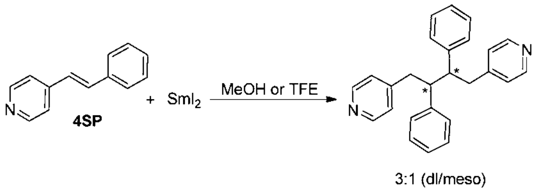
The reactivity order was **BPI** > **BMI** > **BAI**. This reactivity order is not in accord with the electron affinity of these substrates but rather with the accessibility of the lone pair on the nitrogen. The purpose of the present work is to examine the effect of removal of the nitrogen from the reaction center to a side location. Thus, using **BAI** as the starting point we moved the nitrogen atom from the reaction center—the central double bond—to one of the rings to give 4-styrylpyridine (**4SP**).



4SP

Preliminary experiments have indeed shown that **4SP** reacts with SmI_2 at least an order of magnitude faster than **BAI**. In addition, as will be shown below, the reaction displays a novel role for the proton donor with a high probability of a proton coupled electron transfer (PCET) mechanism.

The reaction of **4SP** with SmI_2 yields the dimer cleanly (eq 1). However, as will be shown below, the kinetics of this simple reaction are rather complex. Therefore, kinetic traces instead of rate constants will be presented throughout this paper.



(1)

In this work, the effect of the following additives on the reaction was examined using a stopped flow spectrometer to follow the disappearance of SmI_2 at 619 nm: MeOH, trifluoroethanol (TFE), HMPA, and SmI_3. Figures 1 and 2 show the effect of the concentration of MeOH and of TFE.

As can be seen in the highest trace in each figure, in the absence of a proton donor the reaction manifests autocatalytic behavior as do the imines **BAI**, **BMI**, and **BPI**.[1] The catalyst generated in the course of the reaction is most

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(1) Rao, C. N.; Hoz, S. *J. Am. Chem. Soc.* **2011**, *133*, 14795.

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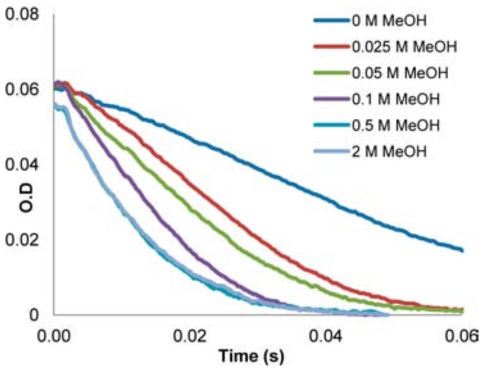

Figure 1. Kinetic traces showing the effect of MeOH concentration on the reaction of SmI_2 (0.5 mM) with **4SP** (5 mM).

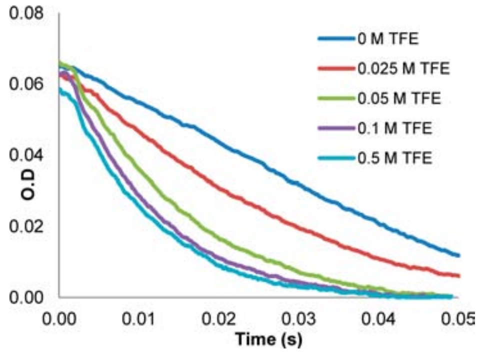

Figure 2. Kinetic traces showing the effect of TFE concentration on the reaction of SmI_2 (0.5 mM) with **4SP** (5 mM).

probably the Sm^{3+}. As more and more proton donor is added to the reaction mixture, the autocatalytic nature gradually disappears and the kinetics become more characteristic of a pseudo-first-order reaction. Consequently, to determine the kinetic order in the substrate, which turned out to be 1, we have used 4 M MeOH (Table S1 and Figure S1).

