Circularly Polarized Luminescence Studies of the Ternary Complexes Formed between Terbium(III), Pyridine-2,6-dicarboxylic Acid, and Amino Acids

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Abstract: Ternary complexes formed between pyridine-2,6-dicarboxylic acid (DPA), Tb(III), and various amino acids have been prepared and studied by circularly polarized luminescence (CPL) spectroscopy. The CPL spectra were found to be reliable reporters of the bonding changes undergone by the complexes as both complex structure and solution pH were varied. Weak unipositive CPL was observed in the $Tb(DPA)_2(AA)$ system when the amino acid coordinated in a unidentate manner, while double-signed CPL of comparable magnitude was observed if the amino acid was able to coordinate in a bidentate manner. If the pH was raised to 8–10, a precipitate of Tb(DPA) formed and left $Tb(DPA)_3(AA)$ in solution. For most amino acids, double-signed CPL was observed in this pH region, the sign pattern being opposite to that seen at low pH for the bidentate amino acid chelation. This new optical activity is due to closure of a $-NH_2CHCOO-$ chelate ring after deprotonation of the amino acid ammonium group.

Introduction

The stereochemistry and electronic structure of metal complexes have been probed extensively by chiroptical techniques in the past, with optical rotation, optical rotatory dispersion (ORD), and circular dichroism (CD) techniques being used. Most of the interest in chiral transition metal complexes has centered on the CD of d–d transitions, and the theory relating to CD band shapes and intensities is reasonably well developed.[1-4] The optical activity associated with chiral lanthanide complexes has received far less attention, and theories dealing with f–f chiral properties have not yet been advanced.

Lanthanide f–f absorption transitions tend to be quite weak in almost all cases, and typical values for molar absorptivity (ϵ) are usually less than 5.[5,6] The resultant CD spectra of chiral lanthanide complexes tend to be very difficult to measure, since the values obtained for $\Delta\epsilon$ are unobtainable except with very high concentrations of complex. The CD spectra of various lanthanide complexes have been recorded, however, but the resulting features display a profound pH and concentration dependence that makes quantitative interpretation difficult.[7] The CD spectra of lanthanide complexes with amino acids, for example, display more CD extrema than bands present in the absorption spectrum,[7] and subsequent studies involving intermolecular energy transfer among lanthanide amino acid complexes have indicated that polymeric association of complexes takes place above neutral pH values.[8] This association undoubtedly contributes to the complexity of the CD spectra.

Recently, a new chiroptical technique has been developed in which the optical activity of the emitting state is measured.[9] In general, when the luminescence of a chiral molecule is examined, there will be a differential emission of left and right circularly polarized light, and this technique is referred to as circularly polarized luminescence (CPL). CPL is particularly well suited to the study of chiral lanthanide complexes since a few of the lanthanide ions emit with reasonable intensity in fluid solution at room temperature. The luminescence spectra of Tb(III) and Eu(III) have the greatest emission intensity, and the luminescence spectra of complexes of these two ions consist of well-separated emission bands. Spectroscopic assignment of these emission bands are quite straightforward since the peak maxima are shifted only slightly from known transition energies of the aquo complexes.

CPL studies on chiral lanthanide complexes have been carried out primarily by Richardson and co-workers since these compounds serve as useful model compounds for lanthanide–protein complexes.[10,11] The studies that have been performed so far involve lanthanide complexes of carboxylic and amino acids[12,13] and chiral lanthanide β-diketone complexes.[14] In more recent studies, we have measured the CPL induced in an achiral Tb(III) β-diketone complex by chiral solvents, and have found a correlation between the sign pattern of the induced CPL and the absolute configuration of the solvent,[15] while Davis and Richardson have probed the interactions of Tb(III) and nucleosides with CPL spectroscopy.[16]

Detailed theoretical studies of the lanthanide CPL spectra have not yet been reported even though the general theory of CPL phenomena has been advanced.[9,17] In most cases, the solution geometry about the emitting lanthanide ion has not been known with certainty, and in situations involving amino and carboxylic acid complexes one is not certain of the number of ligands attached to the metal ion.

In order to develop the CPL technique as applied to chiral lanthanide complexes, we have carried out the synthesis and characterization of a series of lanthanide complexes in which the solution chemistry is well defined. It is well known that pyridine-2,6-dicarboxylic acid (dipicolinic acid, DPA) forms strong tris complexes with lanthanide ions,[18] and that the ^1H NMR of these complexes can be explained by invoking a molecular D_3 symmetry in solution. In the study reported here we have attempted to separate vicinal contributions to optical activity from configurational effects by preparing compounds containing two molecules of DPA and one molecule of L-amino acid per lanthanide ion. Analogous studies on transition-metal complexes have already been reported.[20,21] In these studies ternary complexes were prepared which contained one amino acid molecule and several achiral ligands per metal ion, and these studies enabled a direct determination of the contribution made by the presence of a single chiral ligand to the optical activity of a d–d transition (vicinal effect).

