Luminescent chiral lanthanide(III) complexes as potential molecular probes

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This perspective gives an introduction into the design of luminescent lanthanide(III)-containing complexes possessing chiral properties and used to probe biological materials. The first part briefly describes general principles, focusing on the optical aspect (*i.e.* lanthanide luminescence, sensitization processes) of the most emissive trivalent lanthanide ions, europium and terbium, incorporated into molecular luminescent edifices. This is followed by a short discussion on the importance of chirality in the biological and pharmaceutical fields. The second part is devoted to the assessment of the chiroptical spectroscopic tools available (typically circular dichroism and circularly polarized luminescence) and the strategies used to introduce a chiral feature into luminescent lanthanide(III) complexes (chiral structure resulting from a chiral arrangement of the ligand molecules surrounding the luminescent center or presence of chiral centers in the ligand molecules). Finally, the last part illustrates these fundamental principles with recent selected examples of such chiral luminescent lanthanide-based compounds used as potential probes of biomolecular substrates.

1 Introduction and background

The importance of the trivalent lanthanides ions (Ln(III)) in spectroscopy is a consequence of their electronic structure. Since numerous and extensive reviews are devoted to the basic, photophysical, and chemical properties of lanthanides in the literature,[1–13] only a brief overview of the luminescence aspect of these will be given here.

The absorption and emission spectra of lanthanides consist of sharp and narrow bands corresponding to the Laporte-forbidden *f*–*f* transitions and are characteristic to the metal ion. Eu(III) and Tb(III), are among the most emissive lanthanide ions, and have an electronic configuration of [Xe]4f^6 and [Xe]4f^8, $^7F_0$ and $^7F_6$ as their ground state, and long-lived $^5D_0$ and $^5D_4$ excited states, respectively (Fig. 1). Some transitions have variable intensities resulting from the sensitivity to the structural details of the metal ion environment. For Eu(III), the most intense bands are usually

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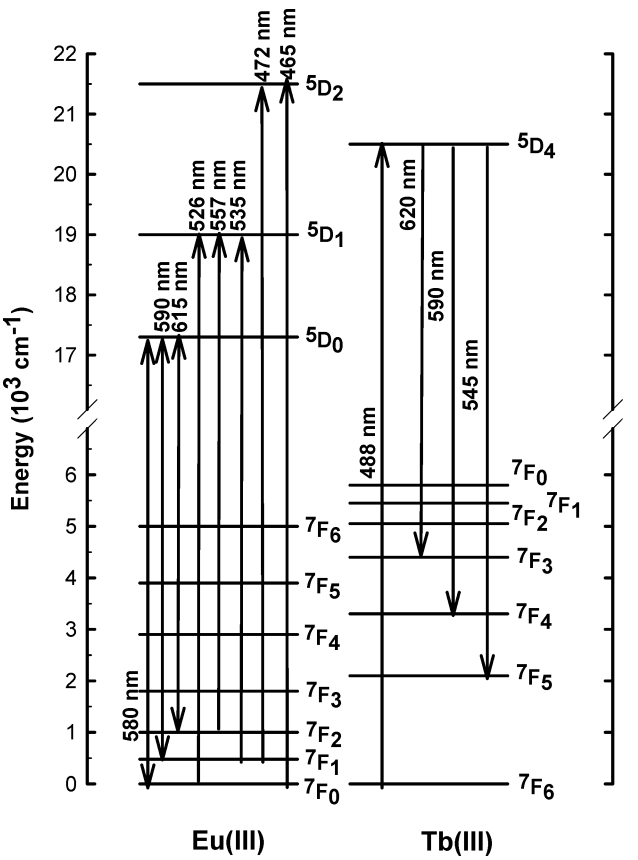

Fig. 1 Approximate partial energy level diagrams for Eu(III) and Tb(III).

the $^5D_0 \rightarrow {}^7F_1$ and $^5D_0 \rightarrow {}^7F_2$ transitions located around 595 and 615 nm, respectively. The latter is described as "hypersensitive" due to its high sensitivity to the chemical environment. The $^5D_0 \rightarrow {}^7F_1$ transition, which satisfies the magnetic dipole selection rules, $\Delta J = 0, \pm 1$ (except $0 \leftrightarrow 0$),[14] is widely used as a probe of chiral structures (see below). For Tb(III), the strongest transition ($^5D_4 \rightarrow {}^7F_5$) is located around 540 nm and is also extensively employed for investigating chiral structures. Even if most of the luminescence applications involve Eu(III) and Tb(III), other lanthanides such as Sm(III), Dy(III), or Yb(III) and Nd(III) in the near-IR have stimulated interest,[6,7,12,13,15,16] despite their usually much weaker luminescence properties.

Although Ln(III) ions have weak absorption and emission intensities, due to the fact that the intraconfigurational *f–f* transitions are Laporte forbidden, this disadvantage can be overcome by indirect sensitization through the absorption bands (indirect excitation) of the ligand molecules coordinated to the Ln(III) ions using UV light (Fig. 2). In situations where one is concerned with possible photochemical changes that may easily alter the organic parts of the Ln(III) complexes caused by UV light,[17] it is possible to minimize these photochemical degradations using a direct laser excitation of the lanthanides in the visible region of the spectrum. This is realized by direct excitation from the $^7F_0$(Eu) or $^7F_6$(Tb) ground level to the excited $^5D_0$, $^5D_1$ or $^5D_2$ (Eu), or $^5D_4$(Tb) states requiring a high power laser source. For instance, terbium may be excited with the 488 nm line of the argon ion laser which corresponds to the $^5D_4 \leftarrow {}^7F_6$ transition, whereas the excitation of europium at 525–529, 550–565 or 578–582 nm is accomplished by using a tunable dye laser pumped by an argon ion laser (using coumarin 6, rhodamine 110 or rhodamine 6G as dyes), which matches the $^5D_1 \leftarrow {}^7F_0$, $^5D_1 \leftarrow {}^7F_2$ or $^5D_0 \leftarrow {}^7F_0$ transitions, respectively. However, the most widely strategy used is the indirect excitation through the ligand absorption bands as it allows modulating the metal ion physicochemical properties.

The concept is to bind to the Ln(III) ion a selected chromophoric group that can improve the absorption and luminescence efficiency (called sensitization or antenna effect) of the resulting Ln(III)-based edifice (Fig. 2). The advantage of the indirect excitation is that the various energy conversion processes occurring in the Ln(III)-based systems (*i.e.* intersystem crossing transfer, efficiency of the luminescence sensitization by the ligand, efficiency of the long-lived triplet state-to-Ln energy transfer *etc.*) may be optimized by choosing selected sensitizing moieties.[4–7,9,11,13,16,18–20] Another important aspect of the judicious design of ligands is to maximize the protection of the Ln(III) ion from external quenching processes such as the intrusion of solvent molecules (*i.e.* H_2O) into the inner sphere coordination of the metal ion. It is well established that the luminescent properties of Ln(III) ions are largely influenced by the radiationless deactivation processes that occur upon interaction with OH, NH, and CH oscillators of the solvent molecules. The *simplest* way to reduce these radiationless deactivations is to fill entirely the first coordination sphere (usually coordination number of 8–9) with multidentate ligands such as diethylenetriaminepentacetic acid (DTPA) and 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraaceticacid-based (DOTA) systems, or analogue macrocycle platforms bearing functionalized pendant arms.[9,11,20] Other classes of molecules used include, *i.e.*, terpyridine, 1,10-phenanthroline, β-diketonate, porphyrin, bipyridyl-functionalized macrocycle, cryptand, or calixarene derivatives (Fig. 3).[21,22] The numerous strategies tested and used result from the influence of the information encoded in the ligands and the metals used, which play a preponderant role in the auto-assembling process based on the "lock-and-key" and/or "induced fit" principles.[23,24] The nature of the metal (*i.e.* lanthanide or transition metal), characterized by its coordination number and its predisposition for a preferential geometry, is one of the principal factors influencing the number of ligands involved in the formation of such edifices. Among other parameters that were considered one can cite various types of ligands, their denticity, noncovalent secondary interactions (*i.e.* π-stacking, hydrogen bonding, steric repulsion *etc.*), experimental conditions, or the number of metallic cations, among others. These aspects are summarized in various review articles.[6,7,22,25]

Luminescent Ln(III) complex-based molecular probes are commonly employed for analytical and biomedical applications, where they are used either as diagnostic or as therapeutic tools.[3,5,13,24,26,27] The considerable surge of interest in using luminescent Ln(III) complexes is a consequence of their unusual spectral characteristics when compared to conventional organic fluorophores (*i.e.* long excited-state lifetimes, line-like emission bands that are easily recognizable and well separated from the broad fluorescence bands of the organic fluorophores, large Stokes shift, or time-resolved separation between Ln(III) luminescence and short-lived background fluorescence *etc.*). Since Eu(III) and Tb(III) possess the desirable characteristics (high quantum yields, long-lived luminescence lifetimes in the ms-range, and less sensitive to vibrational quenching by energy transfer to OH, NH or CH oscillators) for developing commercial biomedical applications, one can understand why most of these latter are mainly based on the two most luminescent Ln(III) ions, Eu(III) and Tb(III). For instance, the optical properties of these Ln(III) ions are taken advantage of in time-resolved fluoroimmunoassays, in luminescent responsive systems to assay various analytes, or in color-tailored fluorophores for simultaneous detection of multiple targets on DNA strands.[3,5,13,24,26,27] On the other hand, Ln(III) ion luminescence—namely Eu(III) and Tb(III)—may provide useful information concerning the structure of metal-containing biological systems in aqueous media. Of special importance in the numerous published studies are to identify, locate, and characterize the metal-binding sites as well as the overall solution structure.[28,29] Aspects of particular interest include the characterization of individual binding sites, the number of metal-coordinated water molecules, the stoichiometry, the binding affinity, the metal-ion selectivity, the inter-metal ion distance, or the investigation of any conformational changes by looking at (Eu) excitation spectroscopy, luminescence decay lifetimes, NMR pseudo-contact shifts, or energy-transfer distance measurements.[7,24,29,30]

