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CHIRAL LANTHANIDE COMPOUNDS

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CONTENTS

ABBREVIATIONS

CD	circular dichroism
ORD	optical rotatory dispersion
g_{abs}	Kuhn dissymmetry factor
g_{lum}	luminescence dissymmetry factor
CPL	circularly polarized luminescence
ODA	oxydiacetic acid
DPA	dipicolinic acid
FACAM	trifluoroacetyl-*d*-camphor
HFBC	heptafluorobutyryl-*d*-camphor

* See ref. 1.

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ATC	acetyl-*d*-camphor
DPM	dipivaloylmethane
FOD	6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedione
TTFA	theonyltrifluoroacetone
BZAC	benzoylacetone
DBM	dibenzoylmethane
PDTA	1,2-propanediaminetetraacetic acid
CDTA	1,2-*trans*-cyclohexanediaminetetraacetic acid
EDDS	ethylenediaminedisuccinic acid
ATP	adenosine triphosphate
EDTA	ethylenediaminetetraacetic acid

A. INTRODUCTION

Since the first report by Cotton [2] that circular dichroism (CD) could be observed in the absorption bands of Cr(III) and Cu(II) complexes with L-tartaric acid, considerable effort has been made to understand the chirality of metal complexes. Much of this work has centered on how the *d–d* transitions of transition metals sense the dissymmetry of their environment, and on how the properties of these orbitals are altered when all S_n symmetry is removed from the complex. A general review regarding the optical activity of coordination compounds has been presented [3], and Richardson has summarized the most recent conceptions about the theory of *d–d* optical activity [4]. Saito has provided detailed evaluations of the absolute configurations of metal complexes [5,6], and the problem of isomerism in complexes has been addressed [7].

While intense efforts have been made to detail the nature of *d–d* optical activity, much less interest has been focused on analogous studies of the *f–f* optical activity associated with chiral lanthanide complexes. This situation has arisen partly from the difficulty of resolving the very labile lanthanide complexes, partly from a general lack of interest in lanthanide solution chemistry, and partly from an ill-conceived concept of the rarity of the members of the series. The so-called "rare earths" are not rare at all, and actually are more abundant than many transition metals. As a result, applications in phosphor technology, catalysis, bioinorganic chemistry, etc., have begun to abound.

The information available from chiroptical methods has only begun to receive systematic attention from a few groups, in spite of the fact that chiral lanthanide compounds have been prepared in great numbers but never studied from that particular point of view. For instance, while lanthanide complexes of β-diketones have been widely used in NMR spectroscopy as paramagnetic shift reagents for the clarification of overlapping resonance

lines [8], most groups have not taken advantage of the fact that many of the compounds used were inherently chiral. Almost all of the studies which have been reported have merely been contented with questions of spectral simplification and stereochemical predictions. For example, the very first report involving the use of lanthanide chelates as shift reagents considered an adduct containing cholesterol [9].

It is the purpose of this review to discuss the types of studies which have examined a chiral lanthanide compound for some reason, and to attempt a correlation of the various types of results which have been obtained. Hopefully, this will permit an evaluation for future directions of research in the field. While early studies involving *f–f* optical activity attempted to use circular dichroism as a chiroptical probe [10], more recently it has been established that circularly polarized luminescence (CPL) studies on emissive compounds is a much more suitable tool for these studies [11]. This latter method involves detection of the differential emission of left- and right-circularly polarized light by a chiral molecule. Since the absorptivity of lanthanide ions in the visible region is so weak, measurements involving luminescence methods can provide useful data at moderate concentrations.

B. EXPERIMENTAL METHODS FOR THE STUDY OF CHIRAL LANTHANIDE COMPOUNDS

The optical activity within the *f–f* spectroscopic transitions of chiral lanthanide complexes has been studied by the conventional methods of optical rotatory dispersion (ORD) and circular dichroism (CD). The CD technique measures the differential absorption of left- and right-circularly polarized light within an absorption band, and it is convenient to obtain the ratio of the differential absorption to the total absorption

$$g_{abs} = \frac{\epsilon_L - \epsilon_R}{\frac{1}{2}(\epsilon_L + \epsilon_R)} \tag{1}$$

In eqn. (1), ϵ_L and ϵ_R represent the extinction coefficients for absorption of left- and right-circularly polarized light, respectively, and g_{abs} is known as the Kuhn dissymmetry factor [12,13]. The use of dissymmetry factors in chiroptical spectroscopy is significant in that these may be related to the rotational strengths of the transitions, and that they provide a diagnostic test for the nature of a particular band [14].

However, the low absorptivities associated with *f–f* absorption bands requires that solutions of high concentration or long path length be used to obtain suitable signal/noise ratios. This difficulty may be overcome for luminescent lanthanide complexes by measuring the spontaneous differential emission of left- and right-circularly polarized light by a chiral complex, and

this technique is known as circularly polarized luminescence (CPL) spectroscopy. This method combines the sensitivity of luminescence spectroscopy with the selectivity of chiroptical spectroscopy, and given the simple patterns of lanthanide ion luminescence (a limited number of non-overlapping emission bands of known origin) CPL spectroscopy is the preferred method for the study of *f–f* optical activity. A dissymmetry factor can be defined for CPL in analogy with the Kuhn dissymmetry factor of CD [11]

$$g_{\mathrm{lum}} = \frac{I_{\mathrm{L}} - I_{\mathrm{R}}}{\frac{1}{2}(I_{\mathrm{L}} + I_{\mathrm{R}})} \tag{2}$$

I_{L} and I_{R} stand for the emitted intensities of left- and right-circularly polarized light, respectively, and g_{lum} is the luminescence dissymmetry factor.

Finally, chiral lanthanide compounds may be studied by NMR methods, and a vast literature exists on this subject [8]. Direct determinations of enantiomeric purity via the NMR technique have been made by taking advantage of the fact that the spectra of enantiomers are nonequivalent in a dissymmetric environment. The magnitude of lanthanide induced shifts, $\Delta\delta$, has been shown to be a valuable probe of steric environments, and it is no surprise that differential shifts, $\Delta\Delta\delta$, can distinguish between equivalent nuclei of an enantiomeric pair.

C. THEORY OF *f–f* OPTICAL ACTIVITY

While a detailed discussion of the general theory of *f–f* optical activity (as it exists today) is beyond the scope of this article, it is helpful to briefly outline the work of several groups active in the field. Most of the published work has dealt with the chirality of lanthanide ions in trigonal environments, and with the optical activity resulting from placing the metal ions in chiral crystal space groups. However, Richardson has developed a series of selection rules for lanthanide optical activity based on the S, L, and J angular momentum quantum numbers of 4-*f* states perturbed by spin-orbit coupling and crystal field interactions [15]. The term-to-term transitions were classified as to their predicted electric dipole and rotatory strengths, and to the dissymmetry factors within a chiral environment. Certain transitions were identified as being particularly favorable for chiroptical studies on the basis of their inherently large values for the rotatory strength and dissymmetry factor. One very interesting result obtained in this study was the prediction that the hypersensitive ($\Delta J = \pm 2$) transitions of lanthanides would not generally be the most favorable transitions for chiroptical investigations.

A great deal of experimental and theoretical work has centered around the chiroptical properties of lanthanide ions in trigonal environments. Lanthanide

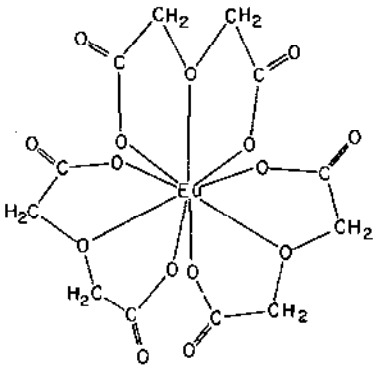


Fig. 1. A view of the tris(oxydiaceto)europium(III) ion down the threefold crystal and molecular axis. (Adapted from Fig. 1 of ref. 23 and used with permission of the copyright owner.)

complexes of oxydiacetic acid (ODA) or diglycolic acid are prepared in aqueous solution as a racemic mixture (since the metal ion site symmetry is essentially D_3), but it happens that these complexes crystallize in an optically active space group [16]. A second-order crystalline phase transition is known to occur between 120 and 5 K, and this changes the space group from *R32* to either $P3_121$ or $P3_221$ [17]. Thus, in these trigonal systems, chiroptical studies are possible at a variety of temperatures, but only in the solid state. The trigonal nature of the ODA complexes is illustrated in Fig. 1, and it will be important in Section F of this review to recall the trigonal nature of tris(terdentate ligand) lanthanide complexes.

