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Electronic spectroscopic characterization of the formation of iron(III) metal complexes: The 8-HydroxyQuinoline as ligand case study



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Keywords: Density-functional theory Metal-to-ligand-charge-transfer Low-spin/high-spin states Trensox Microcalorimetry Synthetic siderophores derivated from 8-HydroxyQuinoline (HQ) present various biological and pharmacological activities, such as anti-neurodegenerative or anti-oxydative. However, their affinity towards iron(III) seems to depend on the position (*i.e.*, 7 or 2) of the HQ substitution by an electron withdrawing group. Two esterderivatives of HQ at 2- and 7-position are synthesized and their respective iron-complexation is characterized by a joined experimental and theoretical work. By investigating the stability of all the possible accessible spin states of the iron(III) complexes at density-functional theory (DFT) level, we demonstrate that the high-spin (HS) state is the most stable one, and leads to a UV/vis absorption spectrum in perfect match with experiments. From this DFT protocol, and in agreement with the experimental results, we show that the ester functionalization of HQ in 2-position weakens the formation of the iron(III) complex while its substitution in 7-position allows a salicylate coordination of the metal very close to the ideal octahedral environment.

1. Introduction

8-HydroxyQuinoline (HQ) is a well-known ligand within the fields of materials science, supramolecular and medicinal chemistry. The deprotonation of its phenolic-like function added to the proximity of its heterocyclic nitrogen imparts it a strong bidentate character allowing the formation of stable hexa- or tetra-coordinated complexes with a broad range of transition metal and lanthanide cations [1-4]. Over the past 20 years, its popularity has never stopped to grow as an aluminium (III) chelating agent. It produces the tris(8-hydroxyquinoline)aluminium(III) [Al(HQ)₃], a hexa-coordinated complex widely involved in promising low-molecular-weight precursor suitable for organic light emitting diode (OLED) applications [5-7].

In parallel, the interest in HQ has increased for medicinal inorganic chemistry as a robust alternative to the usual catechol, hydroxamic acid and α -hydroxycarboxylic acid chelating agents [8]. Some of its derivatives were recently reported for their anti-microbial, anti-cancer, anti-bacterial, and/or anti-neurodegenerative activities [9-11]. One of the pharmacological responses to HQ derivatives *in vivo* is their interaction with metals, such as Cu, Zn or Fe. Iron plays a crucial part in the growth process of living organisms [12]. For example, it participates in respiration mechanisms with the transport of molecular oxygen, DNA

synthesis and repair catalyzed by ribonucleotide reductase, and electron transport chains across membranes. Nevertheless, iron is also involved in Fenton- and Haber-Weiss-type chemistry which generates highly reactive oxygen radicals that cause irreversible damage to cells and their environment [13]. Furthermore, in its most stable oxidation state (*i.e.*, iron(III)), the cation is insoluble in physiological conditions and precipitates as an iron(III) oxide. For this reason, in microorganisms, the metal is chelated by low-molecular-weight ligands called siderophores with affinities between 10^{15} and 10^{40} [14,15].

In case of iron-overload disorders such as thalassemia or haemochromatosis, chelation therapies with natural or synthetic siderophores are carried out to remove the excess of iron from the organism [16-18]. Deferoxamine is a common example of natural siderophore extracted from the bacteria *Streptomyces pilosus* [19]. However, the development of synthetic siderophores is of particular interest since they allow the development of new metal chelators with improved selectivity and affinities.

Within this framework, a tripodal tris(bidentate) family of ligands containing 3 HQ units were synthesized. They present biological functions as cellular protection, antiproliferative and apoptotic effects [20-23]. Known as TRENSOX, the skeleton of the tripodal ligand consists of 3 HQ-5-sulfonate subunits linked by amide bond to tris(2-aminoethyl)

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Fig. 1. Representation of the free ligands investigated herein.

amine (TREN). According to the HQ substitution position (*i.e.*, at 7- or 2-position, see Fig. 1), the tripodal ligand is dubbed O-TRENSOX or N-TRENSOX, respectively. Both chelators exhibit a high affinity for iron (III), but the pFe value of N-TRENSOX is calculated as 7 orders of magnitude lower than that of O-TRENSOX (22.5 versus 29.5, respectively) [24,25]. Furthermore, we had synthesized 3-isoxazolidone derivative and a ciprofloxacin conjugate, both bearing by an amide bond HQ at position 2. These molecules present high activities against *Chlamydia trachomatis* but were not able to chelate iron(III) through their HQ moieties [26,27].