Although the use of luminescent Ln(III) complex-based probes is now commonplace in fields like biochemistry, biology, medicine, and related biomedical disciplines, there is a considerable surge of interest to develop luminescent Ln(III) compounds possessing chiral properties in addition to their interesting spectral features discussed above. As a result, the focus of this paper is to review some of the developments made in this field aimed at taking advantage of the chiral feature introduced in the design of luminescent Ln(III) complexes acting as potential biomolecular probes. However, it is not intended to present a comprehensive and extensive review of this emerging discipline, but rather to

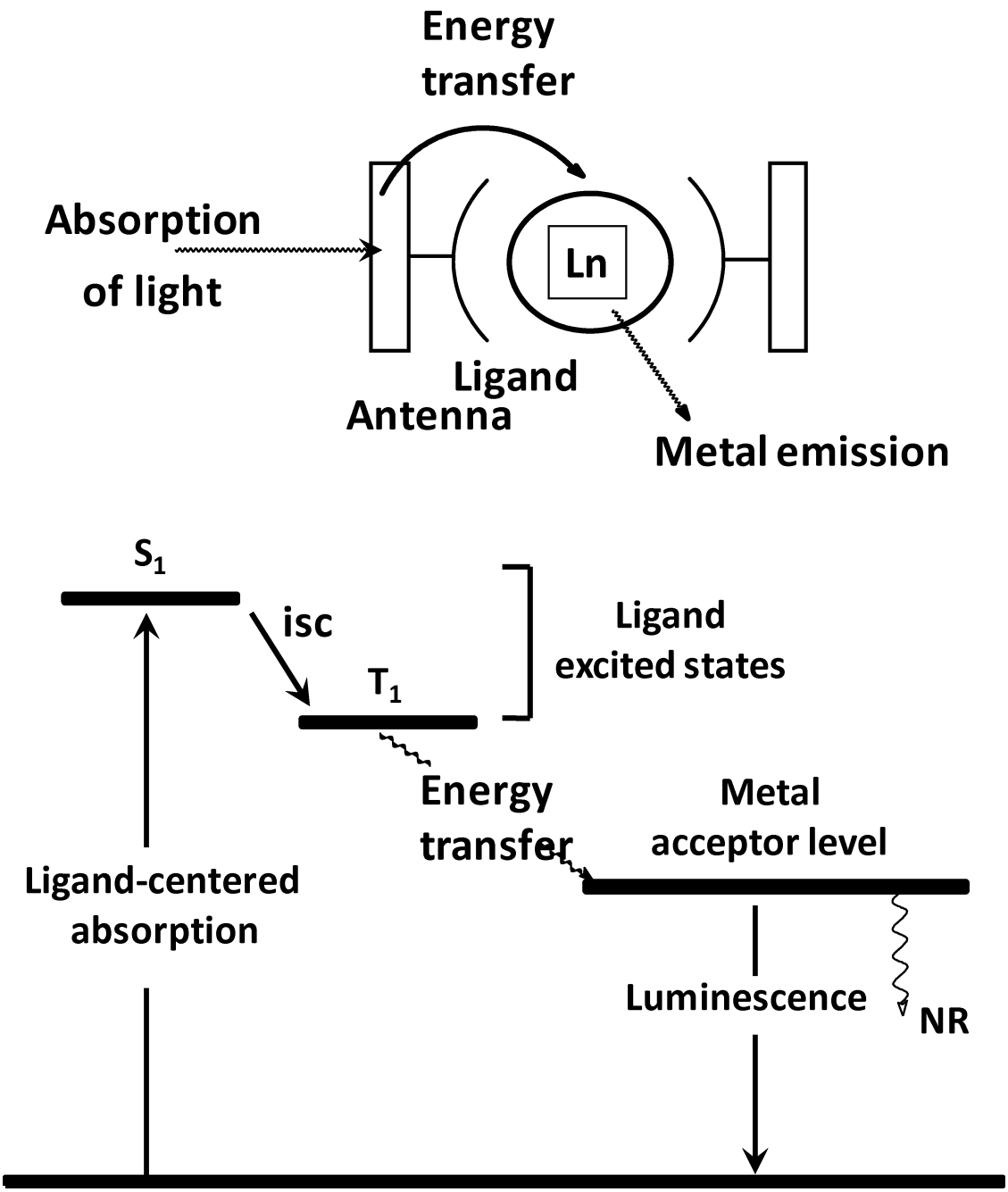

Fig. 2 Simplified illustration (top) and diagram (bottom) showing the indirect sensitization of Ln(III) luminescence through the absorption bands of the ligand molecules coordinated to the Ln(III) ion in a Ln(III) complex (singlet state ^{1}S, triplet state ^{3}T, non-radiative pathway NR, intersystem crossing ISC).

emphasize the importance of chirality in the Ln-based systems that offers technical advantages for the development of a wide-range of new applications. This review begins with a short introduction to the importance of chirality in the biological and pharmaceutical fields and an assessment of the chiroptical spectroscopic tools employed, followed by a section defining the two sources of chirality present in Ln(III) complexes. The last section surveys recent selected examples of chiral luminescent Ln(III) compounds as potential probes of biomolecular substrates. The discussion will also focus on highlighting potential biomedical applications that are currently under investigation.

2 Molecular chirality: significance and relevance

Molecular chirality—the property whereby two mirror images of a molecule cannot be superimposed on each other—is crucial to modern drug research.[31,32] While the difference between chiral structures may *seem* trivially small,[33] the slight change in the compounds' three-dimensional structure profoundly alters the given compound's interaction with its surroundings.[34] For example, in the 1960s, racemic thalidomide was widely used to treat morning sickness. One of the enantiomers was effective at reducing morning sickness,[35] but unfortunately the drug's other enantiomer caused

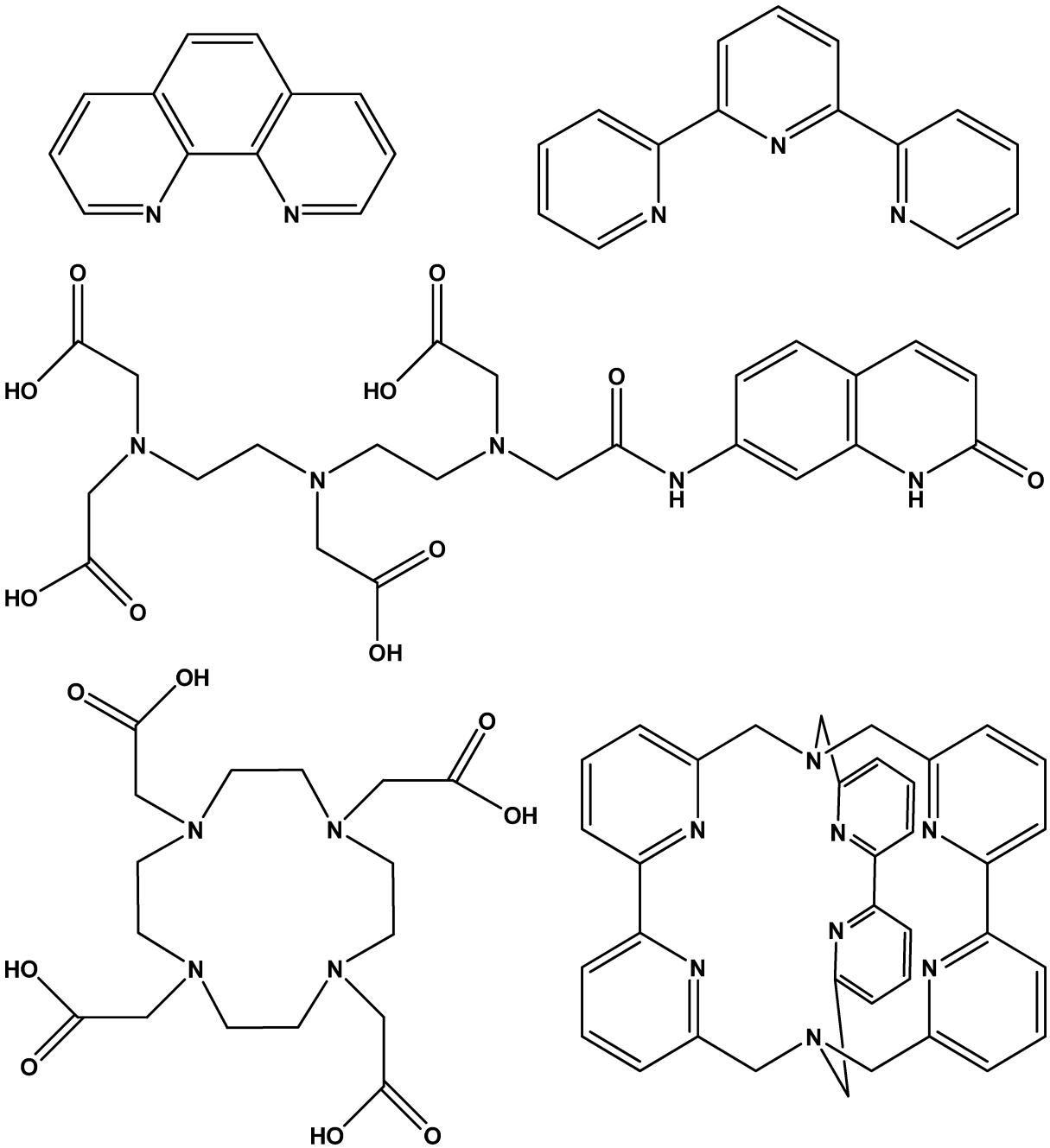

Fig. 3 Selected examples of classes of molecules based on the 1,10-phenanthroline (top left), terpyridine (top right), linear aminocarboxylate (DTPA, middle), macrocyclic (DOTA, bottom left), and cryptate (bottom right).

