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Mechanistic Study of β-Substituent Effects on the Mechanism of Ketone Reduction by SmI_2

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Abstract: The rate constants for the reduction of 2-butanone, methylacetoacetate, N, N-dimethylacetoacetamide, and a series of 4′- and 2′-substituted acetophenone derivatives by SmI_2 were determined in dry THF using stopped-flow absorption decay experiments. Activation parameters for the electron-transfer processes in each series of compounds were determined by a temperature-dependence study over a range of 30 to 50 °C. Two types of reaction pathways are possible for these electron-transfer processes. One proceeds through coordination (Scheme 1) while the other involves chelation (Scheme 2). The results described herein unequivocally show that both coordination and chelation provide highly ordered transition states for the electron-transfer process but the presence of a chelation pathway dramatically increases the rate of the reduction of these substrates by SmI_2. The ability of various functional groups to promote a chelated reaction pathway plays a crucial role in determining the rate of the reaction. Among the 2′-substituted acetophenone series, the presence of a fluoro, amino, or methoxy substituent enhances the rate of reduction compared to the 4′-analogues. In particular, the presence of a 2′-fluoro substituent on acetophenone provides a highly ordered transition state and considerably enhances the rate of ketone reduction.

Introduction

Since Kagan's pioneering work in 1980,[1] Samarium diiodide (SmI_2) has become a powerful tool in the arsenal of synthetic chemists. There are essentially three classes of transformations mediated by SmI_2 that are discussed in Kagan's seminal paper: functional group reductions, reductive coupling of two Π bonds, and reductive coupling between halides and Π bonds. In particular, the reduction of ketones to alcohols and the reductive coupling of carbonyls with olefins provide entry into a diverse range of natural products[2] including, (±)-muscone,[3] upial,[4] paeoniflorigenin,[5] (−)-grayanotoxin,[6] and (−)-steganone.[7] Although SmI_2 is clearly a useful reagent in organic synthesis, its mode of action in the reduction of carbonyls is only beginning to be understood at a basic level.

The reduction of dialkyl ketones to alcohols or pinacols by SmI_2 tends to be a slow process in the absence of additives such as HMPA,[8] alcohols,[9] or inorganic salts.[10] Conversely, the intramolecular reductive coupling of ketones containing pendant olefins is a fast reaction.[11] On the basis of this evidence, Curran postulated that the reductions of ketones is a fast reversible reaction with the equilibrium lying to the side of unreacted dialkyl ketone and SmI_2 (1).[12]

(1)

While additives can increase the rate of ketone reduction, the presence of an amide or ester in close proximity to a ketone also enhances the rate of reduction to a ketyl. In fact, Molander has reported that β-ketoamides can be reduced preferentially in the presence of a pendant alkyl iodide.[13] This is surprising because the redox potentials of alkyl iodides are typically 1 V less negative than dialkyl ketones, and this indicates that chelation may enhance the rate of reduction of ketones significantly.

In the realm of enantioselective reactions, chelation is the predominant feature of most transition-state models that are used to explain the stereochemical outcome of reactions mediated by SmI_2. Molander,[14] Keck,[15] and Matsuda[16] have utilized chiral

