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Stereoselectivity in Lanthanide Complexes of Malic Acid

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A variety of spectroscopic and potentiometric studies have been carried out detailing the nature of the complex formation between lanthanide ions and malic acid. Formation constants calculated below pH 7 (where the complexes are mononuclear) demonstrate that both Gd^{3+} *and* Dy^{3+} *complexes of DL-malic are more stable than corresponding complexes of either D- or L-malic acid. Studies of intermolecular energy transfer, on the other hand, indicate that above pH 7 (where the complexes are found to self-associate) complexes of resolved ligand associate to a greater extent than complexes prepared from racemic ligand. Supporting evidence is obtained from measurements of differential absorption. It appears that the weaker D- or L-MAL complexes are more prone to hydrolysis than the DL-MAL complexes, and evidence is presented from measurements of luminescent titrations that dimeric complex units are apparently bridged by either one or two –OH bridges. No evidence was found at 1:5 metal-to-ligand ratios for the existence of 1:3 lanthanide/malic acid complexes and no experimental effects could be detected which pointed toward participation of the malic acid hydroxy group in the complex bonding.*

Introduction

The solution chemistry of lanthanide complexes of malic acid (MAL) has been the subject of several studies and continues to be of interest. The labile nature of the complexes, a fairly variable coordination number, and a tendency toward polymeric association of complexes at high pH makes it fairly difficult to describe the nature of the complexes with certainty. However, with the growing use of lanthanide ions as structural probes in protein research [1, 2] and as shifting reagents in the proton NMR spectra of aqueous solutions [3–5], the need for detailed studies of the solution chemistry of lanthanide complexes becomes greater.

Formation constants have been measured by Cefola *et al.* using potentiometric titration methods, and these workers reported stepwise formation constants up to 1:3 Ln^{3+}/MAL complexes [7]. Neither group considered the effect of the ligand's enantiomerism on the strength of the lanthanide complexes, and both groups interpreted their data considering only monomeric complexes. Through their detailed potentiometric studies, Rajan and Martell [8] found that both the Cu^{2+} and UO_2^{2+} complexes of malic acid were extensively associated into dimers and higher species, and that hydrolysis of the complexes led to new and more complicated forms. Later potentiometric work of Martin and others [9] demonstrated that inflection points in the titration curves of Ln^{3+}/MAL complexes could only be attributed to complex hydrolysis and the nature of the data strongly suggested the presence of polynuclear species at high pH.

Circularly polarized emission studies [10, 11] of Tb^{3+} and Eu^{3+} complexes of L-malic acid show a marked pH dependence, which changes gradually as the pH of the solution is raised. A previous report from this laboratory demonstrated that electronic energy could be absorbed by Tb^{3+}/MAL complexes and transferred to Eu^{3+}/MAL complexes, and that this transfer was more efficient among complexes prepared from D- or L-MAL when compared to the transfer efficiency among complexes prepared from DL-MAL [12].

In the present work, we report potentiometric and spectroscopic measurements of stereoselectivity in several lanthanide complexes of malic acid. The complexes have been studied by potentiometric, luminescence, and differential absorption titrations, pH dependencies of luminescence and differential absorption, and pH dependence of energy transfer. Stereoselective effects have been detected in several of the measurements corresponding to ground and excited state studies, which conclusively shows that

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the stereoselectivity has its origins in the ground state properties of the complexes.

Experimental

Oxides of Tb^{3+}, Eu^{3+}, Ho^{3+}, Gd^{3+} and Dy^{3+} (99.9% pure) were obtained from Kerr-McGee, while DL-, D- and L-malic acids were purchased from Aldrich; all materials were used as received. Rare earth oxides were dissolved in a stoichiometric amount of 35% perchloric acid (with heating) and standardized spectrophotometrically with calmagite [13]. Malic acid was added from a stock solution (which was standardized by potentiometric titration) to yield a final metal-to-ligand ratio which was kept at 1:5 for all of the studies reported here. The Ln^{3+}/MAL complexes were not actually isolated from solution.

