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Cooperative Binding of Amine Substrate Molecules by Chiral Europium(III) Shift Reagents

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Abstract: Various techniques of emission spectroscopy have been used to study the adduct formation of two chiral europium(III) β-diketonate complexes with *n*-propylamine, isopropylamine, *n*-butylamine, *sec*-butylamine, and *tert*-butylamine. The emission intensity of the ${}^5D_0 \rightarrow {}^7F_2$ Eu^{3+} transition was found to be sensitive to the binding of substrate molecules by the lanthanide chelates. It was found that both chelates bound two molecules of amine substrate, and did so in a cooperative fashion. Intermolecular energy transfer from corresponding Tb^{3+} chelates to Eu^{3+} chelates was used to demonstrate that the chelates were not associated in CCl_4 solution, so it was concluded that the cooperative binding of substrates reflects a reorganization of the β-diketone ligands about the lanthanide ion. Formation constants were calculated for all the adducts formed and it was found that steric effects were important in the binding of substrates by the chiral shift reagents.

Introduction

The usefulness of chiral lanthanide(III) β-diketonate complexes as reagents for the NMR determination of enantiomeric purity has been demonstrated.[1,2] Eu(III) and Pr(III) chelates of β-diketones prepared from derivatives of *d*-camphor have received the widest application. Little attention has been paid, however, to the stoichiometry and conformation of the chelate–substrate adducts that actually exist in solution. The crystal structure of the dimethylformamide adduct of $Eu(facam)_3$ (facam = 3-trifluoroacetyl-*d*-camphorato ion) has been reported,[3] but it is not presently clear what relation this crystal structure bears to the actual solution conformation that is of interest to NMR spectroscopists. Until detailed bonding and steric requirements of these chiral lanthanide chelates are better understood, the use of chiral chelates as probes of enantiomeric purity will not be fully understood and the application of theoretical calculations will be severely impeded.

It is well-known that Eu^{3+} complexes of β-diketones can be highly luminescent, and that this emission is strongly dependent on the geometry of the chelate and on the possible presence of adducts.[4] Adducts of $Eu(dpm)_3$ (dpm = 2,2,6,6-tetramethylheptane-3,5-dionato ion) have been studied, and information regarding the association of this achiral shift reagent with some phosphines has been obtained.[5] Circular polarization of emission (CPE) has been used to study the adduct formation between simple substrates and $Eu(facam)_3$.[6] In addition, CPE spectroscopy has been used to examine the adducts formed between achiral Eu^{3+} β-diketones and chiral substrates.[7] These studies have shown that emission spectroscopy can be an effective probe of the chelate–substrate complex, and that, under certain conditions, examination of the splittings observed in the sharp lanthanide emission lines can reveal information regarding the geometry and conformation of the complexes.

In general, emission from a Eu^{3+} β-diketonate chelate is weak if the chelate is dissolved in a noncoordinating solvent and intense if a strongly binding substrate is added to the solution. This observation has made it possible to carry out emission titrations on the achiral Eu^{3+} chelate of 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dione with a variety of substrates.[8] This study was extended in a subsequent work[9] in which five achiral chelates were titrated with a variety of simple amine and alcohol substrates. Stoichiometries and formation constants were determined for all adducts in solution, and it was demonstrated that the formation of 1:2 chelate–substrate adducts is fairly widespread within the range of substrates examined.

In the present work, emission titrations have been carried out for $Eu(facam)_3$ and its more substituted derivative, $Eu(hfpc)_3$ (hfpc = 3-heptafluoropropylhydroxymethylene-*d*-camphorato ion). The structures of these compounds are shown in Figure 1. In addition, Job's method of continuous variations was used to identify the stoichiometry of the adducts formed in the titrations.

Experimental Section

$Eu(facam)_3$ and $Eu(hfpc)_3$ were both purchased from Aldrich. Each complex was sublimed before use, and then dried over P_4O_{10} in a vacuum desiccator. Spectroquality CCl_4 was used as the solvent in titrations and was dried over molecular sieves before use. Spectrograde *n*-propylamine, isopropylamine, *n*-butylamine, *sec*-butylamine, and *tert*-butylamine were also dried over molecular sieves to ensure that no water was present in any of the samples. All manipulations were carried out in a glovebag under a dry nitrogen atmosphere to prevent possible water contamination. Failure to maintain the rigorous exclusion of water from all solutions resulted in somewhat irreproducible data. Lanthanide chelate concentrations were all kept at 2×10^{-3} M. The titrations were carried out by adding microliter quantities of