In general, if the protonation is by proton donors from the bulk, the kinetic order in the proton donor should be 1. If it is done from within the complex of the proton donor and SmI_2, the log−log plot will exhibit a sigmoidic shape with leveling off around a 4 M solution.[3] This is achieved when all the coordination sites on samarium are occupied as in the case of MeOH. In the present case we see a different behavior. In spite of the absence of exact rate constants, it is clear that the reactions are enhanced by the proton donors. However, rate leveling takes place much before the proton donor concentration reaches 4 M. This behavior does not correspond to protonation from the bulk nor to protonation from within the SmI_2 coordination sphere. The latter is evidenced by the fact that the leveling off takes place at a proton donor concentration much smaller than 4 M and by the behavior with TFE which does not complex to SmI_2. The leveling off concentration is in line with the formation of a hydrogen bond between the pyridine nitrogen of **4SP** and the alcohol. Once saturation is achieved, an additional amount of alcohol will not affect the rate. In accordance with this is the fact that the more acidic alcohol, TFE, reaches saturation at 0.1 M, whereas MeOH levels off only around 0.5 M. The rate enhancement due to this hydrogen bonding may be due to either an increase in the electron affinity of the substrate or a PCET (proton coupled electron transfer).[4] This point will be discussed below.

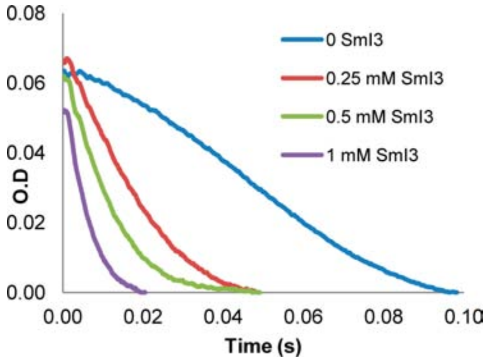

Figure 3. Kinetic traces showing the effect of Sm^{3+} concentration on the reaction of SmI_2 (0.5 mM) with **4SP** (5 mM). No proton donor was added.

As we have seen, the reaction is autocatalytic, and as was the case with **BAI**, it is highly likely that the catalyst is the Sm^{3+} generated in the course of the reaction. It is postulated that it causes a rate enhancement by complexing to the pyridine nitrogen of the substrate, increasing thereby its electrophilicity. To test this postulate, SmI_3 was prepared externally and added to the reaction mixture. Figure 3 shows the effect of Sm^{3+} on the reaction.

It is clear that even at a concentration which is a fraction of the millimolar concentration (concentrations similar to those generated in the course of the reaction), Sm^{3+} significantly catalyzes the reaction. To assess its complexation

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(2) For reviews on SmI_2 over the past 10 years, see: (a) Szostak, M.; Procter, D. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 9238. (b) Sautier, B.; Lyons, S. E.; Webb, M. R.; Procter, D. J. *Org. Lett.* **2012**, *14*, 146. (c) Sautier, B.; Procter, D. J. *Chimia* **2012**, *66*, 399. (d) Procter, D. J.; Flowers, R. A., II; Skrydstrup, T. *Organic Synthesis Using Samarium Diiodide: A Practical Guide*; The Royal Society of Chemistry: Cambridge, U.K., 2010. (e) Concellón, J, . M.; Rodrkguez-Solla, H.; Concellón, C.; Amo, V. *Chem. Soc. Rev.* **2010**, *39*, 4103. (f) Honda, T. *Heterocycles* **2010**, *81*, 2719. (g) Nakata, T. *Chem. Soc. Rev.* **2010**, *39*, 1955. (h) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7140. (i) Dudnik, A. S.; Sromek, A. W.; Rubina, M.; Kim, J. T.; Kel’in, A. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 1440. (j) Gopalaiah, K.; Kagan, H. B. *New J. Chem.* **2008**, *32*, 607. (k) Ichikawa, S. *Chem. Pharm. Bull.* **2008**, *56*, 1059. (l) Faugeroux, V.; Genisson, Y. *Curr. Org. Chem.* **2008**, *12*, 751. (m) Jung, D. Y.; Kim, Y. H. *Synlett* **2005**, 3019. (n) Concellón, J. M.; Rodríguez-Solla, H. *Chem. Soc. Rev.* **2004**, *33*, 599. (o) Dahlén, A.; Hilmersson, G. *Eur. J. Inorg. Chem.* **2004**, 3393. (p) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371.