Luminescence and Energy Transfer Measurements

Solutions of Tb^{3+}/MAL were excited at 365 nm, and the integrated peak area of the $^5D_4 \rightarrow {}^7F_5$ transition of Tb^{3+} (545 nm) was followed (integrated intensities proved necessary rather than peak heights since band splitting was observed at high pH values). The initial concentrtation of Tb^{3+} in all solutions was 2×10^{-3} *M*, and variations in excitation light intensity were compensated for by referencing all intensities to the intensity of a 2×10^{-3} solution of Tb^{3+}/H_2O. The pH dependence of emission and luminescence titrations were carried out by addition of microliter quantities of standard $HClO_4$ or NaOH directly to the Tb^{3+}/MAL solution in the fluorescence cuvette (pH measurements were then taken by inserting a microcombination glass electrode into the cuvette). All solutions were 0.10 *M* in $NaClO_4$ to insure constant ionic strength. Changing the inert salt to either $NaNO_3$ or NaCl did not change any of the results.

The quenching experiments were carried out by adding microliter quantities of 1:5 Eu^{3+}/MAL (2.0×10^{-2} *M* in metal) solution whose pH had previously been adjusted to be the same as the Tb^{3+}/MAL solution to which it was being added. The decrease in emission intensity of the Tb^{3+} luminescence was followed as Eu^{3+} quencher was added, and the final Eu^{3+} concentration was kept below 6×10^{-4} *M*. Immediately after the emission intensity was obtained, the emission lifetime was also recorded. Identical quenching results were obtained in every case for complexes prepared from either L- or D-MAL; identical results were also obtained when racemic ligand was either used from the bottle or prepared from equimolar mixtures of D- and L-malic acid.

Differential Absorption Measurements

Measurements of differential absorbance (DA) were obtained on the 0.1 and 0.25 absorbance scales of a double-beam spectrophotometer. The reference was a 0.03 *M* solution of Ho^{3+}/H_2O at pH 4.0, while the sample was a 1:5 solution of HO^{3+}/MAL (0.03 *M* in HO^{3+}). The pH of the sample was adjusted by adding microliter quantities of standard $HClO_4$ or NaOH and any volume changes were reproduced in the sample by adding an equivalent amount of H_2O. The integrated absorbance of the $^5I_8 \rightarrow {}^5G_6$ Ho^{3+} transition was followed as a function of pH, and two peaks at 451 and 454 nm were examined in detail. Differential absorption titrations were made by following the changes in differential absorption with known quantities of NaOH titrant.

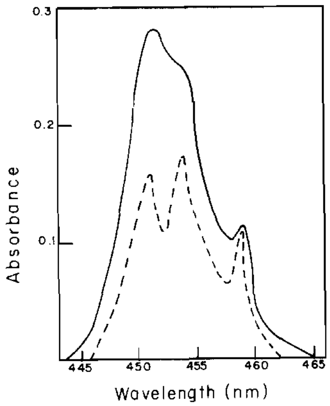

Fig. 1. Total (solid line) and differential (dashed line) absorbance of 1:5 Ho^{3+}/MAL at pH 5.0, with $[Ho^{3+}] = 0.03$ *M*.

Potentiometric Titrations and Calculations

pH titrations were carried out at 25 ± 0.1 °C in a thermostated beaker, through which purified N_2 could be flushed to purge CO_2 and O_2. Titrations were carried out on 1:5 solutions of Gd^{3+}/MAL and Dy^{3+}/MAL (0.012 *M* in metal) that were 0.10 *M* in $NaClO_4$ to insure constant ionic strength. Formation constants for the complexes existing below pH 7 were calculated using a variety of methods in the literature [14–16].

Apparatus

Absorption measurements were made on a Beckman 25 UV/VIS recording spectrophotomeer, while all luminescence measurements were taken on apparatus constructed in this laboratory and similar to that previously described [17]. pH data were taken on either a Fisher Accumet 144 or an Orion 701A pH meter, using standard glass combination electrodes. The electrodes were calibrated daily using either phosphate or phthalate buffers.