birth defects. For this reason, it is easy to understand why single-enantiomer drugs are attractive, and researchers are looking at them as possible treatments for cancer, cardiovascular disease, and central nervous system (CNS) defects.[35] In 2009, estimates suggest that enantiopure drugs will produce $15 billion in revenue.[36] To fully understand how chiral molecules produce their biological effects, science needs to develop reliable tools and/or effective probes.

During the last decade, a growing interest in the development of molecular recognition of guests by artificial hosts has emerged.[37,38] This can be explained by the increasing importance of the host–guest chemistry, since it represents a fundamental process for a variety of chemical and biological phenomena and for the regulation of various functions in living systems. For these reasons, synthetic receptors have become an attractive target for chiral recognition studies. In particular, these studies have been focused on the development of receptors having an increased selectivity and/or binding affinities, since such selectivity and affinities can provide valuable information for a better understanding of the interactions between molecules. Moreover, the continued efforts to improve the design of targeted artificial hosts may also lead to the development of useful practical applications including catalysis,

separation processes, sensing, or transport through membranes. Among the large variety of synthetic hosts designed, considerable attention has been devoted to the chiral recognition of amino acids, since they are the basic building blocks of many biologically important molecules. It is often the chiral nature of amino acid R-groups that governs structure-function relationships of peptides and proteins in aqueous media (*i.e.* chiral discrimination in active sites or dictate the folding/unfolding of proteins). Since there are a large variety of biomolecules, this research field has generated considerable interest and is still growing with the continuous discovery of new processes and functions involving proteins. Thus, new tools in chiral separation and resolution must be found to meet this growing demand.[32]

3 Chiroptical tools: from CD to CPL spectroscopy

Currently, the most commonly used tools in drug discovery, structural resolution, and elucidation include circular dichroism (CD), NMR, X-ray diffraction, mass spectrometry, HPLC, and molecular imprinting methods.[38,39] X-Ray diffraction is the most commonly used technique in resolving absolute structures; however the caveat for this approach is the difficulty of obtaining suitable crystals from small amounts of material. NMR methods for determining stereochemical activity based on modified Mosher's Methods[40] or the Trost-Type approach[41] are commonly used in the resolution of primary amines, secondary alcohols, and carboxylic acids. A study by Marathias *et al.*,[42] where Ibuprofen's enantiomers were identified using NMR and residual dipolar couplings, serves as an example of the recent shift to *ab initio* methods. This is due to the complexity in resolving ambiguous proton environments through routine NMR methods. More recently, CD has been used extensively when the structure and specific optical rotation values are known.[43] This technique serves as a staple in current DNA structure analysis, where the absorption bands and intensity can yield substantial information on the structural activity. The use of CD has given rise to newly modified techniques including the spectroscopic approach of comparing observed and calculated vibrational circular dichroism spectra, exciton chirality, electronic circular dichroism, or optical rotation values which have gained popularity due to commercially manufactured software and supercomputers, powerful PC's and Linux clusters.[44,45] Although these conventional tools including NMR, chiral HPLC, capillary electrophoresis, optical rotation, or CD are widely used, each may have their own limitations (*i.e.* time consuming, large sample preparation, high cost, not being sensitive enough to distinguish one enantiomer over another *etc.*) or be more appropriate for specific chiral biomolecules. For instance, CD and molecular mechanics calculations rarely provide unambiguous data[46] as corroborated by the revised assignment of the helical handedness initially proposed of peptide nucleic acid double helices.[47] It is also interesting to note that Polavaraplu recently summarized the importance to use several chiroptical spectroscopic tools for obtaining chiral molecular structural information (*i.e.* independent verification, single methods may only provide partial information or give ambiguous conclusions *etc.*).[45]

Consequently, an attractive complementary tool is the use of Ln(III) luminescence spectroscopy, and especially CPL spectroscopy, the emission analog to CD.[48] CD allows one to detect the differential absorption of left and right polarized light, whereas CPL measures the *difference* in the emission intensity of left circularly polarized light *vs.* right circularly polarized light.

The considerable increase in the use of CPL most probably originated from the discovery that luminescence from intraconfigurational *f–f* transitions of the Ln(III) ions obeying magnetic-dipole selection rules often showed large circular polarization.[49] Transitions that satisfy the formal selection rules of $\Delta J = 0, \pm 1$ (except $0 \leftrightarrow 0$) are magnetic-dipole allowed, where J stands for the total angular momentum quantum number found in the definition of the term symbol, $^{2S+1}L_J$, describing the electronic states of lanthanides.[14] It is common to report the degree of CPL in terms of the luminescence dissymmetry factor, $g_{lum}(\lambda) = 2\Delta I/I = 2(I_L - I_R)/(I_L + I_R)$, where I_L and I_R refer, respectively, to the intensity of left and right circularly polarized emissions. A value of 0 for g_{lum} corresponds to no circular polarization, while the absolute maximum value is 2.

The emphasis in much of the CPL-based work developed over the past decade is a result of the unusual spectral characteristics of the luminescent chiral Ln(III) complexes (see above) and the technical advantages resulting from the use of CPL.[48] One can expect the measurement of larger g_{lum}—as high as 1.38—for selected transitions of Ln(III) compounds, compared to chiral organic molecules for which the extent of circular polarization is almost always less than 1×10^{-2}.[48] For example, chiral triarylamine-based helicenes[50] and Eu(III) complexes[51,52] with chiral 3-heptafluoro-butylryl-(+)-camphorato-, hydroxy-2-isophthalamide-, pyridyldiamide- or 1-hydroxy-2-pyridinone-based ligand derivatives exhibited g_{lum} values of 1×10^{-3} and +1.38, +0.29, +0.18 or –0.12, respectively.

CPL became increasingly useful as a probe of luminescent Ln(III) complexes as sensory systems for anion binding in aqueous media and as a test for the existence of chiral Ln(III) structures (*i.e.* predominant isomer in solution or if the solution of a complex containing an achiral ligand is indeed a racemic mixture).[48] It is also an indicator of changes in chiral structure (*i.e.* importance of the helical wrapping of the ligand strand contribution, and therefore its influence on the diastereomeric induction). In addition, information concerning metal-ion environments and the associated chiral structures of metal-containing biological systems could be obtained through CPL measurements. This information complements data obtained using CD spectroscopy, a much less sensitive chiroptical absorption technique. The latter is mainly used for determining macromolecular information about protein's secondary and tertiary structures, whereas CPL rather reflects local chiral structure changes associated with the local environment surrounding the emitting chromophore. Lunkley *et al.* recently showed the importance of using CPL for selectively studying only luminescent chromophores present in the systems of interest, in contrast to CD, which is affected by most chromophores and/or equilibrium mixtures in an additive manner.[51] Unlike the constant CPL activity observed for the cesium tetrakis(3-heptafluoro-butylryl-(+)-camphorato = (+)-hfbc) Eu(III) complex solution in EtOH upon 10-fold dilution (Fig. 4 and Table 1), the concentration dependence of its exciton CD activity resulted from the dissociation of the tetrakis (+)-hfbc Eu(III) compound into the tris (+)-hfbc Eu(III) complex. The former species exhibited a strong CPL activity in solution, whereas the CPL activity of the latter compound was negligible. On the other hand, the weak CD signals of the Ln(III) complexes, resulting from the very low

Table 1 Summary of CPL results for Cs[Eu((+)-hfbc)$_4$] and [Eu((+)-hfbc)$_3$] at 295 K (λ_{exc} = 335–359 nm range)[51]

Complex	Solvent	concentration/mM	g_{lum} ($^5D_0 \rightarrow {}^7F_1$)	g_{lum} ($^5D_0 \rightarrow {}^7F_2$)
Cs[Eu((+)-hfbc)$_4$]	EtOH	2	+1.32 (595 nm)	–0.19 (612 nm)
		0.2	+1.32 (595 nm)	–0.19 (612 nm)
[Eu((+)-hfbc)$_3$]	EtOH	2	—	+0.003 (612 nm)
		0.2	—	+0.002 (612 nm)