In the present report, we present CPL spectra of a series of ternary complexes containing Tb(III), DPA, and various amino acids. The data obtained during the course of this work represent the first determinations of vicinal effects in f–f transitions, and the known geometry of the complexes permits explanation of the observed trends in terms of structural features. The CPL method was found to be a sensitive probe of the solution environment about the lanthanide ion and permitted an evaluation of the various types of complexes formed by an amino acid when it binds to a lanthanide ion.

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Table I. Analytical Data for $Tb(DPA)_n$ Complexes with Alanine

		I[a]	II[b]	III[c]
% C	found	19.69	36.10	40.01
	calcd	19.46	36.19	39.58
% H	found	3.79	2.35	1.97
	calcd	3.50	2.32	2.08
% N	found	3.20	5.07	5.61
	calcd	3.24	4.96	5.77
% Tb	found	37.0	28.3	22.1
	calcd	36.78	28.17	21.82

[a] Compound I was actually isolated as $Tb(DPA)\cdot 6H_2O$. [b] Compound II = $Tb(DPA)_2(Ala)$. [c] Compound III = $Tb(DPA)_3(Ala)$.

Experimental Section

A. Reagents. Solutions of Tb(III) in H_2O were prepared by dissolving Tb_4O_7 (99.9% pure from Kerr-McGee) in a minimum amount of 70% $HClO_4$, diluting with glass-distilled H_2O, neutralizing excess acid with NaOH, and finally diluting to the desired volume. The final pH of all Tb(III) solutions prepared in this manner was approximately 3. Standardization of the metal stock solutions was carried out spectrophotometrically.[22] Dipicolinic acid was obtained from Aldrich and used without subsequent purification. The amino acid ligands used in this study were (1) alanine (Ala); (2) valine (Val); (3) leucine (Leu); (4) isoleucine (Ileu); (5) phenylalanine (Pala); (6) tyrosine (Tyr); (7) serine (Ser); (8) threonine (Thr); (9) aspartic acid (Asp); (10) glutamic acid (Glu). All amino acids were the L isomer, and their purity was determined using potentiometric titrations. Ionic strengths were all adjusted with $NaClO_4$ and a total ionic strength of 0.10 M was used throughout.

B. Synthesis and Characterization of Complexes. Complexes having a general formula of $Tb(DPA)_2(AA)$ (where AA refers to any amino acid) were prepared by mixing stoichiometric amounts of Tb(III) and DPA, and then adding excess AA to the solution (usually in solid form). Addition of excess AA was found to be necessary to fully form the $Tb(DPA)_2(AA)$ complex owing to the weakness of binding of amino acid ligands by the $Tb(DPA)_2(H_2O)_n$ complex. Precipitation of both types of Tb(III) complexes was possible by adding concentrated solutions of Ag(I), and analysis of the isolated material (Schwarzkopf Microanalytical Laboratory) was within satisfactory agreement with the predicted structure. These compounds were all obtained when the solution pH was less than 7.

Above pH 7, the $Tb(DPA)_2(AA)$ complex was found to be unstable. Upon raising the pH to approximately 8 a white precipitate of Tb(DPA) formed; this material was collected and analyzed. The complex remaining in solution was precipitated with Ag(I) and analyzed; the resulting empirical formula was found to be $Tb(DPA)_3(AA)$. It was found that the $Tb(DPA)_3(AA)$ complex decomposed slowly with time to yield the $Tb(DPA)_3$ complex; this decomposition was found to be greatly accelerated with strong acid or base. This decomposition was not found to be reversible, since once the complex was treated with either strong acid or base subsequent reversal of the pH change to more moderate pH values only yielded the $Tb(DPA)_3$ complex. A summary of the analytical data for the Tb(DPA) complexes with alanine is found in Table I.

C. Apparatus. All luminescence measurements of total emission (TE) and CPL were made on a high-resolution emission spectrometer constructed in our laboratory, in which the luminescence is recorded at 180° to the exciting beam. The excitation source was a 200-W Hg-Xe arc lamp (Oriel Associates), and the output of this lamp was selected by an Instruments SA H10-UV-V 0.1-m grating monochromator. All samples were excited at 295 nm, and an excitation band-pass of 16 nm was used. The light emitted by the sample was allowed to pass through a solution filter designed to remove all traces of excitation energy (5 M KNO_2) and immediately into an optical phase modulator whose modulation frequency was 50 kHz (Model PEMFS-3, Morvue Electronics). The phase modulator is immediately followed by a plane polarizer, and this combination of optical elements serves as an analyzer for the circularly polarized components of the luminescence. The 50-kHz signal that reaches the detector is directly proportional to the differential emission of left and right circularly polarized light emitted by the sample.

