

The Effect of Proton Donors on the Facial Stereoselectivity in SmI₂ Reduction of Norcamphor

Sarasij Kumar Upadhyay and Shmaryahu Hoz* Department of Chemistry, Bar-Ilan University, Ramat-Gan 52900, Israel

shoz@mail.biu.ac.il

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The *endo/exo* product ratio in the reactions of SmI_2 with norcamphor in the presence of various proton donors was determined. The effect of MeOH, EtOH, trifluoroethanol (TFE), ethylene glycol (EG), and water was investigated at various concentrations of these proton donors. At low concentrations of EtOH, TFE, and EG, an endo/exo ratio near unit was found. This ratio increased as the concentration of the proton donor increased. However, MeOH and water gave a U-type curve, in a plot of the endo/exo ratio vs proton donor concentration. The difference between the two groups of proton donors was shown not to result from differences in their acidities or polarity effects. It is suggested that at low MeOH and water concentrations, the second electron transfer takes place from the dimer of SmI_2 rather than from the monomer. This bulky electron donor approaches the radical anion preferentially from the *exo* direction giving rise to the high *endo/exo* ratio at the left arm of the U-shaped curve. Comparison of kinetic and product H/D isotope effects shows that protonation on carbon, the step that locks the stereochemistry, is a post rate determining step.

Introduction

Since its discovery, samarium iodide has proven itself as a useful reagent in organic synthesis.¹ It has been widely applied in the synthesis of important building blocks and natural products.² Its ability to form complexes with various reagents³ such as HMPA,⁴ methanol,⁵ glycols,⁶ water,^{5a,7} etc. has added to its versatility in terms of reactivity and stereoselectivity.⁸ A judicious choice of these additives and their fine-tuning may turn out to be extremely helpful in synthetic processes. Still, our understanding of the role of the

from complete. HMPA, one of the most commonly used additives, coordinates effectively with SmI_2 and increases its reduction potential from -1.3 to -2.05 V, rendering the reduction reaction more facile.⁹ On the other hand, alcohols

various additives in the chemistry of samarium iodide is far

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such as glyme coordinate to SmI₂ but do not change its reduction potential.¹⁰ Coordination by methanol greatly enhances various reactions. The rate enhancement, which in this case is not due to a higher reduction potential, must be realized by a different mechanism. We have shown¹¹ that when the electron transfer is highly endothermic, the lifetime of the radical anion formed is too short to enable an encounter with a proton donor from the bulk solution before back transfer of the electron to the Sm³⁺. However, if a methanol molecule is coordinated to the samarium cation in the ion pair, it can rapidly transfer its proton to the radical anion, capturing it in a unimolecular reaction. This is demonstrated by the reduction of α -cyanostilbenes as shown in eq 1, where no reaction was observed in the presence of trifluoroethanol (TFE) as the proton donor, yet a facile reaction took place in the presence of MeOH.



In this case, MeOH efficiency is due to its coordination to the SmI₂. Therefore, once the SmI₂ transfers its electron to the substrate, the MeOH being in the close vicinity of the radical anion can protonate it before back electron transfer takes place. The same concept of capturing an unstable radical anion before it donates its electron back to the samarium cation was employed also in photochemical reactions achieving some previously unattainable reactions.¹² Thus, through various mechanisms, additives can significantly shorten reaction times and in some cases convert a "no go" reaction into a "go" reaction. However, there may also be a down side to this coordination. It was shown in several instances that coordination by HMPA, for example, hampers inner-sphere electron transfer reactions.^{44,66,13}

In the present paper we report the effect of the coordination of SmI_2 on the stereochemical outcome of a carbonyl reduction reaction. It should be pointed out that coordination to lanthanides has been shown to increase the acidities of alcohols by ca. 15 orders of magnitude.¹⁴ Thus, in most of these cases, the protonation that locks the stereochemistry takes place either from a proton donor which is precoordinated to the samarium or in a transition state in which the

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incipient alkoxide is stabilized by a neighboring Sm^{3+} cation. It is clear that the size of the coordination shell of the SmI_2 increases with the concentration of the ligand in the reaction mixture (up to a saturation level). Thus, whenever there are two possible approach directions to the substrate differing in their steric accessibility, the stereoselection will vary with the size of the protonating complex, and hence, with the concentration of the ligand.

We have chosen to use norcamphor, one of the classical substrates for such studies,¹⁵ for our investigation. Its reduction yields two isomers, *endo* and *exo* (eq 2).