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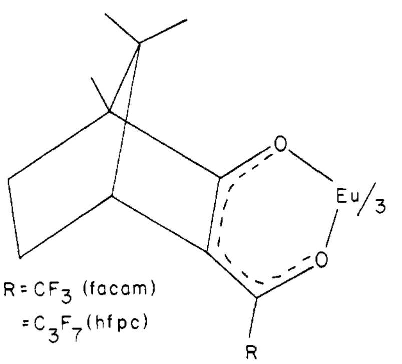

Figure 1. Structures of the chiral Eu(III) β-diketonate chelates used in this study.

substrate from a 0.1 M stock solution to 3.0 mL of the chelate solution already in the fluorescence cuvette.

Tb(facam)$_3$ and Tb(hfpc)$_3$ were synthesized using the method of Schurig,[10] with the ligands being obtained from acid hydrolysis of the corresponding Eu^{3+} complexes. Purification of the Tb^{3+} chelates was carried out in the same fashion as for the Eu^{3+} chelates. The energy-transfer studies were performed by adding microliter quantities of the Eu^{3+} chelates (from a 0.01 M stock solution) to a 1×10^{-3} M solution of the corresponding Tb^{3+} chelate. With each addition of Eu^{3+} quencher, the intensity of Tb^{3+} and its emission lifetime were both measured.

All emission measurements were made on a medium-resolution emission spectrometer constructed in this laboratory and previously described.[11] Samples were excited by the 365-nm output of a 200-W Hg-Xe arc lamp, the emission collected at 90° to the exciting beam and subsequently analyzed by a double-prism monochromator, and finally detected by an EMI 9798B photomultiplier tube (S-20 response). The emission titrations were conducted by monitoring the *integrated* intensity of the $^5D_0 \rightarrow {}^7F_2$ Eu^{3+} emission band at 615 nm as increasing quantities of substrate were added to the chelate solution. All emission intensities were referenced to the emission intensity of a 1×10^{-3} M solution of quinine sulfate in 0.1 N H_2SO_4; with this correction all intensity data were reproducible to within 1%. Emission lifetime measurements were made by exciting the samples with a pulsed xenon flashlamp (EG & G FY-5D supply and FX-6A tube) and photographing the emission decay as displayed on a Tektronix Model 564 storage oscilloscope. Standard exponential decay routines were used to evaluate the emission lifetime.

Results and Discussion

Addition of substrate dissolved in CCl_4 to a solution containing one of the chiral europium β-diketonate complexes always resulted in an increase in Eu^{3+} emission. The emission was found to increase up to an intensity value that could not be exceeded no matter how much substrate was added. This limiting intensity was found to be dependent on the nature of the substrate used and, in general, the more sterically hindered a substrate that was used the lower the limiting intensity that could be achieved. Since the increase in Eu^{3+} emission intensity that takes place when substrate molecules bind to the chelate is thought to arise as a result of shielding the metal ion from the solvent,[12] it seems apparent that the limiting intensity is related to the strength of the chelate-substrate adduct.

The shapes of the emission titrations differed greatly on passing from Eu(facam)$_3$ to Eu(hfpc)$_3$, as the data presented in Figures 2 and 3 illustrate. The addition of the first equivalent of substrate to Eu(facam)$_3$ results in only a very slight emission enhancement, while the addition of the second equivalent yields a great deal of enhancement. On the other hand, when the first equivalent of substrate is added to a solution of Eu(hfpc)$_3$ a much larger relative enhancement is seen. Addition of the second equivalent results in still more emission enhancement, with the rate of increase being somewhat higher than for the addition of the first equivalent.

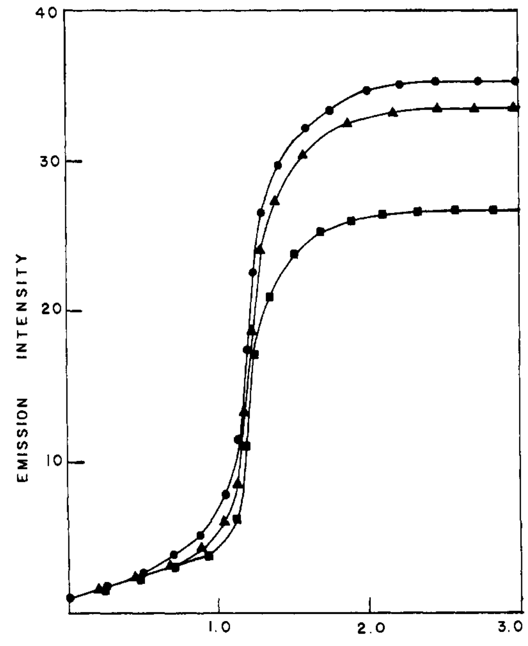

Figure 2. Emission titrations of Eu(facam)$_3$ with *n*-butylamine (●), *sec*-butylamine (▲), and *tert*-butylamine (■). The intensity units are arbitrary.