Results

pH Dependence of Differential Absorption

The $^5I_8 \rightarrow {}^5G_6$ transition of Ho^{3+} is found in the visible region of the spectrum, and the band envelop

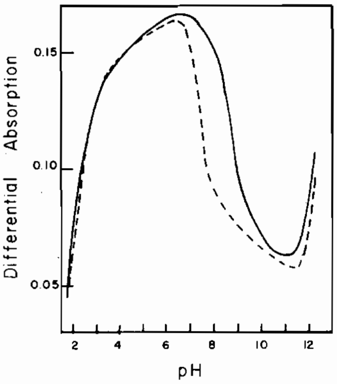

Fig. 2. pH dependence of differential absorption for 1:5 Ho^{3+}/MAL solutions. Data taken from the 451 nm band for L-MAL (solid line) and DL-MAL (dashed line) complexes.

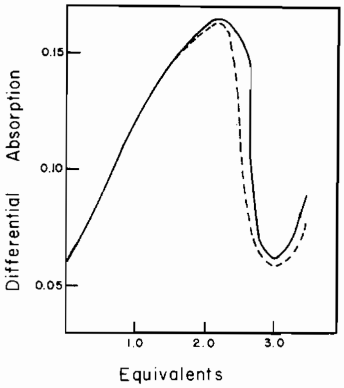

Fig. 4. Differential absorption titration of 1:5 Ho^{3+}/L-MAL (solid line) and Ho^{3+}/DL-MAL (dashed line) solutions. Data were obtained from the 451 nm band.

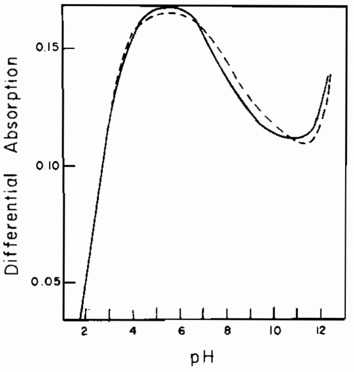

Fig. 3. pH dependence of differential absorption for 1:5 Ho^{3+}/MAL solutions. Data taken from the 454 nm band for L-MAL (solid line) and DL-MAL (dashed line) complexes.

extends from approximately 450 to 460 nm. Formation of the Ho^{3+}/MAL complex does not result in any spectral shifts but does intensify the absorptivity of this transition, as is to be expected from the 'hypersensitive' nature of the absorption [18]. The differential absorption of Ho^{3+}/MAL *versus* Ho^{3+}/H_2O clearly reveals the presence of at least three components within the band, and these crystal-field split components occur at 451, 454, and 460 nm, as may be seen in the typical example illustrated in Fig. 1.

The pH dependence of the differential absorption within the 451 and 454 nm bands was studied in detail since it was found that the DA exhibited a strong dependence on solution pH. A stereoselective effect was clearly seen in the DA within the 451 nm peak (as is shown in Fig. 2), since the DA of Ho^{3+}/L-MAL was measurably greater than the DA of Ho^{3+}/DL-MAL over the 6–10 pH interval. On the other hand, very little evidence of stereoselectivity was found in the corresponding pH region when the DA of the 454 nm band was examined (Fig. 3). Both bands did display generally similar behavior, with the DA rising rapidly from pH 2 through 6, dropping equally fast from pH 6 to 11, and finally rising very rapidly as the pH was raised from 11 to 12.

A titration was carried out in which the differential absorption of Ho^{3+}/MAL (451 nm band) was followed as known quantities of base were added. This DA titration is shown in Fig. 4, and yields new information regarding the stereoselective effect. For Ho^{3+} complexes of L- and DL-malic acid addition of the first two equivalents of base per mol of ligand yields identical values for the DA. The addition of the third equivalent causes a great decrease in the DA and is also responsible for the differences in DA observed when the complexes were prepared from L- or DL-malic acid. Addition of more than three equivalents of base per mol of ligand results in another sharp rise in DA.

