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Potentiometric and Spectrophotometric Studies on the Binding Ability of a Flexible Tripodal Catecholamine Ligand toward Iron(III)

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ABSTRACT: The tripodal catecholamine ligand N^1,N^3,N^5-tris(2-(2,3-dihydroxybenzylamino)ethyl)cyclohexane-1,3,5-tricarboxamide (CYCOENCAT, L) has been synthesized and characterized. The ligand was investigated as a chelator for Fe(III) in an aqueous medium of 0.1 M KCl at (25 ± 1) °C by potentiometric and spectrophotometric methods. Six protonation constants for the ligand were determined and were used as input data to determine the stability constants of the metal complexes. The stability constants for the $FeLH_3$, $FeLH_2$, FeLH, and FeL complexes are reported. The ligand showed the potential to form a tris(catecholate) type complex with a pFe value of 24.76 at pH = 7.4.

1. INTRODUCTION

Biomimetic approaches in research have gained immense interest in recent years due to the interface between chemistry and biology. Many biomolecules are identified in living systems, which act as chelators for the assimilation and transport of metal ions. These natural chelators have received considerable interest due to their selective and strong binding efficiency for a specific metal ion in the presence of other metal ions in living systems. Therefore, to design new chelators for a metal ions, effort has been made to mimic the molecular structure and binding sites of natural chelators through simple synthetic molecules.[1] Also, such synthetic biomimetic molecules are implemented for metal ion sequestration due to their similar selective and strong binding properties toward the metal ion. One of the most studied biomolecules for designing biomimetic synthetic chelators for iron(III) is enterobactin (Scheme 1), which is produced and excreted by bacteria in iron deficient media to bind and assimilate extracellular iron.[2] It contains three catechol groups appended to tripodal cyclic L-serine through an amide linkage, which has been found to be the best iron-chelating agent with the highest formation constant (log K = 52).[3] The enormous iron(III) complexing ability and effective selectivity has led to the synthesis of new biomimetic analogs containing three catechol units in the tripod for: (i) their potential applications as clinical iron removal agents (iron overload is one of the most common types of poisoning),[4] (ii) the use of their iron complexes in agriculture for the prevention or treatment of chlorosis,[5] and (iii) to mimic the essential structural features that are responsible for the different biological functions of natural compounds.[6]

In this communication, a novel biomimetic tripodal catecholamine ligand N^1,N^3,N^5-tris(2-(2,3-dihydroxybenzylamino)ethyl)-cyclohexane-1,3,5-tricarboxamide (CYCOENCAT, L) was investigated as a chelator for iron(III) in an aqueous medium of 0.1 M KCl at (25 ± 1) °C by potentiometric and spectrophotometric methods. The stability constants of the various complexes and their possible structures in solution are explained.

2. EXPERIMENTAL SECTION

2.1. Materials and Measurements. The triamine CYCOEN was synthesized by following a reported method.[7] All chemicals required for the synthesis: 1,3,5-benzenetricarboxylic acid, platinum dioxide, ethylenediamine, 2,3-dihydroxybenzaldehyde, and sodium borohydride were obtained from Sigma-Aldrich and were used directly. Anhydrous $FeCl_3$, absolute ethanol, methanol, KOH, HCl, and KCl were obtained from Ranbaxy Chemicals Ltd., India.

Proton NMR spectra were recorded on a Bruker DPX-300 spectrometer in DMSO-d_6 or D_2O, and chemical shifts were reported relative to Me_4Si. IR (KBr pellets, (450 to 4000) cm^{-1}) spectra were recorded on a Perkin-Elmer RX I FT-IR spectrometer. The electronic spectra were recorded on an Agilent-8453 diode array spectrometer. Elemental analyses were determined for C, H, and N using the Exeter Analytical CE-440.

2.2. Synthesis of CYCOENCAT. The Schiff base intermediate was prepared by dropwise addition of 2,3-dihydroxybenzaldehyde (0.39 g, 28.24 mmol) in 5 mL of absolute ethanol to a magnetically stirred suspended solution of CYCOEN (0.32 g, 9.33 mmol) in 10 mL of absolute ethanol. A bright yellow coloration appeared immediately. The mixture was refluxed for one hour. A dark yellow solution was obtained. On cooling in a freezer, a dark yellow precipitate was obtained, which was filtered off and washed with cold ethanol followed by ether and then dried in a vacuum. Yield = 0.49 g (75 %); IR (KBr pellet, cm^{-1}): 3372, 3215, 2918, 2717, 1623, 1581, 1512, 1445, 1354, 1310, 1235, 1155, 1115, 1021, 962, 851, 774, 652, and 636. ^{1}H NMR (DMSO-d_6, δ ppm): 1.58 (3H, d), 1.83 (3H, d), 2.21 (3H, t), 3.42 (6H, t), 3.69 (6H, t), 6.62 (3H, m), 6.76 (3H, q), 6.86 (3H, m), and 8.30 (3H, s).

