Stability of Metal Complexes with a Ligand of Biological Interest: Noradrenaline

J. Chem. Research (S), 1999, 90–91
J. Chem. Research (M), 1999, 0471–0488

Christian Gérard,* Hanane Chehhal and Michel Aplincourt

GRECI (Groupe de Recherche En Chimie Inorganique), Université de Reims Champagne-Ardenne, BP 1039, F 51687 Reims Cedex 2, France

Stoichiometry, equilibrium constants and spectra of iron(III) complexes with noradrenaline have been determined from spectrophotometric measurements; in addition equilibrium constants of complexes with Mg^{II}, Cd^{II} and Pb^{II} have been determined from potentiometric measurements.

Knowledge of the coordination of simple bidentate ligands such as catechols is important for the synthesis of iron(III) sequestring agents able to replace desferrioxamine for the treatment of iron overload; they also can be used for the synthesis of chelators which mimic siderophores.[1] In addition to their chelating properties, catecholamines are of high biological interest. This work is a part of a series concerning catecholamines such as dopamine[4] and adrenaline.[5] Complexes of three little studied divalent metal ions (Mg^{2+}, Cd^{2+} and Pb^{2+}) have also been investigated.

Protonation constants of noradrenaline H_3L^+ [$pK_a = 8.71$, 9.63, 12.2 (25 °C, $I = 0.1$ M $NaClO_4$)] and equilibrium constants of the complexes with Mg^{II}, Cd^{II} and Pb^{II} were determined by fitting the protometric titration curves with the program Protaf[7] (Table II). Precipitatation which occurs at pH = 8 and 8.5 for lead and cadmium, respectively, prevented determination of a complete set of equilibrium constants.

Electronic spectra of solutions containing a 1:4 Fe(III): noradrenaline ratio at various pH values, exhibit two series of isosbestic points (Fig. 4). The first (pH range = 4.45–5.20) at 705 nm ($\varepsilon = 1620$ L mol^{-1} cm^{-1}) corresponds to the equilibrium between $Fe(HL)^{2+}$ and $Fe(HL)_2{}^+$ while the second (pH range = 6.5–8.7) at 365 nm ($\varepsilon = 2200$), 395 (2150) and 545 (3840) corresponds to the equilibrium between $Fe(HL)_2{}^+$ and $Fe(HL)_3$. In acidic medium three species are simultaneously in equilibrium: spectrophotometric titrations in the pH range 0.4–1.2 reveal a further protonated 1:1 $Fe(H_2L)^{3+}$ complex ($\varepsilon = 725$ at 390 nm). Stability constants of the four iron(III) complexes were determined from spectrophotometric titrations by using least square methods as previously described.[4] Above pH = 8.5 the three amino groups of $Fe(HL)_3$ are successively deprotonated to $FeL_3{}^{3-}$ and the corresponding equilibrium constants were determined by fitting the protometric titration curves.

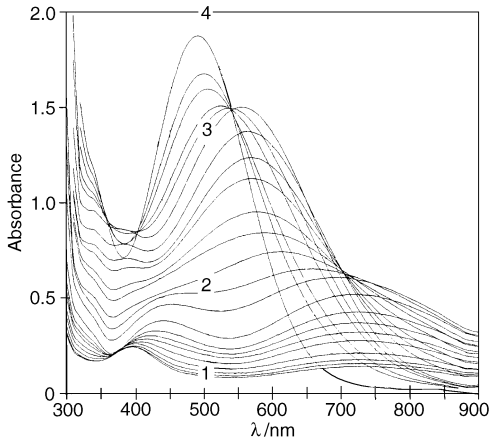

Fig. 4 Electronic spectra for the Fe^{3+}–noradrenaline system (0.5 cm pathlength) $C_{Fe} = 7.52 \times 10^{-4}$ mol L^{-1}; $C_L = 3.02 \times 10^{-3}$ mol L^{-1}: (1) pH = 2.56, (2) pH = 4.45, (3) pH = 6.66, (4) pH = 7.90

*To receive any correspondance (*e-mail:* christian.gerard@univ-reims.fr).