Out of some macroscopic conclusions, the iron(III) affinities measured for 2- and 7-substituted HQ by electron withdrawing groups still remain nonrationalized. To disentangle the different effects acting on this chelation mechanism, we propose to assess a mixed experimental and theoretical spectroscopic study aiming at understanding the ability of 2- and 7-ester HQ, dubbed here as NHQ and OHQ, respectively, to chelate the metal cation (Fig. 1).

Among theoretical methods, the Kohn-Sham approach [28] of density-functional theory [29] (DFT) and its time-dependent variant [30] (TDDFT) in its linear-response formulation [31] are the best suitable methods to study the targeted metalloquinolate complexes. Their trade-off between computational cost and accuracy, enriched by the recurrent developments led to improve the estimate of the unknown exchange-correlation energy, turn them into an approach of choice to study the spectroscopic properties of systems of hundreds of atoms [32]. In their global and range-separated variants, hybrid and double-hybrid density functional approximations [33,34] partly cure the self-interaction error in DFT (SIE) [35]. In this respect, they are underlined by several benchmark tests to be part of the most accurate class of approximation to estimate ground- and excited-state properties of organic molecular systems [36-38]. However, due to their large variety of possible spin states and the low energy gap between themselves, transition metal complexes are still a challenge for DFT approaches. Numerous investigations show that a too large excess of exact-like exchange (EXX > 25%) may emphasize a stabilization of the high-spin (HS) state while semilocal density functionals (EXX = 0%) tend to favor a low-spin (LS) state configuration as ground-electronic state [39,41,42]. This methodological ambiguity avoids systematic and blind investigations and requires a careful check of all the accessible states using different levels of theory, especially when the investigations deal with the computations of spectroscopic features [43].

By carefully analyzing all the possible spin states and computing the absorption spectroscopic features of a declination of iron(III) complexes chelated by quinolate derivatives, comparing them with experimental measurements, we intend here to rationalize and explain the different affinities of NHQ, HQ and OHQ for the metal cation.

2. Experimental section

The esters NHQ and OHQ were obtained after esterification of the corresponding acid (both purchased from Sigma-Aldrich), in refluxing thionyl chloride or, methanol and sulfuric acid, respectively (Fig. 2).



Reagents: (a) SOCl₂,MeOH, 65 °C. (b) H₂SO_{4.} MeOH, reflux.

Fig. 2. Synthesis of NHQ and OHQ esters from HQ carboxylic acids.

2.1. Methyl 8-hydroxyquinoline-2-carboxylate (NHQ) synthesis

Thionyl chloride (0.127 mL, 1.74 mmol) was added dropwise to a cooled suspension of 8-hydroxyquinoline-2-carboxylic acid (0.22 g, 1.16 mmol) in MeOH (5 mL). The yellow suspension was heated at 65° C for 4 h. After cooling at room temperature, water (10 mL) was added dropwise to the solution. Then, the suspension was filtered under vacuum to provide NHQ as yellow solid (0.200 g, 85%).

IR (ν cm⁻¹): 3333, 1657, 1610. ¹H NMR (CD₃OD) δ ppm: 8.36 (d, J = 8.60 Hz, ¹H), 8.33 (d, J = 8.56 Hz, ¹H), 7.54 (t, J = 8.04 Hz, ¹H), 7.38 (dd, J = 8.24 and 1.08, ¹H), 7.15 (dd, J = 7.68 and 1.12 Hz, ¹H), 4.06 (s, 3H). ¹³C NMR (CD₃OD) δ ppm: 164.0, 152.7, 145.1, 143.9, 134.8, 132.9, 132.6, 122.4, 119.6, 116.3, 54.7. HRMS m/z calcd for C₁₁H₉NO₃ [M+H]⁺ 204.0661; found: 204.0659.