To the suspension of Schiff base (0.50 g, 0.71 mmol) in 50 mL of dry methanol, sodium borohydride (0.22 g, 5.81 mmol) was

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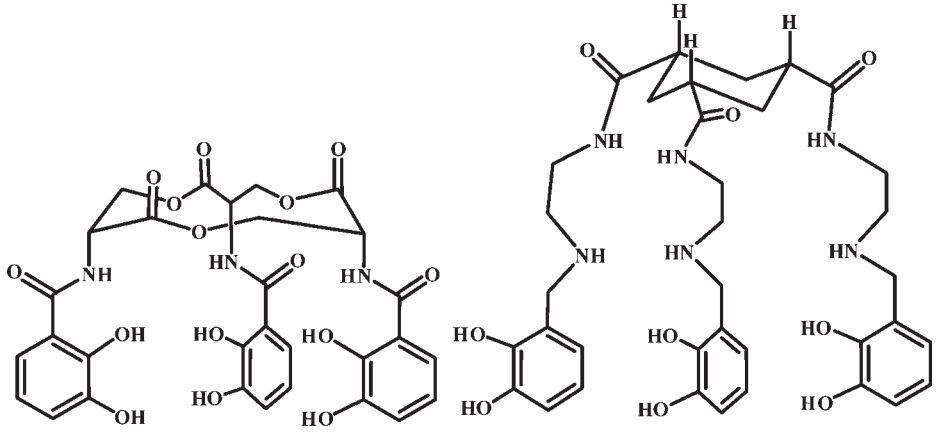
Scheme 1. Molecular Structures of Enterobactin and CYCOENCAT (L)



added with stirring over a period of two hours under nitrogen atmosphere. When the solid phase disappeared and the solution became colorless, 2 mL of concentrated HCl taken in 10 mL methanol was added and kept overnight at −40 °C. A white residue was removed by filtration. The solvent was evaporated under reduced pressure. The crude product obtained was dissolved in dry methanol and evaporated. This process was repeated 3−4 times, and then the residue was dissolved again in dry methanol and to it decolorizing charcoal was added. After vigorous shaking, the charcoal was filtered off. The filtrate was collected, and the solvent was evaporated under reduced pressure. A white product was obtained, which was dried under vacuum. Yield = 0.39 g (65 %); IR (KBr pellet, cm^{-1}): 3374, 3220, 2922, 2718, 1634, 1576, 1504, 1446, 1356, 1304, 1240, 1160, 1126, 1066, 1020, 960, 838, 764, 696, 640, and 616. ^{1}H NMR (D_2O, δ ppm): 1.35 (3H, q), 1.83 (3H, d), 2.38 (3H, t), 3.12 (6H, t), 3.46 (6H, t), 4.15 (s, 3H), 6.70−6.85 (6H, m), and 6.87 (3H, d). Elemental analysis: Anal. Calcd. (Found) for $C_{36}H_{48}N_6O_9 \cdot 3HCl \cdot 2H_2O$: C, 50.58 (50.62); H, 6.47 (6.49); N, 9.89 (9.84).

2.3. Titration Procedure. The apparatus used, experimental details, calibration of the electrode, and titration procedures were as described before.[8] A standard hydrochloric acid solution was titrated with a standard KOH solution, and the calculated hydrogen ion concentrations (pK_w = 13.77) were used to convert the pH-meter reading to hydrogen ion concentration. All solutions were prepared prior to the experiments in double-distilled deoxygenated water. KOH solution of 0.1 M was prepared and standardized against potassium hydrogen phthalate. HCl solution (0.1 M) was prepared and standardized against standard KOH. The ionic strength was maintained at 0.1 M by adding the appropriate amount of 1 M KCl. Stock solutions of 0.01 M ligand and 0.01 M iron(III) were also prepared in deoxygenated water. The final concentrations of ligand ($1 \cdot 10^{-3}$ M) and metal ($1 \cdot 10^{-3}$ M or $5 \cdot 10^{-4}$ M) were maintained for the different potentiometric titrations. The following titrations with metal-to-ligand molar ratios of C_{Fe}/C_L = 0:1, 1:1, 1:2 were carried out, and the potentiometric data were refined using the computer program Hyperquad 2000[9] to get the protonation constants of the ligand and the formation constants of the metal complexes. Literature data ($\log \beta$) on the iron(III) hydroxo complexes were included in the refinement process to obtain the formation constants of the ferric complexes.[10] The method adopted for the spectrophotometric titrations are similar to the potentiometric titrations except that dilute solutions of ligand ($4.02 \cdot 10^{-5}$ M) and metal ion ($4.02 \cdot 10^{-5}$ M) were used. After each adjustment of pH, an aliquot was removed, and spectra were recorded.