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to the nitrogen lone pair, we have performed ab initio calculations at the B3LYP/SDD level,[5] on the interaction energy between pyridine and $SmCl_3$. We have examined multiplicities 2, 4, 6, and 8 for Sm^{3+} (Tables S2, S3). The complexation energies of the most stable electronic configuration (multiplicity 6) and that of the lowest multiplicities were −38.1 and −39.3 kcal/mol, indicating a strong affinity of the pyridine to the positively charged samarium.

Thus, the two additives discussed above, ROH and Sm^{3+}, act by coordinating to the pyridine nitrogen lone pair. The question is, does SmI_2 itself also coordinate to the pyridine nitrogen? This was examined by spectral analysis as well as by ab initio calculations. Generally, complexation is evident from a change in the absorption spectrum of SmI_2. However, the high reactivity of **4SP** does not enable such a spectral measurement. Pyridine, the complexing part of the substrate, also reacts with SmI_2. Therefore, the spectrum of SmI_2 with a pyridine derivative, 4-methoxypyridine, which shows a relatively low reactivity toward SmI_2, was examined. It was found that, even at a 50 mM concentration of 4-methoxypyridine, the double humped spectrum of SmI_2 is significantly distorted, indicating complexation to SmI_2. The spectrum is further distorted at higher concentrations (Figure S2). Interestingly, HMPA induces upon complexation the coalescence of the two humps and a blue shift.[6] MeOH causes a coalescence with no shift,[7] and the 4- methoxypyridine causes coalescence with a red shift.[8] Ab initio calculations were carried out examining multiplicities 1, 3, 5, 7, 9, and 11 of $SmCl_2$ (Table S4). The interaction of pyridine with Sm^{2+} at the most stable multiplicity (7) and at its lowest multiplicity (1) was found to have complexation energies of −29.4 and −29.5 kcal/mol, respectively (Table S3).

Thus, the spectral and computational evidence support the complexation of SmI_2 to the substrate. To demonstrate that this complexation has indeed a significant effect on the reaction rate, we examined the effect of HMPA on the reaction. In general, HMPA accelerates such reactions due to the increase in the reduction potential of the SmI_2 coordinated to HMPA.[9] If the electron transfer is of an inner sphere nature,[10] the addition of HMPA may reduce the reaction rate. In the present case, in the absence of HMPA the reaction reaches 90% completion in less than 0.1 s. The addition of HMPA slows the reaction until, at 0.6 mM HMPA, the reaction reaches 90% completion after more than 1 s (Figure 4). A further increase in HMPA concentration induces rate enhancement, probably due to the formation of fully HMPA-coordinated SmI_2. At intermediate concentrations, complex behavior is exhibited because of a competition between Sm^{2+} and the generated Sm^{3+} for HMPA. Thus, at concentrations of 0.3 and 0.6 mM HMPA, the HMPA is inhibitive.

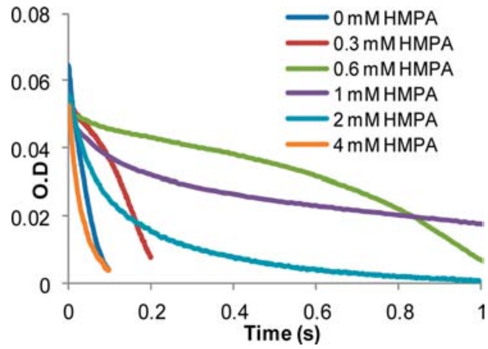

Figure 4. Effect of HMPA on the reaction of SmI_2 (0.5 mM) with 4SP (5 mM) in the presence of 25 mM MeOH.

It should be noted that the autocatalytic behavior observed in these cases does not follow the traditional scenario, namely generation of a catalyst in the course of the reaction, but rather is due to the removal of the inhibitor (HMPA) by Sm^{3+}.