Richardson and coworkers have developed a general theory of the *f–f* optical activity of lanthanide ions in complexes having trigonal dihedral symmetry [18]. A crystal field model was adopted, with both the chiral and achiral components of the crystal field being represented in terms of multipole-point charge and multipole-induced dipole interactions of the lanthanide ion with its ligands. Expressions for the electronic rotatory strengths, dipole strengths, and dissymmetry factors were obtained, and these quantities were relatable to the electronic and stereochemical properties of the coordination environment and electronic structure of the metal ion. Finally, a computational model based on the formal theory was developed, such that qualitative predictions regarding 4*f*–4*f* chiroptical spectra could be evaluated. Such calculations were then carried out for the Pr(III), Eu(III), Tb(III), and Ho(III) ions in a trigonal dihedral (D_3) environment [19]. Correlation of the calculated dipole strengths, rotatory strengths, and dissymmetry factors with experimental data demonstrated that the theoretical model correctly accounted for most of the qualitative aspects of the observed chiroptical

behavior. However, the authors indicated the need for further refinement of the model to permit reliable calculations of chiroptical properties at the level of crystal field component resolution.

A variety of experimental work on the chiroptical spectra of trigonal lanthanide complexes has been carried out by several groups. Chowdhury and co-workers reported the first chiroptical investigation involving single-crystal CD (where the chirality was due solely to a dissymmetric environment) when they discussed the ORD within the *f–f* absorption region of $Pr(ODA)_3$ [20]. Subsequently, the CD and magnetically induced CD spectra of the same transitions were reported [21], and a simple model based on the Judd–Ofelt theory of transition intensities was used to interpret the sign and magnitude of a CD anomaly in the $Pr(ODA)_3$ system [22].

Schwartz and co-workers reported the first correlation of CD spectra and absolute configuration of the metal ion for any lanthanide complex [23] when they determined that the Δ-isomer of $Eu(ODA)_3$ exhibited negative CD for the $^7F_0 \rightarrow {}^5D_1$ and $^7F_0 \rightarrow {}^5D_2$ absorption bands. More extensive CD work on the same system has also been reported by Sen et al. [24]. Very detailed work on the CPL spectra of the $Eu(ODA)_3$ system has been reported by Richardson and co-workers [25], and a detailed analysis of the spectra within the confines of the theoretical model created by the same group [18] reveals good agreement in almost every case. The nature of the CPL spectra were found to differ when excitation was performed parallel and perpendicular to the trigonal axis. Mason and co-workers have examined the anisotropic ligand polarization contributions to the *f–f* transition probabilities of Eu(III): $GdAl_3(BO_3)_4$ [26]. This crystal host also provides a trigonal environment for the Eu(III) ion, as the space group is *R32*.

The CD spectrum of $Gd(ODA)_3$ has been discussed in terms of a "soft" selection for optical activity, ΔJ and $\Delta L \leqslant 1$ [27]. In this study, relative values of the ratio of rotational strength to the square root of the dipole strength were reported, and compared to the gross magnetic dipole moments of the *f–f* transitions. Richardson and co-workers have carried out a very detailed series of investigations involving polarized luminescence studies on $Tb(ODA)_3$ [28], examining both linear as well as circular polarization in the emission spectra. Unlike the Pr(III) system, the Tb(III)–ODA complexes apparently do not undergo a phase transition at cryogenic temperatures. As before, the theoretical model developed by Richardson [18] is well-suited for fitting and interpretation of the observed spectra. Finally, the CD spectra of lanthanide ions in the double nitrate crystal system, $K_3Nd_2(NO_3)_9$, has been reported recently [29], and the results of this investigation used to evaluate the selection rules proposed by Richardson [15]. The double nitrate system is interesting in that the crystal system is cubic and hence optically isotropic (the space group is $P4_32$), while the ODA systems are axial. As a

result, no orientation effects exist in the spectra associated with the $K_3Nd_2(NO_3)_9$ host and the results should be more easily interpreted.

D. LANTHANIDE COMPLEXES OF β-DIKETONES

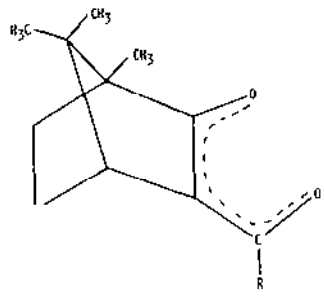
(i) Complexes derived from chiral β-diketone ligands

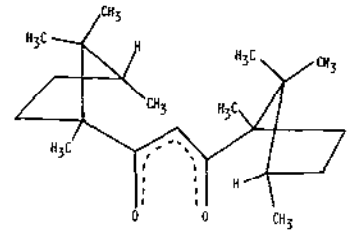
The need to obtain degrees of enantiomeric purity has long been important in synthesis, and it has become established that one of the most useful methods for such determinations has been that of NMR spectroscopy. While the two enantiomers of any dissymmetric compound exhibit identical proton resonances, complexation with a chiral material leads to the existence of diastereomeric compounds and the resonances of these are generally distinguishable in the NMR spectrum. Lanthanide chelates of chiral β-diketone ligands have been widely used for this purpose, as these metal ions are also capable of inducing spectral simplification through paramagnetic-induced shifts.

The ligands used for these studies have generally been derived from *d*-camphor, and the lanthanide ions which are most useful for NMR studies are Eu(III), Pr(III) and Yb(III). Summaries of how the chiral shift reagents have been used in NMR studies have appeared either as separate reviews [30,31] or as a portion of reviews devoted to NMR applications of paramagnetic shift reagents [32–36]. The first complexes of this type were all structurally related to acetylcamphor and substitution on the β-diketone chelate ring has led to the synthesis of a variety of chiral ligands capable of bonding to lanthanide ions. In Fig. 2, the general structure of the β-diketone ligand system (and suitable abbreviations) is shown. These ligands are normally prepared from (+)-3-bromocamphor, a material of known absolute configuration [37].

While transition metal chelates containing chiral β-diketone ligands derived from *d*-camphor were known previously [38], the first reported lanthanide complex was $Eu(BHC)_3$ [39]. Using this complex, Whitesides and Lewis [39] were able to demonstrate that the enantiomeric purity of α-phenylethylamine could be determined from an examination of the NMR spectrum. These studies were subsequently extended [40] to include new chelates derived from the basic *d*-camphor system, and others where different chiral groups were bound at various places on the β-diketone ring.

Other workers had shown earlier [41,42] that β-diketone complexes which contained perfluoro groups could function much more efficiently as NMR shift reagents (a property which resulted from their greater Lewis acidity), and fluorinated derivatives of the camphorato ligand system were prepared. Goering et al. [43] reported the preparation and applications of





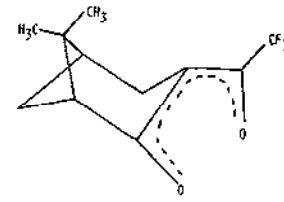
V DCM

I ATC R = CH_3

II BHC R = $C(CH_3)_3$

III FACAM R = CF_3

IV HFBC R = C_3F_7



VI TFANP

Fig. 2. Structures for the nomenclature associated with chiral β-diketone ligands derived from *d*-camphor.

Fig. 3. Structures of the *d,d*-dicampholymethanato (DCM) and 3-trifluoroacetyl-*d*-nonpinonato ligands.

$Eu(FACAM)_3$, while Fraser et al. [44] communicated similar studies for $Eu(HFPC)_3$. The increased Lewis acidity of these compounds greatly extended the range of compounds whose enantiomeric purities could be established by the NMR methods. The synthesis of these chelates was improved by simplifying the procedures [45], and the Pr(III), Eu(III), Sm(III), Dy(III), Ho(III) and Yb(III) complexes were fully characterized.

The shift reagent studies eventually culminated in summary papers by the Whitesides [46] and Goering [47] research groups. Goering et al. carried out extensive studies on the shift differences for enantiotopic protons using $Eu(FACAM)_3$, $Pr(FACAM)_3$, $Eu(HFBC)_3$, and $Pr(HFBC)_3$ [47], although studies involving other β-diketone chelates were mentioned. As would be expected, the fluorinated complexes served as the most useful shift reagents. Whitesides and co-workers [46] reported the synthesis of 8 nonfluorinated and 6 fluorinated Eu(III) β-diketone complexes, most of which had not been previously reported. Interestingly, the most effective reagent was found to belong to the nonfluorinated class. Tris(*d,d*-dicampholymethanato)Eu(III) was found to be more efficient as a shift reagent when compared to either $Eu(FACAM)_3$ or tris(3-trifluoroacetyl-*d*-nonpinonato)Eu(III); the structures

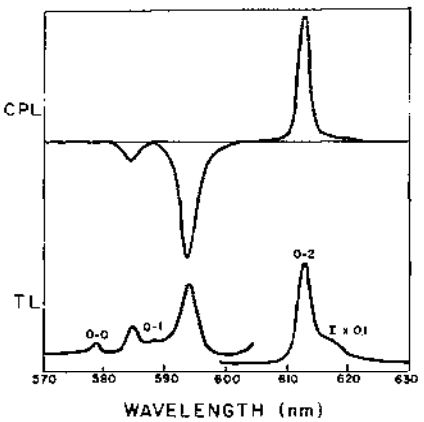
of these two chelate systems may be found in Fig. 3. However, $Eu(FACAM)_3$ and $Eu(HFBC)_3$ are easier to synthesize (as well as being commercially available), although the recent availability of synthesized $Eu(DCM)_3$ should increase the use of this material.