Luminescence Titration

The pH dependence of Tb^{3+}/MAL luminescence has already been published [12] as part of our previous study. No stereoselective effects were found in the luminescence studies, and none were found in the present work. A titration was carried out in which the luminescence intensity of the $^5D_4 \rightarrow {}^7F_5$ transition of Tb^{3+}/MAL (approximately 545 nm) relative to the intensity of Tb^{3+}/H_2O was followed as known quantities of base were added. This plot is shown in Fig. 5, and it may be seen that a first inflection is observed after the addition of 2.0 equivalents of base per mol of ligand. This rather weak inflection is followed by a rapid increase in luminescence intensity as more base is added, and the intensity reaches a maximum after a total of 2.7 equivalents are added. Addition of more base results in a rapid decrease in luminescence intensity.

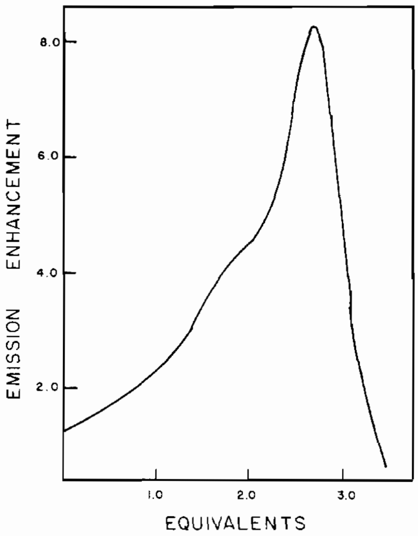

Fig. 5. Luminescence titration of a 1:5 solution of Tb^{3+}/MAL. The intensity scale is relative to the intensity of Tb^{3+}/H_2O.

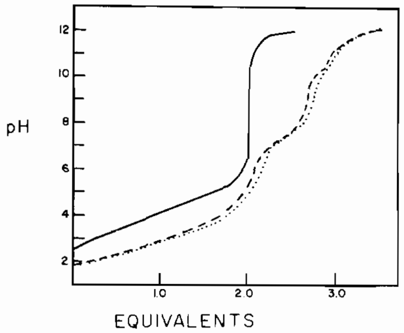

Fig. 6. Potentiometric titration of free malic acid (solid line, 1:5 Gd^{3+}/L-MAL (dashed line), and 1:5 Gd^{3+}/DL-MAL (dotted line).

Potentiometric Titration

In the potentiometric titration of free malic acid, the two carboxylic acid protons ionize in a single buffer system. The first inflection found in titrations of 1:5 Gd^{3+}/MAL and Dy^{3+}/MAL occur at 2 equivalents of base per mol of ligand, which indicates that the malic acid ligands bind predominately in a bidentate fashion below pH 7. Two further inflections are noted as a third equivalent of base is added, and these are assigned to complex hydrolysis [9]. It was found that the titration curves of complexes prepared from DL- and L-malic acids were not superimposable in different pH regions, as shown in Fig. 6.

This stereoselectivity was investigated by calculating formation constants for the various complexes, and these are collected in Table I. All values for ligand protonation constants and complex formation constants agree reasonably well with published results [7]. No evidence was found in the titration curves for the existence of 1:3 Ln^{3+}/MAL complexes in solutions having a metal-to-ligand ratio of 1:5, and indeed the only literature report having detected 1:3 Ln^{3+}/MAL complexes did so at metal-to-ligand ratios of 1:12 [6].

TABLE I. Formation Constants of Malic Acid Complexes.

	Gd^{3+}	Dy^{3+}
(a) *L-Malic acid Ligand*		
log K_1	4.74 ± 0.03	4.76 ± 0.03
log K_2	2.94 ± 0.05	3.16 ± 0.05
log B_{12}	7.68 ± 0.08	7.92 ± 0.08
(b) *DL-Malic acid Ligand*		
log K_1	4.75 ± 0.03	4.77 ± 0.03
log K_2	3.08 ± 0.05	3.31 ± 0.05
log B_{12}	7.83 ± 0.08	8.08 ± 0.08

Energy Transfer Studies

We have previously reported [12] the transfer of electronic energy from Tb^{3+}/MAL complexes to Eu^{3+}/MAL complexes at Eu^{3+} quencher concentrations where the energy transfer could be described by a linear Stern-Volmer quenching equation:

$$\frac{I_o - I}{I} = K_{sv}\phi[Q] \qquad (1)$$

In equation (1), I_o is the luminescent intensity without quencher present, I is the intensity with quencher, [Q] is the molar concentration of quencher, and $K_{sv}\phi$ is the Stern–Volmer quenching constant for luminescence quenching. An analogous equation may be written for quenching of the luminescent lifetime, and yields $K_{sv}\tau$ as the Stern–Volmer quenching constant for lifetime quenching.