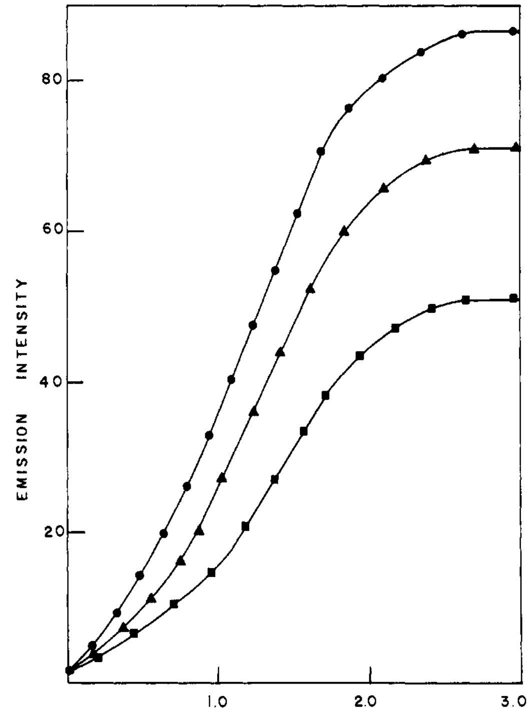

Figure 3. Emission titrations of Eu(hfpc)$_3$ with *n*-butylamine (●), *sec*-butylamine (▲), and *tert*-butylamine (■). The intensity units are arbitrary but are on the same relative scale as Figure 2.

Application of Job's method of continuous variation to the study of chelate-substrate adducts was carried out by preparing a series of solutions containing the same total number of moles of substrate and chelate, but in which the mole fraction of each component was varied from zero to one. The emission intensity of each solution was measured and it was found that a maximum in intensity occurred when the mole

Table I. Formation Constants of the Eu(facam)$_3$: Substrate Adducts[a]

substrate	$K_1 \times 10^{-1}$	$K_2 \times 10^{-3}$	$K_{12} \times 10^{-4}$
n-PrNH$_2$	6.68	1.35	9.01
i-PrNH$_2$	5.88	1.03	6.05
n-BuNH$_2$	6.20	1.36	8.43
sec-BuNH$_2$	5.47	1.07	5.83
t-BuNH$_2$	4.43	1.09	4.82

[a] The units of K_1 and K_2 are liter/mole and each is associated with an error of ±0.05. The units of K_{12} are liter^2/mole^2 and each constant carries an error of ±0.1.

Table II. Formation Constants of the Eu(hfpc)$_3$: Substrate Adducts[a]

substrate	$K_{12} \times 10^{-5}$	substrate	$K_{12} \times 10^{-5}$
n-PrNH$_2$	2.43	sec-BuNH$_2$	2.06
i-PrNH$_2$	2.28	t-BuNH$_2$	1.96
n-BuNH$_2$	2.38		

[a] The units of K_{12} are liter^2/mole^2 and each constant is associated with an error of ±0.08.

fraction of substrate was equal to ⅔ (this behavior was noted for both the Eu(facam)$_3$ and Eu(hfpc)$_3$ chelates and occurred with all substrates). It was therefore inferred that at the limit of emission intensity observed in the titration curves a 1:2 chelate–substrate complex was formed. One-to-two complexes with Eu(facam)$_3$ and amines have been reported previously, although the chelate apparently prefers a 1:1 type of complex with less strongly binding substrates.[13]

Formation of 1:2 chelate–substrate complexes has been observed in emission titrations of Eu(dpm)$_3$ and Eu(fod)$_3$ with the substrates used in this study,[9] but the titration curves of these achiral chelates were always characterized by a linear portion at low ratios of substrate to chelate. The titration curves of the chiral chelates are characterized by nonlinear plots at low substrate to chelate concentrations (although the hfpc chelate less so than the facam), so it seems clear that a different mode of binding is taking place with the chiral lanthanide β-diketonate complexes. The titration curves of Eu(facam)$_3$ suggest that the first molecule of substrate is added with difficulty, but that once that molecule is bound the addition of a second is much more facile. On the other hand, addition of the first molecule of substrate to Eu(hfpc)$_3$ is much easier than the corresponding Eu(facam)$_3$ addition, but it is still somewhat more difficult than the addition of the second molecule.