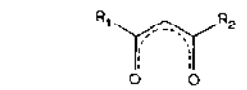
Much less attention has been paid to the inherent optical activity of these complexes, even though they offer excellent situations for the study of *f–f* optical activity. Unlike the acetylacetone complexes, the camphorato chelates are monomeric in solution [48] and therefore one may examine contributions to the overall optical activity made by vicinal, conformational, and configurational effects. However, while the low molar absorptivities of the *f–f* absorptions has prevented useful circular dichroism studies from being carried out, the use of circularly polarized luminescence spectroscopy has permitted extensive investigations of the stereochemistry of these lanthanide complexes.

The first CPL studies carried out on lanthanide complexes of chiral *β*-diketones concerned the Eu(III) derivative of 3-trifluoroacetyl-*d*-camphor, $Eu(FACAM)_3$. The optical activity of $Eu(FACAM)_3$ was studied in 28 neat solvents, but CPL was only observed in eight of these [49]. When CPL could be observed, it was found that the lineshapes were solvent independent, and only differed in magnitude as the solvent was changed. With dimethyl sulfoxide, one of the components of the $^5D_0 \rightarrow {}^7F_1$ transition was found to be totally circularly polarized. The CPL spectra within selected Eu(III) emission bands may be found in Fig. 4.

The origin of this optical activity, and an explanation for the lack of CPL in many solvents, requires that an understanding of the processes accompanying the solvation of these complexes be understood. Brittain and Richardson also examined the behavior of $Eu(HFBC)_3$ (HFBC = 3-heptafluorobutyryl-*d*-camphor) in a variety of solvents [50], and found that in dimethyl sulfoxide solvent the sign of the optical activity was opposite for $Eu(HFBC)_3$ relative to $Eu(FACAM)_3$ even though the *β*-diketone ligands were both prepared from *d*-camphor. These results suggested that the metal chirality was due primarily to configurational effects, as the sign of the vicinal effect was required to be the same in each case (no contribution could be expected from the conformational effect as the *β*-diketone ring is planar).

The configurational nature of this solvent-induced optical activity was conclusively demonstrated by Chan and Brittain, who prepared and characterized a series of mixed-ligand Eu(III) compounds [51]. The CPL spectra of $Eu(DK)_2(TFAC)$ or $Eu(DK)_2(HFBC)$ could be obtained in non-coordinating solvents, the signs of the observed CPL bands were solvent independent, and the magnitude of the observed optical activity was only 10% that seen in the tris TFAC or HFBC chelates in the coordinating solvents. In the mixed-ligand chelate systems, only vicinal contributions are possible and the





VII	ACAC	$R_1 = CH_3$	$R_2 = CH_3$
VIII	DPM	$R_1 = C(CH_3)_3$	$R_2 = C(CH_3)_3$
IX	FOD	$R_1 = C(CH_3)_3$	$R_2 = C_3F_7$
X	TFFA	$R_1 = CF_3$	$R_2 = C_4H_3S$
XI	DFHD	$R_1 = CF_3$	$R_2 = C_3F_7$
XII	BZAC	$R_1 = CH_3$	$R_2 = C_6H_5$
XIII	DBM	$R_1 = C_6H_5$	$R_2 = C_6H_5$

Fig. 4. Total luminescence (TL, lower trace) and CPL spectra (upper trace) associated with the Eu(III) $f-f$ emission bands of Eu(FACAM)$_3$ dissolved in neat dimethyl sulfoxide. Data are shown for the $^5D_0 \rightarrow {}^7F_0$, $^5D_0 \rightarrow {}^7F_1$, and $^5D_0 \rightarrow F_2$ emission bands. (The results are adapted from Figs. 3 and 4 of ref. 49, and are quoted with permission of the copyright owner.)

Fig. 5. Structures for the nomenclature associated with achiral β-diketone ligands.

weak CPL associated with these systems identifies the source of the optical activity in the pure complexes. It was hypothesized that formation of the solvent adduct causes crowding of the bulky camphorato ligands, and these adopt the configuration of lowest energy. However, since all three ligands in the pure compounds are inherently chiral, the preference for any isomer is in fact a partial resolution of the complex.

With this assumption, it is clear that the solvents which do not cause extensive crowding of the ligands (and therefore have small steric requirements themselves) will not lead to measurable CPL. The substrates which lead to the largest CPL actually are observed to form 1 : 2 chelate/substrate adducts, and these have been recently studied in great detail. The effect associated with the steric nature of the substrate was investigated by measuring the CPL of Eu(FACAM)$_3$ and Eu(HFBC)$_3$ with a series of sulfoxides, sulfones, and phosphate esters [52], and also with a series of formamide and acetamide derivatives [53]. The stereoselective interaction of these chelates containing chiral β-diketones has also been studied with Tb(ATC)$_3$ (ATC = 3-acetyl-*d*-camphor), and the different acidity of the nonfluorinated ligand permitted quite different chemistry to take place [54]. Depending on the steric nature of the substrate, different diastereomers of the Tb(III) complex could be produced in excess.

(ii) Complexes derived from achiral β-diketone ligands

Most of the applications in which lanthanide complexes of β-diketones have been used as NMR shift reagents have employed ligand systems which are inherently achiral. The structures of the important chelate systems (and suitable nomenclature) have been collected in Fig. 5. Although a tris(β-diketone) lanthanide complex is actually a racemic mixture (being trigonal), no resolutions have been reported. However, complexation of a chiral substrate in the inner-coordination sphere of the lanthanide ion yields a chiral compound, as, for instance, in the first report made by Hinckley [9]. It is impossible to describe here the range of compounds which have been studied via the NMR method after complexation with lanthanide shift reagents, but we shall restrict the discussion to the results of chiroptical investigations.

A variety of investigations has been carried out in which correlations have been made between the absolute configuration of a chiral substrate and the sign of the CD induced in a lanthanide β-diketone chelate. Nakanishi and Dillon have described a method for the determination of the chirality of α-glycols and α-amino alcohols based upon the CD and ORD resulting in $Pr(DPM)_3$ and $Eu(DPM)_3$ [55–57]. In this method, chirality developed in the ligand absorptions of the complexes (near UV region) is studied as a function of the added substrate, but CD within the $^7F_0 \rightarrow {}^5D_1$ absorption band of $Eu(DPM)_3$ can also be used for the determination of absolute configurations [58]. Using these methods, the chirality of C_{18} juvenile hormone has been established [59]. In another report, the chirality of simple amines and cyclic 1,2-amino alcohols has been determined with $Pr(DPM)_3$ [60].

Much more extensive chiroptical studies have been carried out for luminescent β-diketone complexes using the CPL technique. Brittain and Richardson were able to induce dissymmetry in $Eu(DPM)_3$ and $Eu(FOD)_3$ upon dissolution into resolved α-phenylethylamine [50], and also studied the changes in $Eu(FACAM)_3$ CPL when this chiral lanthanide chelate was dissolved in the chiral solvent. Later, Brittain extended the investigations begun by Nakanishi to include CPL determinations of absolute configuration, when it was shown that the sign of the CPL within the $^5D_4 \rightarrow {}^7F_5$ transition of $Tb(DPM)_3$ could be related to the chirality of the bound substrate [61].

By studying the CPL spectra of complexes in which the chiral substrate is able to attach to the Eu(III) β-diketone complexes in a bidentate fashion, it has been possible to examine the conformational effect in these chelate systems. Adducts of $Eu(TTFA)_3$ (TTFA = theonyltrifluoroacetone) with cinchona alkaloids revealed that the sign of the observed CPL could be correlated with the absolute configuration of one of the substrate asymmetric

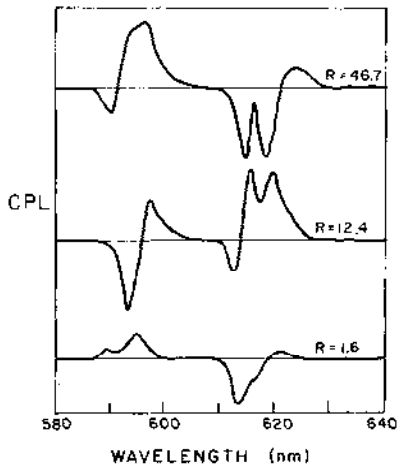


Fig. 6. CPL spectra obtained for $Eu(BZAC)_3$ during titration with D-phenylglycinol. Spectra are shown for the $^5D_0 \rightarrow {}^7F_1$ and $^5D_0 \rightarrow {}^7F_2$ emission bands, and the mole ratio of phenylglycinol to $Eu(BZAC)_3$ is shown with the corresponding spectrum. (The data are found as Fig. 4 in ref. 66 and are used with permission of the copyright owner.)

atoms, and that the different alkaloids were able to induce varying degrees of chirality at the metal ion [62]. CPL studies were also carried out using aliphatic amino alcohols to induce optical activity in $Eu(TTFA)_3$ [64] and $Eu(FOD)_3$ [65], and in these works the emission intensities were also used to calculate the formation constants of the adduct complexes. Finally, in a comprehensive study involving 10 chiral phenylalkylamines and phenylalkylamino alcohols and their adducts with $Eu(FOD)_3$ and $Eu(TTFA)_3$, it was shown that the optical activity associated with monodentate substrate binding was significantly different from that observed upon bidentate attachment, and different yet from chirality arising from terdentate bonding by a substrate [65].