The detector was an EMI 9798B photomultiplier tube (S-20 response), and was housed at room temperature. The current developed by the PMT was converted to a voltage signal and amplified by a current-sensitive preamplifier (Model 181, Princeton Applied Research). At this point, the luminescence signal was split; the TE was immediately recorded by one channel of a potentiometric recorder (Houston Instruments), while the CPL was first processed by phase-sensitive detection (Model 5101 or 128A lock-in amplifiers, Princeton Applied Research) before being recorded by the other channel of the recorder. Simultaneous recording of TE and CPL is necessary to ensure reproducibility of features.

The two quantities which are measured in our experiment are therefore I (TE) and ΔI (CPL); these are recorded in arbitrary units and not in absolute quantal efficiencies. However, taking the ratio of these two quantities eliminates any instrumental considerations. The instrumentation was calibrated by comparison to previously reported data,[14a] and by measuring the CPL and TE magnitudes of a totally circularly polarized emission (obtained by passing the TE of fluorescein through a Fresnel rhomb). No attempt was made to correct the TE and CPL spectra for monochromator and detector response; the sharpness of the emission bands and the consequent small spectral region scanned made such corrections unnecessary. An emission bandwidth of 10 Å was used in all studies.

All pH measurements were taken on an Orion 701A pH meter using a glass microcombination glass electrode that could be directly inserted into the fluorescence cuvette. The electrode was calibrated daily with phosphate buffer. Variations in solution pH were effected by adding microliter quantities of standardized $HClO_4$ or NaOH directly to the Tb(III) complex solution in the cuvette.

Results

The luminescence spectrum of Tb(III) complexes in fluid solution at room temperature consists of a series of emissions from a single excited state, $^5D_4$, to several ^7F_J term levels with transitions having $J = 3, 4, 5, 6$ exhibiting the greatest intensity. Previous work in a wide variety of studies has demonstrated that the most intense of these transitions, $^5D_4 \rightarrow {}^7F_5$, displays the greatest optical activity. For this reason, only CPL data obtained for this particular f–f transition are reported in this work. It was found that very intense Tb(III) luminescence could be obtained if excitation energy was directly absorbed by the aromatic DPA ligands (at 295 nm), since the electronic excitation energy is transmitted to the Tb(III) ion with great efficiency.[23] Very little dependence of total luminescence upon solution pH was noted, with only a doubling of Tb(III) emission intensity being found on passing from pH 3 to 7, and essentially no increase in intensity when the pH was raised from 7 to 10. There was a rapid increase in total luminescence intensity at very low pH values (2.0–2.5) when the DPA ligands attach to the Tb(III) ion. We interpret these observations to imply that the DPA coordination environment is formed once pH 2.5 is exceeded and that little change occurs after that. This would then imply that the energy transfer from DPA to Tb(III) is essentially a constant factor over the pH regions of study.

In general, two classes of complex behavior were noted in the CPL spectra recorded for the various Tb(III) complexes, and two pH regions were found to exhibit markedly different behavior. At pH values below 7, complexes of the type $Tb(DPA)_2(AA)$ were found to be formed. The CPL of complexes having AA = alanine, phenylalanine, valine, leucine, isoleucine, tyrosine, and glutamic acid (which shall be referred to as the "alanine class" amino acids) consisted of a plain positive CPL maximum at 544 nm, and this CPL peak coincided with the maximum in the TE spectrum. Representative examples of the CPL spectra are found in Figure 1. Experiments performed with several D amino acids (AA = alanine, phenylalanine, or aspartic acid) led to the observation of CPL patterns equal in magnitude but opposite in sign to the line shapes found for complexes containing L amino acids.

It is possible to place the CPL results on a quantitative basis by defining the luminescence dissymmetry factor, g_{lum}, in terms of the experimental observables:[9]

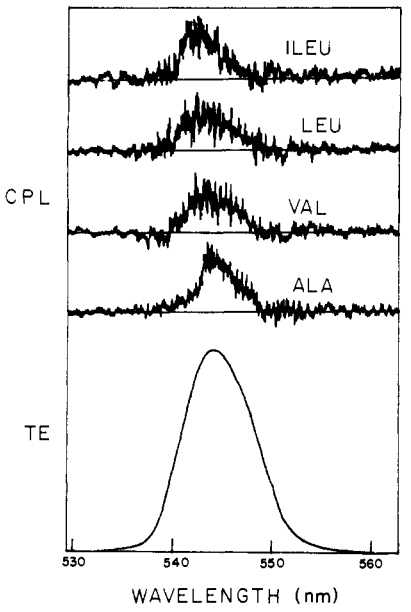

Figure 1. Total emission (TE) and circularly polarized luminescence (CPL) of $Tb(DPA)_2(AA)$ complexes, where AA = alanine, valine, leucine, and isoleucine. All intensity scales are completely arbitrary.

