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Optical Activity in Tb(III) Mixed-Ligand Complexes Containing Pyridine-2,6-Dicarboxylic Acid and Hydroxyphenyl Derivatives

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Addition of hydroxyphenyl derivatives to tris-(dipicolinate)Tb(III) results in the generation of optical activity within the Tb(III) spectroscopic transitions. Unlike earlier work, in many cases the bonding was found not to be totally outer-sphere in nature, but the adducts could be best described as 1:1 $Tb(DPA)_3^{3-}$/substrate complexes. At low pH values the interactions appeared to be outer-sphere in nature, but ionization of the hydroxyphenyl group resulted in the formation of the inner-sphere complex. Presumably, one of the dipicolinates partially dissociates to permit bonding of the ionized hydroxyphenyl portion of the substrate. The chiral substrates examined during the course of this study were hydroxyphenylglycine, tyrosine, dihydroxyphenylalanine (L-DOPA), tyrosinol, noreinephedrine, and epinephrine.

Introduction

The tris lanthanide complexes of pyridine-2,6-dicarboxylic acid (dipicolinic acid, or DPA) are of considerable interest in that the metal ion experiences trigonal symmetry [1], and that this trigonal environment is preserved even in aqueous solution [2]. If it were not for the extremely labile nature of the central lanthanide ion, one theoretically would be able to resolve the optical enantiomers and thus obtain fundamental chiroptical information on the compounds. However, we have found that through outer-sphere complexation with a variety of chiral substrates (the Pfeiffer effect), partial resolution of the $Ln(DPA)_3$ complexes is possible. So far, we have demonstrated that optical activity may be induced in the tris(DPA) complexes of Tb(III) and Eu(III) by resolved cationic transition metal complexes [3], L-ascorbic acid [4], monoamino and diamino carboxylic acids [5, 6], tartrate substrates [7], and phenylalkylamines, phenylalkylamino alcohols, and phenylalkylamino acids [8].

During the course of the last series of Pfeiffer effect studies involving the phenylalkylamino acids [8], it was observed that when a hydroxy group was presented on the phenyl ring, irreversible formation of an inner-sphere compound was evident from examination of the chiroptical data. In the present work, we wish to report on the studies carried out to understand the nature of this inner-sphere complex, and on the conditions under which the complexes form. As in the preceding studies [3–8], chiroptical data were obtained from measurements of circulary polarized luminescence (CPL) spectra rather than the more conventional method of circular dichroism. This situation is necessitated by the low absorptivity of the lanthanide f–f transitions, and the high quantum yield of emission associated with the Tb(III) complexes.

Experimental

The $Tb(DPA)_3^{3-}$ complexes were prepared by mixing stock solutions of Tb(III) and pyridine-2,6-dicarboxylic acid in a 1:3 stoichiometric ratio. The lanthanide ions were obtained as the 99.9% oxides (Kerr–McGee), and the stock solutions were prepared by dissolving the oxide in a very slight excess of 11.6 *M* $HClO_4$, neutralizing to pH 3.0 with NaOH, and then diluting to the desired volume. The dipicolinic acid and all chiral substrates were used as received from either Aldrich or Sigma. In a previous work, $Na_3Tb(DPA)_3 \cdot 15H_2O$ was prepared and used for Pfeiffer effect studies [5], but absolutely no difference in data was noted when comparing results obtained on Tb(III) compounds prepared in the two fashions. The concentration of $Tb(DPA)_3^{3-}$ used for all spectroscopic studies was found to be 14 mM after all dilutions were performed.

In the absence of any added chiral substance, no CPL could be noted in any of the Tb(III) luminescence bands. The chiral environment substances were added to the stock $Tb(DPA)_3^{3-}$ solution from

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concentrated stock solutions whenever possible, but for several of the dihydroxy derivatives weighed amounts of chiral material were simply dissolved in the Tb(III) solution. In some cases, fairly rapid decomposition of the chiral material was evident from slow changes in the CPL intensities, and as a result quantitative determinations of equilibrium parameters proved difficult to obtain.

All CPL and total luminescence (TL) spectra were obtained on a medium-resolution CPL spectrometer constructed in this laboratory, and whose detailed description has been provided [9]. The Tb(III) complexes were excited at 295 nm, taking advantage of the fact that the DPA ligand absorbs quite strongly at this wavelength and is capable of efficiently transferring this absorbed energy to the Tb(III) ion. The emission spectra were analyzed by a 0.5 meter grating monochromator at 1 nm resolution, as further increases in spectral resolution did not lead to any observable improvement of the bandshape features. As with most luminescence measurements, the TL and CPL intensities were obtained in proportional arbitrary units. However, by taking the ratio of CPL/TL one is able to generate a dimensionless quantity referred to as the luminescence dissymmetry factor (g_{lum}) [10]. No other absolute quantal parameters were measured.