It is always assumed in NMR spectroscopy that formation of the adduct complex does not alter either the conformation or structure of the substrate. This is not always the case, as was demonstrated during the course of CPL investigations in which chiral amino alcohols were bound to $Eu(BZAC)_3$ (BZAC = benzoylacetone) and $Eu(DBM)_3$ (DBM = dibenzoylmethane) [66]. In the normal situations [61–65], addition of the chiral substrate results in the development of a particular CPL lineshape which intensifies as the adduct becomes more fully formed. Full complexation of the chelate yields CPL spectra which are unaffected by further addition of substrate. However, with $Eu(BZAC)_3$ and $Eu(DBM)_3$, the CPL spectra underwent drastic changes as a function of substrate concentration, as has been illustrated in Fig. 6. These CPL changes were finally determined to arise as a result of Schiff base

formation between the amino alcohol substrates and the coordinated β-diketone ligand [66]. Such behavior was not observed with the fluorinated β-diketone ligands, as the Schiff base complexes of these ligands are prone toward hydrolysis.

Very recently, Calienni and Brittain have begun to synthesize and characterize a series of Schiff base complexes, in which salicylaldehydes and β-diketones have been condensed with chiral amines and amino alcohols. The Eu(III) derivatives of these are often highly luminescent, and display very strong optical activity characteristic of a merged sum of vicinal, conformational, and configurational effects [67].

E. LANTHANIDE COMPLEXES OF AMINO AND CARBOXYLIC ACID LIGANDS

(i) Complexes containing chiral amino acids

Lanthanide ions generally display only a small affinity for α-amino acids, since these ligands bind solely at the carboxyl portion of the ligand. However, when the ligand contains two carboxyl groups capable of forming a chelate (as in the case of L-aspartic acid), the formation constants can be substantial [68,69]. In spite of the weakness of the complexes, the amino acid complexes of lanthanide ions have received some degree of attention since the paramagnetic members of the series may be used as aqueous shift reagents for the study of proteins, as will be seen in Section G of this review. Central to an understanding of the lanthanide/protein complexes is a comprehension of the simpler complexes, and approaches have been made along several lines.

Potentiometric titrations have proved extremely useful in the determination of stability constants, and these have been tabulated [70,71]. Of course, these measurements do not provide stereochemical information, but are useful in evaluations of thermodynamic properties. Martin and co-workers [72] have observed that even in the presence of a 10-fold excess of ligand, lanthanide ions titrate 2.4–2.8 equivalents of base per mole of Ln(III) associated with hydrolysis of the metal ion. These workers suggested that this nonintegral portion of the titration curves was due to the formation of polymeric species, with the bridging being effected by hydroxide ions. This polymeric association was studied by Brittain, who used intermolecular energy transfer between Tb(III) donor complexes and Eu(III) acceptor complexes to study the influence of aspartic acid [73], histidine [74], and hydroxy amino acids [75] on the polynuclear association. A very interesting result found during the course of the quenching studies was the existence of stereoselectivity in the energy transfer: complexes prepared from D- or

L-ligands exhibited different transfer efficiencies when compared to complexes prepared from D,L-ligands in the high pH region.

In conjunction with efforts to develop the use of lanthanide ions as reagents to aid the study of protein and polypeptide conformations in solution, a wide variety of NMR studies have been carried out on simple amino acid complexes of lanthanide ions. The applicability of nitrotyrosine residues as potential specific lanthanide ion binding sites was evaluated from studies on the Eu(III), Pr(III), Gd(III), and La(III) complexes with *N*-acetyl-L-3-nitrotyrosine [76]. During the course of this work, several limitations regarding lanthanide induced shifts were uncovered, but the probe technique was shown to be a valuable conformational aid. General methods for the determination of the conformation of small molecules in solution by means of paramagnetic shifts and relaxation perturbations have been described [77], and specific examples involving amino acids and peptides were quoted.

Complexes of Nd(III) with alanine, histidine, threonine, and serine have been studied by NMR methods [78], and during the course of this investigation it was learned that formation constants of the amino acid complexes calculated from both NMR and potentiometric methods agreed quite well. Sherry and Pascual [79], examined the proton and carbon lanthanide induced shifts obtained when L-alanine was complexed to each of the members of the lanthanide series, and concluded that structural changes took place across the series. A monodentate coordination geometry was proposed for Pr(III) to Tb(III), while bidentate carboxyl coordination appeared to dominate for Dy(III) to Yb(III). This behavior was thought to parallel known hydration sphere alterations which are known to take place along the lanthanide series. However, such changes were not found in subsequent work involving sarcosine [80], and a number of explanations for the discrepancy were advanced.

Other spectroscopic techniques have been used with great success to study the solution chemistry of the lanthanide amino acid complexes. Birnbaum and Darnall have used difference absorption spectroscopy to uncover details in the Nd(III) binding of alanine, histidine and other ligands [81]. Legendziewicz et al. have used a combination of NMR, absorption and luminescence spectroscopies to study a wide variety of lanthanide complexes with L-aspartic acid, L-glutamic acid, L-asparagine, L-alanine, and L-glutamine [82–84].

As would be expected, chiroptical techniques can provide extremely detailed stereochemical information, if the structure of the chiral complex is known with some degree of certainty. Katzin and Gulyas studied the pH dependence of the CD spectra associated with the Pr(III) complexes of alanine, valine, leucine, serine, asparagine, ornithine, lysine, aspartic acid and glutamic acid [85], and found that the CD spectra were extremely sensitive to pH changes. In Fig. 7, spectra obtained for Pr(III)/L-valine

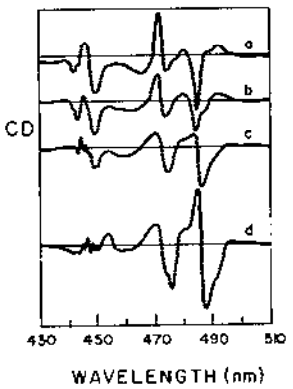


Fig. 7. Circular dichroism spectra obtained for a 3:1 Pr(III)/L-valine mixture over the 7–9 pH interval. (The spectra were taken from Fig. 2 of ref. 85 and are used with permission of the copyright owner.)

complexes are shown as the pH was raised from 7 to over 8. However, in this work the presence of 1:1 complexes was assumed even though large excesses of ligand were used, and the possible polynuclear association of the complexes was not even considered. As a result, many incorrect conclusions were reached, such as bidentate coordination by glutamic acid via its two carboxyl groups. The CD of these ligands with a variety of metals was reported by Martin and co-workers [72], who carefully considered all the parameters necessary to comprehend the data.

One approach to overcoming the problem of polynuclear complex association is to use a lower concentration of lanthanide complex for the chiroptical determinations. Due to the low absorptivity of the *f–f* transitions, CD studies could not be carried out at lower concentrations, but CPL studies of complex chirality were quite possible. Luk and Richardson carried out the first studies involving chiral lanthanide amino acid complexes in aqueous media [86,87]. These survey studies demonstrated that CPL spectroscopy was an excellent probe of the solution-phase stereochemistry of Eu(III) and Tb(III) complexes. Most of the work involved studies of the Tb(III) complexes due to the greater quantum yield of emission for this metal ion, although the chemical similarity of lanthanide ions ensures that the results would be translatable to most of the members of the series. A 5:1 ratio of ligand/metal was used for much of the work, with the chiral ligands under study being L-malic, L-aspartic, L-glutamic and L-lactic acids, as well as L-alanine and L-serine.

Subsequently, CPL spectroscopy was used to detail the interactions between Tb(III) and Eu(III) ions and a series of potentially terdentate amino acids (L-aspartic acid, L-serine, L-threonine and L-histidine) [88]. In both of

these works, the 5 : 1 ratio of ligand/metal was used and it was found that while direct correlations between observed spectra and plausible solution-phase structures were elusive, nonetheless the CPL spectra were extraordinarily sensitive to details of pH. Generally, it was noted that the most intense CPL was found above neutral pH values.