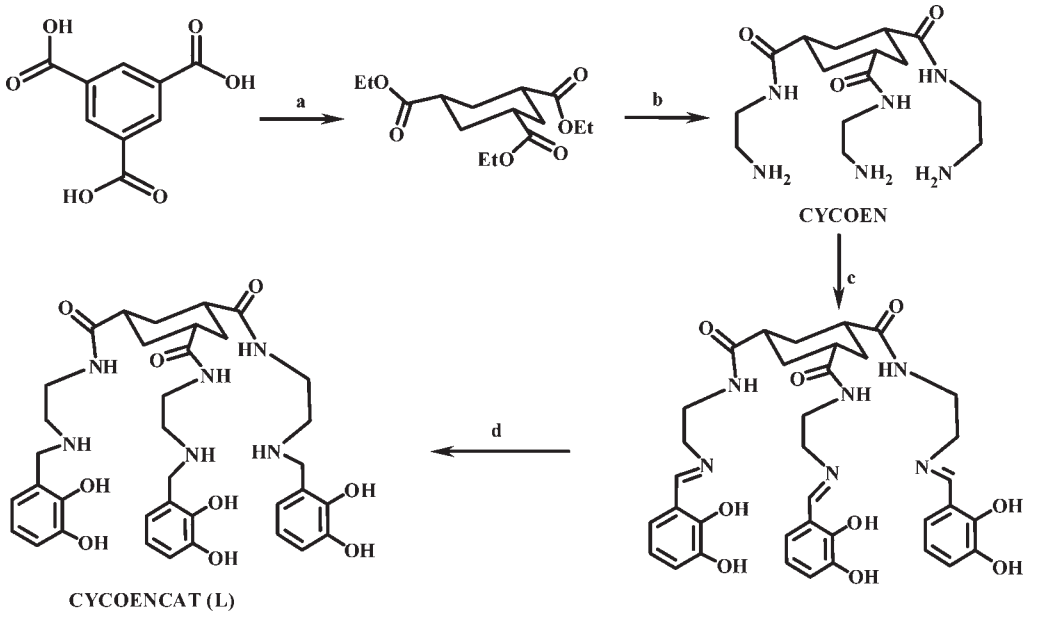
3. RESULTS AND DISCUSSION

3.1. Ligand Synthesis. The synthetic procedure of CYCOENCAT (L) is presented in Scheme 2. The ligand was isolated as a hydrochloride salt, and care was taken to avoid contact with the atmosphere throughout the procedure. This compound is highly hygroscopic and soluble in water, methanol, and ethanol but insoluble in chloroform, ether, and acetonitrile. The ligand was characterized on the basis of elemental analyses and various spectral (electronic, IR, and ^{1}H NMR) data.

The infrared spectrum of the unreduced form of CYCOENCAT showed a weak band at 1623 cm^{-1} for $\upsilon_{C=N}$ that merged with the broad $\upsilon_{C=O}$ band. Upon reduction, the infrared spectrum of L showed only the $\upsilon_{C=O}$ band at 1634 cm^{-1}. Usually, the normal position for the stretching vibration of non-hydrogen bonded or free hydroxyl groups absorbs strongly in the range of (3700 to 3584) cm^{-1}.[11] In the present case, the ligand showed a broad ν_{O-H} stretching vibration at 3374 cm^{-1} indicating the presence of intramolecular hydrogen bonding. The deformation δ_{O-H} peak was observed at 1356 cm^{-1}. The band observed at 1240 cm^{-1} was attributed to ν_{C-O}. Aromatic carbon−carbon stretching vibrations were observed at (1574 and 1504) cm^{-1}, whereas two bands at (838 and 764) cm^{-1} were assigned to the ring substituted bending vibrations.

The experimental ^{1}H NMR spectrum of the unreduced form of CYCOENCAT displayed a resonance signal at 8.30 ppm due to imine hydrogens and three distinct peaks at (1.58, 1.83, and 2.21) ppm for three different types of protons present in the cyclohexane ring. Triplets at (3.42 and 3.69) ppm were characterized for the methylene groups attached to the imine and amide functional groups, respectively. Other peaks at (6.62, 6.76, and 6.86) ppm were characterized for the aromatic protons. Upon reduction, the characteristic imine band at 8.30 ppm disappeared, and the ^{1}H NMR spectrum of CYCOENCAT (Figure 1) showed the presence of benzylic signals at 4.15 ppm.

