Pergamon

Tetrahedron Letters 39 (1998) 8063–8066

TETRAHEDRON LETTERS

Calorimetric Determination of the Solution Affinity of $YbCl_3$ for HMPA in Tetrahydrofuran

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Received 30 June 1998; revised 27 July 1998; accepted 12 August 1998

Abstract Isothermal titration calorimetry (ITC) is employed to determine the energetics and stoichiometry of binding of HMPA to $YbCl_3$ in THF. The calorimetrically obtained stoichiometry for the trivalent ytterbium/HMPA complex agrees with the previously reported crystal structure.

The ligand HMPA plays an important role in many lanthanide mediated organic reactions.[1] The addition of HMPA to reactions mediated by SmI_2 and YbI_2 dramatically accelerates the electron transfer process. Inanaga and coworkers reported an increase in the rate of reduction of organic halides when HMPA was added to SmI_2-THF solutions.[2] Curran and Hasegawa have demonstrated that the time of SmI_2 reductions can be reduced from days to minutes in the presence of HMPA.[3] Although there are numerous crystal structures available for various lanthanide-HMPA complexes, relatively little is known about the solution structures of these complexes. Information on the solution structure can provide insight into how electronegative functional groups may interact with a given lanthanide-HMPA complex in solution. Herein, we report an isothermal titration calorimetric experiment designed to determine both the affinity of HMPA for $YbCl_3$ and the stoichiometry of the $YbCl_3$-HMPA complex in THF.

ITC is a well-established technique for probing the thermodynamics of biomolecular interactions.[4,5] Although this technique is also suitable for determining the binding stoichiometry and thermodynamics of metal ligand interactions, there has been little work performed in this area. Recently, Morel-Desrosiers and coworkers developed a microcalorimetric method[6] to allow the simultaneous determination of the association constant and enthalpy in water for a series of lanthanides with ribose,[7] alditols,[8] and nitrate ions.[9] They found that the association constant and enthalpies for these processes were small. We expected that the heats evolved from the binding of basic ligands like HMPA to lanthanides in THF would be much larger than the heats of binding observed by Morel-Desrosiers in water. Energetic and stoichiometric information on cosolvent-metal assemblies can provide useful insight into their reactivity.

We employed a MicroCal Omega Isothermal titration calorimeter to determine the number of HMPA ligands bound to $YbCl_3$ and the enthalpy and equilibrium binding constants of these interactions. We have outfitted our instrument with the appropriate inert seals and introduced a small port capable of keeping a static inert gas environment over the sample. These changes enabled us to carry out calorimetric analysis of air

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01774-2

sensitive compounds in organic solvents. Figure 1 contains the calorimetric data and a plot of the heat evolved for the titration of HMPA into $YbCl_3$ vs. the mole fraction of HMPA/$YbCl_3$ in THF at 25 °C.[10]