In the present study, these quenching studies have been extended to cover quencher concentrations where the simple linear equation does not hold. Above pH values of 7.5 we have found it necessary to use the equation:

$$\frac{I_o - I}{I} = K_A[Q] + K_B[Q]^2 \qquad (2)$$

Values for K_A and K_B as a function of pH are collected in Table II. A stereoselective effect is clearly visible, with energy transfer among complexes prepared from L-malic acid being much more efficient than transfer among complexes made from DL-malic acid.

TABLE II. Results of Non-linear Quenching Studies.[a]

pH	L-MAL		DL-MAL	
	$K_A \times 10^4$	$K_B \times 10^{-6}$	$K_A \times 10^{-4}$	$K_B \times 10^{-6}$
7.5	0.175	0.365	0.174	0.360
8.0	0.182	0.480	0.183	0.485
8.5	0.183	0.495	0.184	0.510
9.0	0.199	0.735	0.188	0.570
9.5	0.204	0.810	0.190	0.600
10.0	0.241	1.37	0.200	0.750
10.5	0.398	3.90	0.277	1.79
11.0	0.469	6.60	0.313	2.60
11.2	0.885	24.5	0.428	7.61
11.4	5.97	339	1.19	56.3
11.6	14.1	938	4.81	308
11.8	20.6	1370	11.7	701
12.0	35.4	2350	17.0	1095

[a] Approximate error with each constant is ±10%.

Discussion

All of the data presented here indicate that the nature of the lanthanide complexes with malic acid is quite sensitive to pH, and that there is a further dependence of complex stability with ligand chirality. The formation constants that we have calculated were computed in pH regions where the malic acid complexes were already determined to be mononuclear [12]. These constants demonstrate that the origin of the stereoselective effect is associated with the binding of the second ligand molecule to the metal ion; in none of the cases we have examined was an enantiomeric preference noted for binding of the first ligand molecule. It was found for Gd^{3+}/MAL and Dy^{3+}/MAL that the complexes formed from DL-malic acid were measurably more stable than those prepared from either D- or L-malic acid.

The results of the energy transfer studies clearly indicate that association of Ln^{3+}/MAL complexes becomes important once the solution pH is raised much above 7, and that this association becomes very complex in the 11–12 pH region. It has proved extremely difficult to detail the predominate species existing at these extreme pH values, but the presence of hydrolyzed polynuclear complexes has been previously inferred from potentiometric titration studies [9]. While it is rather unlikely that only one type of complex would exist at a given alkaline pH, certain calculations involving the energy transfer which assume the presence of only one emitting and quenching species are possible and a simple calculation of this sort has some information to present.

Boaz and Rollefson [19] have shown that when luminescence quenching is found to occur by a combination of dynamic (collisional quenching) and static (complex formation) quenching, then the constants of equation (2) have the form:

TABLE III. Association Constant at Medium pH Values.[a]

pH	L-MAL $K_1 \times 10^{-2}$	L-MAL $K_1 \times 10^{-2}$
7.5	2.43	2.40
8.0	3.20	3.23
8.5	3.30	3.40
9.0	4.90	3.80
9.5	5.40	4.00
10.0	9.10	5.00
10.5	22.30	10.20

[a] Approximate error with each constant is ±10%.

$$K_A = K_Q + K_1 \tag{3}$$

$$K_B = K_Q K_1 \tag{4}$$

where K_Q is the Stern–Volmer constant for collisional quenching, and K_1 is the association constant for the 1:1 donor/quencher complex. Studies of lifetime quenching yielded a value of 1.5×10^3 for K_Q, so it was possible to calculate values of K_1 and these are found in Table III. The stereoselective nature of the energy transfer is quite apparent in that the extent of donor/quencher complexation is more extensive among Ln^{3+}/L-MAL complexes than among Ln^{3+}/DL-MAL complexes.