2.2. Methyl 8-hydroxyquinoline-7-carboxylate (OHQ) synthesis

Five drops of sulfuric acid were added to a solution of 8-hydroxyquinoline-7-carboxylic acid (0.050 g, 0.26 mmol) in MeOH (5 mL). The reaction mixture was heated to reflux and stirred for 6 h. Then, the solvent was removed in vacuum and the crude residue purified by dematellated silica gel chromatography (eluent: $CH_2Cl_2/MeOH$, 85:15, v/ v) to afford OHQ as solid (0.054 g, quantitative).

IR (ν cm⁻¹): 1550, 1597, 2843. ¹H NMR (DMSO- d_6) δ ppm: 9.01 (dd, J = 4.8 and 1.5 Hz, ¹H), 8.81 (dd, J = 8.4 and 1.4 Hz, ¹H), 8.0 (d, J = 8.7 Hz, ¹H), 7.94 (dd, J = 8.4 and 4.8 Hz, ¹H), 7.49 (d, J = 8.72 Hz, ¹H), 3.37 (s, 3H). ¹³C NMR (DMSO- d_6) δ ppm: 170.8, 158.0, 146.2, 142.2, 133.9, 132.1, 128.1, 124.2, 115.7, 112.5, 52.8. HRMS m/z calcd for C₁₁H₉NO₃ [M+H]⁺ 204.0661; found: 204.0655.

2.3. Stock solutions

Because of their poor solubility in aqueous media, the compounds synthesized were first dissolved in EtOH or DMSO at 10^{-2} or 10^{-3} M. These solutions were then diluted to 1 or $5 \cdot 10^{-4}$ M in the final buffer. Solutions at pH < 2.0 were not buffered; formiate, acetate, Hepes and carbonate buffers were used for pH 2.0–3.5, pH 3.5–6.0, pH 6.0–8.5 and pH > 8.5, respectively. Buffer salt concentration was 50 mM, and the ionic strength was adjusted to 0.2 with KCl. The final pH was reached by micro-injections of concentrated HCl or NaOH. FeCl₃ solutions were

prepared in acidic media (pH 2.0). The Fe^{3+} complexes were prepared in acidic media by adding the required amount of FeCl_3 to the ligands. Then, the pH was gently raised to the final values by micro-injections of a concentrated NaOH solution. Fe(III)-citrate was prepared as previously described [44].

2.4. pH Measurements

pH values were measured at $25.0 \pm 0.5^{\circ}$ C with a Jenco pH-meter equipped with an "Ingold" combined calomel/glass microelectrode. The pHmeter was standardized at $25.0 \pm 0.5^{\circ}$ C by the standard pH buffer values of 7.00 and 10.01 (Sigma). In the presence of DMSO and EtOH, the pH values were corrected according to published procedures [45].

2.5. Spectrophotometric measurements

Affinity constants and acid-base constants were determined spectrophotometrically with the SPECFIT32 Global Analysis program [46,47]. Spectroscopic measurements were performed at $25.0 \pm 0.5^{\circ}$ C on a Cary 4000 spectrophotometer equipped with a Peltier-thermostated cell-carrier.

2.6. Microcalorimetry

Isothermal titration calorimetry (ITC) experiments were carried out on a TA Instruments microcalorimeter system with a gold cell and an active cell volume of 166 μ L. All ITC titrations were performed at 25.0°C and a stirring rate of 250 rpm, using a titrating syringe volume of 50 μ L. Typically, an automated sequence of 24 injections, each of 2 μ L FeCl₃ or Fe(citrate), titrant into the sample cell containing the ligand, spaced at 7.5 min intervals, at pH 2.0 or pH 7.0, respectively. Reverse titrations were also performed with an automated sequence of 24 injections of ligand into the cell containing the metal solution, spaced at 7.5 min intervals. The ITC data were analyzed after subtraction of the control injection in buffer alone, using the Nanoanalyze software, to yield the association constant, stoichiometry, and the enthalpy variation of the binding reactions.