It is possible to calculate formation constants for the chelate–substrate adducts using the data of the titration curves and methods that have been previously outlined.[8] The break in the titration curves observed for Eu(facam)$_3$ made it possible to determine both K_1

$$K_1 = \frac{[\mathrm{LS}]}{[\mathrm{L}][\mathrm{S}]} \tag{1}$$

and K_2:

$$K_2 = \frac{[\mathrm{LS}_2]}{[\mathrm{LS}][\mathrm{S}]} \tag{2}$$

where [L] is the concentration of free lanthanide chelate, [S] is the concentration of free substrate, and [LS] and [LS$_2$] are the concentrations of 1:1 and 1:2 adducts. Only K_{12}

$$K_{12} = \frac{[\mathrm{LS}_2]}{[\mathrm{L}][\mathrm{S}]^2} \tag{3}$$

could be determined for Eu(hfpc)$_3$ since no clear-cut break was observed in the titration curves obtained for this chelate. Results found for Eu(facam)$_3$ are summarized in Table I, while the results obtained for Eu(hfpc)$_3$ are found in Table II.

The formation constants found for Eu(facam)$_3$ reveal some very interesting features. Within experimental error, it is found that only two values of K_2 are observed and that these clearly reflect the steric requirements of the lanthanide "pocket" into which the second molecule of substrate enters. Both primary amines have values of K_2 that are essentially 1.35×10^3, while both secondary amines and the one tertiary amine have values of K_2 that average to 1.06×10^3. This grouping indicates that the extra steric hindrance provided by the tertiary amine relative to the secondary is unimportant in the binding of the second molecule of substrate. On the other hand, the steric difference between primary and secondary amines is found to be significant, with the primary amines having less difficulty binding the second molecule of substrate.

The binding of the first molecule of substrate by Eu(facam)$_3$ also displays a dependence on the steric nature of the substrate. In general, primary amines add the first molecule with the greatest ease, secondary amines find it slightly more difficult, and the tertiary amine had the greatest degree of difficulty in binding to the chelate. It was not possible to find K_1 for the Eu(hfpc)$_3$ chelate, but similar trends were observed in the K_{12} values that were calculated for this chelate. It may be noted in passing that the K_{12} values found for Eu(hfpc)$_3$ are somewhat greater than the corresponding values found for the Eu(facam)$_3$ chelate, but this behavior is not unexpected since the extra fluorination on the β-diketone ring present for the hfpc ligand should increase the Lewis acidity of its Eu^{3+} complex.

It should be pointed out that the formation constants calculated from emission data could contain inaccuracies due to the nature of the measurements. If LS is a weak emitter due to its unique stereochemistry, then the values of K_1 could actually be larger than were calculated here. Likewise, if LS$_2$ is an unusually strong emitter due to its stereochemistry, then the calculated values of K_2 might be too high. These possibilities were not considered in the calculation of formation constants, but are not expected to influence the results to a large extent. It is fairly well established that the predominant mode of radiationless deactivation of the Eu^{3+} excited state is solvent quenching, and that strong emission intensities are observed if the lanthanide ion is well protected from the solvent molecules by its inner coordination sphere.[12] Previous work on other lanthanide β-diketonate chelates has shown that a single molecule of substrate can be quite effective in promoting strong Eu^{3+} chelate emission,[8,9] and these results were obtained with less bulky ligands than used in the present study. It would appear, therefore, that the less intense Eu^{3+} emission of the LS complex compared to the LS$_2$ complex is due to a smaller degree of complexation between the lanthanide ion and the substrate, and not to any inherent difference in the nature of the radiationless decay pathways of the LS and LS$_2$ adducts.

Two explanations may be advanced to explain the cooperative binding of amine substrates by these two optically active chelates (the titration curves found for Eu(hfpc)$_3$ are not nearly as nonlinear as the Eu(facam)$_3$ curves, but they do reflect the same type of behavior). It is possible that the chelates are associated in solution, and that the addition of the first molecule of substrate only serves to break up the oligimers. The second equivalent is then able to add in a much easier fashion since the chelate molecules are now discrete and monomeric. Association of Eu(facam)$_3$ molecules has been detected in the solid state, but evidence for association vanished when the complex was dissolved in solvent.[6] Nevertheless, since other lanthanide β-diketonate complexes become more associated in noncoordinating solvents (such as CCl$_4$) than in solvents capable of adduct formation,[14] this possibility cannot be ruled