In this substrate the *exo* approach of the proton donor (leading to an endo product) is sterically less hindered than the *endo* one. We may therefore expect an effect of the concentration of proton donor on the facial stereoselectivity. When the proton donating system (coordinated SmI_2) is large, the *exo* approach will be preferred and hence, the production of the *endo* alcohol will be favored. However, as will be shown later on, this naïve hypothesis does not describe the reality in full.

Results and Discussion

All the reactions were conducted in THF at room temperature under nitrogen. The standard concentration of the norcamphor was 0.023 M and that of SmI_2 0.048 M. Unless otherwise indicated, the reactions were conducted until discoloration of the SmI_2 was observed.

In general, the mechanism for reduction of carbonyl compounds by SmI_2 consists in most cases of the following sequence: electron, proton, electron, proton transfer steps.¹⁶ The step that locks the stereochemistry is the protonation on the carbon atom. Since the reactions are conducted in a solvent of low polarity, the incipient alkoxide in the transition state of the proton transfer step is most likely stabilized by a samarium cation.¹⁷ The effect found upon variation of MeOH concentration on the stereochemistry is given in Table 1 and Figure 1.

 TABLE 1.
 Yield and Endo/Exo Percentage in the Reduction of Norcamphor with SmI2 in the Presence of Various Concentrations of MeOH

MeOH], M	time, h	yield, %	endo, %	exo, %
0.1	96	87	81	19
0.3	96	80	77	23
0.5	48	80	62	38
1	20	76	55	45
2	15	62	65	35
4	10	42	83	17

Surprisingly, the data show that as the MeOH concentration increases, the *endo/exo* ratio first decreases to a minimum

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FIGURE 1. The effect of MeOH concentration on the *endo/exo* ratio in the reduction of norcamphor with SmI_2 .

TABLE 2. Yield and Endo/Exo Percentage in the Reduction of Norcamphor with SmI₂ in the Presence of Various Concentrations of EtOH

[EtOH], M	time, h	yield, %	endo, %	exo, %
0.5	144	83	67	33
1	96	85	75	25
2	60	86	80	20

TABLE 3. Yield and Endo/Exo Percentage in the Reduction of Norcamphor with SmI₂ in the Presence of Various Concentrations of TFE

[TFE], M	time, h	yield, %	endo, %	exo, %
0.1	240	31	53	47
0.3	240	65	65	35
0.5	192	70	79	21
1	120	86	84	16

TABLE 4. Yield and *Endo/Exo* Percentage in the Reduction of Norcamphor with SmI₂ in the Presence of Various Concentrations of EG

[EG], M	time, h	yield, %	endo, %	exo, %
0.05	96	84	64	36
0.1	48	100	67	33
0.3	10	89	75	25
0.5	0.25	91	89	11
1	0.1	91	92	8

around 1 M and then increases again to close to the initial value. Because of this unexpected result, the effect of four additional proton donors—EtOH, trifluoroethanol (TFE), ethylene glycol (EG), and water—was examined.¹⁸ The results are shown in Tables 2-3,4,5 and in Figures 2 and 3.

As can be seen, there is no uniform behavior among the various proton donors. MeOH and H_2O show a minimum, whereas the three other alcohols display a continuous increase in the *endo/exo* ratio as the proton donor concentration increases. The behavior of these three alcohols can be explained as follows. In the absence of a proton donor, or at low concentration thereof, the oxygen atom of the radical anion generated upon the first electron transfer is coordinated to the Sm³⁺ (1). This would constitute a bulky group that would prefer to occupy the *exo* position. On the other hand, regardless of the intimate details of the mechanism, protonation of the carbanion at a later stage must involve a party of two, the proton donor and a samarium cation, which

TABLE 5. Yield and *Endo/Exo* Percentage in the Reduction of Norcamphor with SmI_2 in the Presence of Various Concentrations of H_2O

	-			-
[H ₂ O], M	time, h	yield, %	endo, %	exo, %
0.05	96	86	82	18
0.1	72	79	80	20
0.3	10	85	63	37
0.5	0.1	92	57	43
0.8	0.05	96	58	42
1	0.03	87	63	37
4	0.008	79	75	25



FIGURE 2. The effect of EtOH, TFE, and EG concentration on the *endo/exo* ratio.