Table II. Luminescence Dissymmetry Factors of $Tb(DPA)_2(AA)$ Complexes in the Low-pH Region. Alanine Class Amino Acids[a]

amino acid	$g_{lum} \times 10^4$ (544 nm)	amino acid	$g_{lum} \times 10^4$ (544 nm)
Ala	+8.80	Pala	+10.6
Val	+9.38	Tyr	+15.8
Leu	+9.86	Glu	+7.68
Ileu	+9.30		

[a] The approximate error in the values is ±0.05 and each value is obtained from multiple averages over the entire 3–7 pH region.

$$g_{lum} = \frac{2\Delta I}{I} = \frac{2(I_L - I_R)}{(I_L + I_R)} \quad (1)$$

where I_L and I_R are the respective intensities of the left and right circularly polarized light emitted by the sample, I is the mean TE intensity, and ΔI is the differential CPL intensity. The g_{lum} factor associated with the luminescent transition is related to the rotatory strength, R_{ab}, and the dipole strength, D_{ab}, with[12b]

$$g_{lum} = 4(R_{ab})/D_{ab} \quad (2)$$

where

$$D_{ab} = |\langle \psi a|\hat{\mu}|\psi b\rangle|^2 \quad (3)$$

and

$$R_{ab} = \mathrm{Im}\,\langle \psi a|\hat{\mu}|\psi b\rangle\langle \psi b|\hat{m}|\psi a\rangle \quad (4)$$

Equations 1–4 are valid for randomly oriented emitting systems in which the emitting state is thermally equilibrated prior to emission. Both of these conditions are expected to hold for the lanthanide complexes examined under the conditions used in the present work. It should be noted that, while the value of g_{lum} has no theoretical significance without a detailed analysis of the CPL line shape, values of g_{lum} may be compared with each other to determine trends in the data that may be correlated with changes in complex structure.[9]

Values for g_{lum} of the $Tb(DPA)_2(AA)$ complexes were calculated, and the results obtained over the 3–7 pH region have been collected in Table II. General features observed in all of our studies are that no CPL is obtained for any of the systems below pH 2.5, rapid development of the CPL occurs from pH 2.5 to 3.0, and then the CPL band shape persists unchanged over the 3–7 pH region. Values obtained for g_{lum} at various pH values are equal to within experimental error over the entire range.

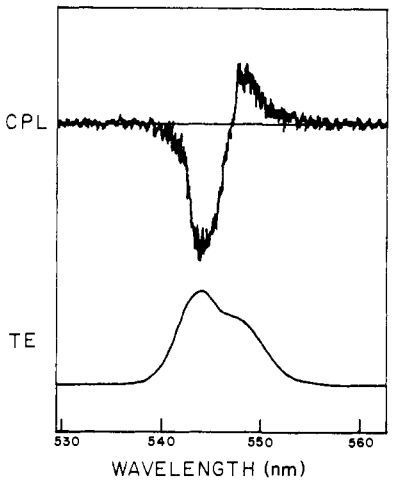

Figure 2. Total emission and circularly polarized luminescence spectra of $Tb(DPA)_2(Asp)$. Both intensity scales are in arbitrary units.

Table III. Luminescence Dissymmetry Factors of $Tb(DPA)_2(AA)$ Complexes in the Low-pH Region. Aspartic Acid Class Amino Acids

amino acid	$g_{lum} \times 10^4$ (543 nm)	$g_{lum} \times 10^4$ (548 nm)
Asp	−10.4	+2.70
Ser	−9.88	+2.48
Thr	−5.30	+1.34

Spectra obtained for the $Tb(DPA)_2(AA)$ complexes where AA = aspartic acid, serine, or threonine (which shall be referred to as the "aspartic acid class" amino acids exhibit a very different CPL line shape over the same 3–7 pH interval. The CPL of $Tb(DPA)_2(ASP)$ is of comparable magnitude to the CPL obtained in the same pH region with the alanine class ligands, except that now the CPL is double signed, as is shown in Figure 2. Values for g_{lum} were calculated at both CPL extrema (543 nm for the negative peak and 547 nm for the positive peak), and these are found in Table III. A difference in complex behavior for ASP relative to the alanine class amino acids is not surprising since Asp is capable of bidentate coordination to the Tb(III) ion through its two carboxylic acid groups (Glu is not capable of such coordination owing to the presence of an extra CH_2 group between the terminal carboxylates).