However, with the observations of Martin and co-workers [72], indicating the presence of polynuclear species at elevated pH, and the energy transfer results of Brittain [73–75] actually proving the presence of these compounds, the observation that most CPL was obtained at high pH values compromised some of the results. In order for the results to have the greatest utility, one had to obtain information on complexes known to be monomeric in the pH ranges of interest.

However, one ligand system was found in which the complexes were found to be monomeric at all pH values. Pyridine-2,6-dicarboxylic acid (dipicolinic acid, or DPA) complexes of Tb(III) and Eu(III) apparently displayed no tendency to associate, probably as a result of the extreme bulkiness of the ligands. The coordinatively saturated 1 : 3 metal/DPA complexes displayed no associative tendencies [89] and nor did the coordinatively unsaturated 1 : 1 and 1 : 2 metal/DPA complexes [90].

Brittain was able to take advantage of the fact that $Tb(DPA)^+$ and $Tb(DPA)_2^-$ contain bound solvent molecules which may be displaced by a second chiral ligand, thus permitting CPL studies to be carried out on complexes known to be monomeric at all pH values. These studies permit an easy method where one may study the interaction of the lanthanide ion and only one (or at most two) chiral ligands, and thus isolate the bonding situations where vicinal or vicinal/conformational effects determine the chirality of the Tb(III) ion. The DPA ligand thus serves a number of purposes: (1) it acts as a means by which polymeric association of the complexes is prevented, even at high pH; (2) it acts as a filler and restricts the number of chiral ligands which may enter the inner coordination sphere of the Tb(III) ion; and (3) it serves as an efficient sensitizer of the Tb(III) emission (the DPA ligand is irradiated, and the absorbed energy is transferred nonradiatively to the metal ion). The very large binding constants of DPA for lanthanide ions [91], ensure that it will not be displaced from the metal coordination sphere.

Brittain studied the CPL spectra obtained in mixed-ligand Tb/DPA complexes containing L-alanine, L-valine, L-leucine, L-isoleucine, L-serine, L-threonine and L-aspartic acid, and in this work was able to see that the CPL spectra associated with chirality due solely to vicinal effects was quite different in sign and magnitude when compared to chirality due to a combination of vicinal and conformational effects [92]. In Fig. 8, the CPL spectra obtained within the $^5D_4 \rightarrow {}^7F_5$ Tb(III) transition is shown for

$Tb(DPA)_2$(L-alanine) and $Tb(DPA)_2$(L-aspartic acid), and one may easily note the difference between the situations where the chiral ligand can only bind in a monodentate fashion (leading to the vicinal effect determining the chirality) as opposed to the bidentate fashion (permitting the conformational effect to contribute). It was also demonstrated that both serine and threonine could bind to the Tb(III) ion in a bidentate manner [92]. The distinction between CPL spectra associated with pure vicinal effects versus spectra obtained when vicinal/conformational effects can contribute was subsequently addressed, and found to be a general effect for the Tb(DPA) complexes: if the CPL of the $^5D_4 \rightarrow {}^7F_5$ transition is single-signed only, then only the vicinal effect is operative [93]. The sign of the vicinal effect CPL is directly relatable to the absolute configuration of the asymmetric atom in the chiral ligand.

(ii) Complexes containing chiral carboxylic acids

Carboxylic acid/lanthanide interactions can be quite strong in aqueous solution, and generally other functional groups do not interact with a Ln(III)

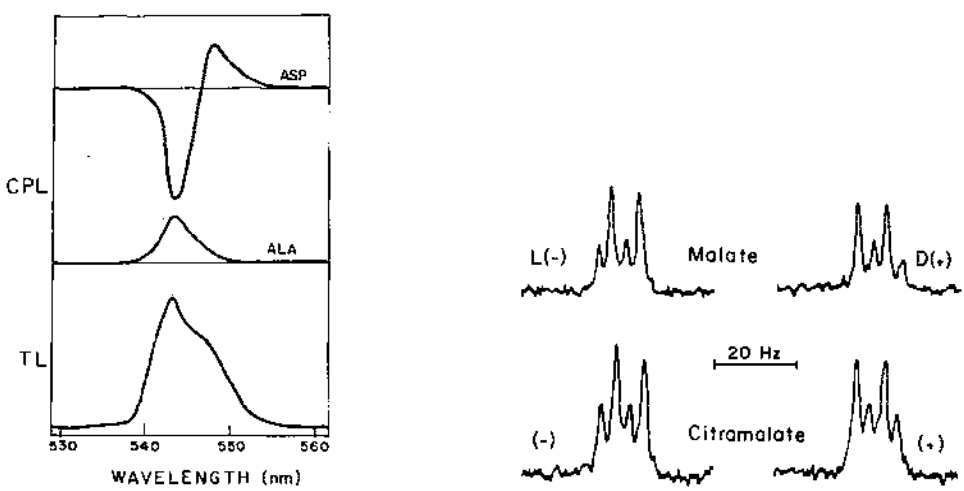


Fig. 8. CPL spectra obtained within the $^5D_4 \rightarrow {}^7F_5$ emission band system of the L-aspartic acid (upper trace) and L-alanine (middle trace) complexes with $Tb(DPA)_2^-$. The TL spectrum was essentially identical for each complex, and is shown as the lower trace. (The spectra were adapted from Figs. 1 and 2 of ref. 92, and are shown with permission of the copyright owner.)

Fig. 9. The methyl proton resonances (at 60 MHz) of enantiomeric mixtures (L/D = 2) of L-lactic acid (50 mM) in solutions containing 100 mM of a malate or a citramalate enantiomer and 20 or 30 mM, respectively, of $PrCl_3$. (These data are taken from Fig. 5 of ref. 102, and are used with permission of the copyright owner.)

ion unless the ligand is first bound by carboxylate ligands. For example, pyridine apparently has no affinity for lanthanide ions in aqueous solution; with Gd(III) and pyridine-2-carboxylic log $K_1 = 4.0$ [94], and with pyridine-2,6-dicarboxylic acid log $K_1 = 8.74$ [91]. However, the formation constants associated with monocarboxylic acids are very low (see, for example, the values quoted in Vol. 3 of ref. 70), and as a result all significant lanthanide complexes containing chiral carboxylic acids are characterized by the presence of multidentate bonding.

Undoubtedly, most attention has focused on complexes of α-hydroxycarboxylic acids since early work indicated that this class of ligands could be used to aid the ion-exchange separation of the members of the lanthanide series. Katzin [95] examined the CD spectra associated with the Pr(III) complexes of 16 hydroxy and sugar acids, although the complex conditions were not controlled as closely as is now known necessary. Nevertheless, this study and the subsequent work of Martin and co-workers [72] with complexes of L-malic acid demonstrated the sensitivity of chiroptical spectroscopy to changes within the coordination environment of the lanthanide ions.

The lanthanide complexes of malic and tartaric acids have received special attention due to the multitude of coordination possibilities presented by these ligands. The CD within the infrared region of the spectrum has been presented for Pr(III)/tartrate complexes [96], with data being obtained within several f–f absorption bands. The thermodynamics of complexation between tartaric acid and La(III) has also been determined, and formation constants obtained for a variety of protonated metal complexes [97]. The formation constants for L-malic acid with a series of lanthanide ions have been calculated from potentiometric determinations [98], and it has also been shown that stereoselectivity exists in the formation constants [99]. While the log K_1 values associated with the Gd(III) and Dy(III) complexes of L-malic and D,L-malic acids are identical to within experimental error, the log K_2 values are significantly different. These formation constants were all obtained at sufficiently low pH as to avoid the polynuclear association which also exists with the malic acid complexes [100].

Nuclear magnetic resonance studies of the Pr(III) complexes of chiral hydroxycarboxylic acid complexes have provided interesting information regarding the stereochemistry of these compounds [101,102]. The paramagnetic nature of the lanthanide ion permitted the resolution of enantiomeric nuclei, as is shown in Fig. 9 for the malate complexes. Spectral resolution is obtained in 1 : 3 metal/ligand complexes and is lost in 1 : 2 complexes, indicating that steric crowding in the 1 : 3 complexes forces the ligands into stereochemically persistent positions. Configurational assignments of absolute configurations were found to be possible in a comparison of known and unknown resonances for related compounds.

CPL investigations on hydroxycarboxylate complexes have received a great deal of attention. Luk and Richardson presented preliminary details associated with studies of Tb(III) and Eu(III) complexes with L-malic acid [87], and these investigations were greatly extended for the Eu(III)/malate complexes [103]. Strong CPL was observed above pH 8, but with the later energy transfer results [75] indicating considerable polynuclear association in this same pH region a need was indicated for further work.