3. Computational details

All the computations were performed with the release B.01 of the Gaussian'16 program package [48]. The structures of the free ligands and hexa-coordinated iron(III) complexes in their low, intermediate and high spin electronic states were fully optimized at DFT level with the PBE0 global-hybrid density functional [49,50] using the Pople 6-

 $31 + G^*$ double- ζ basis set for the H, C, N and O atoms [51,52], and the LanL2DZ double- ζ basis set associated to the corresponding pseudopotential for Fe [53]. Structure optimizations of the high spin state complexes were also performed at the PBE0-D3(bj) level of theory by adding on top of the PBE0 density functional the D3(bj) empirical dispersion correction [54]. Bulk solvent effects were added in an implicit fashion employing the polarizable continuum model (PCM) and setting the dielectric constant to the one of water [55]. To confirm the spin multiplicity of the ground electronic state of each iron(III) complex, structure optimizations were also carried out with OPBE [56,57], a semilocal density functional recognized to provide a reliable estimate of the high- and low-spin energy gaps [39].

Excited-state properties were computed with linear response TDDFT using the methodology mentioned above. More precisely, the first 30 vertical electronic excitations were estimated with the PBE0 global- and CAM-B3LYP [58] range-separated hybrid density functionals from the PBE0 optimized structures with the same basis sets and pseudopotentials as mentioned above. Both density functionals and basis sets are recognized to provide reliable energies depending on the type of electronic transitions [59], and a sufficient enough energy convergence [60,61], respectively. The band-shaped absorption spectra were obtained by convoluting the stick spectrum (energy and oscillator strength) into a sum of Gaussian functions centered on each vertical transition, fitting the full width at half maximum of each Gaussian function to the corresponding experimental spectra [62,63]. Densitybased analyzes and the mean charge transfer distance D_{CT} index values were computed from ground- and excited-cube densities according to the model described by Ciofini and coworkers [64].

4. Results and discussions

4.1. Free ligands

4.1.1. UV/vis absorption spectra of the ligands

The scaffold of HQ and its both NHQ and OHQ ester derivatives consists of a quinoline core substituted in 8-position by a phenol-like hydroxyl function (Fig. 1). The resulting electronic delocalization over the whole molecule, modulated by a functionalization in 2- or 7-position by an electron withdrawing group (NHQ and OHQ, respectively), induces large absorption bands within the UV/vis region. The position of these bands is experimentally demonstrated as sensitive to the pH and results from the protonation state of the hydroxyl phenol-like function and the nitrogen atom carried by the heterocyclic quinoline skeleton.

Fig. 3 depicts the influence of the pH on the absorption properties of HQ. The first set of absorption spectra is recorded from pH 6.10 to 2.35

Fig. 3. Experimental absorption spectra of HQ (5 \cdot 10⁻⁴ M) acquired at different pH values in (left) sodium acetate 50 mM, KCl 140 mM, 20% EtOH, pH 2.35–6.10 (right) carbonate 50 mM, KCl 150 mM, 20% EtOH, pH 7.35–12.45. All the experiments are performed at 25 ± 0.5°C. Arrows indicate the direction of spectral changes when pH value decreases.



Table 1

Energies (*e*, in eV), wavelengths (λ , in nm), oscillator strengths (*f*, in a.u.) and charge-transfer distance (D_{CT} in Å) of the main vertical electronic transitions computed for the acid (LH₂⁺), neutral (LH) and basic (L⁻) forms of the HQ molecule at PCM-TD-PBE0 and PCM-TD-CAM-B3LYP level of theory with the 6-31 + G^{*} basis set. Only transitions with sufficiently large enough oscillator strength are retained. Experimental energies and wavelengths of the main absorption bands are provided as a matter of comparison.