Scheme 2. Synthesis of CYCOENCAT. Reagents and Conditions: (a) i. EtOH, Dry HCl; ii. PtO_2/H_2, Room Temp., 24 h; (b) Ethylenediamine (en); (c) 2,3-Dihydroxybenzaldehyde, EtOH; (d) $NaBH_4$, Conc. HCl, MeOH



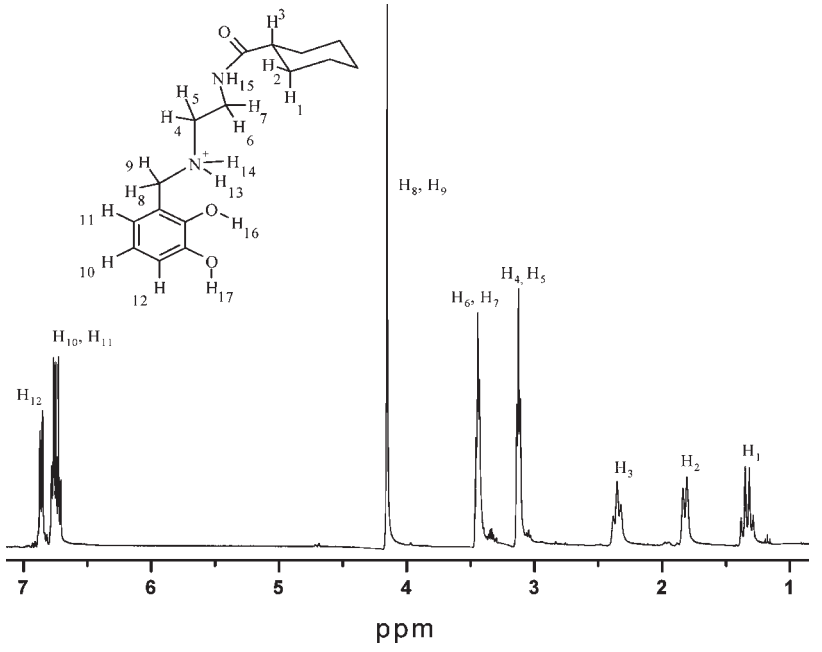


Figure 1. ^1H NMR spectrum of CYCOENCAT (D_2O, 300 MHz).

The spectrum showed three distinct peaks for the cyclohexane ring protons. A quartet and doublet were obtained at 1.35 ppm and 1.83 ppm for the axial and equatorial protons of methylene groups, respectively, whereas a triplet at 2.38 ppm was observed for the three axial protons attached with the appended groups in the cyclohexane ring, which confirmed a *cis*,*cis*-equatorial configuration for the ligand. Other peaks at (3.12 and 3.46) ppm were characterized for the methylene groups attached to the amine and amide functional groups, respectively. Peaks due to aromatic protons showed multiplets between (6.70 to 6.85) ppm and a doublet at 6.87 ppm.

3.2. Ligand Protonation Constants. Potentiometric and spectrophotometric titrations of the ligand CYCOENCAT were carried out in an aqueous medium to determine the protonation constants. In the potentiometric method, the ligand was first acidified with 10-fold excess of a measured amount of standard HCl and then titrated against standard KOH at an ionic strength of μ = 0.1 M KCl and (25 ± 1) °C. Equilibrium points (pH = $-\log_{10}[H^+]$) were collected by adding base into the acidified solution of ligand. The titration curve of the ligand is shown in Figure 2. The analysis of the potentiometric titration curve using the program Hyperquad 2000 gave the best fit for six protonation

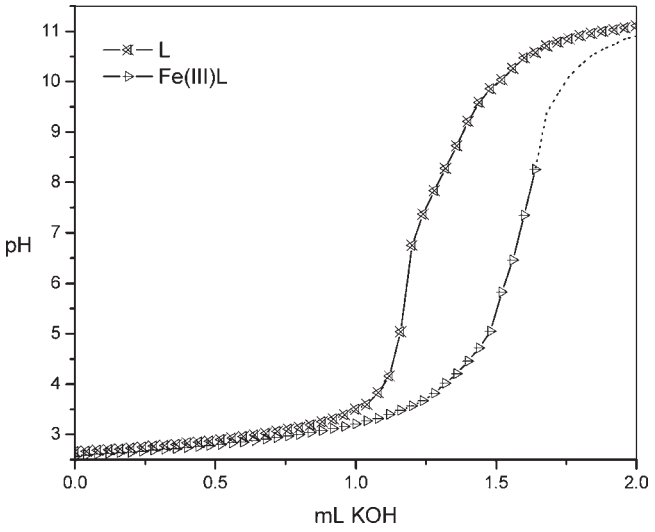


Figure 2. Potentiometric titration curves of CYCOENCAT (L) in the absence and presence of Fe(III) at a 1:1 ligand−metal molar ratio.

constants (Table 1) for the ligand as proposed by the eq 1 (charges are omitted for simplicity):

$$LH_{n-1} + H \rightleftharpoons LH_n \qquad K_n = \frac{[LH_n]}{[LH_{n-1}][H]} \qquad (1)$$

