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Chelating alcohols accelerate the samarium diiodide mediated reduction of 3-heptanone

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Abstract—Initial rate studies of samarium diiodide mediated reduction of 3-heptanone to 3-heptanol are reported. The reduction of 3-heptanone with the polydentate tri(ethylene glycol) methyl ether is 16 times faster than without a proton donor, and 4.3 times faster than methanol. The primary kinetic isotope effect (KIE) was measured as $k^{H}/k^{D} \approx 2$, indicating a rate-determining proton transfer. Diols are superior to mono-alcohols as proton donors, the reduction of 3-heptanone is 255 times as fast with di(ethylene glycol) than in the absence of a proton donor. A mechanism of glycol accelerated samarium diiodide reduction is discussed. © 2001 Elsevier Science Ltd. All rights reserved.

Samarium diiodide (SmI_2) is rapidly becoming an important reagent in synthetic organic chemistry for its versatility in single and two electron transfer reactions. Samarium diiodide promotes reduction of halides, aldehydes, ketones, carboxylic acids, reductive eliminations, deoxygenations and many other reactions.[1] SmI_2-catalyzed reactions are known to be group selective, and the development of SmI_2 for asymmetric synthesis is under exploration.[2] However, the lack of detailed mechanistic knowledge prevents the full use of this promising reagent.[3]

Despite the extensive use of SmI_2 in THF, little is known about the structure of SmI_2 in other ethereal solvents and chelating groups. The seven coordinate solvate $\{SmI_2(THF)_5\}$ has been shown by Evans et al. to crystallize from a THF solution.[4] The *cis* and *trans* isomers of 8-coordinated samarium have been reported by Sen et al. for the dimethoxyethane (glyme) complex of SmI_2, $\{SmI_2(diglyme)_2\}$.[5] Recently we crystallized the chiral 8-coordinated complexes $\{\Delta-$ and Λ-$SmI_2(glyme)_3\}$.[6]

We now report on the kinetics of SmI_2 reduction of 3-heptanone using various alcohols as proton sources. The first studies of SmI_2 reductions of aldehydes and ketones showed that a proton source should be present to obtain high yields of alcohol,[1,3] but the actual role of the alcohol has not been investigated in detail. We have determined the role of the proton source or alcohol in the reduction of ketones by investigating the kinetics of simple alcohols, glycols and other chelating alcohols.

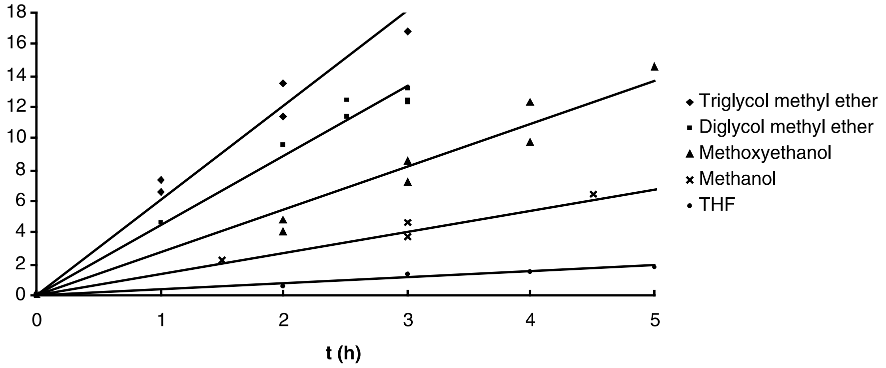

Figure 1. Initial rates of reduction of 3-heptanone with SmI_2 (0.1 M in THF) with various alcohols as proton sources.

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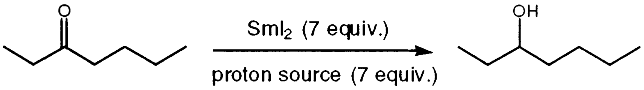
The results from mono-alcohols were also compared with those of the corresponding diols. We have studied the reduction of 3-heptanone in THF in the presence of various proton sources. An excess of SmI_2 and the proton source were used in order to keep the concentration of reactants approximately constant over the time for initial rate determinations. The progress of the reduction was followed by GC.[7]



The most commonly used proton sources (H^+) in SmI_2-mediated reactions are methanol and *t*-butanol. We found by IR studies that the alcohols (MeOH and *t*-BuOH) do not coordinate strongly to samarium, and therefore the stability of SmI_2 in THF is high, resulting in slow decomposition. The initial rates of the reduction with and without simple alcohols are shown in Fig. 1. The initial rate of reduction without a proton source appears very slow (0.3×10^{-4} M h^{-1}). Clearly there is an increase in rate observed when a proton source such as methanol, *t*-butanol or water is added to the THF solution of SmI_2 and 3-heptanone. The initial rate with methanol is 1.4×10^{-4} M h^{-1} or about 3.5 times the value without an added proton source. It is important to notice that in the absence of a proton source, the pinacol product is favored, especially in the case of phenyl substituted ketones.[4] The reactions involving methanol were rather slow and after 3 days at room temperature, only a 20% yield of heptanol was detected by GC. Prolonged reaction time, up to 3 weeks, did not improve the chemical yield. This is likely to be due to a slow reaction between the samarium diiodide and either THF or the alcohol.