Free Exp.		PBE0				CAM-B3L	CAM-B3LYP				
ligands	Туре	e (eV)	λ (nm)	e (eV)	λ (nm)	f (a.u.)	D _{CT} (Å)	e (eV)	λ (nm)	f (a.u.)	D _{CT} (Å)
LH_2^+	$\pi \to \pi^{\bigstar}$	3.36	369	3.36	369	0.04	2.1	3.71	334	0.06	2.1
-	$\pi \rightarrow \pi^{\star}$	5.12	242	5.25	236	0.83	2.0	5.40	229	0.88	1.7
LH	$\pi \to \pi^{\bigstar}$	4.02	308	3.88	319	0.06	2.1	4.21	295	0.09	2.0
	$\pi \to \pi^{\bigstar}$	4.92	252	5.40	229	0.87	1.7	5.53	224	0.96	1.5
L^{-}	$\pi \to \pi^{\bigstar}$	3.44	360	3.04	408	0.08	2.2	3.37	368	0.09	2.2
	$\pi \rightarrow \pi^{\star}$	3.71	334	3.87	320	0.14	1.5	4.02	309	0.14	1.3
	$\pi \to \pi^{\bigstar}$	4.77	260	5.10	243	0.40	1.3	5.21	238	0.42	0.4

in acetate buffer. The resulting spectra show an absorbance increase (decrease) of the low-lying band at 369 (308) nm, gone along with a red shift of the maximum of absorption from 242 to 252 nm. These variations generate the appearance of 3 isosbestic points at 245, 265 and 335 nm. We ascribe these spectroscopic changes to the protonation of the nitrogen atom belonging to the heterocyclic quinoline core. Computations at TD-PBEO level accurately confirm and precise the pHsensitivity of HQ with an error lower than 0.1 eV on the positions of the first low-lying transitions (Table 1). The protonation of the nitrogen atom induces a red shift of the first low-lying vertical electronic transition from 319 to 369 nm (3.88 to 3.36 eV, respectively), accompanied by a decrease of the corresponding oscillator strength from 0.06 to 0.04. In both case, the low-lying vertical absorption is of $\pi \rightarrow \pi^*$ type and is governed by a highest occupied to a lowest unoccupied molecular orbital (HOMO \rightarrow LUMO) transition delocalized over the whole quinoline core. The red shift of the maximum of absorption is also accurately modeled when the pH decreases. It goes from 229 nm (5.40 eV) for the neutral HQ molecule to 236 nm (5.25 eV) for the nitrogen-protonated system.

A second series of absorption spectra is acquired in carbonate buffer (Fig. 3) making the pH to vary from 12.45 to 7.35. We observe a concomitant blue shift and absorbance decrease of both characteristic absorption bands from 334 (at pH 12.45) to 308 nm (at pH 7.35) and from 260 (at pH 12.45) to 252 nm (at pH 7.35), together with the appearance of a low-lying band at 360 nm. 3 isosbestic points at 224, 276 and 318 nm come out from these spectral variations. Computations show that the modification of the absorption spectrum comes from the deprotonation of the phenol-like hydroxyl function (Table 1). Indeed, for the anionic system, TDDFT models the outbreak of a new low-lying $\pi \rightarrow$ π^{\star} absorption band at 408 nm (3.04 eV) governed by a HOMO \rightarrow LUMO transition, and the persistence of both other $\pi \rightarrow \pi^{\star}$ bands at 320 and 243 nm (3.87 and 5.10 eV), respectively. In direct comparison with experiment, the $S_0 \rightarrow S_1$ absorption band computed at TD-PBE0 level of theory is red-shifted by 0.4 eV (Table 1). This larger error with respect to the neutral and cationic HQ molecules is rationally explained by the expansion of the electronic conjugation of the system. In this specific case, semilocal or hybrid density functionals casting a low fraction of exact-like exchange overdelocalize the density due to SIE [35]. At excited state, this error is translated by a stronger chargetransfer character of the transition which results in a small electronic overlap between the donor and acceptor regions of the molecule [64-66]. The analysis of the D_{CT} index value, which provides an information about the mean charge-transfer distance between donor and acceptor centers [64], agrees and provides a small increase of charge-transfer length when going to the anionic form (2.1 to 2.2 Å). The computation of the vertical transitions with the CAM-B3LYP range-separated hybrid density functional confirms this hypothesis (Table 1) and finds the positions of the 3 absorption bands of the anionic system at 368, 309 and 238 nm (3.37, 4.02 and 5.21 eV, respectively).