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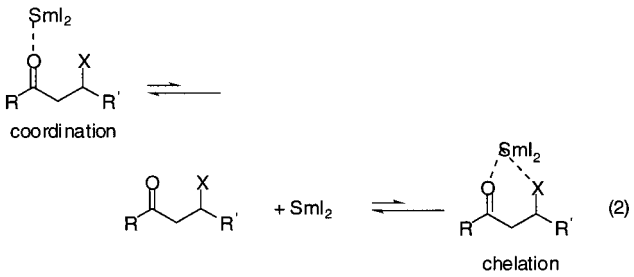
(1) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.
(2) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307.
(3) Suginome, H.; Yamada, S. *Tetrahedron Lett.* **1987**, *28*, 3963.
(4) Nagaoka, H.; Shibuya, K.; Yamada, Y. *Tetrahedron Lett.* **1993**, *34*, 1501.
(5) Corey, E. J.; Wu, Y.-J. *J. Am. Chem. Soc.* **1993**, *115*, 8871.
(6) Kan, T.; Hosokawa, S.; Nara, S.; Oikawa, M.; Ito, S.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 5532.
(7) Monovich, L. G.; Heuron, Y. L.; Ronn, M.; Molander, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 52.
(8) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485.
(9) (a) Kagan, H. B.; Namy, J. L.; Girard, P. *Tetrahedron* **1981**, *37*, 175; (b) Dahlen, A.; Hilmersson, G. *Tetrahedron Lett.* **2001**, *42*, 5565.
(10) (a) Kamochi, Y.; Kudo, T. *Tetrahedron Lett.* **1991**, *32*, 3511; (b) Fuchs, J. R.; Mitchell, M. L.; Shabangi, M.; Flowers, R. A., II. *Tetrahedron Lett.* **1997**, *38*, 8157.
(11) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 872.
(12) Curran, D. P.; Fevig, T. L.; Jasperse, C. P.; Totleben, M. J. *Synlett* **1992**, 943.
(13) Molander, G. A.; Etter, J. B.; Zinke, P. W. *J. Am. Chem. Soc.* **1987**, *109*, 453.
(14) Molander, G. A.; Harris, C. R. *J. Org. Chem.* **1998**, *63*, 812.
(15) Keck, G. E.; Wager, C. A.; Sell, T.; Wager, T. T. *J. Org. Chem.* **1999**, *64*, 2172.

multifunctional templates to control the stereoselectivity of carbonyl reductions and ketyl-olefin couplings. While chelation between SmI_2 and multifunctional substrates is reasonable, in the absence of kinetic studies, it is uncertain whether such chelates are intermediates or products of nonproductive equilibrium (2).



We initiated rate and mechanistic studies of the reduction of 2-butanone, methylacetoacetate, *N*,*N*-dimethylacetoacetamide, acetophenone, and a series of 4′-substituted and 2′- substituted acetophenone derivatives. Reduction of these substrates by SmI_2 proceeds without complicating side reactions. Activation parameters for different SmI_2-substrate systems were determined and evaluated. The results reveal an important role for several functional groups and their ability to stabilize either a chelated or a coordinated transition state.

Experimental Section

Materials and General Procedures. THF was distilled from sodium benzophenone ketyl, under nitrogen atmosphere. Dried solvents were stored in an Innovative Technology, Inc. drybox containing a nitrogen atmosphere and a platinum catalyst for drying. The SmI_2 was prepared according to a reported procedure.[17]The concentration of the SmI_2 was determined by iodometric titration.[18]Butanone, methylacetoacetate, *N*,*N*-dimethylacetoacetamide, and all acetophenone derivatives were received from Aldrich and distilled under vacuum from CaO before use.

SX.18 MV Stopped-Flow Reaction Analyzer. Kinetic experiments in THF were performed with a Computer Controlled SX.18 MV Stopped-Flow Spectrophotometer (Applied Photophysics Ltd., Surrey, UK). The SmI_2 and substrates were taken separately in airtight Hamilton Syringes from a glovebox (Innovative Technology, Newburyport, MA) and injected in to the stopped-flow system. The cellblock and the drive syringes of the Stopped-Flow Reaction Analyzer were flushed at least three times with dry degassed THF to make the system anaerobic. The concentration of SmI_2 used for the study was 0.005 M. The concentration of the ketone substrates was kept high relative to [SmI_2] (0.05−0.45 M) to maintain pseudo-first-order conditions. The pseudo-first-order rate constants were determined using standard methods.[19]Reaction rates were determined from the decay of the SmI_2 absorbance at 555 nm. The decay of SmI_2 displayed first-order behavior over >4 half-lives for all SmI_2–substrate combinations. A representative stopped-flow trace for the reduction of methylacetoacetate by SmI_2 is contained in Figure 1. The temperature studies were carried out over a range between 30 and 50 °C using a Neslab circulator connecting to the sample-handling unit of the stopped-flow reaction analyzer. The step size used for the temperature study was 5 °C and each kinetic trace was recorded at a known temperature that was measured by a thermocouple in the reaction cell.

