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Characterization of the complex formed between samarium diiodide and the dehydro dimer of HMPA (diHMPA)

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ABSTRACT

A new ligand that facilitates samarium diiodide-mediated reductions has been developed. Addition of a solution of samarium diiodide to the dehydro dimer of hexamethylphosphoramide results in a purple complex which is an excellent reductant for a variety of organic functionalities. The complex was characterized by the kinetics of reduction of 1-bromodecane, visible spectroscopy, and cyclic voltammetry.

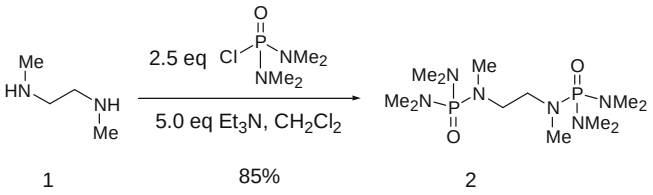
Samarium diiodide as a useful reductant was introduced to the synthetic organic community by Kagan.[1] It was subsequently determined that the addition of HMPA as a co-solvent to a THF solution of SmI_2 can accelerate reductions of alkyl halides.[2] The complex formed between SmI_2 and 4 equiv of HMPA has evolved into one of the most versatile reagents for performing reductions, often with concomitant formation of carbon–carbon bonds.[3] Due to its importance, this complex has been the subject of much elegant mechanistic scrutiny. In THF solution, substantial evidence points to the complex $[Sm(HMPA)_4(THF)_2]^{2+}2I^-$ as the reactive species.[4–6] Hou has reported the crystal structure of $SmI_2(HMPA)_4$.[7]

Although of great synthetic value, HMPA is also known to cause nasopharyngeal cancer in laboratory animals. Rats were shown to develop nasal tumors when HMPA was inhaled (50 ppb for one year)[8] but tumor formation was not observed when HMPA was administered orally to rats (6.25 mg kg^{-1} day^{-1} for two years).[9] There is evidence that this carcinogenicity is related to hydroxylation at *N*-methyl positions of HMPA by cytochrome P450 enzymes with concomitant release of H_2CO within the nasopharyngeal cells.[10] The propensity of intracellular H_2CO to crosslink DNA ultimately leads to intra-locus and multi-locus deletions within the genome.[11] In spite of this, chemists use SmI_2 with HMPA as a co-solvent on a routine basis.

A small number of potential HMPA surrogates have been investigated. Electron-rich ligands such as *N*,*N*′-dimethylpropyleneurea (DMPU)[12], 1,1,3,3-tetramethyl-guanidine (TMG), and 1,8-diazabycyclo[5.4.0]undec-7-ene (DBU)[13] have been employed with some success. Mixtures of samarium diiodide with water and amines, especially *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylene triamine (PMDTA), were shown to be effective for the reduction of a variety of functionalities.[14] Various transition metal salts have also shown efficacy in facilitating reduction by samarium diiodide.[15] Recently it has been demonstrated that 1,3-dimethyl-2-imidazolidinone (DMI) has shown promise as an alternative to HMPA.[16,17] None of these, however, have been demonstrated to be generally applicable to the wide range of synthetic applications for which SmI_2 has proven useful.

We have examined the dehydro dimer of HMPA (diHMPA, **2**) with regard to its ability to facilitate SmI_2-mediated reductions. We presume that diHMPA would be less mutagenic than HMPA due simply to its lower volatility. This compound was first synthesized by Naarman via radical dimerization of HMPA.[18] It has been used previously to facilitate alkylations[19] and conjugate additions[20] of alkali metal enolates. There are no published reports of the use of diHMPA in combination with samarium diiodide. We chose to synthesize diHMPA by bisphosphorylation of *N*,*N*′-dimethylethylenediamine (Scheme 1). Purification was accomplished by silica gel column chromatography. Storage of this compound under argon at room temperature for up to a year resulted in no decomposition as evidenced by ^1H NMR or discoloration.

When a 0.1 M solution of SmI_2 in THF was exposed to 2 equiv of diHMPA, a deep purple solution resulted. Initial evidence for the reactivity of this mixture was obtained by the addition of 0.3 equiv of 1-bromodecane to the solution. This resulted in rapid and



1 85% 2

Scheme 1. The synthesis of diHMPA.

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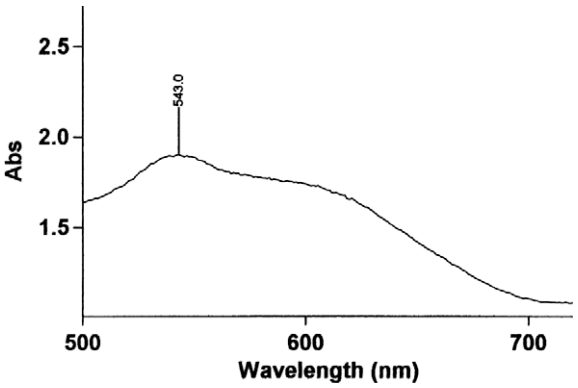


Figure 1. Visible spectrum of 5 mM THF solution of SmI_2 with 10 mM diHMPA.

complete conversion of the alkyl bromide to decane as evidenced by gas chromatography.