A surprising result obtained during the course of the low-pH studies involving complexes where AA = serine or threonine was that the CPL spectra for these complexes were identical with that obtained when AA = ASP, as may be seen in Figure 3. Through their studies of potentiometric titrations, Martin and co-workers concluded that only weak coordination was possible through the terminal hydroxy group.[7] The present results suggest that strong interaction may be possible in the proper coordinative environment. Values for g_{lum} were calculated at the CPL extrema (543 and 547 nm), and it may be noted that the values obtained for AA = serine were essentially identical with the ASP data, while the THR g_{lum} values were appreciably less. The data are found in Table III.

In the pH region of 7–8, precipitation of a Tb(III) product was observed. This material is highly emissive in the solid state, and elemental analysis indicated that its simplest formula was Tb(DPA). The precipitate could be removed from the solution by passing the suspension through a 0.8-μ Millipore filter. The

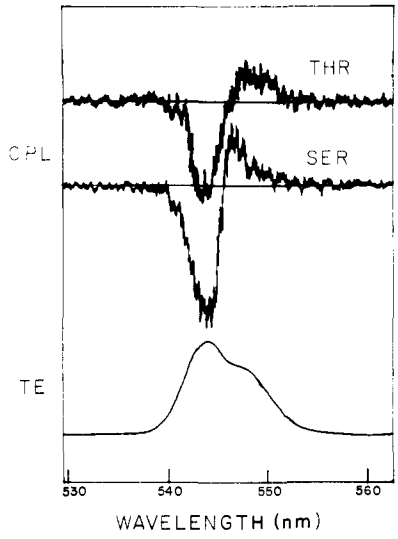

Figure 3. Total emission and circularly polarized emission spectra obtained for $Tb(DPA)_2(Ser)$ and $Tb(DPA)_2(Thr)$ at low pH. The intensity scales are arbitrary.

Table IV. Luminescence Dissymmetry Factors of $Tb(DPA)_3(AA)$ Complexes in the High-pH Region. Alanine Class Amino Acids

amino acid	$g_{lum} \times 10^3$ (544 nm)	$g_{lum} \times 10^3$ (548 nm)
Ala	+3.52	−1.46
Val	+2.16	−0.86
Leu	+3.16	−1.72
Ileu	+4.06	−1.94
Pala	+3.82	−1.90
Tyr	+15.2	−6.78

solution was shown to contain a $Tb(DPA)_3(AA)$ complex, and we conclude that the following reaction takes place:

$$2Tb(DPA)_2(AA) \rightarrow Tb(DPA)_{(s)} + Tb(DPA)_3(AA) + AA \quad (5)$$

Solutions filtered in this manner display differing CPL behavior, and once again a difference between alanine and aspartic acid classes is found. In both cases, the TE rises by approximately a factor of 2.5 after concentration effects are taken into account.

Filtration of complexes prepared from aspartic acid ligands removed all traces of CPL (limit of detection is $g_{lum} = 10^{-5}$), in spite of the fact that complexes having the general formula $Tb(DPA)_3(AA)$ may be precipitated from solution with Ag(I). Strong CPL was obtained from alanine class amino acids, however, and a few typical examples are shown in Figure 4. As in all preceding cases, the value of g_{lum} was independent of pH over a fairly wide pH range (here being 8–10). A double-signed CPL was noted for these complexes, but the sign pattern was opposite to the CPL obtained for aspartic acid complexes at low pH. Values of g_{lum} were calculated at both extrema (now at 544 and 548 nm) for all alanine class ligands, and these results are found in Table IV. If the pH of a $Tb(DPA)_3(AA)$ solution (where AA refers only to alanine class ligands) was lowered below 3 or raised above 10, complete abolition of CPL was observed and the CPL could not be fully restored upon return of the pH to the 8–10 region. Optimal formation of the high-pH CPL spectra was noted if the solution pH was raised to 9.25–9.5 before filtration. One interesting feature of the complex formed at high pH values is that, if the pH was lowered to the 4–6 region, then the CPL decreased in intensity by only a factor of 2, and that the CPL could be fully restored if the pH was immediately raised back to the 8–10 region.