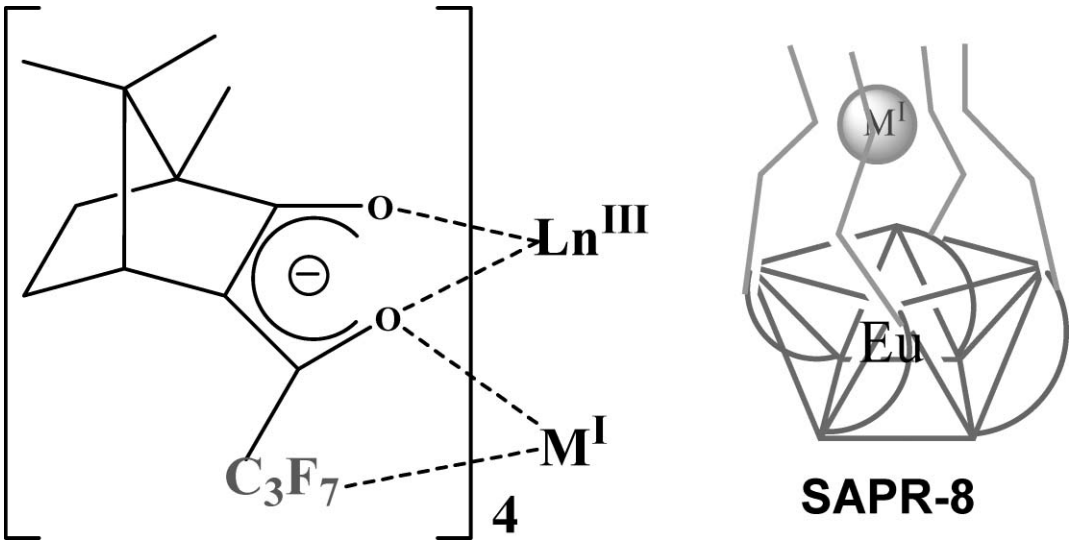

Fig. 4 Chemical structure of M^I[Ln((+)-hfbc)$_4$] (left) and its proposed structure in solution (side view, right).

molar absorptivities associated with the Laporte-forbidden $f \leftrightarrow f$ transitions, have considerably limited their usefulness in chirality sensing. It should be noted that most of the CD applications in chirality sensing involving Ln(III) systems are based on the exciton CD activities due to the presence of chromophoric moieties in the ligand molecules coordinated to the Ln(III) ions.[53,54]

4 Origin of chirality in luminescent Ln(III) complexes

In order for a luminescent Ln(III) compound to possess chiral properties, the Ln(III) ion must be in a chiral environment. The introduction of this chiral feature into such edifices is based on two strategies. One results from the formation of a chiral structure due to the chiral arrangement of ligand molecules surrounding the luminescent center, the formation of double or triple helices, or the helical twist of a macrocycle ligand. For instance, it has been shown that three ligand molecules can be wrapped in a helical way about one or two trivalent Ln ion resulting in the formation of mononuclear triple helical complexes or triple-stranded bimetallic helicates, respectively.[22,55] The use of achiral (non-chiral) ligands usually leads to the formation of a racemic mixture of the right-handed (*P*) and left-handed (*M*) enantiomeric forms,[56] except in rare cases in which a spontaneous crystallization results in the resolution of this racemic equilibrium.[57] The formation of an enantiomerically pure compound requires, in general, the separation of the two constituents of the racemic mixture, which is based on the physical properties of the diastereoisomers (*i.e.* difference of boiling point or of solubility *etc.*). Although separation of enantiomers by selective crystallization of diastereoisomers or other classical chemical separation techniques are well established for transition metal compounds,[58] the situation is more complicated with Ln(III) systems since the ligands are generally very labile. As a result, the *simplest* way of resolving the racemic mixtures of Ln(III)-containing edifices is to introduce a chiral center in the ligand molecules surrounding the Ln(III) ion that will result in a partial or complete diastereoisomeric resolution of the Ln(III)-based systems. This method will be successful only if the possible diastereoisomers have significantly different formation energies. In addition to favouring one of the diastereomeric forms of the Ln(III) complexes, the use of chiral ligands may also determine the overall chirality of these Ln(III)-based edifices. A recent review by Crassous has emphasized the importance of the chiral notion and, in particular, the chiral transfer aspect in coordination complexes.[59] It should be noted that the introduction of at least one asymmetric carbon atom in the ligand molecules surrounding the luminescent Ln(III) ion is the predominant strategy used in the formation of luminescent chiral Ln(III) complexes. The resulting effect of using chiral ligands in the lanthanide(III)-containing species is that its luminescence must be chiral.

5 Survey of luminescent chiral Ln(III) complexes as potential biomolecular probes

Because the focus of this review is to highlight the use of luminescent chiral Ln(III) complexes as potential molecular probes, this section emphasizes recent selected examples of exciton CD- and/or CPL-based Ln(III)-containing probes for chirality sensing or recognition. The key point of introducing chirality into luminescent Ln(III) complexes is to develop strongly luminescent probes that also possess chiral properties with the expectation

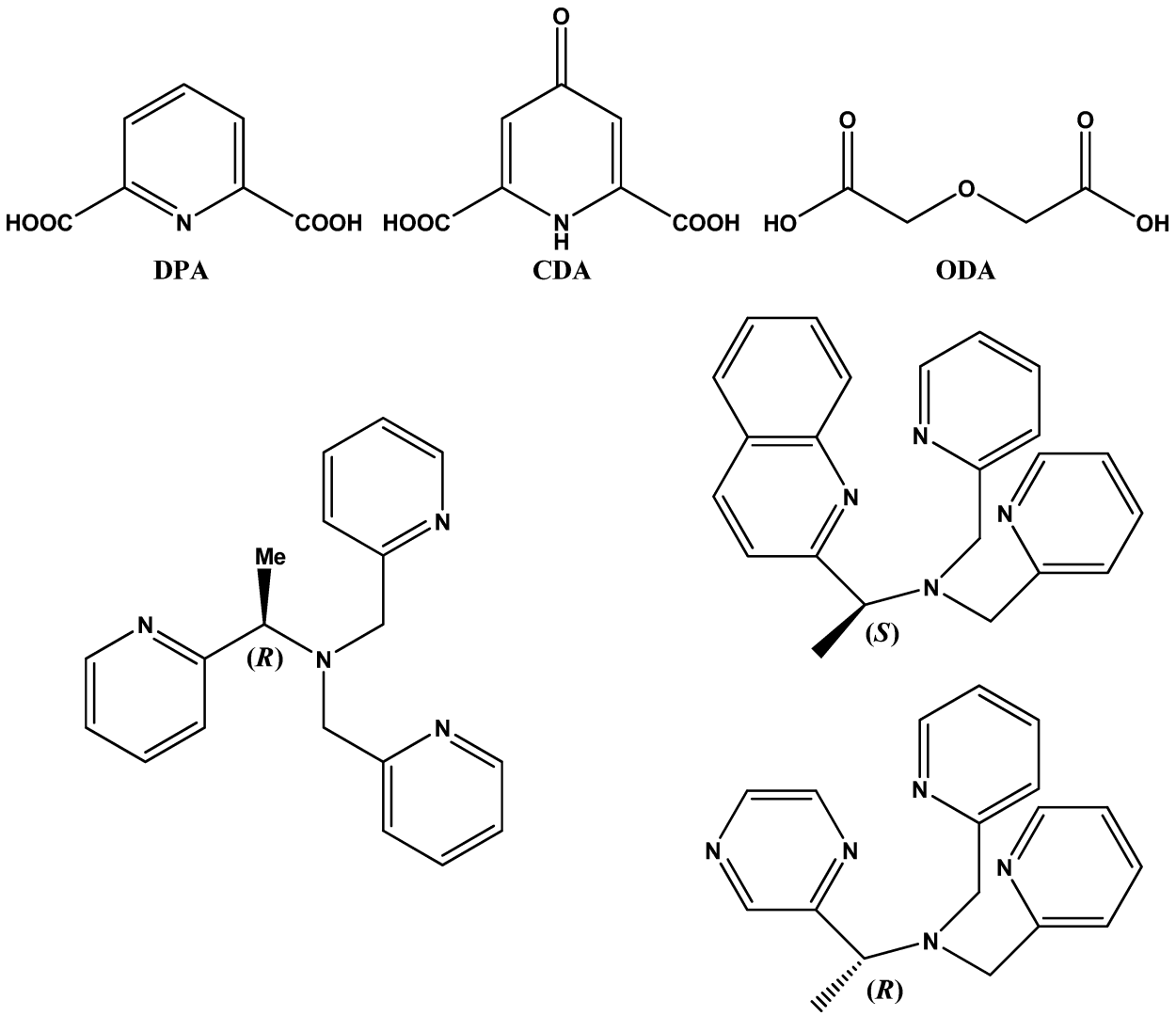

Fig. 5 Chemical structures of achiral (DPA, CDA and ODA, top) and chiral tri(2-pyridylmethyl)amine (bottom left) and tripode-based ligands (bottom right).

of improving the selectivity toward biological systems. One of the enantiomers/diastereoisomers of the chiral Ln(III) complex will preferentially interact with an optically active molecule and quantitatively reflect the result of the interaction with the chiral environment of the molecule of interest. This new property will add considerable power (*i.e.* flexibility, applicability, sensitivity, specificity, selectivity *etc.*) to chiroptical luminescent probes since it can provide valuable information concerning molecular recognition mechanisms in biological materials. The judicious selection of chiral and/or achiral ligands in the preparation of chiroptical active functional Ln(III)-based materials may be used to mimic complexed biological systems and provide useful information on their mechanisms, or enhance their chiral recognition and sensing properties. Since the development of applications for the chiral luminescent Ln(III) compounds with chiral properties depends on how the chirality feature was introduced in these systems (*i.e.*, chiral structure resulting from a chiral arrangement of the ligand molecules about the Ln(III) ion or presence of asymmetric carbon atoms in the ligand molecules), the selected examples have been grouped by type of ligands present in chiral systems containing Ln(III) ions, achiral (non-chiral) and chiral (non-racemic) ligands.