The ligand CYCOENCAT contained nine deprotonation sites: six catechols and three *sec*-amines. However, due to the very low acidity of the catechol (pK_{a1} = 9.13 and pK_{a2} = 13.00)[12] subunits, only one proton could be deprotonated. Therefore, the neutral CYCOENCAT was considered as triprotic acid and addressed as LH_3, whereas the fully protonated form as LH_6^{+3}. The species distribution diagram as a function of pH (Figure 3) indicates that in acidic solution CYCOENCAT initially exists 100 % in the fully protonated form as LH_6^{3+} below pH < 4.0. As the pH increases, deprotonation starts with the formation of LH_5^{2+} which exists between pH 5−8 with a maximum concentration (70 %) at pH ∼ 7. Species LH_4^+, LH_3, and LH_2^- are formed successively with an increase in pH and show a maximum concentration of 55 %, 70 %, and 55 % at pH∼ 8, ∼9, and ∼10, respectively. At pH ∼11, the species LH^{2-} shows the maximum concentration of 50 %, and thereafter the deprotonated ligand L^{3-} starts to predominate.

Spectrophotometrically, the electronic spectra [(225 to 340) nm] of the ligand were recorded in the pH range 3.2−10.2 (Figure 4a). No appreciable change in the electronic spectra was observed below the experimental pH of 3.2, and the spectra overlapped each other. With an increase in pH, the spectra showed a bathochromic shift in the absorption band for the $\pi \rightarrow \pi^*$ transition from (281 to 288) nm with a concomitant increase in absorbance. The shift continued until pH 8.12, and within this range, two isosbestic points at (266 and 286) nm were observed. The formation of isosbestic points indicate the state of equilibrium between the deprotonated and the protonated ligand and can be attributed to the formation of catecholate ions. Since the catechol group is the only significant chromophore in CYCOENCAT, the red shift in the electronic spectra is attributable to deprotonation of the hydroxy group. As the pH rises further, a hyperchromic shift was prominent, and no more isosbestic points were observed. This observation can be characterized for the deprotonation process from $-NH_2^+$ groups. The inclusion of the whole range of data in the least-squares fitting program pHAb[13] resulted in six protonation constants (Table 1), which accords well with the potentiometric results. The predicted electronic spectra of the species whose protonation constants have been determined are shown in Figure 4b. According to these results, the six protonation constants calculated for CYCOENCAT can now be assigned to the three amine groups and three most acidic hydroxyl groups of the catechol units.

3.3. Metal−Ligand Complex Formation. Potentiometric titrations of the ligand CYCOENCAT (L) were carried out in the presence of Fe(III) at 1:1 and 1:2 metal-to-ligand molar ratios to study the formation of metal complexes. The titrations were carried out in an aqueous medium at an ionic strength of μ = 0.1 M KCl and (25 ± 1) °C. The potentiometric curve for the 1:1 metal−ligand molar ratio is shown in Figure 2. The solid symbols represent equilibrium points collected when no solid phase was present in solution, while dotted lines represent points collected when turbidity or precipitation appeared in the solution. The deviation in the metal−ligand titration curves from the free ligand curve implies the formation of metal complexes. As the pH increases, precipitation/solid phase starts to appear from pH = ∼8.0. Considering these preliminary observations, the experimental data represented in symbols were only tested in the minimization program with many sets of possible models. The best-fit models were obtained, when the formation of the species $FeLH_3$, $FeLH_2$, FeLH, and FeL were considered. No additional species were detected from the data obtained between the 1:1 and the 1:2 metal−ligand molar ratios. The overall formation constants (log β) of the species were calculated using the Hyperquad 2000 program and are summarized in Table 2. The equilibrium reactions for the overall formation of the complexes are given below by the eqs 2 to 5 (charges are omitted for simplicity):

$$Fe + LH_6 \rightleftharpoons FeLH_3 + 3H \qquad \beta_{113} = \frac{[FeLH_3][H]^3}{[Fe][LH_6]} \qquad (2)$$

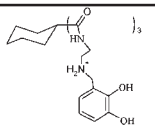
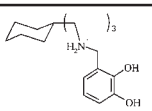
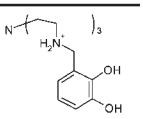
$$FeLH_3 \rightleftharpoons FeLH_2 + H \qquad \beta_{112} = \frac{[FeLH_2][H]}{[FeLH_3]} \qquad (3)$$

$$FeLH_2 \rightleftharpoons FeLH + H \qquad \beta_{111} = \frac{[FeLH][H]}{[FeLH_2]} \qquad (4)$$

$$FeLH \rightleftharpoons FeL + H \qquad \beta_{110} = \frac{[FeL][H]}{[FeLH]} \qquad (5)$$