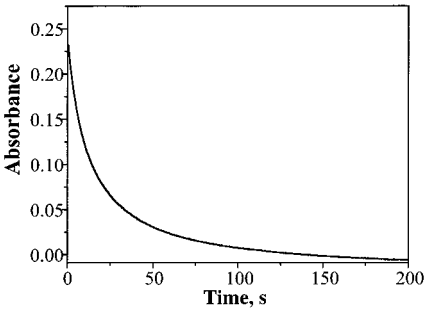


Figure 1. Stopped-flow trace showing the decay of SmI_2 absorbance at 555 nm in the presence of methylacetoacetate (0.25 M) at 25 °C.

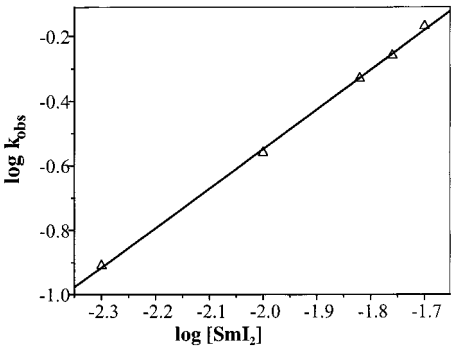


Figure 2. Plot of log k_{obs} versus log[SmI_2] for the reduction of methylacetoacetate (0.50 M) in THF at 25 °C.

Table 1. Rate Constants Obtained for Electron Transfer between SmI_2 and 2-Butanone, Methylacetoacetate, and *N*,*N*-Dimethylacetoacetamide

substrate	rate constant, $M^{-1}s^{-1}$[a]
2-butanone	$7 \pm 3 \times 10^{-4}$[b]
methylacetoacetate	$2.2 \pm 0.4 \times 10^{-1}$
N,*N*-dimethylacetoacetamide	$7.5 \pm 0.4 \times 10^{-2}$

[a] Experimental values are reported as $\pm\sigma$ and experimental uncertainties were propagated through these calculations. [b] The natural decay of SmI_2 obtained was 4.4×10^{-4} s^{-1}. All rate data are the average of at least two independent runs.

Results and Discussion

The goal of this work was to determine the relative importance of chelation versus coordination in SmI_2 reductions of ketones containing pendant functional groups. All studies were carried out in the absence of inter- and intramolecular proton donor sources to simplify the kinetic analysis. The pseudo-first-order rate constants for the reduction of all of the ketones studied display a first-order dependence on [SmI_2] (Figure 2) and on [ketone]. The data are consistent with the rate law shown in eq 3. The rate constants for the reduction of 2-butanone, methylacetoacetate, and *N*,*N*-dimethylacetoacetamide are contained in Table 1.

$$\text{rate} = k[SmI_2]\,[\text{ketone}] \qquad (3)$$

The rate of reduction of 2-butanone was just above the measured rate for the natural decay of SmI_2 in THF.[20] Nonetheless, the data clearly show that the presence of a β-ester or amide function

(16) Kawatsura, M.; Hosaka, K.; Matsuda, F.; Shirahama, H. *Synlett* **1995**, 729.
(17) Curran, D. P.; Gu, X.; Zhang, W.; Dowd, P. *Tetrahedron* **1997**, *53*, 9023.
(18) Shotwell, J. B.; Sealy, J. M.; Flowers, R. A., II. *J. Org. Chem.* **1999**, *64*, 5251.
(19) Pedersen, S. U.; Lund, T.; Daasbjerg, K.; Pop, M.; Fussing, I.; Lund, H. *Acta Chem. Scand.* **1998**, *52*, 657.

(20) The natural decay of SmI_2 was determined by injecting 5 μL of 5 mM SmI_2 into THF and monitoring the decay of the band at 555 nm. The source of the decay is likely due to the presence of small amounts of oxygen in THF. The natural decay of SmI_2 in THF has been reported in other kinetic studies and is within the same order of magnitude reported here (see ref 22).