Brittain then applied the mixed-ligand approach to the study of hydroxycarboxylate complexes, and obtained the CPL spectra for a variety of Tb(III)/DPA complexes. A sequence of studies examined the optical activity of the Tb(DPA) and $Tb(DPA)_2$ complexes containing L-lactic acid [104,106], L-mandelic acid [104,106], L-malic acid [105,106], L-hydroxyisocaproic acid [106], L-arginnic acid [106], L-phenyllactic acid [104,106], L-hydroxyglutaric acid [106], and D-isocitric acid [106]. In these studies, examination of the CPL spectra demonstrated bidentate attachment of the chiral ligands, and with malic acid a transition from the bidentate to terdentate mode was observed [105]. This bonding change was indicated by a total inversion of the CPL spectra, as may be seen in Fig. 10. Das Gupta and Richardson also studied mixed-ligand complexes containing DPA, and also employed *N,N'*-ethylenebis-(α-(*o*-hydroxyphenyl)-glycine) as the achiral ligand [107]. In this latter work, the sequence of α-hydroxycarboxylic acids was extended to include tartaric acid.

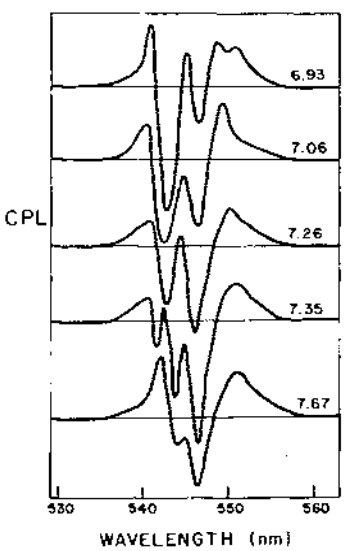


Fig. 10. CPL spectra accompanying the bonding transition from bidentate (lower pH) to terdentate (higher pH) associated with the L-malic acid complex of $Tb(DPA)_2^-$. (The data are taken from Fig. 4 of ref. 105, and are quoted with permission of the copyright owner.)

The effect of the achiral ligand on the observed CPL has been investigated further, and it has been found that replacing the DPA ligand by either sulfosalicylic [108] or phthalic acids [109] cannot only alter the optical activity for a given mode of coordination, but can in fact prevent malic acid from binding in the terdentate mode. Additional work using aminopolycarboxylate ligands as the achiral portion of the coordination sphere confirms these observations [110]. It is presumed that the conformation of the chiral ligand can be perturbed by the other ligands, and that these conformational changes lead to differing *f–f* chirality as experienced by the metal ion.

Lanthanide complexes of carbohydrates and sugar acids have been studied by several physical methods. Katzin has used CD spectroscopy to study the Pr(III) [95] and Eu(III) [111] complexes of a wide variety of sugar acids, and has paid particular attention to gluconic and galactonic acids. Richardson and co-workers [112] have used CPL spectroscopy to study many of the same complexes in aqueous and nonaqueous solution. The binding of La(III) by D-lyxose and D-ribose has been examined using NMR spectroscopy, with weak complexes being detected for aldoses having a *cis* arrangement of three consecutive hydroxyl groups in one of the tautomeric forms of the sugar [113]. A similar binding requirement was noted in the complexation of sorbitol by Pr(III), La(III), Eu(III), and Yb(III) [114].

(iii) Complexes containing chiral aminopolycarboxylic acids

Lanthanide complexes of aminopolycarboxylic acids are known to be extremely stable [70], and several of these ligands are known to be potentially resolvable. 1,2-propanediaminetetraacetic acid (PDTA), 1,2-*trans*-cyclohexanediaminetetraacetic acid (CDTA), and ethylenediaminedisuccinic acid (EDDS) all have been resolved and the lanthanide complexes of these studied by ORD, CD, and CPL techniques. Misumi et al. studied the CD associated with 6 lanthanide compounds of R(−)-PDTA [115], and compared the observed CD intensities. It was found that the ligand-field splittings of the *J*-levels were better resolved in the CD spectra, and certain *f–f* transitions were identified as being "CD sensitive". A similar sequence of studies was carried out on the complexes of L-EDDS [116]. In a later work, the same group examined the effect of pH on the CD sensitive transitions, and observed that the chiroptical spectra were quite sensitive to changes in complex stereochemistry [117].

Essentially at the same time, Pearson and co-workers began to study the ORD and CD spectra of the lanthanide aminopolycarboxylate complexes [118]. A general periodic trend was observed in the ORD spectra associated with eight lanthanide complexes of R(−)-PDTA, and it was found that at any given wavelength (other than inside of an absorption band) the molecu-

lar rotations became more negative as one traversed the lanthanide series. This effect probably arises from perturbations on the ultraviolet bands of the ligand caused by the metal ions. Instrumentation was developed which enabled these workers to study the kinetics of ligand exchange through changes in the chiroptical properties of the R,R(−)-CDTA [119] and R(−)-PDTA [120] complexes of various lanthanide ions. Pearson and co-workers have also developed a spectropolarimetric method for the determination of lanthanide ions, based on titration with R(−)-PDTA [121] and R,R(−)-CDTA [122]. Instrumentation for the automatic recording of ORD [123] and CD [124], and the application of these methods to the study of lanthanide compounds, has also been presented.

Murata and Morita have recently reported the CD [125] and CPL [126] spectra of the Tb(III) complex of L-ammoniaisopropiondiacetic acid, and have also examined some details of the intermolecular energy transfer to the analogous Dy(III) and Ho(III) complexes. Brittain and Pearson [127] have carried out a detailed CPL investigation of the Tb(III) and Eu(III) complexes of R(−)-PDTA and R,R(−)-CDTA, and have demonstrated the extreme usefulness of the chiroptical technique in the study of these complexes. Extensive CPL sign and magnitude changes take place between pH 10 and 11.5, and these observations have been linked to the formation of hydroxy complexes at these high pH values. Presumably, the formation of the mixed-ligand complexes is accompanied by substantial alterations in the conformational and configurational properties of the lanthanide ions.

F. STUDIES OF THE PFEIFFER EFFECT IN LANTHANIDE COMPOUNDS

The observation of optical activity in a racemic mixture of a labile metal complex upon addition of a chiral material was first observed by Pfeiffer [128], and the effect has been named by Brasted and Dwyer after its discoverer. In most instances, the effect is produced when outer-sphere complexation takes place between the metal complex and the chiral environment substance, and this interaction perturbs the enantiomeric equilibrium. The net effect of this perturbation is the production of measurable optical activity, which often is identical in lineshape to that obtained when the metal complex is resolved by chemical means [129]. While CD studies of a wide variety of Pfeiffer-active transition metal complex systems have been reported, no CPL investigations have yet been made.

On the other hand, while no CD studies of Pfeiffer-active lanthanide systems have been reported, CPL studies on trigonal complexes have appeared in the literature. It is known that the $Ln(DPA)_3^{3-}$ series of complexes is approximately trigonal in solution, and therefore the complex consists of a pair of rapidly interconverting enantiomers [130]. That the enantiomeric

equilibrium can be upset was first shown by the addition of resolved tris(ethylenediamine)Cr(III) to a solution of $Tb(DPA)_3^{3-}$ [131]. Formation of the expected ion pair yield strong CPL, and it was shown that decreasing the dielectric constant of the solvent resulted in an intensification of the CPL intensity (as would be expected for an electrostatic attraction).

However, a second mode of bonding between $Tb(DPA)_3^{3-}$ and a potential environment substance was shown when CPL could be observed upon addition of L-ascorbic acid to the Tb(III) complex [132]. Here, the Pfeiffer effect could only be observed as long as the lactone ring remained intact; hydrolysis of this functionality to yield L-diketogluconic acid led to complete loss of CPL. This effect suggested that a hydrophobic site might exist between the DPA rings bound to the metal ion. Positively charged substrates interact favorably with the $Tb(DPA)_3^{3-}$ complex, and the Pfeiffer effect induced by amino acids containing nitrogen atoms bound in a ring system (histidine and proline derivatives) has been reported [133].

The nature of the hydrophobic site has been examined in great detail using a wide variety of environment substances to determine the conditions under which the outer-sphere bonding might take place. The $Tb(DPA)_3^{3-}$ and $Eu(DPA)_3^{3-}$ complexes were all found to exhibit the Pfeiffer effect with monoamino- and diaminocarboxylic acids [134], derivatives of tartaric acid [135] and phenylalkylamines, phenylalkylamino alcohols, and phenylalkylamino acids [136]. In these studies, CPL spectroscopy has been used in conjunction with NMR and absorption spectroscopies to verify the conditions under which binding takes place, what the probable mechanism is, and that the bonding is outer-sphere in nature. A very interesting effect was noted with long-chain diaminocarboxylic acids; here the CPL spectra were found to invert sign at elevated pH values, indicating a change in the mechanism for the association not observed for the short chain substances.

