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# Quantitation of the Interactions of Alcohols and Amines with $SmI_2$: Pros and Cons of VIS and NMR Spectroscopies

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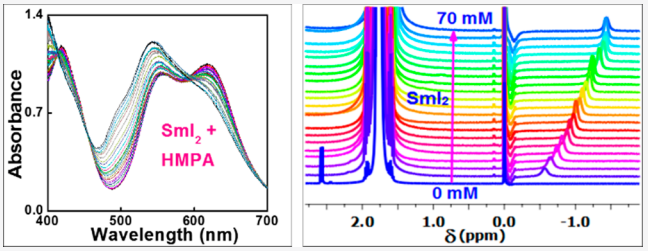
**ABSTRACT:** While additives play an important role in the reactions of samarium iodide, ligand−$SmI_2$ complexation constants are scarce. Here, VIS spectroscopy was harnessed along with NMR to determine the first complexation constant for most of the alcohols and amines used in $SmI_2$ reactions. The second equilibrium constant was determined for selected ligands. In cases where both methods could be applied, in general, a good correlation between the equilibrium constants was obtained.






The chemistry of samarium iodide is dominated by its interaction with ligands prior to the electron transfer step.[1] Several features of $SmI_2$ reactivity are affected by complexation, most notably the reduction potential, which in the case of hexamethylphosphoramide (HMPA), for example, increases from −1.33 to −2.05 V.[2] Another example is complexation with proton donors. Due to internal protonation within the ion pair, which enables unimolecular protonation of short-lived radical anions, reduction of substrates that otherwise cannot be accomplished with $SmI_2$ is enabled.[3] Different proton donors can yield different products,[4] and intensive ligation can change the reaction mechanism from an inner sphere to an outer sphere electron transfer by hampering the direct contact between the substrate and $SmI_2$.[5] Recently, the use of an enantiopure amine-alcohol additive in the first enantioselective radical cyclizations using $SmI_2$was demonstrated.[6] Surprisingly, a quantitative systematic assessment of the interaction between ligands and $SmI_2$ has only recently emerged; equilibrium constants were determined using cyclic voltammetry,[7] and the basis for the general use of NMR was provided.[8] Here, we add another method to the arsenal−visible spectroscopy (VIS). The efficiency and applicability range of this method is compared with NMR spectroscopy, and the first equilibrium constant is provided for most of the known ligands used in $SmI_2$ chemistry.

## COMPARISON OF VIS AND NMR SPECTROSCOPIES

The most important parameter in the determination of equilibrium constants is the magnitude of the response to the binding. Assuming proportionality between the response and the binding, a larger response increases the reliability of the acquired value, in particular for small equilibrium constants. In complexation to $SmI_2$, the NMR method has a huge advantage over VIS, as the implementation of shift reagents was based from its onset on the fact that minor interactions of lanthanides with organic molecules are sufficient to induce a change in their chemical shift.[9] This advantage of the NMR method is nicely exemplified by the complexation of 2-(2-aminoethoxy) ethanol(OON) to $SmI_2$. The chemical shift of OON fully bound to $SmI_2$ is about −10.7 ppm,[8] markedly different than the free ligand (∼2.7 ppm). Another example is the interaction of 1,2-dichloroethane with $SmI_2$. While the VIS spectrum of $SmI_2$ is not affected by addition of 1,2-dichloroethane to its THF solution, its NMR spectrum is clearly shifted downfield (Figure 1), yielding an

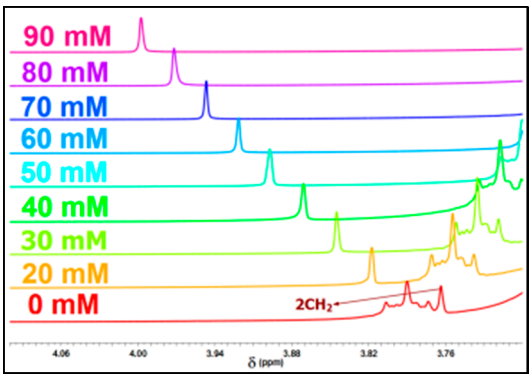



**Figure 1.** Peak shift of 1,2-dichloroethane as a function of $SmI_2$ concentration (multiplet moving upfield arises from THF satellites).

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equilibrium constant of 0.6 $M^{-1}$. As most of the alcohols studied here did not affect the VIS absorption of $SmI_2$, their equilibrium constants were determined only by NMR.