5.1 Lanthanide(III) complexes with achiral ligands

As discussed earlier, the use of achiral ligands usually leads to the formation of Ln(III) complexes, existing as racemic mixtures of complexes with Δ and Λ helicity in solution (Fig. 5). These racemic complex solutions are mainly utilized for chirality sensing due to the observation of induced chirality in these latter upon outer sphere coordination with a variety of optically active organic molecules such as tartrate substrates, amino acid or sugar derivatives.[11,48,53,60–63] Much of this work focuses on the perturbation of the equilibrium between Δ- and Λ-[Ln(2,6-pyridinedicarboxylate = $DPA)_3]^{3-}$ by the added chiral biomolecule. The added chiral species may perturb the racemic equilibrium resulting in a non-racemic ground state. It is assumed here that the effect of adding chiral amino acids (AA*) results in the preferential formation of one diastereomeric outer sphere association complex. The three relevant equilibrium expressions are defined as follows:

$$\Delta\text{-Ln(DPA)}_3^{3-} \rightleftarrows \Lambda\text{-Ln(DPA)}_3^{3-}\ (K_{rac} = 1) \quad (1)$$

$$\Delta\text{-Ln(DPA)}_3^{3-} + \text{AA*} \rightleftarrows \Delta\text{-Ln(DPA)}_3^{3-} : \text{AA*}\ (K_1) \quad (2)$$

$$\Lambda\text{-Ln(DPA)}_3^{3-} + \text{AA*} \rightleftarrows \Lambda\text{-Ln(DPA)}_3^{3-} : \text{AA*}\ (K_2) \quad (3)$$

where the outer sphere association complex is denoted by a colon (:). Studies have demonstrated that the addition of, *i.e.*, chiral amino acids to a racemic mixture of D_3 lanthanide(III) complexes may lead to a perturbation of the ground state equilibrium without changing the local structure of the complexes involved.[48] This perturbation is often referred to as the "Pfeiffer effect".[64] This latter leads to an enantiomeric excess in the ground state, η, defined as follows:

$$\eta = \frac{[\Lambda]-[\Delta]}{[\Lambda]+[\Delta]} \quad (4)$$

where the square brackets in this equation denote ground state concentrations. As also shown in previous studies,[63] in the limit of large concentrations of AA*, the concentration of free (*i.e.* unassociated) complex goes to zero, and η may be related to the diastereomeric association equilibrium constants as follows:

$$\eta = \frac{K_2 - K_1}{K_2 + K_1} \quad (5)$$

It should be noted that in the absence of other chiral effects such as enantioselective excited state quenching, it may be assumed that enantiomeric excesses in the excited and ground states are equal. These differences can be detected by measurement of the circular polarization in the luminescence.

Although several studies based on this concept were published in the past twenty years, limited attention was devoted to understanding the factors that govern the perturbation of the racemic Ln(III) complexes by addition of chiral molecules such as amino acid derivatives.[11,48,53,62,65] The main purpose of these pioneering works was to determine whether or not the solution species formed exhibited CPL. From this standpoint, Muller *et al.* showed that the CPL sign and its magnitude are dependent upon several factors and not only from the chirality of the enantiomerically pure amino acid.[61] They observed that (i) simple modifications in the chiral molecules added to the racemic system did not change the sign of the CPL signal (the same enantiomeric form was favoured), and (ii) the magnitude of the CPL signal was influenced by the presence of additional aromatic groups in the chiral molecules. It is imperative to take into account the effect of the various noncovalent chiral discriminatory interactions such as hydrogen bonding, Coulombic forces, π-stacking, hydrophobic effects, experimental conditions (*i.e.* pH, temperature, ratio of system of interest to amino acid), and steric effects on the CPL sign and magnitude.

Working along these lines, Moussa *et al.* recently demonstrated that the chiral recognition of L-amino acids can be modulated by the nature of the ligand interface of the racemic 9-coordinate terbium(III) complexes and, in particular, by varying the substituent in the *para*-position of the pyridine ring of DPA.[66] For instance, the hydrogen-bond character of the negatively charged hydroxyl group in CDA (chelidamic acid, Fig. 5), the hydroxylated derivative of DPA, led to a larger "Pfeiffer effect" with L-amino acids (*i.e.* L-proline or L-arginine) susceptible to form hydrogen bonds with negatively charged groups, while these hydrogen-bonding effects were less important with DPA. These studies are part of a series of ongoing efforts to provide a further understanding of the intermolecular forces which constitute the base of the "Pfeiffer effect", so that better predictions in future CPL studies focusing on the chiral recognition of amino acids may take place.

One area of particular interest concerns the distinction of optical isomers. To the best of the author's knowledge, Kosareff *et al.* are the first ones who examined the chiral recognition of solutions containing various equivalents of L- and D-amino acids (*i.e.* serine).[67] Although their qualitative results are of a preliminary nature (a complete study focused on investigating and testing various chiral molecules present in the mixture and, also, different lanthanide(III) complex probes will be described in a forthcoming publication),[68] they confirmed that CPL spectroscopy has potential for the chiral recognition of optical isomers of a given amino acid, even if one of the two enantiomers of this latter is in a high excess in solution (see Fig. 6). This is possible because the measured CPL signal is directly proportional to the CPL activity resulting from the chiral-induced equilibrium shift of $[Tb(DPA)_3]^{3-}$ by each amino acid's enantiomeric form. Their results strongly suggest that CPL spectroscopy is responsive to the nature and amount of the added chiral probes present in solution.

Although most of the "Pfeiffer effect" studies are based on the use of CPL spectroscopy (see above), it is worth mentioning that CD has also the ability to probe the perturbation of racemic Ln(III) complex equilibria by adding chiral molecules. Unlike CPL spectroscopy, which probes the excited state structure of chiral molecules, CD is a tool for the study of the ground state of chiral molecules. It is customary to report CD measurements in terms of the absorption dissymmetry factor, g_{abs}, defined as $g_{abs} = 2(\varepsilon_L - \varepsilon_R)/(\varepsilon_L + \varepsilon_R)$ where ε_L and ε_L refer to the molar absorption coefficients for left and right circularly polarized light, respectively. For instance, Parac-Vogt *et al.* demonstrated that the observation of a linear dependence of g_{abs} (the g_{abs} values were plotted against the L-amino acid : $[Ln(2,2'\text{-oxydiacetate} = ODA)_3]^{3-}$ ratios, Fig. 5) was due to the fact that the racemic complex interacts with the added chiral probes in the associated model,[69] as also confirmed by CPL studies.[48,61] They also showed that the chiral discriminatory interactions responsible for the perturbation of the racemic $[Ln(ODA)_3]^{3-}$ by L-proline derivatives were a combination of electrostatic and hydrophobic forces, whereas the hydrogen bonding effects were less important. However, the limited number of lanthanide-CD (or CD signals associated with *f–f* electronic transitions) studies is a consequence of the difficulties inherent to the low molar absorptivities associated with the Laporte-forbidden *f–f* transitions ($< 3\ M^{-1}\ s^{-1}$). These CD measurements are only possible for Pfeiffer-induced systems if relatively high concentrations and long cell path lengths are used (*i.e.* 0.1 M and 5 or 8 cm), supposing that the availability of material or solubility is not a problem.

Unlike the Pfeiffer-induced systems described above, where the non-racemic emitting state is produced by the disturbance of the ground state racemic equilibrium by an added chiral molecule, one may envisage a situation in which the non-racemic emitting state is the result of a time-dependent optically enriched excited state. This is generated through enantioselective quenching by an added chiral quencher molecule. Although this is commonly referred to as an enantioselective quenching process, a more appropriate description of it would be a diastereomeric interaction. The