We introduced additional chelating or coordinating group(s) in the alcohol, i.e. methoxyethanol and the di- and tri(ethylene glycol) methyl ethers. Alcohols with two, three or four available oxygens that can form chelates with samarium are better candidates at competing with THF due to entropy.

We observed that there is a significant increase in rate upon introducing chelating ether function(s) into the alcohol. The initial rate is almost 2 times larger with methoxyethanol (the initial rate is 2.7×10^{-4} M h^{-1}) than with methanol. With di- and tri(ethylene glycol) methyl ether the initial rates are 3.3 and 4.5 times as large as with methanol, respectively. The initial rate of reduction with tri(ethylene glycol) methyl ether is 6.0×10^{-4} M h^{-1}, or 16 times that without a proton source.

We also performed the reduction with half an equivalent of di(ethylene glycol) methyl ether versus SmI_2. However, the initial rate decreased by less than 20%, and doubling the amount of proton source resulted in less than a 10% increase in the initial rate. This small initial rate dependence on concentration indicates saturation kinetics. This could be the result of the formation of a complex between the SmI_2 and the chelating alcohol.

Furthermore, with the glycol methyl ethers the reactions did not stop at low conversion, as was the case with for example methanol. Instead, we observed yields above 90% after a reaction time of one week. Clearly the possibility of forming chelates between the alcohol and SmI_2 are crucial for the success of this reaction. We also added methanol to a SmI_2–THF solution containing one equivalent of triglyme. The initial rate of reduction of 3-heptanone using this mixture is much slower than that with only methanol. This result clearly shows that the rate of reduction increases significantly with alcohols that coordinate to the electron source, i.e. samarium diiodide.

Kinetic isotope effect

The large increase in rate upon addition of chelating glycols encouraged us to look for a primary kinetic isotope effect. The alcohols were deuterated by treatment with NaH followed by immediately quenching the alkoxide with D_2O.

The reduction performed with the deuterated alcohols proceeded at a significantly slower rate. From the initial

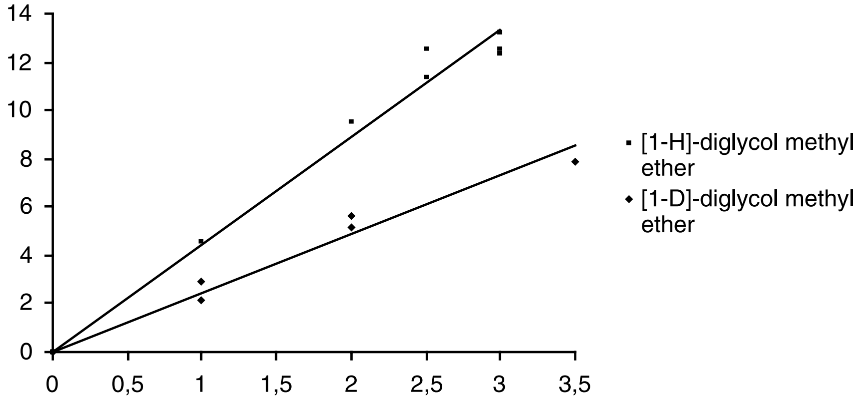


Figure 2. Initial rates of the reduction of 3-heptanone (0.014 M) with SmI_2 (0.1 M in THF) with [1-H]di(ethylene glycol) methyl ether and [1-D]di(ethylene glycol) methyl ether.

rates (see Fig. 2) we estimated a kinetic isotope effect (KIE) $k^H/k^D=2$. This clearly indicates that the rate limiting step in the SmI_2 reduction, using di(ethylene glycol) methyl ether as the proton source, involves a proton transfer.

Diols as proton sources

Encouraged by the observed large increase in rate by introducing ethereal functions into the alcohols, we were led to investigate the corresponding diols. The first diol we studied was 1,2-ethanediol, or glycol, with the oxygens separated by two methylene carbons. The initial rate of reduction with SmI_2 in the presence of one equivalent of 1,2-ethanediol was determined to be 16×10^{-4} M h^{-1}. Adding an ether function between the two alcohols gives di(ethylene glycol) (diglycol) (Fig. 3).