Another prominent difference between the two methods is that VIS follows changes in the spectrum of $SmI_2$, whereas NMR monitors the chemical shift of the substrate. In order to shift the equilibrium in eq 1 to the right, the concentration of either $SmI_2$ and/or the ligand (L) should be increased.

$$SmI_2 + L \rightleftharpoons SmI_2 - L \quad (1)$$

The NMR complexation shift depends on the molar ratio of the complex to the ligand ($[SmI_2{-}L]/[L]$), while VIS depends on the complex concentration $[SmI_2{-}L]$.Therefore, increasing the ligand concentration to shift the equilibrium to the right and produce more of the complex would be counterproductive, as the lower complex-to-ligand ratio would produce a smaller complexation shift. This is clear from eq 2, which shows that the ratio decreases proportionately with the decreasing concentration of $SmI_2$ that is converted to the complex. Thus, in the NMR method where the chemical shift of the ligand is followed, the concentration of $SmI_2$ should be increased in order to shift the equilibrium to the right while increasing the complex-to-ligand ratio.

$$K[SmI_2] = [SmI_2{-}L]/[L] \quad (2)$$

On the other hand, increasing the concentration of L fits very nicely into VIS where the absorption of $SmI_2$ is followed, as it induces the desired change in absorption. On the technical side, it is clearly much easier to gather VIS than NMR data. The number of data points collected in each measurement is very high (number of nm over which the spectrum is measured) as opposed to the much fewer data points (number of observed chemical shifts) in NMR. Also, unlike NMR measurements, VIS spectra are taken inside the glovebox, accounting for the sensitivity of $SmI_2$ to air. The determination of two successive equilibria was enabled only with NMR.

## ■ ALCOHOLS

Chart 1 shows the alcohols for which equilibrium constants were determined. The values of $K_1$ are given in Table 1.

**Chart 1**

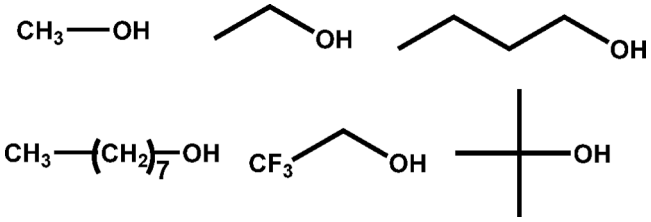


**Table 1. NMR Determined First Equilibrium Constants for Alcohols with $SmI_2$**

| alcohols | $K_1$, $M^{-1}$ |
|---|---|
| TFE | 0.63 |
| *n*-octanol | 1.03 |
| *n*-BuOH | 1.4 |
| EtOH | 1.8 |
| MeOH[8] | 4.4 |
| *t*-BuOH | ~0 |

Addition of alcohols to $SmI_2$ in THF, with the exclusion of MeOH, did not affect much the visible electronic spectrum of $SmI_2$. Even with MeOH, a significant change in the spectrum commences only around 1 M. At this high concentration, the properties of the medium are probably significantly changed, as both homo and hetero hydrogen bonding are formed. Therefore, it is impossible to determine the equilibrium constant based on the changes in the visible spectrum even for MeOH. Thus, for alcohols, only the NMR method, where much lower concentrations of the ligand are needed was applied. Addition of $SmI_2$ to a solution of an alcohol in THF causes a significant change in the chemical shift, enabling to determine the equilibrium constant. Although the constants are small, the sheer fact that an alcohol molecule whose binding site is oxygen can efficiently replace a THF molecule whose binding atom is also oxygen is surprising, all the more so in light of the 1000-fold higher concentration of THF (12.3 M vs ~10 mM for the alcohol). Apparently, this ability of the alcohol to replace THF molecules stems from two origins. First, an alcohol complexed to $Sm^{2+}$ has an enhanced ability to hydrogen bond to a THF molecule. Second, the lower steric size of the alcohol molecules around the binding atoms plays an important role in the complexation to $SmI_2$. Thus, in THF, two $CH_2$ units flank the oxygen atom whereas in alcohol one $CH_2$ unit and one H unit are involved.

Based on the lack of any effect on the VIS spectrum, we assumed in the past that alcohols such as *t*-BuOH and trifluoroethanol (TFE) do not bind to $SmI_2$.[10] While the NMR spectrum of *t*-BuOH was indeed not affected by $SmI_2$, the data (Table 1) shows that TFE binds to $SmI_2$ with an equilibrium constant of 0.6 $M^{-1}$. Nevertheless, the aforementioned assumption stays nearly correct, as under typical conditions (2 mM $SmI_2$ and 0.1 M of TFE used in most of our kinetic studies), only 6% of the $SmI_2$ molecules are bound to a single TFE molecule. It should be noted that the binding site of TFE may be the $CF_3$ group rather than the oxygen due to the higher accumulated negative charge.