Regarding NHQ and OHQ ester derivatives, similar conclusions can be drawn from the Fig. S1 and Table S1 reported within the Supporting Information (SI). Their experimental absorption spectra present similar features and TDDFT confirms the nature and assignation of the bands, keeping an excellent agreement with experiments.

4.1.2. Determination of the thermodynamic constants

The pH-sensitivity of the absorption spectra allows the determination of the $K_{\rm NH}$ and $K_{\rm OH}$ acid-base dissociation constants of the 3 HQ derivatives. The former describes the deprotonation of the nitrogen center positioned on the quinoline scaffold and is defined such as

$$LH_{2}^{+} \Rightarrow LH + H^{+} \quad K_{NH} = \frac{[LH][H^{+}]}{[LH_{2}^{+}]},$$
 (1)

where LH_2^+ and LH are the cationic and neutral form of the ligand, respectively. The latter represents the deprotonation of the phenol-like hydroxyl function and is governed by

$$LH \rightleftharpoons L^{-} + H^{+} \quad K_{OH} = \frac{[L^{-}][H^{+}]}{[LH]},$$
 (2)

with L^{-} the anionic form of the ligand.

Table 2 reports both constants obtained by a Specfit analysis of the absorption spectra of HQ and its NHQ and OHQ ester derivatives. Results are in line with those previously reported at experimental or theoretical levels in Refs [2, 10, 67-69]. The first dissociation constant ($pK_{\rm NH}$) is measured as independent of the electron withdrawing effects induced by the ester substituents and is merely determined as 4.8 for the 3 ligands. However, the $pK_{\rm OH}$ of OHQ (12.5) is estimated as 2 units higher than the ones of HQ and NHQ (10.3 and 9.5, respectively). Indeed, computations show that the energy minimum structure of the neutral OHQ molecule involves the formation of a planar 6-member ring governed by an intramolecular hydrogen bond between the hydroxyl and ester groups. Previously hypothesized by Carris and coworkers [70], this spatial arrangement, which can only occur in case of OHQ, confirms the improved stability of the neutral form and its higher $pK_{\rm OH}$ value.

Table 2

Acid-base dissociation constants of the HQ ligand and its NHQ and OHQ ester derivatives in absence or presence of iron(III).

	Without Fe ³⁺		With Fe ³⁺	
ligands	pK _{NH}	р <i>К</i> _{ОН}	pK _{NH} '	рК _{ОН'}
HQ NHQ OHQ	$\begin{array}{l} 4.85 \pm 0.05 \\ 4.90 \pm 0.10 \\ 4.70 \pm 0.10 \end{array}$	$\begin{array}{c} 10.30 \pm 0.02 \\ 9.50 \pm 0.05 \\ 12.50 \pm 0.10 \end{array}$	3.00 ± 0.04 3.05 ± 0.05 3.00 ± 0.10	$\begin{array}{l} 5.00 \pm 0.05 \\ 5.50 \pm 0.05 \\ 4.85 \pm 0.05 \end{array}$

4.2. Formation of the iron(III) complexes

4.2.1. Stoichiometry of the iron(III) complexes

Owing to their bidentate character, HQ and its both NHQ and OHQ ester derivatives are expected to strongly chelate iron(III). One equivalent of FeCl₃ is added to a solution of HQ, and the absorption spectra are acquired first in formiate and then in acetate buffer (see Table 2 and Fig. S2 in the SI). The Specfit analysis of the spectra shows that in the presence of iron(III), the pK_{NH}' and pK_{OH}' values (Eqs. (1) and (2), the prime factor exponent notation depicting the presence of iron(III)) are decreased by around 1.9 and 5.3 units, respectively. It thus demonstrates the complexation of Fe³⁺ by both acid-base sites of HQ. In the same experimental conditions, the pK_{NH}' of NHQ and OHQ decreases by 1.9 and 1.7 units, while the pK_{OH}' decrease is estimated to 4.0 and 7.6, respectively. In case of OHQ, the larger pK_{OH}' variation indicates the breaking of the 6-member intramolecular hydrogenbonded ring stabilizing the structure and the formation of a iron(III) complex involving its 2 acid-base functions.