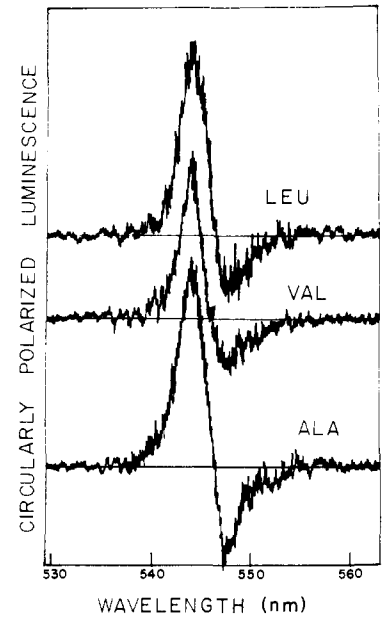

Figure 4. Circularly polarized luminescence spectra obtained at pH 9.25 for the $Tb(DPA)_3(AA)$ complexes, where AA = alanine, valine, and leucine. The intensity scales are in arbitrary units.

Discussion

The CPL spectra presented in this paper are unique in that the observed line shapes and dissymmetry factors are invariant over a particular pH region. All previous CPL data of lanthanide complexes in aqueous solution exhibited CPL spectra which were characterized by strong pH dependences.[12,13] In addition, the CPL of these earlier studies was often obtained at pH values above 7 where polynuclear association of these complexes has been found to be important,[7,8,23] and it is suggested here that the slight variations in CPL band shape as the pH is varied are due to changes in the polymeric structure of the complexes. The invariant CPL spectra obtained in the present study are strongly indicative of the existence of monomeric Tb(III) complexes in solution. It is crucial to the rest of the ensuing discussion that this distinction between the present work and the earlier studies be kept in mind.

It would be highly desirable to obtain spectroscopic assignments for the transitions observed in the present work, but this is not possible at the present time. In octahedral fields, the $^5D_4$ excited state contains four crystal-field components, while the ground $^7F_5$ state is found to contain four components also.[24] Low-temperature luminescence spectra of Tb(III) in cubic hosts have been used to assign the possible transitions, and a total of 9 transitions out of 13 permitted transitions have been identified.[25] The lowering of crystal-field symmetry that exists in the compounds of the present study, and the experimental fact that our spectra were obtained in fluid solution at room temperature, precludes any assignment of individual crystal field transitions. The previous work does point out a very interesting feature, in that the most emission transitions of Tb(III) fall into two spectral envelopes that are only fully resolvable at liquid-nitrogen temperature: (a) two intense peaks are found at 5434 ($T_{1ga} \leftarrow T_{1g}$) and 5440 Å ($T_{1ga} \leftarrow A_{1g}$), and (b) two other intense peaks are located at 5479 ($T_{2g} \leftarrow E_g$) and 5483 Å ($T_{2g} \leftarrow T_{1g}$).[25a] The observation that two extrema are found in the CPL spectra at wavelengths corresponding to these groupings (and a definite shoulder is noted in the TE spectra at corresponding wavelengths) suggests that the CPL transitions have their origin in the O_h states that have been previously described.[25]

Without firm spectroscopic assignments for the various emission bands it is difficult to discuss the absolute values of

the g_{lum} factors calculated for the various complexes. However, the sign patterns observed, the relative values for g_{lum}, and the analytical data relating to the composition of complexes in solution all enable a discussion of the various types of chemical bonding permissible between a lanthanide ion and an amino acid. At low pH, the amino acid ligands of the alanine class can only act as unidentate donors,[27] and one can readily write a plausible equation for the complex formation:

$$Tb(DPA)_2^- + AA^- \rightleftarrows Tb(DPA)_2(AA)^{2-} \qquad (6)$$

This unidentate coordination of an amino acid can lead to measurable CPL, as the data in Table II show. It had been thought at one time that chelation of a ligand was a necessary factor for the observation of optical activity,[26] but it was subsequently shown that CD could be induced through unidentate complexation in complexes of the type $Co(NH_3)_5(AA)$.[21] The data presented here indicate that unidentate coordination is also capable of inducing chirality in the f–f transitions of a lanthanide ion.

At low pH values (below 7), aspartic acid has pK values of approximately 2 and 4,[27] and would be expected to act as a bidentate ligand if possible. The CPL spectra display a clear indication that this is the case, since the observed features are very different from those obtained with alanine class ligands. It is well known that lanthanide ions are capable of exhibiting a wide variety of coordination numbers in solution,[28] so eq 6 would be expected to apply in the case where AA = ASP. Since glutamic acid only displayed CPL spectra characteristic of alanine class ligands, it is concluded here that Glu is incapable of functioning as a bidentate chelate for Tb(III) ions at low pH.