In THF solution, $SmI_2$ is bound to two ligands, THF and iodide ions. In ligand exchange, THF is the first to be replaced, as evidenced from the crystal structure of $SmI_2(DME)_2(THF)$ where THF rather than iodide molecules are replaced by DME.[11a] Increasing the concentration of the ligand or its affinity to $SmI_2$ will eventually replace the iodidesas demonstrated by Flowers et al.[11b,c]

An interesting phenomenon is revealed upon examination of different alcohol chain lengths ($C_n$ in Figure 2). As the length increases, the equilibrium constant decreases, but the decrease levels off very rapidly. The reason seems to be of an entropic origin. The first shell of THF molecules bound to $SmI_2$ hampers the free rotation of the tails of the alcohol molecules embedded in the complex, resulting in a decrease in entropy. For short alcohols this affects the whole molecule, while for alcohols with longer tails, the part which protrudes outside of this shell is not significantly affected and hence does not lead to a substantial further reduction in the equilibrium constant.

## ■ AMINES

Chart 2 shows the cyclic and acyclic amines for which equilibrium constants with $SmI_2$ were determined. The values of $K_1$ are given in Table 2.

Unlike alcohols, the addition of amines caused a significant change in the spectrum of $SmI_2$, as shown for *n*-$BuNH_2$


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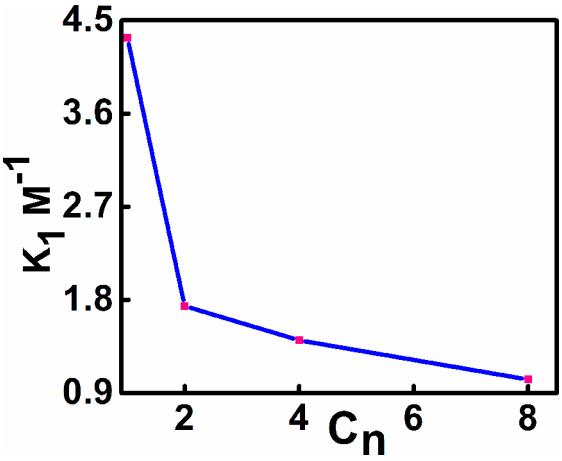


**Figure 2.** $K_1$ as a function of chain length for linear alcohols.

**Chart 2**

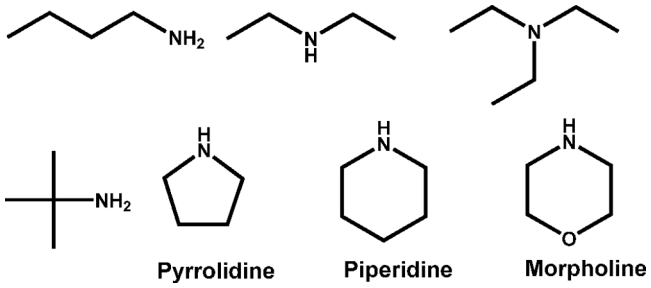


**Table 2. VIS and NMR Determined First Equilibrium Constants of Amines with $SmI_2$**

| | $K_1$, $M^{-1}$ | | |
|---|---|---|---|
| amines | VIS | NMR | avg |
| morpholine | 2.3 | 2.2 | 2.3 ± 0.05 |
| *n*-butylamine | 3 | 2.8 | 2.9 ± 0.1 |
| diethylamine | 3.5 | 3.5 | 3.5 ± 0.02 |
| *t*-butylamine | 5.6 | 6 | 5.8 ± 0.2 |
| pyrrolidine | 6.7 | 6.2 | 6.5 ± 0.3 |
| piperidine | 9.9 | 17.5 | 13.7 ± 3.8 |
| triethylamine | ~0 | ~0 | ~0 |

(Figure 3). Therefore, the equilibrium constants were also determined by VIS.