The pH of all solutions was obtained using an Orion 701A pH meter, and employed a glass microcombination electrode which could be inserted directly into the fluorescence cuvette. The system was calibrated daily with phosphate buffers.

Results

Addition of either a hydroxyphenyl alkylamino acid or a hydroxyphenyl alkylamine to an aqueous solution of $Tb(DPA)_3$ invariably led to the development of optical activity in the Tb(III) emission bands, as evidenced by the appearence of a CPL spectrum. Although the basic CPL lineshape was observed in every situation, the sign and intensity of this CPL was found to vary with solution pH and with the nature of the chiral substrate. Thus, the trends observed in the chiroptical studies will be discussed as part of a systematic variation in the functionalities of the chiral substrate materials.

The optical activity of the Tb(III) complexes was monitored by studying the CPL within the series of well-resolved luminescence bands. As is usual for Tb(III) complexes, the $^5D_4 \rightarrow {}^7F_5$ transition at 545 nm was studied to the largest extend as the most intense TL and CPL spectra are obtained within this band system. This observation is in complete accord with the predictions of Richardson [11]. The other Tb(III) emission bands at 490 nm ($^5D_4 \rightarrow {}^7F_6$), 580 nm ($^5D_4 \rightarrow {}^7F_4$), and 620 nm ($^5D_4 \rightarrow {}^7F_3$) were examined in several instances, but the trends observed upon examination of these systems invariably paralleled those found for the 4–5 Tb(III) emission band. As a result, all discussion will be limited to observations obtained for the 545 nm emission. Examples of CPL spectra obtained for the other emission band systems may be found in the earlier works [5].

Hydroxyphenyl Alkylamino Acids

Substitution of a *p*-hydroxy group onto the phenyl rings of D-phenylglycine and L-phenylalanine yields D-hydroxyphenylglycine (HPG, I) and L-tyrosine (TYR, II):

I II

While addition of both amino acids to a $Tb(DPA)_3$ solution led to the observation of optical activity, the conditions associated with the development of the chirality proved to be very different.

Addition of 2–10 fold excesses of D-HPG was found to induce CPL in the Tb(III) emission bands which is very similar to that presented in earlier work, and which is illustrated in Fig. 1. Raising the solution

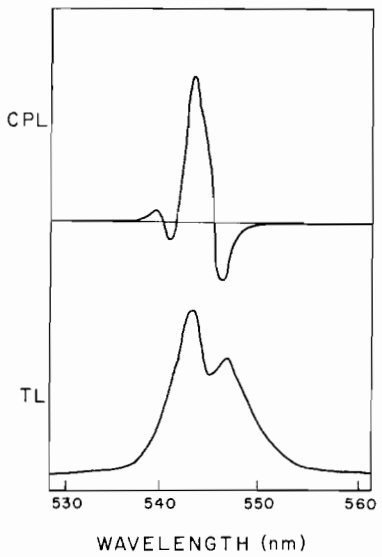


Fig. 1. TL (upper trace) and CPL (lower trace) spectra within the $^5D_4 \rightarrow {}^7F_5$ luminescence band system of $Tb(DPA)_3$ complexed with R-*p*-hydroxyphenylglycine. These spectra were obtained at a substrate/complex ratio of 4.5:1, and at a solution pH of 5.0.

pH, however, led to a complete inversion of the CPL spectrum, and it was found that the CPL spectra obtained at low and high pH conditions were exact mirror images. This sign inversion was observed to take place between pH 7.5 and 8.5, and in Fig. 2 the pH dependence of the CPL spectra (quantitatively

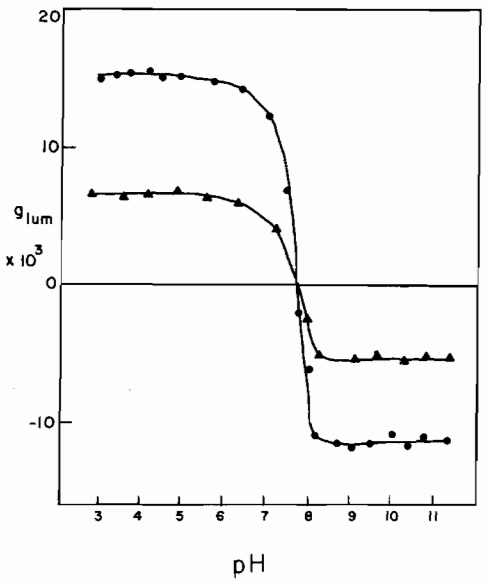


Fig. 2. pH dependence of the dissymmetry factors associated with the adducts of $Tb(DPA)_3^{3-}$ and R-*p*-hydroxyphenylglycine. Data were obtained at a Tb(III) concentration of 14 m*M* and substrate concentrations of 50.0 m*M* (▲) and 113.7 m*M* (●).