With diglycol we observed an initial rate of 97×10^{-4} M h^{-1}. The initial rate of reduction exceeded by 20 times that of diglycol methyl ether. Thus, the reduction of 3-heptanone is increased 255 times when diglycol is added to the THF–SmI_2 solution. Although the actual concentration of the proton donor is twice that of SmI_2, by itself, this does not explain the large rate enhancement. With triglycol, the initial rate was 36×10^{-4} M h^{-1}. Tetraglycol gave a comparably small rate enhancement, the initial rate being only 2.6×10^{-4} M h^{-1}. The number of ether oxygens plays a central role, determining the efficiency of the proton donor. The tetraglycol is probably too large to allow the ketone to coordinate to SmI_2.

We also performed the reduction with half an equivalent of diglycol versus samarium diiodide. The initial rate was determined to be approximately one sixth of that with one equivalent. Thus, the initial rate of reduction is strongly dependent on the concentration of diglycol. This indicates that that there is more than one molecule of diglycol involved in the rate limiting step or that different mechanisms are involved depending on the ratio of glycol versus SmI_2. Furthermore, the initial rate with 0.5 equiv. diglycol is still 4 times as fast as with 1.0 equiv. di(ethylene glycol) methyl ether (Table 1).

Mechanisms of diol accelerated SmI_2 mediated reduction

SmI_2 is a single electron transfer reagent and therefore the reduction reactions involve two SmI_2 molecules and two proton donors. The relatively hard Lewis base SmI_2 is known to be complexed by ethers. Hence, the addition of chelating ethers or ethereal alcohols is expected to form complexes with SmI_2.

The samarium diiodide is likely to be complexed with the glycol methyl ether in THF. To fulfil the coordination number of samarium(II), additional THF molecules may be coordinated. The carbonyl group is a strong dipole and competes with the ether function of the glycol for complexation with the samarium. Once the carbonyl is complexed to the samarium, an inner sphere electron transfer occurs.

Today most researchers have accepted the House mechanism with small variations or modifications.[8] Kagan has already suggested that SmI_2-mediated reductions of ketones proceeds via such a mechanism.[3] However, this mechanism does not adequately explain the large differences in the initial rates of reduction observed with mono-alcohols and the diols of the glymes. Either the rate determining step involves several molecules of the alcohols, or more likely another mechanism is dominating.

There is a recent report on the low-valent lanthanide mediated reduction of ketones, based on the isolation of ketyls or radical anions of ketones. The ketyls were found to be dimers in the solid state, with two bridging alkoxide oxygens between two samarium(III) cations.[9] Based on this, we propose the following mechanism involving a dimeric intermediate with two alcohol groups bridging between two samarium(II) diiodides, see Scheme 1. After electron transfer and proton transfer, the resulting SmI_2 alkoxide should be similar to the known isolated structure $\{YbI_2{\cdot}(OCH_3)(CH_3OCH_2CH_2OCH_3)\}_2$.[10]

Samarium(II) is oxidized to samarium(III) by the electron transfer to the complexed ketone. Since there are two samariums a two-electron transfer results in the formation of the dianion of the ketone. Simulta-

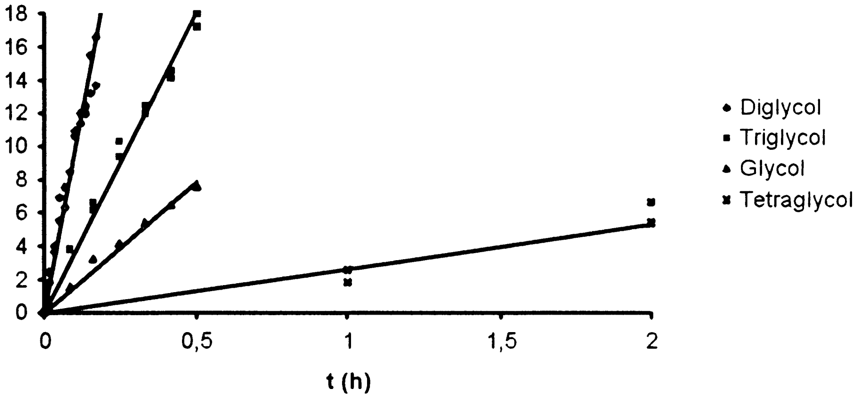
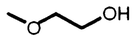
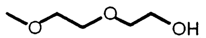
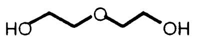
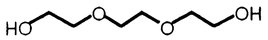
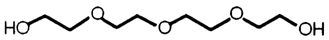
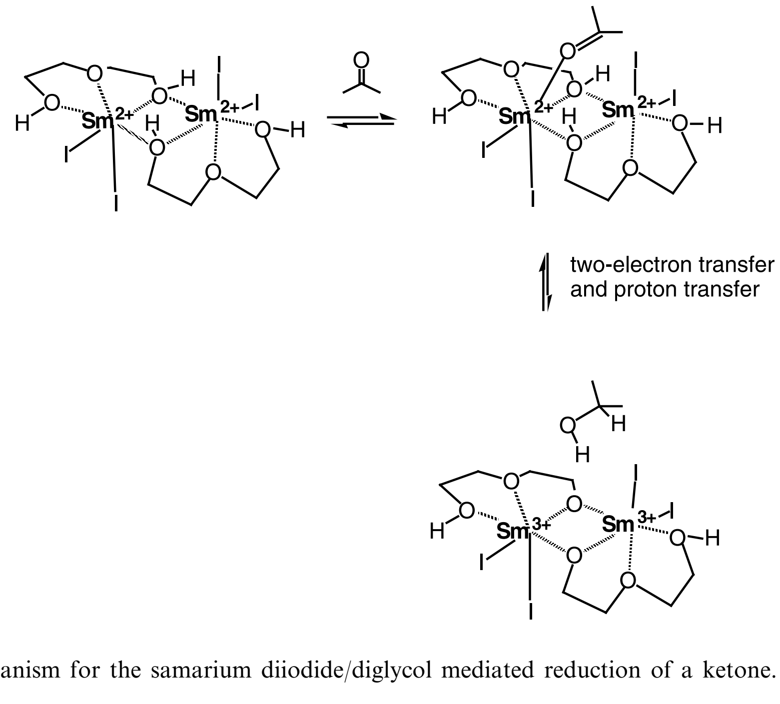