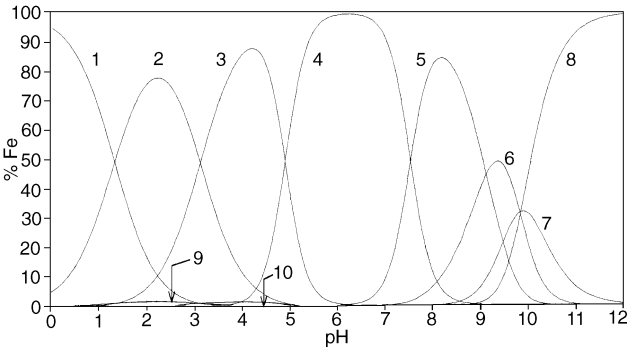

Fig. 7 Distribution curves for the Fe^{III}–noradrenaline complexes ($C_L = 10^{-3}$ mol L^{-1}; $C_{Fe} = 10^{-4}$ mol L^{-1}): (1) Fe^{3+}, (2) $Fe(H_2L)^{3+}$, (3) $Fe(HL)^{2+}$, (4) $Fe(HL)_2{}^+$, (5) $Fe(HL)_3$, (6) $FeL(HL)_2{}^-$, (7) $FeL_2(HL)^{2-}$, (8) $FeL_3{}^{3-}$, (9) $Fe(OH)^{2+}$, (10) $Fe(OH)_2{}^+$

Equilibrium constants (Table II) follow the classical order: $Fe^{III} \gg Pb^{II} > Cd^{II} > Mg^{II}$. Deprotonation constants of the $M(HL)_n$ species (log K between −9.1 and −10.8) are consistent with the dissociation of amino groups in the bidentate ligands *via* the catechol groups. Iron(III) combines with noradrenaline over the whole pH range (Fig. 7). $Fe(H_2L)^{3+}$ which is difficult to detect (weak absorption

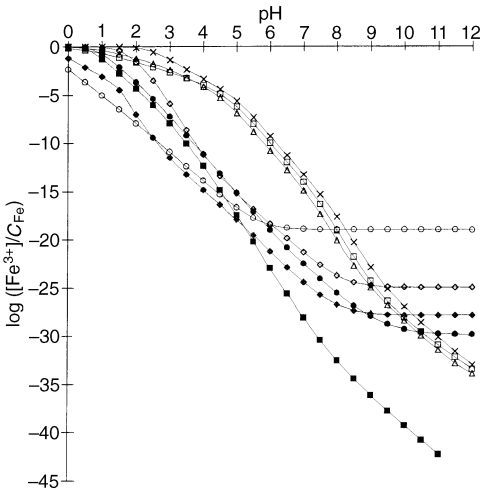

Fig. 8 Plots of log (Fe^{3+}/C_{Fe}) as a function of pH ($C_{Fe} = 10^{-4}$ mol L^{-1}; $C_L = 10^{-3}$ mol L^{-1} for tripodal ligands and 3×10^{-3} mol L^{-1} for the other compounds): (×) catechol (ref. 11), (□) dopamine (ref. 4), (△) noradrenaline, (○) HPNO = 2-hydroxypyridine N-oxide acid (ref. 12), (◇) HQSA = 8-hydroxyquinoline-5-sulfonic acid (ref. 4), (■) enterobactin (refs. 13, 14), (●) trendrox (ref. 15), (◆) *o*-trensox (ref. 16)

Table II Equilibrium constants for noradrenaline complexes[a]

Overall constants	Mg^{II}	Cd^{II}	Pb^{II}	Fe^{III}
$M + H_3L^+ \rightleftharpoons M(H_2L) + H^+$	−7.1(1)	−6.1(1)	−4.9(3)	1.7
$M + H_3L^+ \rightleftharpoons M(HL) + 2H^+$	−16.1(1)	−13.6(1)	−9.03(1)	−1.4
$M + H_3L^+ \rightleftharpoons ML + 3H^+$	−25.44(4)			
$M + 2H_3L^+ \rightleftharpoons M(HL)_2 + 4H^+$	−31.44(6)			−8.1
$M + 2H_3L^+ \rightleftharpoons ML(HL) + 5H^+$	−41.6(1)			
$M + 2H_3L^+ \rightleftharpoons ML_2 + 6H^+$	−52.37(4)			
$M + 3H_3L^+ \rightleftharpoons M(HL)_3 + 6H^+$				−20.0
$M + 3H_3L^+ \rightleftharpoons ML(HL)_2 + 7H^+$				−29.1
$M + 3H_3L^+ \rightleftharpoons ML_2(HL) + 8H^+$				−38.9
$M + 3H_3L^+ \rightleftharpoons ML_3 + 9H^+$				−48.7
Stepwise constants				
$M + H_3L^+ \rightleftharpoons M(HL) + 2H^+$	−16.1(1)	−13.6(1)	−9.03(1)	−1.4
$M(HL) + H_3L^+ \rightleftharpoons M(HL)_2 + 2H^+$	−15.3(2)			−6.7
$M(HL)_2 + H_3L^+ \rightleftharpoons M(HL)_3 + 2H^+$				−11.9
$M + H_3L^+ \rightleftharpoons ML + 3H^+$	−25.44(4)			
$ML + H_3L^+ \rightleftharpoons ML_2 + 3H^+$	−26.94(7)			
Deprotonation constants				
$M(H_2L) \rightleftharpoons M(HL)^+ + H^+$	−9.0(2)	−7.5(1)	−4.1(3)	−3.1
$M(HL) \rightleftharpoons ML + H^+$	−9.3(1)			
$M(HL)_2 \rightleftharpoons ML(HL) + H^+$	−10.1(1)			
$ML(HL) \rightleftharpoons ML_2 + H^+$	−10.8(1)			
$M(HL)_3 \rightleftharpoons ML(HL)_2 + H^+$				−9.12(5)
$ML(HL)_2 \rightleftharpoons ML_2(HL) + H^+$				−9.81(4)
$ML_2(HL) \rightleftharpoons ML_3 + H^+$				−9.83(5)