The formation of the iron(III) complexes with HQ derivatives is further confirmed by direct and reverse ITC titrations (see Fig. S3 in the SI). At pH 2.0, the direct titration, *i.e.* the titration of HQ by FeCl₃, provides a stoichiometry of 0.4 ± 0.1 equivalents of iron(III) cation and an affinity constant of $(2.8 \pm 1.3) \times 10^3$. The reverse titration agrees with the direct one and shows a metal cation chelated by (3.2 ± 0.3) equivalents of HQ and an affinity constant merely equals to the previous one within the uncertainty limits, *i.e.* $(2.1 \pm 0.3) \times 10^3$. As a result, both titrations converge to the thermodynamically favored formation of an iron(III) complex coordinated by 3 HQ molecules. More precisely, the ITC analysis shows that at room temperature and acid pH, the reaction is endothermic ($\Delta H = 0.5 \pm 0.1 \text{ kJ mol}^{-1}$) and driven by entropy (T Δ S > Δ H), *i.e.* that the water/HQ ligand exchanges increase the entropy and drive the reaction to the formation of the complex. At pH7.4, the direct titration of HQ by ferric citrate confirms the thermodynamically favored hexa-coordination of iron(III) with 3 HQ molecules ($n = 0.46 \pm 0.15$, see Fig. S3 in the SI). However, like previously observed for the catechol ligand [44], the reaction is found to be exothermic ($\Delta H = -(53 \pm 1) \text{ kJ mol}^{-1}$) in neutral medium. Thus, it implies that the formation of the coordination bond between the ferric cation and HQ is energetically more important than the decoordination and release of water within the solution $(|\Delta H| > |T\Delta S|)$.

4.2.2. Structure of the iron(III) complexes

The iron(III) complex chelated by 3 HQ ligands can adopt 3 groundstate electronic configurations, each one characterized by a different population of the 3d orbitals of the metal by its 5 valence electrons. In its low-, intermediate- or high-spin state (LS, IS or HS, respectively), iron(III) adopts a $(t_{2g})^5$, $(t_{2g})^4$ $(e_g)^1$, or $(t_{2g})^3$ $(e_g)^2$ electronic configuration. A structure optimization of the neutral form of the complex [Fe (HQ)₃] in its 3 allowed spin states demonstrates that the HS configuration is by far the most stable state of the complex. PBE0 models the HS state 10.0 (14.4) kcal mol⁻¹ more stable than the LS (IS) one. Even if global hybrids are known to overstabilize the HS configuration [39-41,71], the OPBE semilocal approximation confirms the state ordering (HS being 6.0 and 11.8 kcal mol⁻¹ more stable than LS and IS, respectively) and imposes the HS configuration as the most stable electronic state of the complex. Within the sextet spin state multiplicity, the structure of the complex is slightly distorted with respect to an ideal octahedral coordination due to the formation of a constrained 5member ring between Fe and the coordination sites of the ligand. Indeed, the Fe-O and Fe-N mean distances are estimated to be 1.973 and 2.181 Å, respectively (Table 3), with a spin density of about 5.0, 0.1 and 0.0 a.u. localized on the Fe, O and N atoms, respectively. The addition of the D3(bj) empirical dispersion correction does not modify the structure of the complex and confirms the reliability of PBE0 with respect to these systems.

Table 3

Coordination bond distance (Å) between iron(III) and the different chelating sites for a selection of HQ-based complexes. Bond distances are optimized at PCM-PBE0 level of theory with (+D3(bj)) or without (noCor) empirical dispersion corrections with the $6-31+G^*$ basis set. Crystallographic structure parameters of the O-TRENSOX-based complex are reported as a matter of comparison.