The fact that ROH, Sm^{3+}, and SmI_2 compete for coordination to the lone pair on the nitrogen clearly explains why the kinetics of these reactions are not amenable to simple kinetic analysis. Furthermore, the variation in the concentrations of these complexants, as the reaction progresses, adds to the difficulty of the analysis. In the above we have touched only upon first-order effects. A detailed kinetic analysis should also consider the interaction of Sm^{3+} and SmI_2 with ROH and its effect on their ability to coordinate to the nitrogen.

Because of the steric accessibility of the lone pair on the pyridine nitrogen, the additives in the reaction of **4SP** display unique behavior. Alcohols enhance the reaction, but their effect is leveled off after hydrogen bond saturation is achieved at less than 1 M ROH concentration. Sm^{3+} is very effective in enhancing the reaction, and HMPA at a

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(8) It is possible that the direction of the shift is controlled by interactions taking place outside of the σ framework such as back-donation *etc*.

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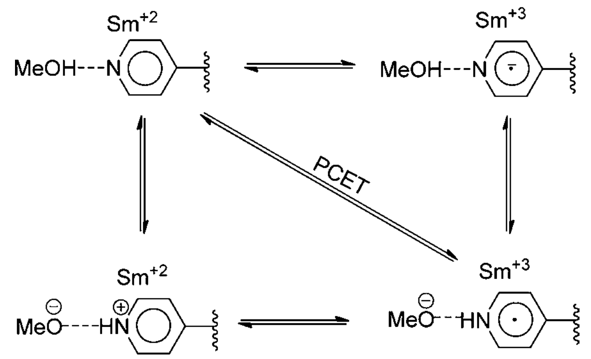

Figure 5. Schematic presentation of possible reaction mechanisms.

low concentration slows down the rate, but enhances it at a higher concentration. Because HMPA usually enhances the reactions of SmI_2, its present effect (at 0.6 mM) of lowering the reaction rate can be used to induce selectivity between substrates (or functional groups within a molecule) containing a pyridine ring and other substrates.[11] This nicely demonstrates the importance of understanding the mechanism and the role of additives in synthetic chemistry. Similarly, the unique dependence on the proton donor concentration could also be employed to discriminate between pyridine containing substrates and substrates that show higher order kinetics in the alcohol.

Figure 5 shows a schematic presentation of possible reaction mechanisms. Motion along the periphery of the scheme implies a sequential proton transfer (PT)/ET followed by ET/PT steps. Motion along the diagonal implies that the proton transfer is coupled to the electron transfer (PCET).[4]

In this mechanism the changes in the geometries of the reactants and the solvent reorganization, which bring the HOMO of the donor to the same energy level as the LUMO of the acceptor, are accompanied by the motion of the proton toward the nitrogen along the hydrogen bond. Counterclockwise motion along the scheme periphery is highly unlikely because of the high endothermicity of the first step in this relatively nonpolar solvent (THF). It is more difficult to decide between the PCET path and clockwise motion because of the electrostatic interactions involved. We have found that the electrostatic interactions contribute ca. 25 kcal/mol to the energy of the electron transfer process.[12] This is in line with Saveant's finding that the electron transfer could be coupled not only to proton transfer but also to the formation of an ion pair.[13] Since the proton transfer is endothermic, according to the Hammond postulate[14] the transition state generating the methoxide anion is late. This gives some advantage to the PCET mechanism over the peripheral clockwise path, as it leads to a hard–hard (MeO^-–Sm^{3+}) interaction rather than to a soft–hard (radical anion–Sm^{3+}) one.[15]

Supporting Information Available. Tables S1–S4, Figures S1 and S2, general information, experimental procedures, copies of ^1H and ^{13}C NMR spectra of starting material, and full characterization spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(11) Using half-lives as a criterion for the reaction rate, in the absence of HMPA, **4SP** is 140 times faster than acetophenone and in the presence of 0.6 mM HMPA acetophenone is 13 times faster than **4SP** ([substrate] 5 mM, [SmI_2] 0.5 mM, [MeOH] 25 mM).

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