FIGURE 3. The effect of H_2O concentration on the *endo/exo* ratio.

will stabilize the alkoxide when formed. This also is a large group of a size similar to that of the ketyl oxygen with its Sm^{3+} . The near similar size of the two groups leads to a lack of steric preference and the *endo/exo* ratio is indeed close to unity. As the concentration of the proton donor increases, the equilibrium depicted in eq 3 will be shifted to the right and a larger proportion of the ketyl oxygen will be protonated.



Since the OH group in 2 is smaller than the bulky protonation complex, it will preferentially assume an *endo* position allowing the ROH \cdot SmI₂ to approach 2 from the *exo*

⁽¹⁸⁾ Side products were observed in some cases, at higher concentrations of the proton donors. Reaction with ethylene glycol (2 M) as a proton donor resulted in poor yield (\sim 20%) because of the loss of material during aqueous workup.

direction. Thus, as the concentration of the proton donor increases the *endo/exo* ratio increases as well. The limited data at hand are insufficient for a suggestion of a detailed unequivocal mechanism for these reactions. This could involve a protonation of the oxygen of **1** by the protonating complex $ROH \cdot SmI_2$ forming **2**, followed by an electron transfer to generate the corresponding carbanion to produce **3**, which subsequently undergoes protonation with retention of configuration to produce preferentially the *endo* product (eq 4).



Alternatively, an electron could be transferred to the radical anion 1, generating the dianion 4, now stabilized by two Sm^{3+} ions, followed by protonation with retention of configuration to generate preferentially the *endo* product (eq 5).



The quandary is: What is the common denominator of the two proton donors, MeOH and water, that distinguishes them from the other proton donors? We have examined the acidity of these proton donors and their effect on the polarity of the THF solution. In the absence of data in THF we used the Bordwell scale in DMSO.¹⁹ The data are given in Table 6. (The value for EtOH is interpolated between that of MeOH and *i*-PrOH.²⁰) In the third column of the table, the calculated proton affinities in THF are displayed. The calculated

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 TABLE 6.
 Acidities in DMSO and the Gas Phase (Calculated) of the Proton Donors

proton donor	p <i>K</i> _a in DMSO	calcd, kcal/mol
TFE	23.45	311.6
MeOH	29.0	325.7
EtOH	29.6^{a}	325.5
H_2O	31.2	324.6
EG	n/a	315.9 ^b
^a Interpolated. ^b In	the cis conformation	



FIGURE 4. The effect of proton donors at 0.1, 0.5, and 1M concentration on the ET30 values of their solutions in THF.

tions were performed with Gaussian 09 at the B3LYP/6- $31+G^*$ level with the PCM solvation model.²¹

For the polarity effect of these proton donors on the THF solutions we used the ET30 scale.²² The results are presented graphically in Figure 4 and in Table S1 in the SI.

Interestingly, the polarity (ET30) of the pure additives decreases in the following order: water (63.1) > TFE (59.5)> EG (56.3) > MeOH (55.5) > EtOH (51.9).²³ Yet, examination of the data shows that water, when mixed with THF, affects the polarity much like the least polar proton donor used—EtOH. It should be noted that the high polarity of water is a colligative property. Namely, the dipole moment of water is 1.87 D, similar to that of MeOH (1.7 D).²⁴ The high polarity of water as a solvent is due to its highly ordered structure.²³ However, in its THF solution at low concentration, water molecules exist, most likely as monomer, dimer, or low molecular weight aggregates which are bound to THF molecules (the concentration of THF in THF is 12.3 M). Under these circumstances, the highly ordered lattice of water and hence the high polarity effect cannot be manifested and the water effect is similar to that of the low molecular weight alcohols.

In both parameters, acidity and polarity, two distinct groups are formed. One consists of TFE and EG and the other of EtOH, MeOH, and water. Thus, none of these properties make methanol and water a group distinguished from the rest of the proton donors. Another parameter one should consider is the ability to form a complex with SmI₂. Methanol and water are known to complex efficiently to

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SmI₂. However, EG is also an efficient complexant to SmI₂; yet, it does not exhibit the U-shaped graph of Figures 1 and 3.

We suggest that the governing factor is a combination of complexation ability and size. At very low proton donor concentrations, the radical anion has the structure of 1. To obtain a large *endo/exo* ratio, the protonating group must approach the radical anion preferentially from the exo direction. For this it must be significantly larger than the $O-Sm^{3+}$ unit of 1. An aggregate of SmI_2 with coordinated MeOH or H₂O molecule(s) satisfies this demand and seems to be the only conceivable protonating species that is considerably larger than the O-Sm⁺³ unit of 1. Recently Flowers et al. reported the existence of a SmI₂ dimer in the presence of water.²⁵ The concentration of the dimer increases with the concentration of water in the solution and the reduction potential of the dimer is much higher than that of the monomer. Thus, one can assume that such a dimer could be formed also with MeOH but not with the larger proton donor EG. We also assume that minute amounts of the dimer are present in the reaction mixture also at low concentrations of these proton donors.