G. LANTHANIDE IONS IN CHIRAL BIOMOLECULAR SYSTEMS

Natural biological systems generally contain centers of dissymmetry, and are often also dissymmetric as a result of molecular conformation and configuration. As a result the lanthanide complexes of these systems may be considered to be chiral lanthanide compounds. As such, the bioinorganic chemistry of the lanthanide ions may be approached from a variety of physical means; absorption and chiroptical spectroscopies, magnetic resonance, and other methods have been used to study the environment of the metal ions. A general review of the bioinorganic chemistry of lanthanide ions has been written by Reuben [137], and the use of lanthanide ions as NMR chemical shift probes in biological systems has been detailed by Glasel [138]. More specific reviews will be mentioned at suitable points in the following sections.

(i) Complexes of nucleosides, nucleotides and nucleic acids

The lanthanide complexes of nucleotides have received extensive attention, since the study of lanthanide induced shifts and line broadenings within NMR spectra can be used to deduce conformations in solution [139]. The lanthanide ions are known to bind at the phosphate group (which functions in a bidentate manner) in the case of nucleotide monophosphates [139], and in adenoside triphosphate the binding appears to be with the terminal phosphate groups [140]. With nucleoside complexes, the bonding undoubtedly exists on the sugar group as the lanthanide ions have little tendency for bonding with the nitrogen donor groups of the base [141]. A conception of these modes of bonding is shown in Fig. 11.

The utility of the shift reagent technique was demonstrated for cyclic β-adenosine-3′,5′-phosphate [142]. Formation of the Pr(III) and Ho(III) complexes at pH 5.3 and subsequent NMR studies of the observed chemical shifts permitted a conclusion that the conformation of the ribose and phosphate groups in solution was consistent with the structure known for the solid state. Williams and co-workers have carried out very detailed and extensive studies of nucleotide conformation using the lanthanide ions as chemical shift reagents. For instance, the conformation of cytidine 5′-monophosphate in solution has been shown to be similar to that of adenosine

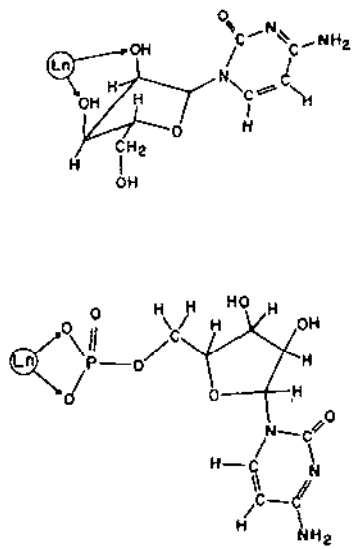


Fig. 11. Plausible modes of lanthanide ion binding to cytidine (upper structure) and cytidine monophosphate (lower structure). Possible coordination of the base carbonyl in the cytidine complex has also been suggested [141].

5′-monophosphate under the same conditions [142]. Dinucleotides have been studied by the same group [143], and the shift reagent method was used to establish the nature of the temperature- and pH-dependent conformational equilibria existing in these complexes.

Cleland and co-workers have also carried out detailed studies of lanthanide nucleotide complexes, but have approached their investigations from a kinetic point of view. A general method for the determination of the dissociation constants of metal–ATP complexes has been advanced [144], and this kinetic method works for any metal complex which can act as an inhibitory substrate analogue for any enzyme that utilizes $MgATP^{2-}$. Since dissociation constant values are available for MgATP under a variety of conditions, the corresponding constants for lanthanide ATP complexes are easily calculated. The utility of this method has been illustrated in the interaction of Ln(III)/ATP complexes with yeast hexokinase, and dissociation constants were obtained for 9 members of the lanthanide series [145].

The utility of lanthanide complexes of ethylenediaminetetraacetic acid as aqueous shift reagents has been demonstrated [146], and the ternary complexes which can be formed with Ln(EDTA) are useful as conformational probes of nucleotide structure in solution. For instance, Williams and co-workers have used the La(III), Pr(III), Eu(III) and Gd(III) complexes of EDTA to study the solution phase conformation of adenosine and cytidine 5′-monophosphates [147], and have shown that the same information is obtained as when the aquo ions are used as the NMR shift reagents. Evidence has been presented which indicates that effective axial symmetry is present in the bidentate chelates formed between lanthanide EDTA complexes and cytidine 5′-monophosphate [148].

Marzilli et al. have examined the lanthanide complexes of nucleosides in detail, using ^{13}C NMR and Raman spectroscopies to study the details of the bonding in aqueous and nonaqueous solution [149–151]. The interactions of cations and anions with the four common nucleosides (uridine, adenosine, guanosine and cytidine) were summarized with respect to the favorable and unfavorable interactions, and these workers proposed that all NMR observations on metal/nucleoside interactions could be explained using the binding criteria specified [150]. It was also determined that the nature of the metal/nucleoside interaction could change substantially when the solution medium was made more basic [151].

The excited states of these compounds have received much less attention, since neither DNA nor any of its constituent nucleotides exhibits easily observable emission in fluid solution at room temperature. However, the Eu(III) ion luminescence may be sensitized after being bound to nucleotides [152], and this property has been used to predict excited state properties and energy transfer characteristics of polynucleotides in aqueous solution. The

emission of Tb(III) may also be sensitized, and a fluorometric method was used to determine the binding constant of Tb(III) with nucleotide monophosphates [153].

No CD investigations of the lanthanide complexes of nucleotides or nucleosides have yet been reported, but Davis and Richardson have reported CPL studies of Tb(III) complexes with nucleosides in aqueous solution [141]. Not all nucleosides were found to induce CPL in the Tb(III) emission, but three systems were found which yielded strong CPL: uridine, cytidine and inosine. Results of the CPL investigations may be found in Fig. 12. Common to all three systems was the presence of two donor hydroxyl groups on the ribosyl group and a carbonyl group on the base with suitable conformations which permit terdentate bonding with the lanthanide ion. Further CPL studies have been carried out in both aqueous and nonaqueous solution by the same group, with the Tb(III) and Eu(III) complexes of nucleosides [154] and nucleotides [155] being studied.

The luminescence of Tb(III) and Eu(III) has been shown to be dramatically sensitized when bound to nucleic acids. Mushrush and co-workers have examined the use of Tb(III) as a luminescent probe for DNA and chromatin [156], and were able to determine that while one equivalent of Tb(III) could be bound per phosphate group in calf thymus DNA, only 0.48 equivalents of Tb(III) could be bound by chromatin. From these data, it was concluded that 52% of the phosphate groups in chromatin were unavailable for

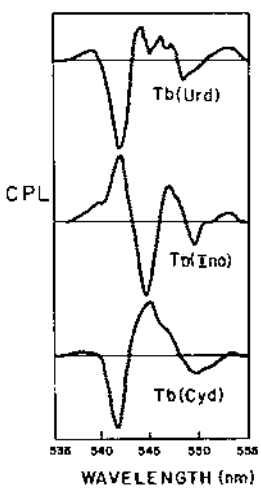


Fig. 12. CPL spectra associated with the $^5D_4 \rightarrow {}^7F_5$ emission band system of 1:2 Tb(III)/nucleoside complexes at pH 6.8. Results are shown for uridine (Urd), inosine (Ino), and cytidine (Cyd), and have been taken from Fig. 1 of ref. 141 with permission of the copyright owner.

lanthanide ion bonding. These workers have also developed several other methods which use Tb(III) binding as a means to study the properties of DNA and RNA [157].

Enhancement of Tb(III) and Eu(III) luminescence has been used to study the transfer-RNA isolated from *Escherichia coli*. This particular nucleic acid is unusual in that it contains a quantity of 4-thiouridine, and the excitation spectrum of Tb(III)-tRNA is identical with the absorption spectrum of this uncommon base [158]. This emission enhancement is observed with $tRNA^{Phe}$, $tRNA^{Glu}$, and $tRNA^{fMet}$ isolated from *E. coli*, but not with yeast $tRNA^{Phe}$ (which does not contain 4-thiouridine). Wolfson and Kearns [159] have carried out further investigations on tRNA isolated from *E. coli*, and have found that binding of the first 3–4 Eu(III) ions is independent and sequential, and the binding of these is approximately 600 times stronger than the binding of Mg(II). In addition, the binding sites are believed to be located near the 4-thiouridine residue found at position 8 in a number of *E. coli* tRNA molecules.

The binding of lanthanide ions by yeast tRNA has also been examined by NMR techniques. It was found that the binding of Eu(III) by yeast $tRNA^{Phe}$ shifts several resonances which have been assigned as being due to protons on the ring nitrogens of the base units [160]. The changes in the NMR spectra as the tRNA is titrated with Eu(III) indicate that 4 or 5 Eu(III) ions are tightly bound, the metal binding is in the fast exchange limit on the NMR time scale, and that the binding to different sites is sequential rather than cooperative.