[a]Values in parentheses represent 1σ standard deviation for the last significant digit; electronic charges are omitted.

coefficient; weak effect on the pH in such an acidic medium) is however present over a large pH range. Although most published papers concerning iron(III) complexes give the sequestering capacity of the ligands in terms of pFe values at pH = 7.4 (biological medium), we prefer to consider the entire pH range with such pH-dependent species. Fig. 8 shows a plot the logarithm of iron(III) molar fractions as a function of pH for a variety of simple ligands: catechol (Afdeef's values[11]), dopamine,[4] adrenaline,[5] hydroxypyridine-*N*-oxide (HPNO),[12] 8-hydroxyquinoline-5-sulfonic acid.[4] In addition three tripodal iron chelators are reported: enterobactin (equilibrium constants from Raymond and coworkers[13,14]), 'trendrox' (Raymond and coworkers[15]) and '*o*-trensox' (Pierre and coworkers[16]). While enterobactin becomes the most efficient above pH = 6, *o*-trensox and HPNO (a non-tripodal molecule) are better iron chelators in acidic media. In simple catechols the strong competition of the protons ($pK_a = 12$–13) keeps the metal from bonding to the ligands in acidic media, but they are as efficient as the synthetic tripods at pH $\geqslant$ 10.

Techniques used: Protometry, visible spectrophotometry

Table I: Deprotonation constants for noradrenaline and related ligands

Table III: Equilibrium constants of the Fe(III)/catecholamines complexes

Table IV: Calculated electronic spectra of iron(III)/catecholamines complexes: maxima of absorbance and isosbestic points

Fig. 1: Noradrenaline (H_3L^+)

Fig. 2: Titration curves for noradrenaline alone and in the presence of Pb^{2+}

Fig. 3: $\bar{p}$ *vs.* pH curves for noradrenaline alone and in the presence of Mg^{2+}

Fig. 5: absorbance as a function of pH for the Fe^{3+}–noradrenaline system

Fig. 6: Calculated electronic spectra of the Fe^{III}–noradrenaline complexes

References: 16

Received, 9th June 1998; Accepted, 16th November 1998
Paper F/8/09069F

References cited in this synopsis

1 M. Aplincourt, C. Gérard, R. Hugel, J. C. Pierrard, J. Rimbault, A. Bertrandie, B. Magny and P. Siret, *Polyhedron*, 1992, **11**, 1161.
4 C. Gérard, H. Chehhal and R. Hugel, *Polyhedron*, 1994, **13**, 591.
5 C. Gérard and H. Chehhal, *Bull. Soc. Chim. Fr.*, 1997, **134**, 1069.
7 R. Fournaise and C. Petitfaux, *Talanta*, 1987, **34**, 385.
11 A. Avdeef, S. Sofen, T. Bregante and K. Raymond, *J. Am. Chem. Soc.*, 1978, **100**, 5362.
12 F. Deida, Thesis, University of Reims Champagne-Ardenne, 1992.
13 W. Harris, C. Carrano and K. Raymond, *J. Am. Chem. Soc.*, 1979, **101**, 2213.
14 L. Loomis and K. Raymond, *Inorg. Chem.*, 1991, **30**, 906.
15 C. Yuen Ng, S. Rodgers and K. Raymond, *Inorg. Chem.*, 1989, **28**, 2062.
16 G. Serratrice, H. Boukhalfa, C. Béguin, P. Baret, C. Caris and J. L. Pierre, *Inorg. Chem.*, 1997, **36**, 3898.