At low concentrations of MeOH or water the reaction is indeed very slow. It is thus possible that the dimer, in spite of its low concentration, by virtue of its high activity, takes part in the second electron transfer. Due to its large size, it approaches the radical anion 1 from the *exo* direction as depicted in 5 (R = Hor Me). This dimer can transfer an electron to the ion-paired radical anion 1 to generate 4 with the C-Sm unit at the *exo* position, followed by protonation on the carbanion (eq 6).



Alternatively it could, as suggested above for the monomer, transfer a proton to the oxygen and concomitantly an electron to the carbon-centered radical to generate 3 (eq 7).



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FIGURE 5. The effect of SmI_2 concentration (solid line 0.084 M, dashed line 0.048 M) on the *endo/exo* ratio in the presence of various MeOH concentrations.

As the concentration of MeOH or water increases, more of the complex $\text{SmI}_2 \cdot (\text{MeOH or } H_2\text{O})_n$, which is of size similar to that of the $\text{O}-\text{Sm}^{3+}$ unit, is formed. This complex competes with the dimer and therefore the *endo/exo* ratio decreases as the proton donor concentration increases. At a certain point, the mechanism shifts to that of the other proton donors. Namely, **1** is converted to **2** and the relative amount of the *endo* isomer starts to increase.

Consistent with the dimer assumption is the result of the experiment in which we increased the SmI₂ concentration from 0.048 to 0.084 M while maintaining the concentration of substrate at 0.023 M. This increase in the SmI₂ concentration should, in principle, increase the concentration of the dimer in the solution. In this case the intervention of the monomeric SmI₂ in the reduction should be attenuated. Indeed, the decrease in the *endo/exo* ratio became more moderate and the minimum was obtained at a higher *endo/exo* ratio (Figure 5, also Table S2 in the SI).

Finally, we wanted to know whether protonation on the carbon is the rate determining step of the reaction. For this purpose we quenched two reactions, one with MeOH and one with MeOD (1M) after 5 and 10 h. The NMR yields were $33(\pm 2)\%$ after 5 h and $40(\pm 1)\%$ after 10 h for both alcohols. Thus, it seems that there is no kinetic isotope effect on the reaction rate. In the second experiment-incorporation isotope effect (6)—we ran a reaction with a mixture of MeOH and MeOD in a ratio of 1:3, respectively. The total concentration of MeOH(D) was 1 M. The ratio of H/D incorporation into the carbinol carbon was 42/58. Thus, the product distribution isotope effect is 2.2. This clearly shows that protonation of the carbon, the step that locks the stereochemistry, is a postrate determining step. It should be noted that the incorporation ratios for the endo and exo isomers were the same within experimental error. Thus, the product

⁽²⁶⁾ In another product distribution isotope effect experiment carried out under irradiation we obtained an isotope effect of 2.1, similar to that of the thermal reaction. (A solution of norcamphor (23 mM) in a 50 mL volumetric flask was allowed to react with SmI_2 (48 mM) in the presence of proton donor [1 M]. The solution was irradiated with a 400 W sun lamp until the blue color of SmI_2 disappeared.) This implies that within the resolution of this technique, the carbanions in the thermal and the photochemical reactions are of identical structure, although in the latter, the *endo/exo* ratio was different from the thermal: 2.4 and 3.2 for 0.1 and 1 M MeOH, respectively.

isotope effect is not sensitive enough to distinguish between these two environments.²⁶