Tb(III) has been shown to bind to ribosomes and ribosomal RNA [161], and evidence was presented which indicated that the Tb(III) bound to the ribosomes primarily through tRNA interactions. Subsequent studies on DNA and RNA employing Tb(III) as a luminescent probe revealed that only the guanine containing nucleotides (Guo-5′-P and dGuo-5′-P) enhanced Tb(III) emission significantly [162]. The guanine moiety in the polymers was found to be much more efficient in its ability to enhance Tb(III) luminescence relative to the guanine moiety existing as a free nucleotide.

The binding of Tb(III) in nucleic acid complexes appears to be a specific probe which can provide information regarding the structure of these materials. Unpaired residues in nucleic acids produced from a break in the hydrogen bonding appear to be particularly able to sensitize Tb(III) luminescence [163]. Base paired residues of nucleic acids induce no emission enhancement. This feature of lanthanide ion binding has led to the development of a method whereby Tb(III) emission enhancement may be used to assess the single-strand content of DNA [164,165].

(ii) Complexes with proteins and enzymes

An extremely vast literature now exists on the lanthanide complexes of proteins and enzymes, as these metals can be excellent structural and spectroscopic probes for binding sites in the macromolecules. Interested readers should consult the review by Reuben [137] for the general features of the field, and in the present work we will be exclusively concerned with studies investigating the chiroptical properties of lanthanide/protein complexes. To date, no CD investigations of the *f–f* optical activity of these systems has been reported, but a sizable amount of work has been carried out on luminescent Tb(III) complexes using CPL spectroscopy.

The biochemical requirements for Ca(II) cannot be overstated, as this ion plays a significant role in a wide variety of regulatory processes [166]. But since the electronic transitions of Ca(II) do not fall into readily accessible regions of the spectrum, and since it does not possess the unpaired electrons or suitable magnetic nucleus required for magnetic resonance spectroscopy, studies involving Ca(II) have been limited to radiotracer experiments. However, the lanthanide ions possess chemical and physical properties which allow these metal ions to function as excellent probes for Ca(II) upon replacement [167]. Martin and Richardson have classified lanthanide ion interactions as belonging to four main categories [168]: Ca(II) proteins inhibited by substitution of Ln(III), Ca(II) proteins which function similarly upon Ln(III) substitution, specific Ln(III) interactions with proteins not normally considered to contain Ca(II), and Ln(III) substitution for metal ions other than Ca(II).

Of all the lanthanide ions, only Tb(III) is found to exhibit luminescence upon UV excitation. The excitation process actually can be sensitized by irradiation of tyrosine or tryptophan aromatic residues between 290 and 300 nm with the absorbed energy being readily transferred in a nonradiative fashion to the Tb(III) ion [168]. Eu(III) is not found to experience this emission enhancement (which can be as large as 10^6 for Tb(III) in some situations) due to an unfortunate charge-transfer absorption [169]. However, both Tb(III) and Eu(III) can be directly excited with a suitable laser line to obtain a considerable amount of information regarding the structure of the metal site [170].

The two Fe(III) atoms of transferrin and conalbumin were replaced by Tb(III), and CPL spectra were then obtained within the Tb(III) emission [171]. In this study (and all subsequent works), only data obtained within the $^5D_4 \rightarrow {}^7F_5$ band were obtained. Examination of several mixed-metal transferrin preparations provided evidence that the two metal sites were equivalent in structure and conformation. It was also found that the metal binding sites of conalbumin were essentially identical in their stereochemical properties, in

spite of the disparity in the origin of these proteins.

Donato and Martin [172] then described the conformation of the metal binding site of carp muscle parvalbumin B by replacing the Ca(II) by Tb(III) and using CPL spectroscopy as the chiroptical probe. In this protein, the excitation energy was channeled into the Tb(III) ion by means of a phenylalanine side chain as there are no tyrosines or tryptophans in this protein. Examination of the CD spectra in the UV region provided evidence that no structural change in the protein secondary and tertiary structure accompanied binding of the Tb(III) ion, even though the lanthanide ion was found to bind much more tightly than did the Ca(II) ion. It should be pointed out that the CPL spectrum shown in Fig. 2 of ref. 172 is inverted, so that the major CPL peak is actually negative and not positive as shown.

The CPL spectrum of rabbit troponin was obtained after Tb(III) replacement, and the resulting optical activity compared to that of parvalbumin [173]. These two muscle proteins share a number of homologies, and it was found that the CPL of the TN-C component of troponin was essentially identical to that of the troponin. In a subsequent study, it was found that the CPL of Tb(III)-substituted bovine cardiac troponin-C was also identical with that of the carp parvalbumin and rabbit troponin-C [174]. An overlay of the amino acid sequences of the three protein systems revealed that in each system, the most easily substituted metal site was near to one of the aromatic residues. Addition of the other troponin subunits, TN-I and TN-T, was found to weaken the total emission and completely quench the CPL.

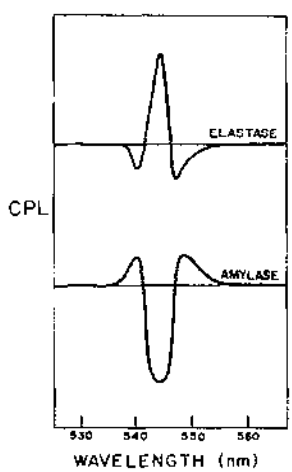


Fig. 13. CPL spectra associated with the $^5D_4 \rightarrow {}^7F_5$ emission band systems of the Tb(III) complexes with porcine elastase and bacterial α-amylase at pH 6.5 in piperazine buffer. (The data are taken from Figs. 2 and 5 of ref. 175 and are shown with permission of the copyright owner.)

The most detailed examination of CPL in Tb(III)-substituted proteins was reported by Brittain, Richardson and Martin [175]. In this study, 40 different protein systems were examined (not all of which were known to bind Tb(III) or Ca(II)), and 36 of these were found to exhibit enhanced Tb(III) emission characteristic of binding at a definite site. However, only nine of these protein systems were found to exhibit CPL: carp parvalbumin, rabbit troponin-C, pronase, porcine elastase, collagenase, bacterial α-amylase, porcine α-amylase and thermolysin. Interestingly, the CPL lineshape invariably took one particular form, and occurred as either mirror image of this form (as is shown in Fig. 13). Comparison of the CPL lineshapes and magnitudes with situations of configurational optical activity [85–90] indicates the origin of the molecular chirality, and a possible explanation as to why CPL is not always observed. If the Tb(III) ion is bound at a site where it is able to experience a chiral environment created by the protein tertiary structure, then CPL will be observed. Binding of the Tb(III) ion at a surface site or in a pleated sheet (and not in a helical environment) does not lead to a configurational effect, and apparently pure conformational or vicinal effects are not sufficient to permit the observation of CPL in the protein systems.

However, other reasons may exist for the lack of observable CPL. Brittain et al. [175] did not observe CPL in Tb(III)-substituted trypsin when the protein was obtained from a commercial source. Epstein and coworkers [176] carefully purified trypsin and separated components which did exhibit CPL upon Tb(III) binding. Presumably, the negative result obtained in the earlier study [175] arose from cancellations within overlapping CPL spectra, which in turn were derived from the presence of different types of binding sites in the different protein components present.

The CPL of Tb(III)-substituted elastase was re-examined by Bieth and co-workers, and the conformational changes induced by the binding of inhibitors was also considered [177]. Turkey ovomucoid, human plasma α_1-proteinase inhibitor, and α_2-macroglobulin did not prevent the binding of Tb(III), although the latter two proteins induced considerable conformational changes in elastase. These conformational changes could be studied from detailed studies of the CPL spectra for the free and inhibited enzymes.

The CPL spectrum of lasolocid A (X537A) has been used to study the conformation of this antibiotic, and the conformational changes which accompany the binding of K(I), Na(I), Rb(I), Cs(I), Mg(II), Ca(II), Sr(II) and Ba(II) [178]. The CPL spectra were found to be solvent dependent, as well as being metal ion dependent. Richardson and Das Gupta [179] used CPL spectroscopy in conjunction with a variety of photophysical measurements to examine the binding of lanthanide ions by the same antibiotic system. During the course of these latter studies, it was established that the probable metal ion binding site was at the salicylate functionality.

H. SUMMARY

Clearly, a wide variety of chiral lanthanide compounds have been prepared and studied, although not always from a chiroptical point of view. Much information of a fundamental nature has been obtained, and a great deal remains to be done. Better correlation of the theory of *f–f* optical activity with observed chiroptical spectra, and the extension of these methods is a highly desirable goal. The interrelation of the various physical techniques discussed in this review is apparent, and future studies would be more useful if several techniques could be brought to bear on a given problem. Nevertheless, it is probably true that the field of lanthanide chemistry stands today where the field of transition metal chemistry stood 15 or 20 years ago, and the study of chiral compounds should be as useful to lanthanide chemistry as it proved to be for transition metal chemistry.

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