Table 2. The Activation Parameters for Electron Transfer between SmI_2 and Methylacetoacetate and *N,N*-Dimethylaetoacetamide

substrate	energy of activation, E_a kcal/mol[a]	entropy of activation, $\Delta S^{\ddagger}$ cal/mol K[b]	enthalpy of activation, $\Delta H^{\ddagger}$ kcal/mol[b]	free energy of activation, $\Delta G^{\ddagger}$ kcal/mol[c]
methylacetoacetate	16.8 ± 1.0	-6 ± 1	16.1 ± 1.0	18.0 ± 1.1
N,N-dimethylacetoacetamide	10.6 ± 0.4	-15 ± 1	10.0 ± 0.4	14.6 ± 0.5

[a] Calculated from $E_a = \Delta H^{\ddagger} + RT$. [b] Eyring activation parameters were obtained from $\ln(k_{obs}h/kT) = \Delta H^{\ddagger}/RT + \Delta S^{\ddagger}/R$. [c] Calculated from $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$. Experimental values are reported as $\pm\sigma$. Experimental uncertainties were propagated through these calculations.

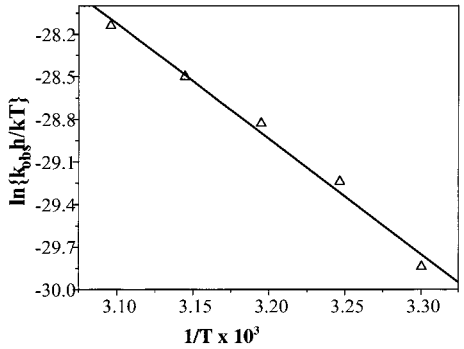


Figure 3. Eyring plot for SmI_2/methylacetoacetate system over a temperature range of 30 to 50 °C.

dramatically accelerates the reduction of ketones. For a dialkyl ketone, the presence of a β-ester changes the rate constant by over 2 orders of magnitude, while the presence of a β-amide alters the rate constant by 6 orders of magnitude.

To gain a more detailed understanding of the electron-transfer process and the possible role of chelation, rates were measured over a 30−50 °C temperature range to obtain activation enthalpies ($\Delta H^{\ddagger}$) and entropies ($\Delta S^{\ddagger}$) from the linear form of the Eyring eq 4.

$$\ln(k_{obs}h/kT) = -\Delta H^{\ddagger}/RT + \Delta S^{\ddagger}/R \qquad (4)$$

Since the rate of reduction of 2-butanone was within the same order of magnitude as the natural decay of SmI_2 under our experimental conditions, only activation data for methylacetoacetate and *N,N*-dimethylacetoacetamide were obtained. The results are contained in Table 2. Figure 3 contains a representative Eyring plot for the reduction of methylacetoacetate by SmI_2. We are fully aware that without a rigorous analysis, activation parameters are susceptible to systematic errors.[21] Nonetheless, comparison of the data provides valuable insight into the activation process for a series of related reactions.

Comparison of $\Delta H^{\ddagger}$ for the reduction of the ketone function by SmI_2 in methylacetoacetate and *N,N*-dimethylacetoacetamideshows that the energy required for bond reorganization in the transition state is 6 kcal/mol lower for the latter case. The negative $\Delta S^{\ddagger}$ values for the reduction of the β-ketoamide and ester are consistent with an ordered transition state. The lower $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ values for the β-ketoamide (compared to a β-ketoester) suggest that the more basic amide is better at stabilizing a chelated transition state compared to an ester. The combination of the rate and activation studies clearly support a chelation mechanism for the reduction of β-ketoesters and amides.

Since the rate of reduction of dialkyl ketones by SmI_2 is very slow, we examined acetophenone and a series of 4′- and 2′-substituted derivatives ($-OCH_3$, $-NH_2$, $-F$, and $-Cl$). The rate of reduction of acetophenone by SmI_2 was recently examined in an elegant study by Daasjberg and co-workers and shows that the rate is in an accessible range for stopped-flow kinetic analysis.[22] The acetophenone derivatives were studied to make a direct comparison between the rates and activation parameters obtained upon both chelation and coordination. The 4′-substituted derivatives only afford access to a coordinated intermediate (or transition state) while the 2′-derivatives should be capable of providing a chelated pathway to reduction of the ketone. The substituents should provide similar electronic effects whether they are in the 4′- or 2′-position of the phenyl ring. The pseudo-first-order rate constants and the activation parameters for the reduction of the 4′-acetophenone derivatives by SmI_2 are contained in Table 3.