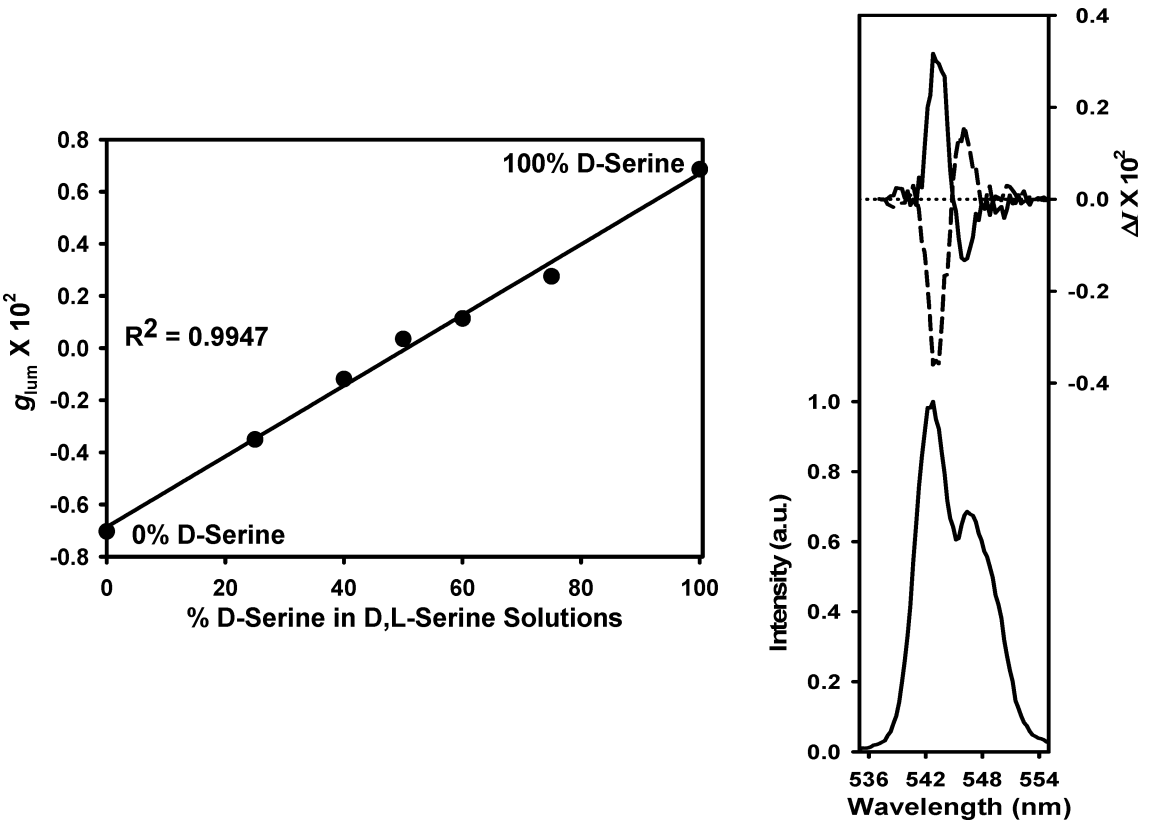

Fig. 6 Left: plot of the g_{lum} values for the 543 nm component of the $^5D_4 \rightarrow {}^7F_5$ transition of 0.01 M $[Tb(DPA)_3]^{3-}$ after addition of 0.40 M of L- and D-serine as a function of the percent of D-serine in the D,L-serine solution. Right: CPL (upper curves) and total luminescence (lower curves) spectra for the $^5D_4 \rightarrow {}^7F_5$ transition of 0.01 M $[Tb(DPA)_3]^{3-}$ after addition of 0.40 M of L- and D-serine (dashed and solid lines), respectively, ($\lambda_{exc} = 293$ nm, pH 7, 295 K).

discriminatory interactions between the excited enantiomers of a racemic Ln(III) complex and a chiral quencher molecule results in a difference in excited state populations due to the quenching of one enantiomer over the other by the added chiral quencher. In terms of the experimental procedure, an unpolarized beam excites the racemic mixture to an emitted state leading to the presence of equal concentrations of the two excited enantiomers. Then, the chiral quencher, also present in the solution, interacts with the excited enantiomers in such a way that one of the enantiomers is quenched at a faster rate than the other. The result of this differential excited-state quenching process is that the excited state becomes chiral (or a non-racemic emitting state) over time, which can be analyzed using the time-resolved feature of the CPL instrumentation. Since the complete mechanistic details of the quenching processes were described numerous times in the literature[48,70,71] and that limited studies have appeared since the last full reviews,[72] only a brief overview of the findings is highlighted here. Most of these studies originated in the research laboratory of Richardson and, then, in some of the research groups of his former students, postdoctoral fellows or visiting scientists who continued related projects on their own and/or with him (see below). Although most of this work uses $[Ln(DPA)_3]^{3-}$ and $[Ln(CDA)_3]^{6-}$ as the racemic donors since they are well characterized and known to be quite emissive and emit light with a high degree of circular polarization, various optically active quenchers (or chiral acceptor molecules) were considered (*i.e.* transition metal-nucleotide complexes, metalloproteins, vitamin B_{12} derivatives, organic dye molecules, dicopper trefoil knots *etc.*)[72–78] with the intent of developing a better understanding of the characteristics of the observed chiral recognition/discrimination properties. In particular, the influence of experimental conditions such as temperature, ionic strength, pressure, solvent type or solution viscosity on the enantioselective excited-state quenching of the racemic systems by these chiral quenchers provided important information about the structure and excited state energetics of the racemic donor and chiral acceptor molecules (*i.e.* shape, size, electrostatic charge distributions, stereochemical dynamics, electronic state structures *etc.*). Of special importance is that the studies by the research groups of Meskers and Dekkers,[73–75] Richardson,[70,72,77] and Riehl[78] showed that the effectiveness of the enantioselective quenching processes is dependent on the strength of the intermolecular interactions between the racemic donor and chiral acceptor molecules and, therefore, responsible for the chiral recognition/discrimination abilities. In other words, the degree and sense of enantiomeric preference in these quenching processes are governed by the electronic and stereochemical properties of the optically active quenchers. In fact, these studies demonstrate that this approach, consisting in generating a differential excited-state quenching system, can be used to probe structural aspects of a series of optically active quenchers. This is possible due to the high sensitivity of the intermolecular chiral recognition/discrimination processes to changes in the structures of the accepting molecules.

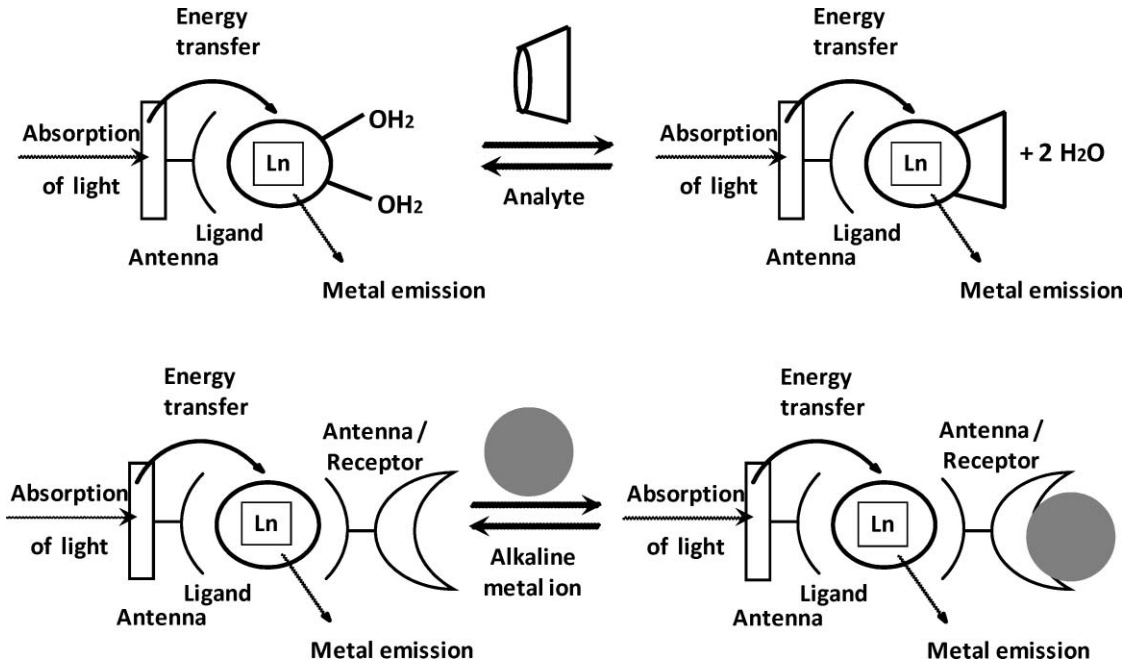

Fig. 7 Illustration on how to design Ln(III)-containing sensors based on the direct coordination of the targeted analyte to the Ln(III) ion (top) and on the covalently or coordinatively binding of the targeted cation to the antenna/receptor group (bottom).

Small structural changes in the chiral quencher systems can result in large changes in the chiral recognition/discrimination properties of the systems of interest. For instance, replacing the amide groups on the side chains of the corrin ring in vitamin B_{12} derivatives by ester moieties resulted in a considerable decrease in the magnitude of the enantioselectivity in the quenching parameter (E_q values went from –0.20 to almost zero).[74] This result suggested that the presence of the amide groups in B_{12} vitamins is critical for effective hydrogen bonding-type intermolecular interactions between its amide protons and the carboxylate groups of the DPA ligands of $[Tb(DPA)_3]^{3-}$. In fact, these hydrogen bonding interactions are responsible for the efficiency of the enantioselectivity processes and, thus, can be used to probe structural aspects of the chiral quencher molecules. It is interesting to note that Meskers and Dekkers also envisioned that such quenching reaction studies could be used to investigate the enantioselectivity of metal containing membrane proteins in the near future.[75]

5.2 Lanthanide(III) complexes with chiral ligands

As can been seen in the above section, the molecular recognition of chiral biological substrates is the result of the chiral perturbation of a racemic Ln-containing complex by an optically active molecule through outer-sphere interactions. However, the considerable interest in chiral Ln(III) compounds, where the chirality is introduced through the use of chiral ligands with the purpose of controlling the diastereoselectivity of these systems, led to the development of numerous chiral sensing/recognition applications. Of special importance is the use of chiral luminescent Ln(III) complexes as anion and cation sensors. The next part of this section details some of the successful recent examples demonstrating the design principles for targeting anions and/or proteins that are of biological relevance (direct coordination to the metal center), followed by a survey of similar studies for analyte sensing (*i.e.* cations and/or proteins) in which the coordination occurs between the analytes and some of the antenna/receptor groups of the chiral Ln(III)-based probes.