Summary and Conclusions

In this paper we explored the effect of the size of the coordination shell around the SmI₂ on the stereochemical outcome in the reduction of norcamphor. We find two groups of proton donors. The first consists of water and methanol which at low concentrations yield a high endo/exo ratio. This ratio decreases to a minimum as the proton donor concentration is raised and then rises again yielding a U-type profile. EtOH, TFE, and EG start at an endo/exo ratio around one showing no facial preference. This ratio increases with the concentration of the proton donor. The increasing endo/exo ratio with the concentration of the proton donor could be easily understood. On the other hand, the counterintuitive observation that MeOH and water at low concentrations display a high endo/exo ratio that then decreases is less understood. It implies that the second electron transfer followed by protonation on the carbon takes place preferentially from the exo position. Namely, the species which approaches the radical anion must be larger than the O-SmI₂ unit, so as to force the later into the more hindered endo position. Such a species could be the dimer of SmI2, which was first discovered by Flowers²⁵ using water as an additive. We suggest that such a dimer is generated also with the other small proton donor—MeOH. This dimer, being the most reactive electron donor and the bulkiest species in the system, approaches the radical anion from the less hindered exo direction leading to the formation of the endo product. Consistent with this mechanism is the observed dependence of the *endo/exo* ratio on the SmI_2 concentration.

These results justify the statement we posited in the introduction saying that it is not enough to select the type of additive for the SmI_2 reductions. Fine tuning of their concentrations may be of no lesser importance.

Experimental Section

General. NMR spectra were recorded at 600 and 300 MHz on a FT-NMR spectrometer. THF was dried and freshly distilled

over Na wire + benzophenone under argon atmosphere. TFE, EtOH, and MeOH were dried according to known procedures.²⁷ Water content was determined and found to be lower than 20 ppm. SmI₂ was diluted as needed from a 0.1 M freshly prepared²⁸ THF solution. The concentration of the SmI₂ solution was spectroscopically determined ($\lambda = 615$ nm; $\varepsilon = 635$). The reactions were performed in a glovebox under nitrogen atmosphere at room temperature. The reduced products (norborneols) of norcamphor are known in literature.²⁹ The product ratios and percentage conversion were determined by high-resolution NMR (600 or 300 MHz) analyses of the crude reaction mixture after extraction, drying, and solvent evaporation.

Reduction with Samarium Iodide: General Procedure. A solution of norcamphor (23 mM) in THF was allowed to react with SmI₂ (48 mM) in the presence of the desired concentration of the proton donor. The reaction was carried out in the glovebox until the deep blue solution became colorless. Phosphate buffer (5%; 15 mL) was added, and the solution was extracted with dichloromethane $(3 \times 25 \text{ mL})$. The combined organic layer was washed with water $(2 \times 15 \text{ mL})$ followed by brine $(2 \times 20 \text{ mL})$, dried over anhydrous Na₂SO₄, and evaporated under reduced pressure to give crude reaction mixture. The percentage conversion and ratio of product distribution were calculated by using NMR signals of the crude reaction mixture (see SI). ¹H NMR (600 MHz) endo alcohol (carbinol proton; δ 4.23–4.2, m, 1H); exo alcohol (carbinol proton; δ 3.76–3.74, m, 1H); ketone (bridgehead protons; $\delta 2.66-2.59$, m, 2H). ¹³C NMR (150 MHz) of the crude; ketone (218.2, 49.8, 45.2, 37.6, 35.4, 27.1, 24.1); endo alcohol (73.0, 42.5, 39.5, 37.5, 37.1, 29.8, 19.8); exo alcohol (74.9, 44.3, 42.3, 35.3, 34.3, 28.1, 24.4).

Incorporation Isotope Effect. The incorporation ratio was determined in an internal competition experiment in which the reaction medium contained both MeOH and MeOD. A solution of norcamphor (23 mM) was allowed to react with SmI₂ (48 mM) in the presence of 1 M proton donor with the composition ratio 3:1 (MeOD, 0.75 M; MeOH, 0.25 M). After 24 h, phosphate buffer (5%; 15 mL) was added, and the solution was extracted with dichloromethane (3 \times 25 mL). The combined organic layer was washed with water $(2 \times 15 \text{ mL})$ followed by brine $(2 \times 20 \text{ mL})$, dried over anhydrous Na₂SO₄, and evaporated under reduced pressure to give crude reaction product. The ratio of product distribution was obtained by integrating NMR (¹³C; 75 MHz) signals of the crude reaction mixture (see the SI). C signals for major product (endo alcohol) were segregated at C-1 (\$\delta 42.39 for H; 42.27 for D isomers) and C-3 (\$\delta 39.30 for H; 39.17 for D isomers), similarly C signals for minor product (exo alcohol) were segregated at C-1 (δ 44.10 for H; 44.39 for D isomers) and C-3 (δ 42.11 for H; 42.01 for D isomers). The NMR spectra are presented in the Supporting Information.

Supporting Information Available: Tables S1 and S2, Gaussian archives for the acidities of the proton donors, and H and C^{13} NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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