The presence of a fluorine, methoxy, or amino substituent in the 4′- position of acetophenone has a deleterious effect on the rate of reduction by SmI_2 with fluoro providing the smallest decrease in the rate and amino substantially reducing the rate of reduction of the ketone. All of these substituents are capable of donating electron density to the ketone, making it more difficult to reduce to a ketyl. The 4′-chloro derivative is reduced at a faster rate than the parent acetophenone. The rate constants for reduction of the 4′- series by SmI_2 parallels their thermodynamic reduction potentials.[23]

The 4′- amino and methoxy derivatives have large negative entropies of activation of -40.3 and -36.3 cal mol^{-1} K^{-1}, respectively, and low barriers for $\Delta H^{\ddagger}$ (7.3 and 8.7 kcal mol^{-1}, respectively) and E_a (7.9 and 9.4 kcal mol^{-1}, respectively). Both are excellent electron-donating substituents and promote a large degree of electron density on the carbonyl. The activation parameters for the 4′-fluoro derivative are within experimental error of those for the parent acetophenone indicating a similar amount of order for the activated complexes of both substrates in their reduction by SmI_2. The 4′-chloro derivative of acetophenone has a $\Delta S^{\ddagger}$ similar to the 4′- fluoro substituent and parent acetophenone while $\Delta H^{\ddagger}$ and E_a are closer to the values for the 4′- amino and methoxy derivatives. All of these results are consistent with ordered transition states for all reductions. Coordination clearly leads to an ordered activated complex and is indicative of a strong interaction between Sm and ketones during reduction to a ketyl.

Next, the reduction of 2′-acetophenone derivatives by SmI_2 was examined in detail. Rate and activation parameters are contained in Table 4. Inspection of the rate constants for the 2′-substituted acetophenones reveals some interesting differences from the 4′-series. The rate constant for the reduction of 2′-methoxyacetophenone is 17 times greater than the rate constant for the same substituent in the 4′-position of the phenyl ring. Even larger changes are apparent for the 2′-fluoro and 2′-amino

(21) Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5573.

(22) Enemaerke, R. J.; Hertz, T.; Skrydstrup, T.; Daasbjerg, K. *Chem. Eur. J.* **2000**, *6*, 3747.

(23) *Encyclopedia of Electrochemistry of the Elements*; Bard, A. J., Lund, H., Eds.; Marcel Dekker: New York, 1978; Vol. XII, pp 59−61.

Table 3. Rate Constants and Activation Parameters for Electron Transfer between SmI_2 and 4′-Substituted Acetophenone Derivatives

substrate	rate constant, k ($M^{-1}s^{-1}$)[a,b]	energy of activation, E_a kcal/mol[c]	entropy of activation, $\Delta S^{\ddagger}$ cal/mol K[d]	enthalpy of activation, $\Delta H^{\ddagger}$ kcal/mol[d]	free energy of activation, $\Delta G^{\ddagger}$ kcal/mol[e]
acetophenone	7.0 ± 0.7	10.5 ± 0.6	-26 ± 2	9.9 ± 0.6	18.0 ± 0.9
4′-methoxyacetophenone	$2.0 \pm 0.3\ 10^{-1}$	9.4 ± 0.4	-36 ± 1	8.7 ± 0.4	20.1 ± 0.5
4′-aminoacetophenone	$4.0 \pm 0.2\ 10^{-2}$	7.9 ± 0.7	-40 ± 2	7.3 ± 0.7	19.9 ± 0.9
4′-fluoroacetophenone	2.9 ± 0.3	10.4 ± 0.1	-28 ± 1	9.8 ± 0.1	18.4 ± 0.3
4′-chloroacetophenone	50 ± 6	8.9 ± 0.9	-27 ± 3	8.3 ± 0.9	16.7 ± 1.3

[a] All rate data are the average of at least two independent runs. [b] Experimental uncertainties were propagated through these calculations and all values are reported as $\pm\sigma$. [c] Calculated from $E_a = \Delta H^{\ddagger} + RT$. [d] Eyring activation parameters were obtained from $\ln(k_{obs}h/kT) = -\Delta H^{\ddagger}/RT + \Delta S^{\ddagger}/R$. [e] Calculated from $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$.