The interaction of Fe(III) with CYCOENCAT was also studied by a spectrophotometric method to explain the different possible coordination modes of the species formed in solution. The spectrometric titration was carried out with a 1:1 metal-to-ligand ratio with the ligand and metal ion concentrations equal to $4.02 \cdot 10^{-5}$ M and varying the pH between 2.5 and 8.0. The experimental electronic spectra of L in the presence of Fe(III) is shown in Figure 5. Major spectral changes were observed after pH ∼3.2 with the appearance of a charge-transfer band at 575 nm due to the formation of ferric complexes. A study of species distribution curves (Figure 6) for the L−Fe(III) system indicates that below pH 3, the free ligand, and the species $FeLH_3$ are present in appreciable amounts. Hence, the peak at 575 nm is due to the formation of $FeLH_3$. On addition of the Fe(III) ion, three protons from LH_6^{3+} are released upon complexation to give the species $FeLH_3$. These three deprotonation/coordination

Table 1. Protonation Constants (log *K*) of CYCOENCAT (L), TAMCHCAT,[8] and TRENCAT[21] Obtained at (25 ± 1) °C and μ = 0.1 M (A = Potentiometry and B = Spectrophotometry)

Equilibrium	CYCOENCAT		TMACHCAT	TRENCAT
				
	A	B	A	A
$L^{3-} + H^+ \leftrightarrows HL^{2-}$	11.36 ± 0.05	11.38 ± 0.07	11.26	11.20
$HL^{2-} + H^+ \leftrightarrows H_2L^-$	10.67 ± 0.04	10.65 ± 0.05	10.65	10.60
$H_2L^- + H^+ \leftrightarrows H_3L$	9.82 ± 0.08	9.80 ± 0.02	9.80	6.59
$H_3L + H^+ \leftrightarrows H_4L^+$	8.49 ± 0.07	8.51 ± 0.08	8.48	8.07
$H_4L^+ + H^+ \leftrightarrows H_5L^{+2}$	7.62 ± 0.06	7.59 ± 0.06	7.61	7.29
$H_5L^{+2} + H^+ \leftrightarrows H_6L^{+3}$	6.27 ± 0.10	6.29 ± 0.09	6.23	6.17

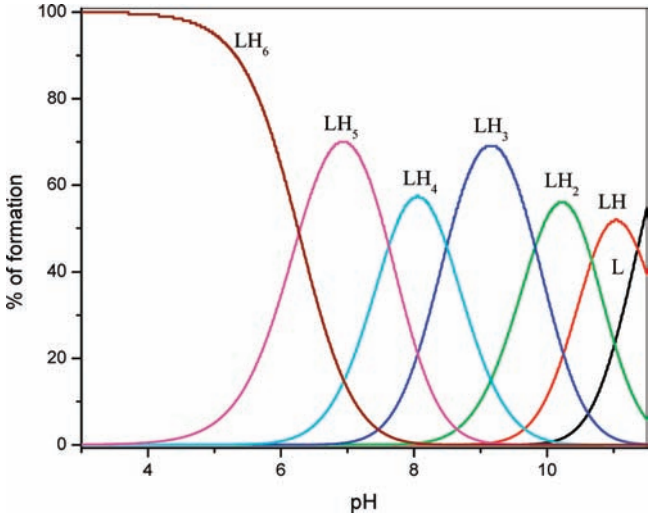


Figure 3. pH-dependent species distribution curves for CYCOENCAT (L) at $[L]_{total} = 5 \cdot 10^{-4}$ M.

processes should have resulted from the three most acidic *ortho*-hydroxy groups of the catechol to form a capped-type geometry. Thus, the peak at 575 nm can now be assigned to be a charge-transfer transition from the ligand to metal (catechol→Fe^{III}). Similar observations have been made for other tripodal catecholate ligands,[14] in which on coordination of the three acidic hydroxyl groups with Fe(III) in acetonitrile, a peak at 528 nm results due to ligand-to-metal charge transfer (LMCT).

At higher pH, the other species $FeLH_2$, FeLH, and FeL are formed in steps with the release of three protons from $FeLH_3$ (Figure 6). The release of these protons from $FeLH_3$ can either take place from the NH_2^+ groups for which the protonation constant values have been evaluated, or from the remaining −OH groups of catechols, for which the protonation constant values are unknown. These two probabilities lead to two distinct geometries: a nitrogen−oxygen encapsulated or oxygen−oxygen encapsulated. In the first case, if the metal ion enters into the nitrogen−oxygen cavity with the release of one/two protons from NH_2^+ upon coordination, it may encounter the repulsive force from the two or one protonated NH_2^+ groups, whereas in the second case, the ligand coordinates through its more basic catecholic oxygens as an anionic donor to