A very surprising result obtained was the observation that the CPL associated with AA = Ser or Thr was identical with that obtained when AA = ASP. In fact, for $Tb(DPA)_2(Ser)$, the magnitude of g_{lum} was essentially the same as for $Tb(DPA)_2(Asp)$, which suggests that serine is capable of acting as a bidentate ligand even at low pH. Threonine appears to be capable of acting in such a fashion also, but the lower values of g_{lum} indicate that the presence of the extra CH_3 group on Thr relative to Ser provides some steric interference with the chelation. It is hardly likely that the OH group can be ionized below pH 7, and we therefore conclude that, when Ser and Thr bind in a bidentate fashion, they do so via an ionized carboxyl and an un-ionized hydroxyl group.

Once the solution pH is raised above 8, different patterns of CPL (and hence of ligand binding) appear. The weak, unipositive CPL band obtained in the alanine class complexes is replaced by a double-signed CPL. This CPL is strongest in the 9–9.5 pH region, and has the opposite sign to the CPL found for aspartic acid class complexes at low pH. The complexes remain monomeric at these elevated pH values[29] (in contrast to earlier work involving other complexes where polynuclear association was important[7,8]). At these pH values, one is able to deprotonate the ammonium group of the amino acid and we assign the high-pH CPL of the alanine class ligands to the formation of an amino acid chelate. It is not surprising that the CPL associated with $-NH_2CHCOO-$ chelation is different than the CPL associated with the $-OOCCH_2CHNH_2COO-$ bidentate binding, since the conformation of the chelate ring is able to contribute (in addition to the existing vicinal effect) to the overall optical activity. Ring closure in lanthanide complexes of glycine has been established in several lanthanide complexes using a variety of physical means.[30]

Complexes of the aspartic acid class display different behavior at high pH, and it was observed that no CPL could be recorded for $Tb(DPA)_3(AA)$ complexes when AA = Asp, Ser, or Thr. We believe that this lack of CPL is merely a manifestation of different modes of bidentate chelation contributing to the total complex formation at high pH. Since the CPL of $-NH_2CHCOO-$ coordination is opposite in sign to and nearly equal in magnitude to $-OOCCH_2CHNH_2COO-$ coordination, a simple 50:50 mixture of the two types of complexes would lead to no net CPL.

It is interesting to note the relative magnitudes of the CPL obtained for both modes of bidentate chelation. A seven-membered ring is formed for $Tb(DPA)_2(ASP)$, six-membered rings for $Tb(DPA)_2(Ser)$ and $Tb(DPA)_2(Thr)$, and five-membered rings for $Tb(DPA)_3(AA)$ where AA = alanine class ligands. It is to be expected that conformational effects would be the dominant source of optical activity when configurational contributions are absent,[1] and one would predict therefore that the conformation of a $-NH_2CHCOO-$ ring is quite different than the possible conformation of a chelate ring formed from terminal group binding. Presumably, the more intense CPL obtained from the former system is due to the fact that the asymmetric carbon is closer in space to the Tb(III) ion in the five-membered rings than in any of the others. One might have expected to find that the CPL associated with the six-membered rings would be intermediate between the values found for the five- and seven-membered rings, but the experimental data do not support this prediction. In the absence of more detailed information regarding ring conformation, we tentatively state that the ring conformations of the six- and seven-membered chelate rings studied in the present work are the same.

The sign patterns and magnitudes of Tb(III) complex CPL spectra appear to be quite sensitive to the asymmetric environment of the metal, and are indicative of the type of bonding existing between the Tb(III) ion and the asymmetric ligands. Care must be exercised before applying CPL analysis of other spectra previously reported in the literature in terms of the results reported in the present study since the effect of asymmetric arrangements of ligands about the Tb(III) ion (configurational effects) has not been evaluated here and these effects must contribute to the other existing data. Studies are now underway to probe the optical activity of Tb(III) complexes (as can be determined from a study of CPL spectra) further.

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Conformational Analysis. 39.[1] ^{13}C NMR Spectra of Saturated Heterocycles. 9.[2] Piperidine and *N*-Methylpiperidine