determined by the magnitude of the luminescence dissymmetry factor) is illustrated for two different ratios of D-HPG/$Tb(DPA)_3$. It is significant to note that the pH values where the two curves cross zero is not a function of substrate concentration. These results are extremely similar to the general trends we have noted for the interaction of $Tb(DPA)_3$ with D-phenylglycine, where an inversion of the CPL patterns could be linked to the deprotonation of the ammonium group.

Another highly important feature observed in the studies is that the pH of the solutions could be cycled as often as desired between pH 3.0 and 10.0, and the dissymmetry factors obtained for a particular pH were not found to depend on the pretreatment procedure of the solution. This observation provides strong evidence that the mode of bonding between the Tb(III) complex and the chiral L-HPG substrate is outer-sphere in nature, and this general trend has been observed in the earlier studies of the Pfeiffer effect [3–9].

Addition of large excesses of D-HPG substrate eventually results in the observation that the dissymmetry factors reach a limiting value which cannot be exceeded. In measuring the CPL intensities at the 544 nm peak, one finds at low pH that the limiting dissymmetry factor equals +0.022, and at high pH the limiting $g_{lum} = -0.022$. In every Pfeiffer study carried out to date, whenever we have been able to reach a limiting dissymmetry factor, the value of ±0.022 has been obtained [3–9]. This observation strongly suggests that this dissymmetry factor corresponds to the full formation of the outer-sphere complex, as the value has been obtained with a vast range of structurally dissimilar environment substances.

With knowledge of the limiting dissymmetry factor, it is quite easy to calculate the formation constants for the adduct complexes:

$$Tb(DPA)_3^{3-} + S \rightleftharpoons Tb(DPA)_3(S)^{3-}$$

by varying the concentration of both initial reagents and then measuring the resulting optical activity. Application of Job's method of continuous variations established the adduct stoichiometry as 1:1, and thus permitted calculation of the association constant:

$$K_1 = \frac{[Tb(DPA)_3(S)]}{[Tb(DPA)_3][S]}$$

We have previously outlined in sufficient detail how this calculation may be performed [6]. The formation constants evaluated at conditions of low and high pH may be found in Table I. Relative to the phenylglycine results [8], the D-HPG adduct complex existing at low pH is found to be considerably more stable, while the high pH adduct is actually slightly less stable. Thus, while the adduct complexes are similar, a quantitative difference attributable to the hydroxy substitution onto the phenyl ring is evident.

TABLE I. Formation Constants for $Tb(DPA)_3^{3-}$ Adducts with Environment Substances which form Outer-Sphere Complexes.[a]

Substrate	K_1 (low pH)	K_1 (high pH)
R-*p*-hydroxyphenylglycine, I	22.48	11.47
S-tyrosinol, IV	14.11	59.26

[a]The error associated with each constant ranges from 7–10%.

Tyrosine, on the other hand, is a difficult substrate to study in that its water solubility is quite low (0.04 g/l at 25 °C). If one begins with a 14 m*M* solution of $Tb(DPA)_3$ at pH 4.0 and saturates this solution with either D- or L-tyrosine, no CPL can be observed. This situation arises since a 0.22 m*M* solution of TYR is insufficient to induce a measurable Pfeiffer effect. Raising the pH until neutral values does not lead to detectable CPL, but optical activity increases rapidly as the pH is raised from 8 to 11. If one then reacidifies the solution, one finds that the CPL does not diminish to any perceptible amount and that the dissymmetry factors remain absolutely constant down to at least pH 3.0. This irreversibility can be taken as proof that a simple outer-sphere association

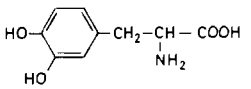
of metal complex and environment substance is not the origin of this chirality, and stands in sharp contrast to the D-HPG studies just described.