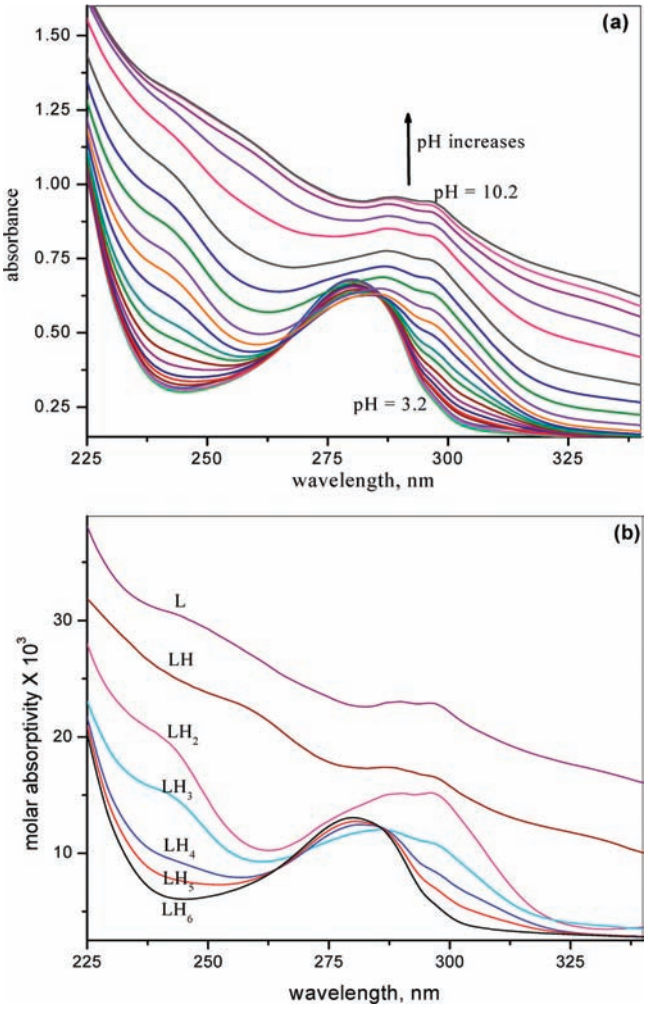


Figure 4. (a) Experimental electronic spectral data of CYCOENCAT (L) as a function of pH (3.2−10.2) during a spectrophotometric titration: [L] = 0.041 mM; [KCl] = 0.1 M, and T = (25 ± 1) °C. (b) Electronic spectra of the seven species as a function of molar absorptivity and wavelength predicted from pHAb using experimental data for CYCOENCAT.

form a tris(catechol) type complex. The latter is more preferable for these hard metal ions, which can be assigned from the shifting

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Table 2. Overall ($\log \beta$) Formation Constants of the Metal Complexes Formed by Ligand CYCOENCAT (L) at (25 ± 1) °C and μ = 0.1 M KCl

equilibrium	$\log \beta$
$[FeLH_3]/[Fe][L][H]^3$	49.82 ± 0.03
$[FeLH_2]/[Fe][L][H]^2$	46.55 ± 0.04
[FeLH]/[Fe][L][H]	42.21 ± 0.07
[FeL]/[Fe][L]	34.61 ± 0.02

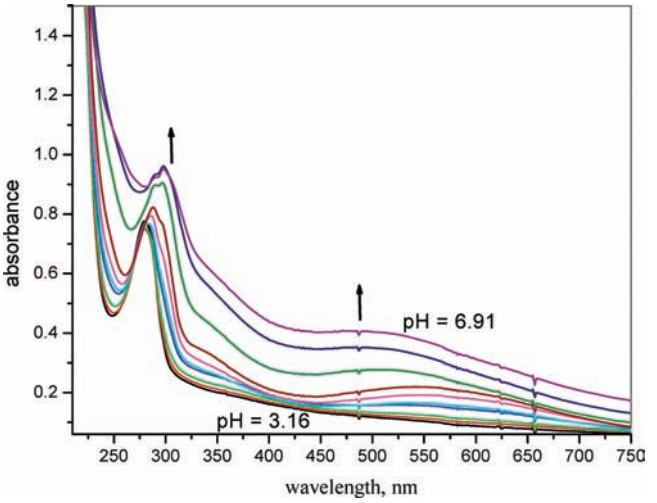

Figure 5. Experimental electronic spectra at 1:1 metal-to-ligand ratio for Fe(III)-CYCOENCAT system.