A visible spectrum of 5 mM solution of SmI_2 in THF with 2 equiv of diHMPA afforded a peak at 543 nm (Fig. 1). A visible spectrum of the related $[Sm(HMPA)_4(THF)_2]^{2+}2I^-$ complex has a peak at 540 nm and the two spectra are qualitatively similar over the scanned range of 500–700 nm.[4,5]

Kinetic studies were performed with 1-bromodecane to determine the relative reactivity of the HMPA, diHMPA, and DMPU complexes of SmI_2 (Table 1). It was decided to include DMPU in this analysis because it is the most common alternative ligand to HMPA for SmI_2-mediated reductions. In each case 1-bromodecane was added to a stirred 0.020 M solution of SmI_2 that contained the indicated amount of each ligand, 1-butanol as the proton source, and tetradecane as an internal standard. Sufficient quantities of SmI_2 and 1-butanol were included to ensure pseudo-first-order conditions for the analyses. Aliquots were removed and immediately quenched with I_2.[21] Gas chromatographic analysis of the resultant mixtures was performed. Linear plots of time versus ln[decane] afforded the results shown in Table 1. The complex formed from 2 equiv of diHMPA and SmI_2 afforded a rate constant fairly similar to that of $[Sm(HMPA)_4(THF)_2]^{2+}2I^-$. When only 1 equiv of diHMPA was used, the rate constant was significantly smaller as expected. Because DMPU has a lesser affinity for SmI_2, 8 equiv of this ligand was used in these studies. The reactivity of the DMPU complex of SmI_2 was approximately the same as that of the 1:1 complex of diHMPA and SmI_2. In the absence of exogenous ligands, but under otherwise analogous conditions, no product was observed in a 4-h period (10 times the length of the other kinetic analyses).

It is known that the addition of 10 equiv of HMPA to SmI_2 in THF affords the complex $[Sm(HMPA)_6]^{2+}2I^-$.[5,22] Kinetic experiments with this complex have shown it to be of comparable reactivity to $[Sm(HMPA)_4(THF)_2]^{2+}2I^-$ with alkyl iodide substrates.[23] In analogous fashion, SmI_2 was added to 5 equiv of diHMPA. The resultant purple complex immediately precipitated from the THF solution. Addition of 1-bromodecane to the stirred mixture did not afford detectable quantities of decane over a 5-h period of analysis.

Cyclic voltammetry (CV) of SmI_2/diHMPA complexes in THF was also undertaken in an effort to characterize the effect of the diHMPA:SmI_2 ratio on the standard reduction potential. In accord with previous studies, relatively high concentrations of the electrolytes n-Bu_4NPF_6 (0.10 M) and n-Bu_4NI (0.020 M) were initially chosen to increase solution conductivity for voltammetry.[24,25] The electrochemical analysis was complicated by the low solubility of the presumed $Sm(diHMPA)_2(THF)_2]^{2+}2I^-$ complex under conditions of high ionic strength, and consequently, no oxidation or reduction waves were observed. When the concentration of n-Bu_4NPF_6 was lowered to 0.025 M (while maintaining n-Bu_4NI at 0.020 M), the SmI_2–diHMPA complex had increased solubility and cyclic voltammetry for the complexes was observed. Under the low electrolyte conditions, the HMPA complex, had a measured standard potential of −2.07 V versus $Ag/AgNO_3$, which is similar to the standard potential measured at higher electrolyte concentration (−2.10 V vs $Ag/AgNO_3$). The effect of diHMPA on reducing strength is illustrated by the data in Table 2. As was shown for complexation of SmI_2 with HMPA[24], the standard potential decreases with the addition of diHMPA. When 2 equiv of diHMPA was introduced, the standard potential was lowered to −2.03 V versus $Ag/AgNO_3$, which is presumably due to the reducing power of the diHMPA complex, $[Sm(diHMPA)_2(THF)_2]^{2+}2I^-$. When smaller amounts of diHMPA (1 equiv relative to SmI_2) were utilized, the standard potential was affected to a much lesser extent (−1.43 V vs $Ag/AgNO_3$). The change in standard potential for $[Sm(diHMPA)_2(THF)_2]^{2+}2I^-$ relative to SmI_2 (−1.33 V vs $Ag/AgNO_3$) was measured to be 0.7 V, which is similar to the change of 0.8 V for $[Sm(HMPA)_4(THF)_2]_2^{+}2I^-$, as measured by Flowers[26] and confirmed in this study.