Table 4. Rate Constants and Activation Parameters for Electron Transfer between SmI_2 and 2′-substituted Acetophenone Derivatives

substrate	rate constant, k ($M^{-1}s^{-1}$)[a,b]	energy of activation, E_a kcal/mol[c]	entropy of activation, $\Delta S^{\ddagger}$ cal/mol K[d]	enthalpy of activation, $\Delta H^{\ddagger}$ kcal/mol[d]	free energy of activation, $\Delta G^{\ddagger}$ kcal/mol[e]
2′-methoxyacetophenone	3.4 ± 0.4	12.2 ± 0.5	-22 ± 2	11.6 ± 0.5	18.6 ± 0.8
2′-aminoacetophenone	6.7 ± 0.9	13.1 ± 0.7	-17 ± 2	12.5 ± 0.7	17.7 ± 0.9
2′-fluoroacetophenone	$2.9 \pm 0.3 \times 10^2$	3.2 ± 0.2	-45 ± 1	2.3 ± 0.2	16.2 ± 0.4
2′-chloroacetophenone	38.5 ± 2.0	7.9 ± 0.6	-32 ± 2	7.3 ± 0.6	17.2 ± 0.8

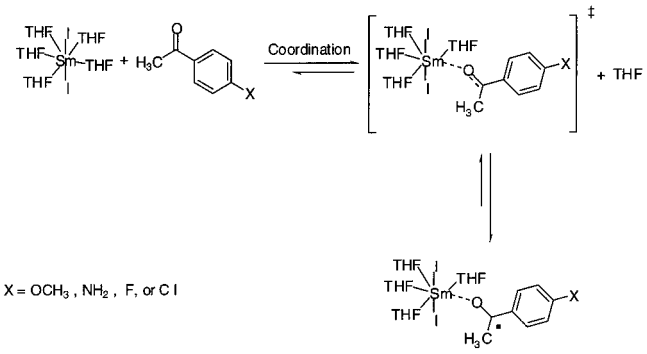
[a] All rate data are the average of at least two independent runs. [b] Experimental uncertainties were propagated through these calculations and all values are reported as $\pm\sigma$. [c] Calculated from $E_a = \Delta H^{\ddagger} + RT$. [d] Eyring activation parameters were obtained from $\ln(k_{obs}h/kT) = -\Delta H^{\ddagger}/RT + \Delta S^{\ddagger}/R$. [e] Calculated from $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$.

substituents. The rate constant for the reduction of 2′-fluoroacetophenone is 100 times larger than for the 4′-derivative while the rate constant for the reduction of 2′-aminoacetophenone is 168 times larger than for the 4′-derivative. Conversely, the rate constant for the reduction of 2′-chloroacetophenone is slightly smaller (ratio of 0.78) than it is for the 4′-derivative. The large differences in rates displayed for the 2′-amino, fluoro, and methoxy derivatives compared with those of the 4′-derivatives suggest that these substituents are capable of providing a chelated transition state during the reduction of a ketone by SmI_2 while the 2′-chloro substituent provides no chelation pathway to reduction.

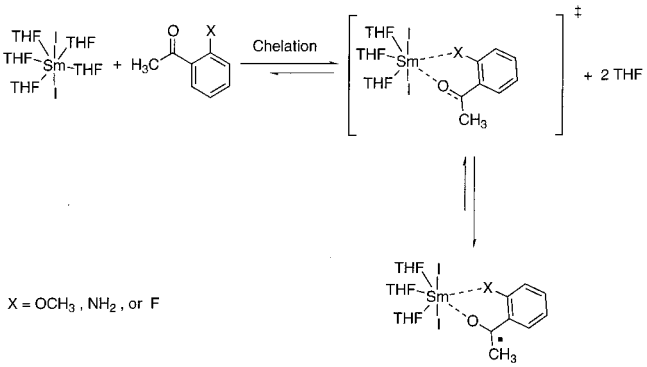
The activation parameters for the reduction of the 2′-acetophenone derivatives provided curious results. While the 2′-methoxy, amino, and fluoro substituents all provide enhanced rates for reduction of the carbonyl compared to their 4′-counterparts, only the fluoro substituent gives a more negative $\Delta S^{\ddagger}$ and smaller $\Delta H^{\ddagger}$ apparently consistent with chelation. Comparison of the activation parameters between 2′- and 4′-methoxyacetophenones shows that the former has a more positive $\Delta S^{\ddagger}$ (by 14 e.u.'s) and a $\Delta H^{\ddagger}$ more positive by nearly 3 kcal/mol. A similar trend, but with more dramatic differences, is displayed by the amino substituent. The activation parameters for the 2′-chloro substituent are within experimental error of those for the 4′-derivative indicating that the β-chloro substituent does not stabilize a chelated transition state.