5.2.1 Sensing through coordination to the metal center. Since anions are essential to life due to their important functions in biological and chemical processes (*i.e.* used to carry out chemical transformations, depend on the presence or transport of these anionic species *etc.*), one can understand why detecting and monitoring the concentration of these species have become an attractive target for chiral sensing/recognition studies.

This approach requires the use of a stable luminescent chiral Ln(III) complex with at least one open coordination site (Fig. 7). This site is occupied by a solvent molecule that can be readily displaced when an anion-like molecule is added to the solution of the coordinatively unsaturated chiral Ln(III)-based complex. The key point is, that upon coordination of a given anion to the Ln(III) ion, the structural changes in the new anion-bound complex formed result in a "fingerprint" chiral signal correlated to the added anion. Although the modulation of the luminescent and/or NMR spectral properties of the Ln(III) complex upon the binding of an anionic molecule is commonly used for sensing/recognition purposes, it is important to mention that such studies are not always conclusive. For instance, Atkinson *et al.* showed that the binding of a series of *O*-phosphorylated amino acids to a coordinatively unsaturated chiral DOTA-based macrocyclic, (*S*,*S*,*S*)-**4a** (Fig. 8), complex of Eu(III) led to the observation of similar ^{1}H-NMR spectral profiles, whereas their chiroptical study resulted in the observation of different CPL spectra.[79] This work also indicated that the Ln(III) complex of interest had a preference for binding *O*-phosphono-L-tyrosine sites.

These results demonstrate the importance of the chirality feature in studies aimed at probing the binding affinity of a series of

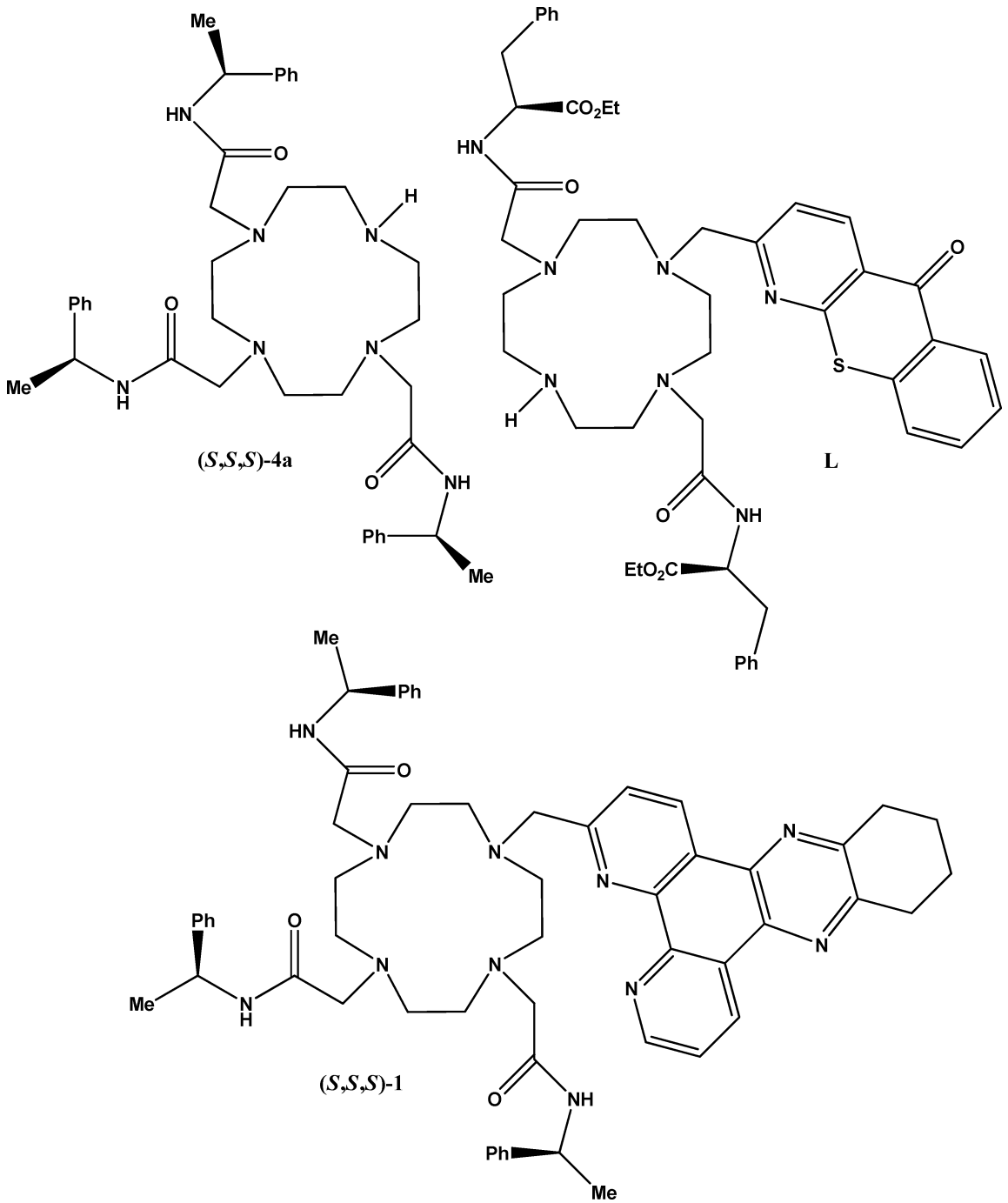

Fig. 8 Chemical structures of ligands based on DOTA-macrocyclic derivatives.

target anionic molecules and/or evaluating the chiral recognition properties of promising functionalized luminescent chiral Ln(III) compounds used as probes for specific target molecules. Indeed, the selectivity for one anion over another may be easier to predict when it is based on a chiral signal. This is because similar binding affinities result in identical chiral signals, whereas different binding affinities give dissimilar chiral spectral features (*i.e.* shape, sign, and/or magnitude). It is interesting to note that these similarities/differences can be investigated by CD and CPL spectroscopy due to (i) the modulation of the chiral properties in the absorption and luminescence spectral profiles of the Ln(III)-containing complexes *via* direct coordination of the anion-like molecules of interest, and (ii) the sensitivity of the chiroptical spectroscopic tools employed to small changes in the chiral environment of the metal centers.

The research groups of Parker and Tsukube are probably the main contributors to this fascinating area of research devoted to the development of chiral luminescent Ln(III) complex probes for anion sensing/recognition. However, it is interesting to note that both laboratories do not use the same type of ligands. Parker *et al.* focus on the design of water-soluble Ln(III) systems with chiral DOTA-based macrocyclic ligand derivatives, whereas Tsukube

et al. currently use chiral tripodal ligand derivatives in their Ln(III) compounds soluble in non-aqueous media (commonly acetonitrile). Since several research articles summarize the early work of Tsukube *et al.* on the enantioselective binding of zwitterionic amino acids by chiral lanthanide tris(β-diketonates) and porphyrinates,[53,54,80] the selected example from Tsukube's research group for illustrating this section comes from recent findings.

Tsukube *et al.* have nicely demonstrated that their chiral tripode-lanthanide systems (Fig. 5) present anion-dependent stoichiometry and, more importantly, some of them offer multiple anion sensing.[81,82] This latter property can be explained by the presence of a fluorescent quinoline and a stereocontrolled methyl group resulting in ligand-fluorescence, ligand-CD, and Ln(III)-luminescence signals of the anion-bound complex, which are controlled by the nature of the targeted anions. The introduction of the stereocontrolled methyl group in the tripodal ligands led to the development of anion-selective CD probes which can provide more specific anion-sensing information than regular fluorescence sensing. The key point is that the use of chiral ligands results in the development of Ln(III) systems with highly sophisticated and selective functions, since the ligand chirality may alter the local environment around the Ln(III) ion and, also, influence the anion selectivity and sensitivity of the chiral Ln(III)-based probes. For instance, Yamada *et al.* showed that their luminescent Ln(III) complexes with chiral tri(2-pyridylmethyl)amine ligands (Fig. 5) exhibited NO_3^- and Cl^- selectivity when the anion sensitivity/selectivity response was modulated by the nature of the Ln(III) ion used (Eu and Tb, respectively).[82] In addition to specific anion selectivity related to the choice of the Ln(III) ion, their studies also confirmed that the observation of an enhanced CD signal at 260 nm (pyridine chromophores) for the Eu(III) complex solution upon addition of three equivalents of the, *i.e.*, NO_3^- anion was due to the replacement of solvent and/or coordinated counterion molecules by NO_3^-. This resulted in a modification of the three-dimensional arrangement of the pyridine chromophores and, also, favoured and stabilized the formation of the highly luminescent 1 : 1 : 3 Ln–ligand–anion complex, in which the NO_3^- anions occupied the three exchangeable coordination sites of Eu(III). One limitation of this approach is when the coordination of a given anion to the Ln(III) ion is stronger than between the chiral ligand molecules and the metal center. This results in the release of the coordinated chiral ligand molecules and the observed CD spectrum is mainly a contribution of the ligand itself present in solution, as recently demonstrated by Masaki *et al.*[83] The consequence of the decomposition of the chiral Ln(III)-based probe is that this system cannot be used for sensing/recognition purposes due to the loss of its chirality feature. It is important to note that these Ln(III)-based sensors also present the disadvantage of common organic fluorophore systems, which usually operate in non-aqueous media.