The pK values for tyrosine are 2.17 (carboxylic acid), 9.04 (ammonium group), and 10.14 (hydroxyphenyl group) [12]. Examination of the data presented for studies involving L-phenylalanine [8] clearly reveal that the new behavior observed with tyrosine must be a consequence of the hydroxyphenyl group, and thus we conclude that the inner-sphere bonding observed with this substrate must reflect interaction of the ionized phenolate group and the Tb(III) ion. In the previous work, it was clearly shown that the hydrophobic end of the amino acids points toward the metal ion [6–8], and thus the ionized phenolate is perfectly suited to bind to the Tb(III) ion. The lack of such interactions with the L-HPG system would indicate that the hydroxyphenyl group cannot get close enough to the Tb(III) ion to interact. The extra methylene group present in tyrosine is then seen to be the crucial factor in determining the nature of the interaction.

Further information on the nature of the inner-sphere complex is available from considerations of TL intensities. After formation of the inner-sphere complex, the Tb(III) emission intensity is found to decrease by approximately 30% relative to that observed at low pH and relative to that seen at comparable pH values with the phenylalanine adducts. Since we have shown that the luminescence of Tb/DPA complexes is approximately proportional to the number of coordinated DPA ligands [9, 13], the tyrosine result indicates that partial detachment of one of the DPA ligands accompanies the formation of the inner-sphere complex. Isolation of the solid adduct proved very difficult, as mixtures of Na_3-$Tb(DPA)_3$ and TYR were produced upon evaporation of the solutions.

The lineshapes obtained with tyrosine as the environment substance appear to be intermediate between those shown for $Tb(DPA)_3$ partially resolved through the Pfeiffer effect (see Fig. 1) and those obtained for inner-sphere complexes of $Tb(DPA)_2$ with α-hydroxycarboxylic acids [14]. With L-TYR (S-isomer) as the environment substance we find that the CPL within the 4–5 Tb(III) emission is always positive at all pH values, and that of the opposite enantiomer is always negative. No CPL sign inversion (as found with the D-HPG studies) was observed with either TYR enantiomer. The value of the dissymmetry factor was found to increase with TYR concentration until solubility limits were reached, but it proved possible to reach g_{lum} values of 0.04 in this manner.

The behavior of the hydroxyphenyl amino acids was investigated further by examining the optical activity induced by L-β-3,4-dihydroxyphenylalanine (L-DOPA, III):



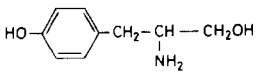
III

With this substrate, all CPL trends pointed toward the existence of inner-sphere complexation. When beginning with the S-isomer, the CPL spectra were uniformly positive at the 544 nm peak and no sign inversions were noted. Decomposition of the substrate in the samples was evident in that the solutions grew dark as work progressed. Working with fresh solutions at concentration values equivalent to those used for study of TYR adducts revealed that the dissymmetry factors obtained for the DOPA compounds were essentially equal to those of TYR compounds.

No estimation of association constants for the addition of either TYR or DOPA to the Tb/DPA complexes could be made as the different mode of bonding existing with these substrates did not permit the use of the methods described in preceding sections.

Hydroxyphenyl Alkylamino Alcohols

Our previous results obtained for the interaction of $Tb(DPA)_3$ with phenylalkyl amino alcohols [8] indicated that these substrates bound the Tb(III) complex much more weakly than did the corresponding amino acids. It therefore proved advisable to examine the interaction of $Tb(DPA)_3$ with L-tyrosinol (TYSL, IV):



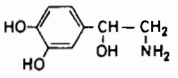
IV

in order to learn about the role of the aminocarboxyl group in fostering the inner-sphere bonding. With L-TYSL as the substrate, we again obtained spectra characteristic of outer-sphere binding, and all the spectral developments were found to be completely reversible. When using the S-isomer as the environment substance, we obtained trends in the CPL spectra which closely paralleled those reported for S-phenylalaninol [8]. The spectra were again found to invert at high pH values, and the CPL of the 544 nm component crosses zero at pH 8.2. With S-phenylalaninol, the CPL crossed zero at pH 7.2, and this difference must be due to the perturbing effects obtained when the hydroxyl group is substituted onto the phenyl ring.

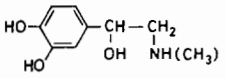
Addition of large excesses of L-TYSL yielded limiting dissymmetry factors of ±0.022 in the low and high pH regions, as had been observed with the D-HPG compounds. This observation permitted the computation of association constants for the outer-sphere complexes existing at low and high pH values, and these may be found in Table I. The effect of substituting the hydroxy group onto the phenyl ring is clearly evident in the results, as these constants are

considerably larger than those we obtained in analogous studies involving phenylalaninol [8].