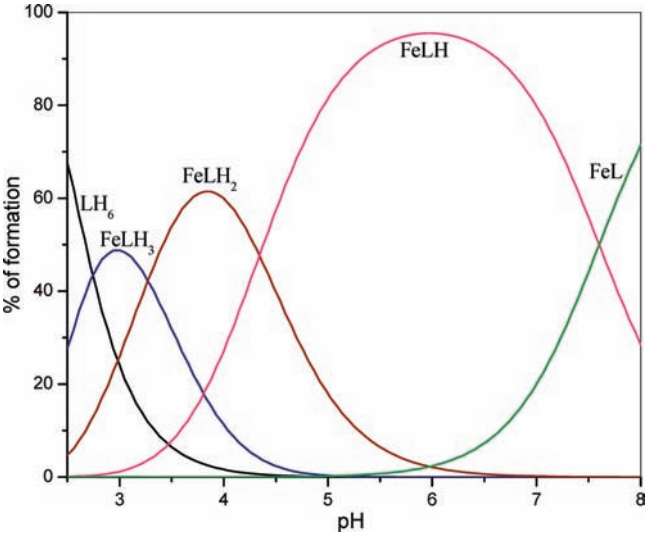

Figure 6. Speciation diagram calculated for the Fe(III)-CYCOENCAT system at an equimolar ferric ion-ligand ratio ($[Fe^{3+}] = [L] = 10^{-3}$ M).

of the peak at 575 nm (pH ~3.2) toward ~500 nm characterized for the formation of the tris(catechol) type complex. Iron(III)-catechol usually gives the LMCT at ~490 nm,[15] which also supports the present proposition. This type of coordination (O,O) is expected for iron(III), because the hard metal ion Fe(III) prefers coordination of hard negatively charged oxygen as compared to the nitrogen donors. X-ray crystal structure studies of tripodal

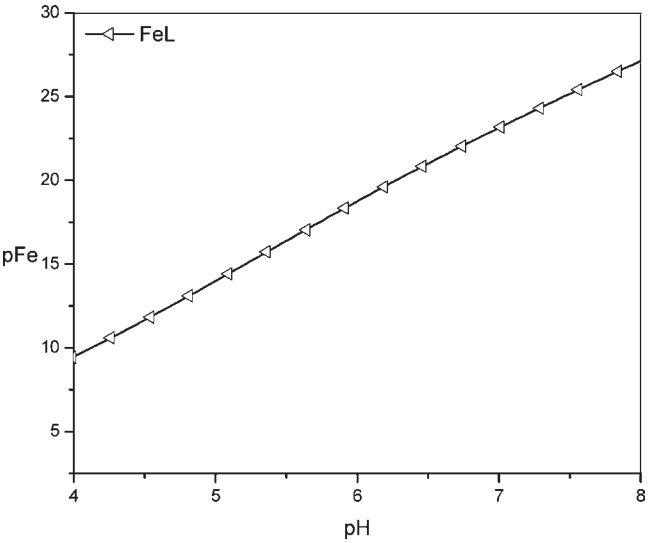

Figure 7. Plot of pFe ($-\log [Fe^{3+}]$) vs pH. pFe was calculated for [L] = $5 \cdot 10^{-4}$ M, $[Fe^{3+}] = 5 \cdot 10^{-5}$ M using the deprotonation constants of ligand L, and the complexation constants β_{11n}.

ligands derived from TREN possessing six oxygen functions show that in their cationic or neutral complexes, nitrogen atoms (imine or amide functions) are not involved in coordination.[16,17] On the basis of above facts, it is suggested that the ferric ion in the tricapped geometry of $FeLH_3$ is not efficiently protected by the wrapped pod and remains accessible for further complexation to give the encapsulated tris(catecholate) complex.

The ligand is a weak acid, and proton competition occurs depending on their pK_a and the pH; therefore, the pFe (= $-\log[Fe^{3+}]$) value was calculated under given conditions of pH and M^{n+} and L concentration to quantify the complexation efficiency of CYCOENCAT. The calculated pFe value of CYCOENCAT at pH = 7.4 by taking $[L]_{total} = 5 \cdot 10^{-4}$ M and $[Fe^{3+}]_{total} = 5 \cdot 10^{-5}$ M is pFe = 24.76, which infers its ability to compete with transferrin (pFe = 20.3).[18] It is well-known that most of the iron circulating in blood plasma is bound to transferrin. Because of the labile nature of the iron transferrin complex, iron overload is cured by sequestering agents like desferrioxamine B (DFO), deferiprone, and deferasirox.[19] Concerning the high iron(III) chelating ability of CYCOENCAT, aqueous solubility over a wide range of pH and no hydroxo species with Fe(III) make the ligand useful for iron(III) sequestration. Moreover, Santos and co-workers[20] suggested that sequestering ligands with free amines as in DFO may improve their usefulness as a drug, where the amine groups are used as a point of attachment to a polymeric solid matrix, which enhance the properties of removing "hard" ions from water solutions. Such free amines are present in CYCOENCAT and also in their complexes depicted in solution. Further, the pH dependence of the selectivity was examined owing to the fact that, in some particular biological compartments or circumstances, pH values exceeding 7 can be observed. The plot of pFe as a function of the pH (Figure 7) reflects that the selectivity of the ligand for Fe(III) is maintained over a pH range 4 to 8.

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