In the water-soluble systems developed by Parker's research group and his collaborators, the responsive and selective probes to anions such as carbonate, phosphate, acetate, or malonate are based on the chiroptical properties of the Ln(III) complexes with chiral DOTA-like ligand derivatives. The coordination of the added anion to the Ln(III) ion also results in the formation of an anion-bound complex in which the helical twist around the center is modified and, thus, leads to different CPL and CD spectra. Of particular note is that the anion affinity can be modulated by the modification of the overall complex charge. Bruce *et al.* showed that the affinity for HCO_3^- decreased as a function of the overall negative charge of the Eu(III) complexes with a series of heptadentate tri-amide or polycarboxylate ligand derivatives.[84] Since most of these studies have already been summarized numerous times in the literature,[9–11,19,20,48,84,85] this section, devoted to the work performed in the research laboratory of Parker, focuses on new results based on the sensing of proteins. A recent work performed by Montgomery *et al.* resulted in the discovery of a very unique chiroptical probe for serum albumin binding.[86] They showed that the Δ-conformer of the Ln(III) complexes with the enantiopure ligand (*SSS*)-**1** (Fig. 8) bound selectively to "drug site II" in serum albumin. The novelty was that this binding process resulted in an inversion of the complex helicity (Δ to Λ), as signalled by a sign change in the CPL spectra, and was only observed for the Eu(III) and Tb(III) compounds with (*SSS*)-**1** and its analogues. No dynamic helicity inversion was observed for the related complexes with (*RRR*)-**1**, nor in the presence of excess of various substrates such as *B*- or *Z*-DNA, chiral anions (*i.e.* tartrate, lactate), (*S*)- or (*R*)-α-phenylsuccinate, or cyclodextrins. This was corroborated by the lack of changes in the sign and form of the measured CPL signals.

This fascinating study by Montgomery *et al.* clearly opens opportunities for developing chiral luminescent Ln(III) complex probes that can be observed by microscopy and, more importantly, have a cell-penetrating feature in addition to their chiroptical recognition properties. This area of research is currently under investigation, as suggested by a series of articles recently published in the literature.[1–3,12,27,87–89] Most of these articles are mainly devoted to the elaboration of various strategies to address this challenging objective. For instance, the preliminary results of New *et al.* seem to indicate that the observed properties (*i.e.* similar toxicity behaviour, similar quenching sensitivity, and common intracellular localization profile) of a series of six pairs of Eu(III) and Tb(III) compounds of macrocyclic ligands, containing a common tetraazatriphenylene sensitizer, are dictated by the nature of the sensitizing moiety.[87] In addition, Yu *et al.* showed that the intracellular speciation of their europium-containing DOTA-based complex (macrocyclic DOTA-based ligand **L**, Fig. 8) was consistent with the presence of various Eu(III)-based species.[89] This was confirmed by the observation of distinctive CPL signals for their Eu(III) complex in the presence of citrate, L-Asp, L-Asn, malate, or oxalate and, also, for this compound localized in the NIT 3T3 cells. Of special note was that these CPL results may suggest that some of the Eu(III)-based species are bound to the proteins and, more importantly, that one can record CPL signals from chiral luminescent Ln(III)-containing compounds present in cells. Although these preliminary studies are investigating the most emissive Ln(III)-based probes (typically compounds of Eu(III) and Tb(III)) for the reasons discussed in the introduction and background section, the use of a Eu(III) ion in these systems is a key factor in the understanding steps due to its advantage over Tb(III). Eu(III) has, in theory, a simpler crystal field energy level pattern than Tb(III), which allows a better interpretation of the luminescence and CPL spectra. On the other hand, one may also envisage that the development of a new application of CPL, namely CPL microscopy, could be on its way at some point in the future.

5.2.2 Sensing through the coordination to the antenna/receptor groups. As discussed above, the sensing/recognition properties of chiral Ln(III)-based probes operate through the coordination of the molecules of interest to the Ln(III) ions of coordinatively unsaturated Ln(III) systems. In this section, the development of chiral luminescent Ln(III)-based probes of relevant biological molecules uses an approach in which they bind to specific receptor groups of the Ln(III) species (Fig. 7). Thus, the changes in the chiroptical properties of the adduct formed are influenced by the recognition processes between the receptor groups and targeted analytes. The Ln(III) complexes commonly used in such sensing studies often require excessive synthetic efforts (typically multi-step syntheses) to make the organic ligands and their derivatives with the desired recognition features. The time and overall yield of these multi-step syntheses are often the limiting factors in the design of new Ln(III)-based luminescent probes. Although it is not a requirement, it is often the case that such Ln(III)-based probes do not possess open coordination sites as seen in the class discussed in the previous section. The approach is that the targeted analyte (often a cation) covalently or coordinatively binds the antenna/receptor groups. This can be assimilated to the "derivatization" (formation of covalent bonds) and "complexation" (bound *via* noncovalent interactions) methods, respectively. In addition to the usual excessive synthetic effort to prepare the Ln(III) complexes, the derivatization technique is also complicated by other factors such as the use of a consequent amount of substrates, the need of coupling reactions and purification steps, the difficulty of substrate recovery, or the possibility of racemizations and/or optical resolutions. One can understand why the complexation method, which is based on noncovalent recognition interactions, is more popular for the sensing of cationic species such as metal ions. However, the result of the recognition (or binding) event is a modulation of the chiroptical properties of the Ln(III) complex-like species that can be detected by CD or CPL.

For instance, Parker *et al.* used this approach for the development of enantiomerically pure luminescent Ln-based probes of biological molecules where the antenna/receptor group (*i.e. N*-methylphenanthridinium or Pd-centered porphyrin) selectively bound to oligonucleotides and nucleic acids. Of special interest was that these binding interactions were mainly due to an intercalative mechanism (intercalation of the antennae between the base pairs), as indicated by measurements using ESMS, ^{1}H NMR, absorption, fluorescence and, in particular, chiroptical spectroscopic techniques consisting of CD and CPL. It was shown that these intercalative interactions were sensitive to the complex's helicity (Λ *vs.* Δ), the type of the base pairs used (*i.e.* $[(CG)_6]_2$, $[(AT)_6]_2$) and, also, the nature of the Ln(III) ion (*i.e.* metal cations emitting in the visible and NIR were considered). Since numerous research articles summarize the work of Parker *et al.* in this area,[10,11,19,20,90] it is also interesting to briefly discuss the recent findings of Kaizaki and his collaborators on the development of chiral Ln-based systems to probe alkaline metal ions.

The study of Shirotani *et al.* showed that the observation of exciton and lanthanide-based CD activities with variation of alkaline metal ions (M^I = Na and Cs) and solvents (EtOH and $CHCl_3$) opens new perspective for the studies aimed at understanding the chiroptical spectral-structure relationships and, in particular, their important roles in configurational chirality for, *e.g.*, chemical sensors.[91] Their X-ray and chiroptical studies demonstrated that the stereospecific formation of chiral Δ-SAPR-(C_4) configurations of their sodium and cesium tetrakis (+)-hfbc Ln(III) complexes was retained in solutions with the aid of intermolecular $M^I \cdots$ FC (fluorocarbon) interactions (Fig. 4). Of special note is that these intermolecular interactions (an example of the "complexation" approach), which play an important role in retaining the chiral solution structure, are dependent on the nature of the alkaline metal ion (chiral arrangement of the four ligands is controlled by the M^I size). The result is that such Ln(III)-based compounds can serve as probes for recognition/sensing of M^I cations. More recently, CPL led to a better understanding of the chiral configuration of these systems of interest in solution (*i.e.* concentration effect on the chiroptical properties) and, more importantly, the advantage of using CPL over CD in such studies (see Chiroptical tools: from CD to CPL spectroscopy section above).[51]

6 Concluding remarks and perspective

In this review, general principles of introducing a chiral feature in the design of luminescent Ln(III) complexes were discussed with a specific emphasis on how to take advantage of it for developing "smarter" biomolecular probes. Of special importance was to demonstrate that the key point of introducing chirality into luminescent Ln(III)-based probes may considerably enhance the molecular recognition/sensing properties (*i.e.* flexibility, applicability, sensitivity, specificity, selectivity *etc.*) of these chiroptical luminescent probes towards biological materials.

Although the focus of this feature article was to exemplify some of the recent successful studies published in the literature, one can envision that a growing interest in using such Ln(III)-based chiral systems for analytical and biomedical applications is on its way. This would be possible due to the considerable and deep understanding of designing luminescent Ln(III)-containing edifices with desired optical properties, as already pointed out by the numerous applications available such as time-resolved fluoroimmunoassays, luminescent responsive systems to assay analytes or, more recently, *in cellulo* gated and non-gated luminescence-based (or microscopy) imaging (see text for selected references). However, the development of new applications taking advantage of the chiroptical properties is probably dependent to the technical advancement in the chiroptical spectroscopic tools such as CD and, more importantly, CPL (*i.e.* CPL imaging). Although CPL is still an underemployed technique, recent studies and developments suggest that CPL would be an attractive complementary tool to CD, a much less sensitive chiroptical absorption technique.[1,51,86,89,92]

Acknowledgements

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