The peak separation between the oxidation and reduction waves (ΔE_p) provides a measure of the electron transfer rate constant (k°). Daasbjerg et al. observed that a significant decrease in k° accompanied complexation of SmI_2 by HMPA, with the retardation attributed to a large increase in the reorganization energy of $[Sm(HMPA)_4(THF)_2]_2^{+}2I^-$.[28] The results in Table 2 indicate an even greater decrease in k° upon introduction of diHMPA. In our study, ΔE_p for SmI_2 was measured to be 0.45 V and increased to 1.2 V for the presumed complex, $[Sm(diHMPA)_2(THF)_2]^{2+}2I^-$, which indicates very sluggish electron transfer kinetics.

The ability of the SmI_2/diHMPA complex to effect the formation of carbon–carbon bonds was also examined. The first example involves the addition of the ketyl radical anion derived from 4-phenylbutanone to styrene (Table 3).[29] Efficient conversion to adduct **4** was observed using either HMPA or diHMPA as a ligand. The use of DMPU as a ligand afforded the product in significantly lower yield.

A second example that illustrates the effect of the ligand on SmI_2-induced formation of a carbon–carbon bond is shown in Table 4. Pummerer rearrangement of sulfoxide **5**[30] affords a very reactive α-trifluoroacetoxy sulfide.[31] After removal of volatile reaction components under vacuum, the substrate was transferred to a mixture of SmI_2, ligand, and t-BuOH. All three ligands examined provided similar yields of cyclized products.[32]

Table 1
Pseudo-first-order kinetic study on the effect of ligand choice on the reduction of 1-bromodecane (21 °C)

Ligand	Equiv ligand/equiv SmI_2	k_{obs}[a] (s^{-1})
HMPA	4	0.0094 ± 0.0009
diHMPA	2	0.0069 ± 0.0007
diHMPA	1	0.0022 ± 0.0003
DMPU	8	0.0020 ± 0.0003

[a] [1-bromodecane] = 0.0030 M, [SmI_2] = 0.020 M, [1-butanol] = 0.040 M.

Table 2
Effect of ligands on the standard potentials of SmI_2[a]

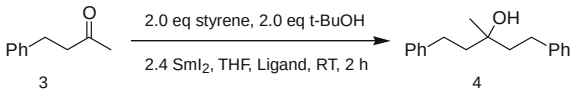
Reductant	Equiv ligand/equiv SmI_2	Standard potential[b] (V vs $Ag/AgNO_3$)	ΔE relative to SmI_2	ΔE_p (V)
SmI_2	—	−1.35 ± 0.03	—	0.45
SmI_2:HMPA	4	−2.07 ± 0.01	0.72	0.83
SmI_2:HMPA	4	−2.10 ± 0.01[c]	0.78	0.93
SmI_2:diHMPA	1	−1.43 ± 0.02	0.08	1.41
SmI_2:diHMPA	2	−2.03 ± 0.06	0.68	1.09

[a] Data were recorded at 5 mM SmI_2 with n-Bu_4NPF_6 (0.025 M) and n-Bu_4NI (0.020 M) at 100 mV/s.

[b] Standard potentials were estimated from cyclic voltammograms and confirmed by semi-integration of the cyclic voltammetry data, Ref. 27.

[c] Data were recorded at 5 mM SmI_2 with n-Bu_4NPF_6 (0.10 M) and n-Bu_4NI (0.020 M).

Table 3
Effect of ligand choice on the SmI_2-mediated addition of 4-phenylbutanone to styrene

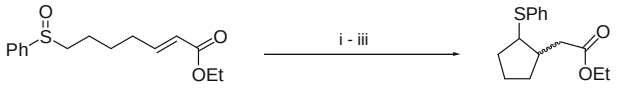


3 4

Ligand	Equiv ligand/equiv SmI_2	Yield[a] (%)
HMPA	4	97[b]
diHMPA	2	82
DMPU	4	52

[a] Isolated yield of chromatographically pure product.
[b] Ref. 29.

Table 4
Effect of ligand choice on the Pummerer rearrangement and SmI_2-mediated cyclization of sulfoxide **5**



5 6

i excess $(CF_3CO)_2O$, 2 eq lutidine, RT; ii remove volatiles; iii 6 eq SmI_2, Ligand, THF, 2 eq t-BuOH, 0 °C

Ligand	Equiv ligand/equiv SmI_2	Yield[a] (%)
HMPA	4	59
diHMPA	2	62
DMPU	4	50

[a] Isolated yield of chromatographically pure product.

In conclusion, diHMPA is a reasonable synthetic alternative to HMPA for SmI_2-mediated reductions. Spectroscopic, electrochemical, and kinetic studies indicate that the complex formed between SmI_2 and 2 equiv of diHMPA is structurally analogous to the complex formed between SmI_2 and 4 equiv of HMPA. Work continues in this laboratory to find alternative ligands for SmI_2 that will be less mutagenic and more reactive than HMPA.

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