At first glance, this last conclusion seems to contradict the earlier observation that mononuclear DL-MAL complexes are more stable than L-MAL

TABLE IV. Association Constants at High pH Values.[a]

pH	L-MAL		L-MAL	
	$K_1 \times 10^{-4}$	$K_2 \times 10^{-3}$	$K_1 \times 10^{-4}$	$K_2 \times 10^{-3}$
11.0	0.269	0.46	0.113	0.31
11.2	0.685	1.58	0.228	1.35
11.4	5.77	3.88	0.990	3.69
11.6	13.9	4.75	4.61	4.69
11.8	20.4	4.72	10.5	4.68
12.0	35.2	4.68	16.8	4.52

[a] Approximate error with each constant is ±10%.

complexes, but a reasonable explanation is possible. We propose that the greater stability of the Ln^{3+}/MAL complexes makes those complexes more resistant to base hydrolysis. Since it is hydrolysis that creates the –OH bridges between the complexes (and thus promoting the polynuclear association), it appears that the weaker MAL complexes are more prone toward –OH bridging.

In the 11–12 pH region, not even the more complicated Stern–Volmer equation (2) sufficiently described the data, and it was necessary to add a third term to fit the data properly:

$$\frac{I_o - I}{I} = K_A[Q] + K_C[Q]^2 + K_D[Q]^3 \qquad (5)$$

Boaz and Rollefson [19] treated this possibility also, and developed an equation which required the presence of two molecules of quencher present in the same solvent cage as the donor. If that situation existed in this pH region for the MAL complexes, then:

$$K_C = K_1(K_Q + K_2) \qquad (6)$$

$$K_D = K_Q K_1 K_2 \qquad (7)$$

where K_2 is now the association constant for attachment of the second quencher molecule to the donor/quencher complex. Studies of lifetime quenching allowed the determination of $K_Q = 2.0 \times 10^3$ in this pH region, so it was possible to calculate values for K_1 and K_2. These are found in Table IV. It may be seen that the K_1 values continue to increase rapidly as the pH is raised, but that the apparent K_2 values reach a limiting value very quickly. Thus, we conclude that some dimer formation does take place at high pH for these Ln^{3+}/MAL complexes, but that the actual extent is not all that great. The dominating mode of static quenching appears to involve donor/quencher dimers.

The various spectroscopic titrations reveal interesting features of the binding in Ln^{3+}/MAL complexes. In all cases, addition of two equivalents of base per mol of ligand results is an inflection of some sort, which indicates that bidentate attachment of the malic acid ligands is the dominate mode of quenching below pH 7. It is possible that the –OH group of the ligand also binds (to provide a terdentate ligand), but the titration results show that if such is the case then the group must bind to the metal without being ionized. The environment necessary to observe differential absorption and luminescence is quite dependent on pH; the DA drops rapidly as a third equivalent of base is added while the luminescent intensity rises rapidly in the same region. Previous work [11] showed that the intensity and complexity of circularly polarized emission increased dramatically in this region also. These results taken together point toward extremely complicated bonding behavior in the hydrolysis region that cannot be detailed at the present time.

It is very interesting to note that the luminescence titration shows a very sharp decrease in emission intensity after 2.7 mol of base per mol of ligand is added. Since the first 2.0 equivalents of base are due to ligand ionization, we conclude that this additional 0.7 mol of base establishes an optimal environment for complex emission. With a metal-to-ligand ratio of 1:5, this amount of base corresponds to 3.5 mol of base per mol of metal ion. This non-equivalent amount of base clearly indicates the presence of polynuclear complexes, and the energy transfer results point toward the presence of dimeric species below pH 11. We propose that a pair of Ln^{3+}/MAL complexes are linked by at least one hydroxide bridge (while not ruling out the possibility of more than one link), and this would yield an effective lanthanide coordination number of 8, which for lanthanide ions is very reasonable [20]. The presence of two hydroxide bridges would imply a coordination number of 9 (also reasonable), but more bridges lead to coordination numbers which are not likely.

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