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Abstract: The ^{13}C NMR spectra of 16 *C*-methyl-substituted piperidines and 19 *N,C*-dimethyl-substituted piperidines as well as *N*-*tert*-butyl-3- and -4-methylpiperidine have been recorded and (separate) methyl substitution parameters for the piperidine and *N*-methylpiperidine chemical shifts have been computed. Shifts calculated using these parameters and experimental shifts are in excellent agreement. Also recorded were the spectra of 25 hydrochlorides of many of the above *N*-alkylpiperidines. Conformational analysis of the C-methylated and dimethylated piperidines and their *N*-methyl derivatives was undertaken through measurement of their spectra at −80 to −100 °C, and the following free-energy differences between equatorial and axial *C*-methyl groups were deduced: N-H compounds, 2-Me, 2.5 kcal/mol; 3-Me, 1.6 kcal/mol; 4-Me, 1.9 kcal/mol; N-Me compounds, 2-Me, 1.7 kcal/mol; 3-Me, 1.6 kcal/mol; 4-Me, 1.8 kcal/mol. The variously substituted *N*-methylpiperidinium hydrochlorides were readily equilibrated in D_2O at a pH of about 5; corresponding $\Delta G°$ values are for 2-Me, 1.4 kcal/mol; 3-Me, 2.2 ± 0.4 kcal/mol; 4-Me, 1.6 kcal/mol. The $\Delta G°$ value for the *N*-methyl group in *N*-methylpiperidinium chloride, 2.1 kcal/mol, is *less* than the corresponding value previously found in the free base. Free-energy values for vicinal interactions in *N*,2-dimethylpiperidinium salts: N-Me_e/2-Me_a, 0.6–0.8 kcal/mol; N-Me_e/2-Me_e, 1.3–1.5 kcal/mol; N-Me_a/2-Me_e, 0.6–0.8 kcal/mol. The e/a and a/e interactions between cis-placed 2,3-dimethyl groups differ by less than 0.1 kcal/mol and the corresponding interactions between *cis*-3,4-dimethyl groups differ by about 0.2 kcal/mol.

Among six-membered saturated heterocycles, the piperidine nucleus is one of the most important ones because of its occurrence in many alkaloids as well as in artifacts of pharmacological importance. Yet literature data concerning the conformation of piperidine and *N*-alkylpiperidines are fragmentary. The stereochemistry of these ring systems has been recently reviewed.[3] The piperidine ring is in a chair conformation with a barrier to reversal of 10.4 kcal/mol[4] and a nitrogen inversion barrier of 6.1 kcal/mol.[5] After some initial confusion[6] it was recognized that the *N*-methyl group in *N*-methylpiperidine prefers the equatorial position, but the extent of the preference was long in doubt.[7] It now seems clear that this preference is quite extreme,[8,9] amounting to 3.15 ± 0.1 kcal/mol in the gas phase, 2.99 ± 0.1 kcal/mol in dodecane, and 2.41 ± 0.1 kcal/mol in chloroform;[10] our own earlier value of $1.35 < \Delta G° < 1.77$ kcal/mol was evidently too low because of difficulties with the adequacy of the model compounds used in the ^{13}C NMR study.[7,11] The question of the N-H equilibrium in piperidine itself has been even more controversial with some investigators holding that the equatorial position was preferred[12] whereas others favored the axial.[13] A recent careful low-temperature NMR study[5] gives a $-\Delta G°$ value of 0.36 kcal/mol for the N-H (a ⇌ e) equilibrium with the equatorial position most likely preferred and an even more recent infrared study of the 8-*tert*-butyl-*trans*-decahydroquinolines[1] now leaves no doubt that equatorial N-H is favored.

Conformational equilibria in *C*-methylpiperidines and N,C-methylated piperidines have been reported only in our own preliminary account[14] and in a brief note by Booth,[15] although there has been extensive work on methyl-substituted *cis*-decahydroquinolines.[16,17] We have also reported, in preliminary form, data on equilibria in *C*-methylpiperidinium salts[18] and their *N*-methyl homologues.

The principal tool used in the present work to elucidate the conformation of *C*-methyl substituted piperidines has been ^{13}C NMR spectroscopy. Earlier work on ^{13}C NMR in piperidines has been carried out by Jones,[19] Feltkamp,[20] Booth,[21] and Duch[22] and an extensive review of ^{13}C NMR spectra of saturated heterocycles (including piperidines) has just become available.[23]

Results

^{13}C NMR Spectra. The ^{13}C chemical shifts of 16 piperidines are presented in Table I and those of 19 *N*-methylpiperidines in Table II. Assignments were made by off-resonance decoupling, by comparison of chemical shifts with literature values, and from signal intensities and were generally straightforward. They were confirmed by the good agreement of experimental and calculated spectra (see below). The NH compounds have previously been studied;[19-22] our data are in only modestly good agreement with those earlier reported, with deviations ranging from 0.2 to 1.0 ppm. Such deviations are not uncommon when comparison is made with data obtained prior to 1973 and may have their origin partly in solvent and referencing differences;[24] we note that, although our shifts are almost uniformly upfield from those in the literature, this is not due to any kind of constant offset, the difference for different signals in one and the same compound ranging from 0.2 to 1.0 ppm.[20b] Only a limited amount of published data concerning *N*-methylpiperidines[19,21,22,25,26] is available; our agreement with them is no better than for the NH compounds.

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