The activation results described above show that the transition state for the 2′- methoxy- and 2′-aminoacetophenones are less ordered than for their 4′-counterparts. Are the data inconsistent with a chelated transition state? A recent crystal structure by Evans and co-workers shows that SmI_2 crystallized from THF is surrounded by five molecules of solvent.[24] Reduction occurring via a coordinated mechanistic pathway is likely to lead to the liberation of one or two molecules of THF (Scheme 1).[25]

Scheme 1



Scheme 2



Reduction proceeding through a chelated mechanistic pathway will certainly liberate more solvent (or an I^-) from the Sm reductant (Scheme 2). The liberation of more solvent or the displacement of an iodide ligand via a chelation pathway is going to offset the entropic cost of chelation leading to a more positive $\Delta S^{\ddagger}$, while the disruption of more solvent- or ligand-Sm interactions will lead to a more positive $\Delta H^{\ddagger}$.

The description above explains the results obtained for the 2′- methoxy and amino derivatives of acetophenone but does not clarify the activation results obtained for the reduction of 2′-fluoroacetophenone by SmI_2. If solvent displacement from Sm offsets the entropic cost of chelation, why does reduction of 2′-fluoroacetophenone proceed through a highly ordered

(24) Evans, W. J.; Gummersheimer, T. S.; Ziller, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 8999.

(25) Schemes 1 and 2 show the liberation of THF solvent from Sm. It is also possible that iodide is being liberated during coordination or chelation. Daasbjerg and co-workers have shown that basic cosolvents such as HMPA can displace iodide from Sm (see ref 21).

transition state? There are two plausible explanations for the data. First, the fluoro substituent is sterically less demanding than the methoxy or amino substituents and less solvent may be displaced in the activated complex. Second, the low E_a and $\Delta H^{\ddagger}$ values (3.2 and 2.3 kcal mol^{-1}, respectively) imply that the electronegative fluorine may have a higher affinity for the Sm that offsets the enthalpic loss because of solvent (or ligand) displacement. While some combination of both scenarios may also be responsible for the ordered transition state, all of these data taken together suggest that Sm is fluorophilic and that pendant fluorine substituents can drastically alter the rate and mechanistic course of ketone reduction. This finding is consistent with the recent work of Daasbjerg that shows that the strongest coordination to the samarium nucleus is observed for the smallest and most electronegative atoms in a series.[22]

Conclusions

The rate studies described in this paper show that the presence of a β-keto ester or amide dramatically accelerates the reduction of a dialkyl ketone by SmI_2 and activation data support a chelation pathway for the reduction. Kinetic experiments on the reduction of acetophenone derivatives by SmI_2 show that the presence of a 2′-fluoro, methoxy, or amino substituent enhances the rate of reduction compared to 4′-derivatives incapable of providing a chelation pathway to reduction, while the 2′-chloroacetophenone shows little difference from its 4′- derivative. The reduction of 2′-fluoroacetophenone by SmI_2 proceeds via a highly ordered transition state compared to the 2′-methoxy and 2′-aminoacetophenone derivatives indicating strong interaction between the fluorine substituent and Sm. The seminal work of Eliel and co-workers shows that the rates of reaction of chiral β-substituted ketones parallel the stereoselectivity of the reaction if chelation lies along the reaction coordinate.[26] Methods directed toward asymmetric synthesis of chiral organofluorine compounds are of current interest in the pharmaceutical industry.[27] The mechanistic studies herein suggest that SmI_2-mediated reductions and reductive coupling reactions of chiral β-substituted fluoroketones will provide high degrees of stereoselectivity. Experiments designed to examine this supposition are currently being carried out in our laboratory.

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Supporting Information Available: Decay traces and plots of rate data (print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778.
(27) Myers, A. G.; Barbay, J. K.; Zhong, B. *J. Am. Chem. Soc.* **2001**, *123*, 7207.