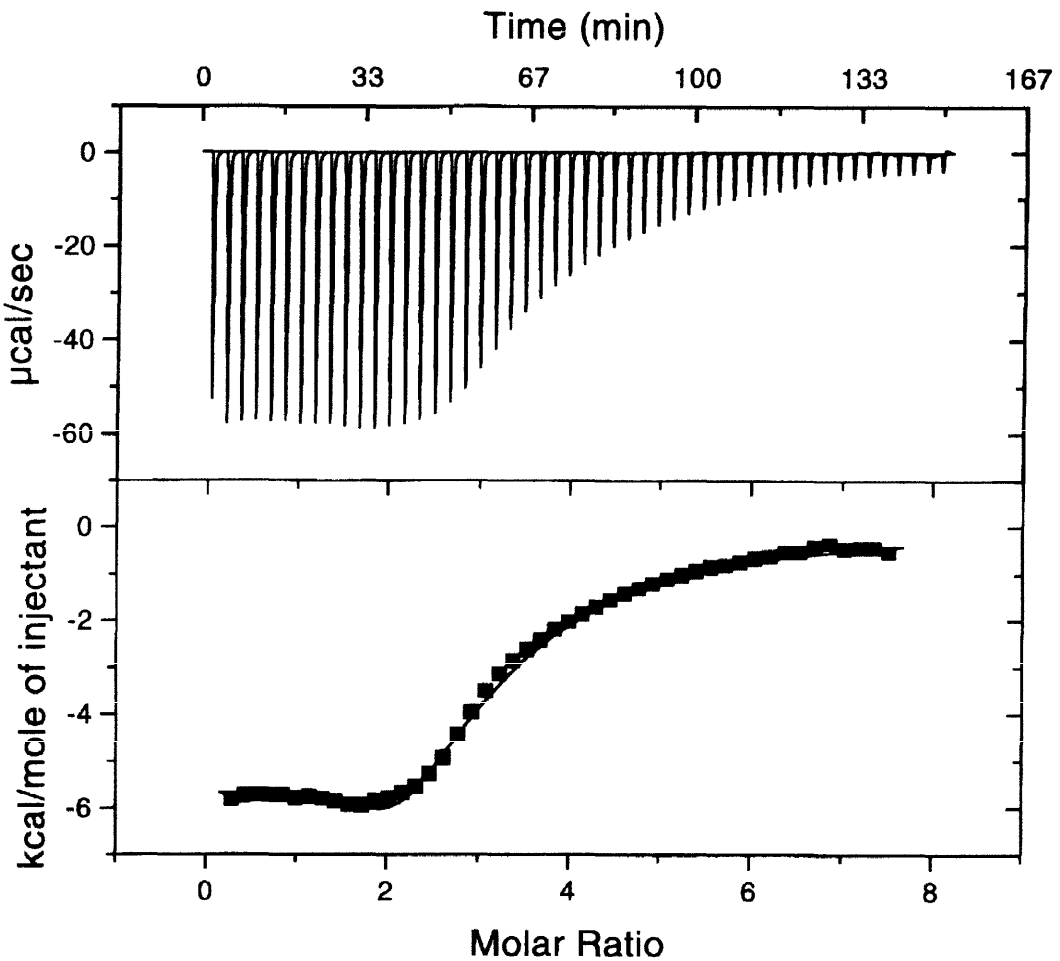

Figure 1 Calorimetric Binding Isotherm for the Titration of $YbCl_3$ with HMPA in THF.[10]

Employing a non-linear least squares analysis of the calorimetric data and an identical interacting sites model developed from a multiple sets of independent binding sites approximation,[11] one can determine the number of binding sites (n), the enthalpy of the interaction, (ΔH), and the binding constant, (K). This approach was employed by Brandts and coworkers[12] at Microcal, Inc. to determine the binding constants and enthalpies for the addition of 4 bromide ligands to a Cd^{2+}. From the experimental data displayed in Figure 1, we find that there are 3 HMPA ligands bound to the $YbCl_3$ (n = 3). The equilibrium binding constants and the enthalpy for each of the three binding interactions between the ytterbium and HMPA can be calculated from the calorimetric data (Table 1). Inspection of the results in Table 1 shows that a model for 2 sets of independent binding sites may also fit the data because the thermochemical values for the first two binding

equilibria are very close. Application of this model provides numerical values that are within 3-8% of those reported in Table 1, however the statistical fit is not nearly as good as that employing the identical interacting sites model. This analysis suggests that although the thermodynamics of association for the first two HMPA ligands are similar, they are not identical.

Table 1.

Thermodynamic Data for the Interaction Between HMPA and $YbCl_3$ in THF

Ligand (HMPA)	K (x 10^4)*	ΔH (kcal/mol)*	Calculated Values	
			ΔG (kcal/mol)**	ΔS (cal/mol)**
First	1.84 ± 0.52	-5.75 ± 0.03	-5.82 ± 0.23	0.235 ± 0.70
Second	1.67 ± 0.56	-6.16 ± 0.01	-5.76 ± 0.24	-1.34 ± 0.80
Third	0.24 ± 0.03	-11.25 ± 1.25	-4.60 ± 0.08	-22.31± 3.90

The data are averaged from the results of three independent runs.
*reported here as ± σ
**values calculated from the average values for K and ΔH employing ΔG = -RTlnK = ΔH - TΔS.

The stoichiometric ITC data for the ytterbium complex correlates very well with the crystal structure for $YbCl_3(HMPA)_3$ reported by Hou,[13] suggesting that the structure of the ytterbium-HMPA complex in solution resembles that in the crystal structure. The binding affinities for the three HMPA molecules (Table 1) suggest that following the formation of a strong association between $YbCl_3$ and 2 HMPA ligands, it is less thermodynamically favorable for the third HMPA to interact with the metal. The ligation of HMPA to $YbCl_3$ is enthalpically driven in the binding of all three ligands. The entropic component of the coordination of the first two HMPA ligands is very small, while the binding of the third ligand displays a large negative entropy term. This can be rationalized in terms of ligand crowding. Following the addition of 2 HMPA molecules to the Yb, the complex becomes sterically congested, making the approach of the third HMPA ligand more difficult. In addition, as more ligands begin to order around the central Yb^{3+}, one would anticipate a corresponding unfavorable entropy of the metal-ligand system. This is consistent with the ΔS values derived from the calorimetric data.

The calorimetric experiment described above provides insight into the solution structure of the $YbCl_3$-HMPA complex in THF. While this technique does not provide definitive structural information like X-ray crystallography, it provides insight into the number of ligands surrounding the $YbCl_3$ in THF and therefore sheds some light on the structure of the lanthanide complex *in solution*, information not provided by crystallographic techniques. The thermodynamic binding data provides insight into the strength of the metal-ligand interactions. We are currently carrying out calorimetric experiments designed to determine the energetics and stoichiometry of cosolvent interaction with divalent ytterbium and samarium. The insight gained from these experiments will enable us to determine the likely solution structure of the cosolvent-lanthanide complex. This information will provide key insights into the reactivity of lanthanide based reagents. These results will be presented in a forthcoming paper.

Acknowledgment: RAF is grateful to the donors of the Petroleum Research Fund, administered by the ACS, (29492-G1) for support of this research. JBS would like to thank the University of Toledo Honors Program for undergraduate research funding.

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10. Experimental details: $YbCl_3$ and HMPA solutions were prepared in distilled degassed THF at concentrations near 1 and 50 mM respectively. The $YbCl_3$ solution was placed in the 1.4 mL calorimetric cell and the HMPA solution was loaded into a 250 μL calorimetry syringe. A 50 injection matrix was employed with each 5 μL injection lasting a duration of 10 seconds. Three minutes was allotted between each injection of HMPA into $YbCl_3$. The enthalpy (ΔH), binding constants (K), and number of binding sites (n) were determined from the calorimetric data employing *Origin*^{TM} data analysis software.

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