The fit between the two methods is reasonable for most of the amines (Table 2), with the exception of piperidine for which, in numerous repetitions, VIS gave a significantly lower value than NMR (a possible explanation for this discrepancy is that piperidine forms with $SmI_2$ aggregates not visible to the naked eye, which maintain a relatively high OD along the series of experiments thatis reflected in thelower equilibrium constant). The simplest amine that was determined, *n*-$BuNH_2$, had, as expected, an equilibrium constant twice as large as the corresponding alcohol, BuOH.[12]

The equilibrium constant of *t*-butylamine is ca. 50% larger than that of diethylamine, suggesting again that the immediate steric effect at the binding atom plays a most important role in determining the binding strength to $SmI_2$. Accordingly, triethylamine does not affect the VIS spectrum of $SmI_2$ or exhibit any NMR chemical shift. Interestingly, while *t*-butylamine has a binding constant twice as large as *n*-butylamine, the opposite trend is displayed by the alcohols where the equilibrium constant of *n*-butanol is around 1, while *t*-butanol does not bind to $SmI_2$. However, the free energy associated with such low equilibrium constant is around zero; therefore, small secondary effects, which are difficult to interpret, can easily affect the binding order.

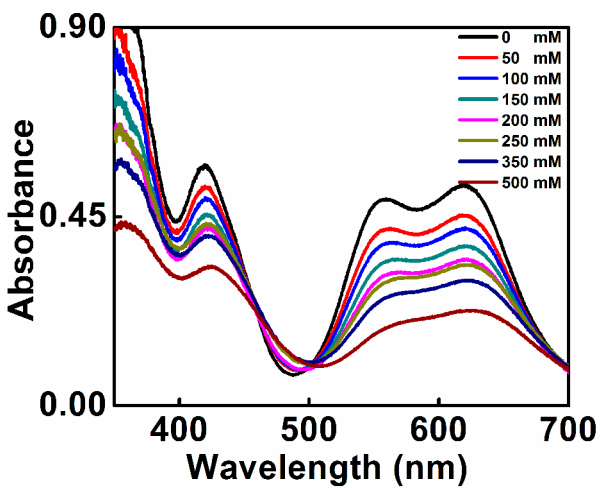


**Figure 3.** VIS spectra of $SmI_2$ at different *n*-$BuNH_2$ concentrations.

Of special interest is the comparison of the three cyclic amines morpholine, pyrrolidine, and piperidine. One may assume that pyrrolidine, a five membered ring like THF, may fit nicely into the first ligation shell comprised of THF molecules and will hence exhibit a relatively large equilibrium constant. Yet, piperidine, a ring of six atoms, has a significantly higher affinity to $SmI_2$ according to both methods. It is clear that there are several factors that determine the binding constants. One of these is no doubt the energy of the lone pair with which, at least a qualitative correlation is expected. It is clear that the binding to $SmI_2$ will take place at the conformation that places the lone pair at the less hindered equatorial position. B3LYP/6-31+G* calculations[13] show that in THF, the axial and equatorial positions of the lone pair have roughly the same preference, within half a kcal/mol. Yet, the energies of the lone pair differ markedly (Figure 4), 8 kcal/mol higher in piperidine than in pyrrolidine; hence, the former is a much better donor for Sm ligation. The importance of the lone pair energy is nicely manifested in the case of morpholine. In this case, due to the "through bond interaction",[14] the lone pair, which is strongly affected by the oxygen, is even more stable and leads indeed to a lower equilibrium constant.

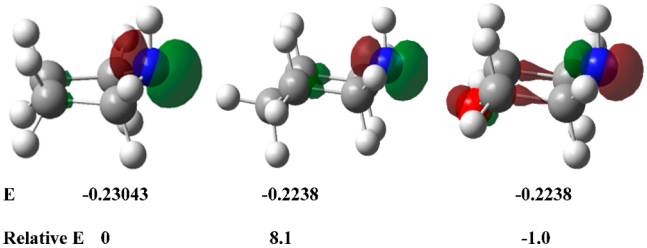


**Figure 4.** Lone pair orbitals on nitrogen; energies (au) and relative energies (kcal/mol).



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## SECOND EQUILIBRIUM CONSTANT

The group of Thordarson[15] developed a software for successive equilibria, enabling the determination of $K_1$ and $K_2$ (eqs 1 and 3).

$$SmI_2{-}L + L \rightleftharpoons SmI_2{-}L_2 \quad (3)$$

In the present study, this method was used for the ligands HMPA, EG, and DEG (see Chart 3). The results in Table 3