The study was completed by examining the optical activity induced by two adrenaline substrates, norepinephrine (NEP, V) and epinephrine (EP, VI):



V



VI

Both of these materials are obtained commercially as the R-isomers, and both were found to bind exclusively in the inner-sphere manner previously described for tyrosine. Quantitative determinations of chiroptical quantities proved quite difficult to obtain (as the substrates were observed to decompose rapidly under our conditions of study), but repeated examination of fresh solutions permitted us to conclude that the dissymmetry factors are essentially pH independent between pH 3 and 7. The CPL of the 544 nm component was uniformly positive at all pH values, the CPL lineshapes were essentially superimposable with those of TYR and DOPA, and dissymmetry factors as large as 0.05 were obtained.

A significant observation was that all CPL was lost once the solution pH exceeded 7. Similar behavior had been noted when studying outer-sphere association of $Tb(DPA)_3$ with norephedrine, norpseudoephedrine, and ephedrine [8], and it was concluded at that time that ionization of the ammonium group (and removal of the positive charge on the substrate) was responsible for the loss of induced optical activity. Given the close similarity in the adrenaline substrates, it would be entirely reasonable to conclude that ionization of the ammonium group causes dissociation of the NEP and EP substrates from the $Tb(DPA)_3$ and results in the observed loss in optical activity.

Discussion

In all previous studies involving optical activity induced in $Tb(DPA)_3$ by chiral environment substances, the substrates invariably bound in an outer-sphere fashion [3–8] characteristic of the Pfeiffer effect. These studies have established that a variety of bonding modes can contribute to the overall stability of the adduct complex. Given that the overall charge on the $Tb(DPA)_3^{3-}$ compound is negative, it is hardly surprising to find that the presence of a center of positive charge on the ligand is a primary requirement for association. However, we have established that a hydrophobic site exists between the DPA ligand rings, and substrates containing either ring systems or large alkyl sidechains tend to place these substituents at this site. Evidence obtained from magnetic resonance studies [6] indicates that the ionic portion of amino acid substrates (the aminocarboxy functionality) lies at maximum distance from the lanthanide ion, and the most hydrophobic portion of the substrate is actually closest to the metal. The ligand apparently is held at a definite distance by a balance of these forces.

Evidence for yet another force capable of influencing the interaction comes from examination of the data obtained for analogous amino acid and amino alcohol or amine substrates. Generally, with either simple amines or amino alcohols, deprotonation of the ammonium group results in the total loss of all induced optical activity [8]. However, upon replacement of the terminal CH_2OH group by COOH, one finds that the CPL invariably invert upon ionization of the ammonium group [8]. This observation would indicate that a new bonding mode must exist for the amino substrates, and this bonding must certainly involve some type of hydrogen bonding between the Tb(DPA) compound and the environment substance.

With this information as background, one may examine the data obtained for substrates I–VI of the current series. Both monohydroxy-(tyrosine) and dihydroxy-phenylalanine are observed to bind to Tb(III) in an inner-sphere manner, while hydroxyphenylglycine binds exclusively outer-sphere in the same manner as phenylalanine or phenylglycine. Since it is known that the phenyl portion of these substrates is situated between the DPA rings at the hydrophobic site, it is certain that after ionization of the phenolate proton(s) direct bonding exists between the substrates and the Tb(III) ion. The HPG substrate cannot exhibit this bonding mode as the phenyl ring is held too far away from the Tb(III) ion by the ionic interactions associated with the aminocarboxy group.

Upon passing to tyrosinol, reversible behavior indicative of outer-sphere interaction is noted. All optical activity is lost after ionization of the ammonium group, and we conclude from these observations that insufficient attraction between $Tb(DPA)_3$ and TYSL exists after the deprotonation. The adduct then dissociates before the phenolate group can bind to the Tb(III) ion. With the adrenaline substrates, however, the presence of a catechol moiety clearly lends sufficient stability to the chelate/substrate adduct as to permit only the presence of inner-sphere bonding.

While it is established that for transition metal ions, coordination at the hydroxyphenyl sites can dominate the metal–ligand bonding [15–18], such conclusions have not yet been shown to be general features of lanthanide ion binding. Similar conclusions have been obtained regarding the mode of coordination between Mg(II) and the uranyl ion with L-DOPA [19], and recent work by Raymond and coworkers [20, 21] seeking to develop specific actinide

sequestering agents has established further the importance of phenolate and catecholate binding of metal cations. Our work demonstrates that such interactions may be of significance in lanthanide chemistry, providing certain other bonding requirements are met.

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