Figure 3. Initial rates of the reduction of 3-heptanone (0.014 M) with SmI_2 (0.1 M in THF) using various glycols.

Table 1. Initial rates of SmI_2 (0.1 M) mediated reduction of 3-heptanone (0.014 M) to 3-heptanol in THF at 20°C, with various proton sources

Entry	Proton source	eq.	SmI_2 eq.	k M h^{-1}×10^{-4}	Initial rate rel. to THF
1	THF	∞	7	0.38	1.0
2	MeOH	7	7	1.4	3.5
3	 methoxy ethanol	7	7	2.7	7.1
4	 di(ethylene glycol) methyl ether	7	7	4.4	12
5	- “ -	3.5	7	3.8	10
6	- “ -	14	7	5.0	13
7	- “ -	7	14	4.3	11
8	 tri(ethylene glycol) methyl ether	7	7	6.0	16
9	 ethylene glycol	7	7	16	42
10	 di(ethylene glycol)	7	7	97	255
11	- “ -	3.5	7	17	45
12	- “ -	14	7	67	176
13	 tri(ethylene glycol)	7	7	36	95
14	 tetra(ethylene glycol)	7	7	2.6	6.9



Scheme 1. Proposed mechanism for the samarium diiodide/diglycol mediated reduction of a ketone.

neously or subsequently to the electron transfer there is a rate determining proton transfer from the coordinated acidic alcohols to the developing dianion.

The rate enhancements are strongly dependent on the number of ethereal oxygens in the polydentate alcohols. The results of the kinetic studies indicate that chiral glycols are promising for asymmetric reductions. Currently, we are preparing chiral ethers to explore their potential in SmI_2-mediated asymmetric synthesis.

Experimental part

The SmI_2 (0.1 M) was purchased from Aldrich and kept inside a glove box (Mecaplex GB80 equipped with a gas purification system that removes oxygen and moisture). Inside the glove box there was a nitrogen atmosphere and the typical moisture content was less than 2 ppm. All glassware was dried in an oven at 140°C for no less than 24 h before use. In a standard procedure, SmI_2 (5.0 ml, 0.1 M, Aldrich) was added to a dry flask, fitted with a septum and containing a magnetic stirrer bar inside the glove box. The flask was kept under a nitrogen atmosphere during the reaction. The proton donor e.g. MeOH (1 equiv.) was added to the reaction vessel containing the THF solution of SmI_2 with stirring. To this mixture was then added the ketone, 3-heptanone (10 μl, 0.14 equiv.), at 20°C. A small portion of the mixture (100 μl) was removed via a syringe and quenched with I_2 in *n*-hexane (0.1 M, 0.1 ml) including 1-hexanol (0.016 M) as internal standard. To the quenched solution was added diethyl ether (1 ml) and HCl (0.12 M, 0.1 ml) to dissolve the inorganic salts. The organic layer was transferred to a vial and 1.0 μl was injected on the GC. The components were separated using a fused silica capillary column DBWX-30W (∅ = 0.25 μm, length = 30 m), using hydrogen as carrier gas at a flow rate of 2 ml/min. The injector temperature was 225°C, the column temperature was initially 70°C for 4 min, then heated to 220°C (10°C/min), and the detector temperature was 250°C. Retention times: 3-heptanone, 4.0 min, 3-heptanol, 6.6 min and 1-hexanol 7.6 min.

The reported initial rates for the reductions are the result of a minimum of three independent measurements, corrected for their individual GC detector responses.

Acknowledgements

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