**Chart 3**

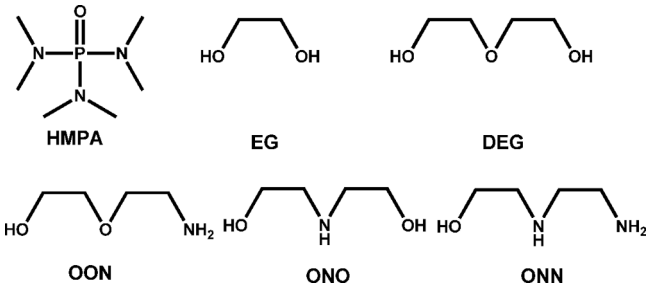


**Table 3. First Two Equilibrium Constants for HMPA, EG, and DEG (Determined by NMR) and for OON, ONO, and ONN (Determined by Cyclic Voltametry[7])**

| ligands | $K_1$, $M^{-1}$ | $K_2$, $M^{-1}$ |
|---|---|---|
| HMPA | 2478 | 761 |
| EG | 103 | 89 |
| DEG | 213 | 298 |
| OON | 405 | 718 |
| ONO | 209 | 444 |
| ONN | 376 | 630 |

were obtained by the NMR method, as these ligands did not lend themselves to reliable VIS determination. Previously, $K_1$ was determined at relatively high $SmI_2$ concentration to ensure mainly mono ligation.[8] For the determination of $K_2$, lower concentrations of $SmI_2$ were used to enable some diligation. In the calculations of $K_2$, the previously determined $K_1$ values were used (see the Supporting Information (SI)). The ligands employed in this study, as well as ligands for which $K_2$ was obtained previously[7] (by cyclic voltammetry), are depicted in Chart 3 and Table 3.

It is interesting to note that while for HMPA, $K_1 > K_2$, for EG the two equilibrium constants are quite similar. Surprisingly, for the tridentate ligands, $K_1 < K_2$, according to both methods. The significantly larger first complexation constant of HMPA is reasonable, as the partial negative charge on the oxygen in the first molecule reduces the effective charge on the samarium ion, resulting in a lower affinity to the second HMPA molecule. The ligation mechanism is elimination–addition; enthalpy invested in the detachment of THF molecules from $SmI_2$ (elimination) is gained in the attachment of the ligands (addition). In the simplest case, one ligand replaces one THF molecule. However, in tridentate ligands, the number of THF molecules displaced by the first ligand may be greater than the number of atoms binding this ligand. As a result, the second ligand entering the complex may benefit from the partial displacement of THF by the first ligand. The enthalpy loss for the first ligation is therefore higher than that of the second one, leading to the observed phenomenon of $K_1 < K_2$.

In conclusion, linear alcohols are much better ligands than THF, by 3 orders of magnitude despite having the same binding atom as THF–oxygen. Amines are better than alcohols, and with the exception of HMPA that carries a large partial negative charge on its oxygen, ligands with more binding sites have higher equilibrium constants.

## EXPERIMENTAL SECTION

Equilibrium constants were calculated using the BindFit online software developed by Pall Thordarson.[15a−c] In NMR (400 MHz) and VIS measurements, a 1:1 fit model was used for mono complexation, while a 2:1 NMR fit model was used for multiple complexation. In most cases, the Nelder–Mead method was used with the initial guess $K_1 = 1$; for HMPA, DEG, and EG, the L-BFGS-B method was used with previously determined $K_1$ values. In NMR experiments the ligand is the host whereas in the UV experiments it is the $SmI_2$. For the determination of $K_1$ the $SmI_2$concentrations were in excess to a fixed concentration of the ligand. For $K_2$ determinations,the concentration of the ligand was increased. In the VIS experiments the $SmI_2$ concentration was kept constant (see the SI).

Tetrahydrofuran was obtained from Bio-Lab, refluxed for 48 h over sodium wire/benzophenone and collected over oven-dried molecular sieve under argon. Most of the other reagents were obtained from commercial sources (Aldrich or Alfa Aesar). All liquid reagents were purified by distillation and degassed using argon. $SmI_2$ was prepared at room temperature in THF inside a glovebox using samarium metal and 1, 2-diiodoethane.[16]

The concentration of $SmI_2$ was determined by VIS spectroscopy at 619 nm. VIS measurements were performed inside a glovebox equipped with a stopped flow spectrophotometer. Data was collected in 10 nm intervals in the range of 540–640 nm. All NMR samples were prepared inside the glovebox in oven-dried tubes 10 min before recording their spectrum. Each NMR tube (0.6 mL) was airtight sealed, and the spectra were taken in nondeuterated THF. The chemical shifts are given in $\delta$ units (ppm) relative to tetramethylsilane (TMS). NMR spectra were recorded in a 400 MHz Bruker spectrometer at room temperature and processed using Bruker TopSpin 3.2 and Mestrenova v6.0.2 software.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01183.

$^1$H NMR (400 MHz) chemical shift data, UV visible studies, Bindfit link for ligands and ab initio calculations (PDF)

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### Notes

The authors declare no competing financial interest.

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