Table III. Stern–Volmer Quenching Constants for the Quenching of Tb(III) Chelates by the Corresponding Eu(III) Chelates in CCl_4 Solution[a]

chelate	K_{sv}^{τ}	K_{sv}^{ϕ}
$Eu(facam)_3$	40.1	40.4
$Eu(hfpc)_3$	37.6	37.8

[a] The units of K_{sv}^{τ} and K_{sv}^{ϕ} are both liter/mole and each is associated with an error of ±0.2.

out. Another possibility is that the first equivalent of substrate induces a reorganization of the β-diketone ligands about the lanthanide ion, and this reorganization makes it possible to add the second molecule of amine with greater ease than the first. This geometry reorganization has been implicated in the binding of 1-phenylethylamine by other chiral Eu^{3+} β-diketonate complexes.[2]

Association of lanthanide complexes in solution can be detected using intermolecular energy transfer from one lanthanide complex to another. Association of lanthanide acetylacetonate complexes was demonstrated by this method,[15] while it was shown that lanthanide complexes of dipivaloylmethane (dpm) are not associated.[16] It is well-known that, if both Tb^{3+} and Eu^{3+} complexes are present in solution, then energy may be transferred from an excited Tb^{3+} ion to an unexcited Eu^{3+} ion.[17] The energy transfer results in a quenching of the Tb^{3+} emission, and this quenching takes place via a dynamic (due to collisional interactions) and static (due to complex formation) quenching mode. Since dynamic quenching decreases both the emission lifetime and intensity of the donor, and static quenching only affects the emission intensity of the donor, a simultaneous measurements of both static and dynamic quenching enables one to conclude whether the donor and quencher are associated in solution or not.[18]

Quenching experiments were carried out in which the emission intensity and lifetime of a CCl_4 solution of either $Tb(facam)_3$ or $Tb(hfpc)_3$ were monitored as quantities of the corresponding Eu^{3+} chelate were added. Standard Stern–Volmer equations for intensity quenching

$$\frac{I_0 - I}{I} = K_{sv}^{\phi}[Q] \tag{4}$$

and lifetime quenching

$$\frac{\tau_0 - \tau}{\tau} = K_{sv}^{\tau}[Q] \tag{5}$$

were used to evaluate the data. In eq 4 and 5, I_0 (or τ_0) refers to the intensity (or lifetime) in the absence of quencher, I (or τ) is the intensity (or lifetime) with the quencher present, and [Q] is the concentration of Eu^{3+} quencher present. K_{sv}^{ϕ} and K_{sv}^{τ} are the respective Stern–Volmer quenching constants for intensity and lifetime quenching, and if these are equal then association of donor and quencher may be assumed to be absent.

The results of the quenching experiments are all collected in Table III, and it is apparent that all of the observed quenching is due to collisional (dynamic) processes. The values found for the quenching are slightly higher than the values found for dpm chelates in CCl_4,[16] but are very close to these values. It is concluded that neither the facam nor the hfpc chelates are associated in solution. In a previous study,[19] $Tb(facam)_3$ was found to be completely dimeric in the long-chain hydrocarbon solvent squalane. The observation made in the present work that facam chelates are monomeric in CCl_4 is consistent with a solvent trend described by Springer and co-workers,[14] in which it was found that self-association of Eu^{3+} chelates was reduced on passing to more polar solvents (the observed order being $n\text{-}C_6H_{14} > CCl_4 > C_6H_6 > CHCl_3$).

It is believed, then, that the cooperative binding of substrate molecules by $Eu(facam)_3$ is due to a geometry reorganization of the β-diketone ligands about the central lanthanide ion. Previous work on $Eu(facam)_3$ had shown that circularly polarized emission (CPE) was not observed in a number of solvents (including the amine solvents used in this study) even though strong total emission and strong CPE were observed and no explanation could be advanced to explain those observations at that time. It is now proposed that the observation of CPE is related to a solution conformation in which a particular diastereomer is found to predominate, and that this conformation is induced by the binding of the substrate molecules. If no particular conformation dominates, the CPE of the different diastereomers cancels and as a result no CPE is observed. This proposal is supported by the observance of four diastereomers in kinetically inert transition metal complexes of chiral β-diketone ligands, and by the observation that the circular dichroism of two of these is equal and opposite in magnitude to the CD of the other two.[20-22] Further work is underway at the present time to further probe the geometry and conformations of chiral shift reagents in solution and to study the process of substrate binding.

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