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Iron(III) complexes	Fe–O		Fe–N		Fe-O(=C)		
	noCor	+ D3(bj)	noCor	+ D3(bj)	noCor	+ D3(bj)	
$\begin{array}{l} {[Fe(HQ)_{3}]^{a}} \\ {[Fe(NHQ)_{3}]^{a}} \\ {[Fe(OHQ)_{3}]^{a}} \\ {[Fe_{oo}(OHQ)_{3}]^{a}} \\ {[Fe(O-TRENSOX)]^{b}} \end{array}$	1.973 1.970 1.970 1.937 1	1.974 1.977 1.970 1.931 .940	2.181 2.307 2.168 - -	2.185 2.274 2.184 - -	- - 2.083	- - 2.090 2.034	

^a Computed at DFT level.

^b Crystallographic structure from Ref. [72].

 $(NHQ)_3$] or $[Fe(OHQ)_3]$ complex show similarly that iron(III) is hexacoordinated by 3 NHQ or OHQ ligands, and lead to an energeticallyfavored HS state configuration. Due to a larger steric hindrance, both resulting complexes are more distorted than $[Fe(HQ)_3]$. The Fe-O mean distance is measured as 1.970 Å and is very similar to the one of $[Fe(HQ)_3]$ (Table 3). However, the Fe–N mean distance is significantly larger (shorter) for $[Fe(NHQ)_3]$ ($[Fe(OHQ)_3]$) with respect to the one of $[Fe(HQ)_3]$ and is estimated to be 2.307 (2.168) Å versus 2.181 Å. This difference in structure impoverishes the spin density of Fe in the NHQbased complex (4.7 versus 5.0 a.u.) and reinforces it to 5.2 a.u in case of the OHQ-based one. Particularly for $[Fe(NHQ)_3]$, these deviations with respect to the ideal octahedral environment of the metal may lead to the formation of less stable complexes with respect to $[Fe(HQ)_3]$.

The OHQ ligand allows however to consider another chelation environment for iron(III) (Fig. 1). Indeed, the spatial proximity of the carbonyl group and phenol-like hydroxyl function of this ligand allows the formation of a less contrained 6-member ring between Fe and both oxygen donor sites. The resulting complex is dubbed [Fe₀₀(OHQ)₃]. With this salicylate coordination, the complex adopts a quasi-ideal octahedral geometry with a Fe–O mean distance estimated to 1.937 and 2.083 Å for the hydroxyl and carbonyl sites, respectively (Table 3). These findings agree with previous works reported by Serratrice and coworkers. They first demonstrated the iron chelation by the carbonyl group by IR spectroscopy, the carbonyl characteristic band being blueshifted in presence of Fe^{3+} [24]. They then confirmed this coordination scheme by crystallizing the iron(III) complex by O-TRENSOX [72]. In this specific case, the distance between the metal cation and the hydroxyl group is in perfect match (1.940 Å). Its distance with the carbonyl site is however 0.04 Å shorter (2.034 Å).

4.2.3. UV/vis spectra of the iron(III) complexes

The formation of the iron(III) complex by HQ-based ligands is now analyzed by UV/vis absorption spectroscopy (Fig. 4). The addition of FeCl₃ to a solution of HQ at pH 2.0 leads to the appearance of 2 new absorption bands within the visible region (653 and 452 nm), and the persistence of the characteristic $\pi \rightarrow \pi^{\star}$ band of the HQ ligand in acidic medium (369 nm) (Table 4). These UV/vis features are in line with what observed experimentally for (8-hydroxyquinoline-5-sulfonic acid) iron(III) and quinolobactine complexes [73-75]. The same experiment performed at pH7.4 leads to a slightly modified absorption spectrum characterized by an absorbance decrease and blue shift of the first lowlying band from 653 to 582 nm, followed by the persistence of both others at 455 and 369 nm, respectively (Fig. 4). The spectrum presents an isosbestic point in the visible region. This feature confirms the ITC experiments (considering a one-third ratio equivalent of iron(III)) and is the signature of the formation of a unique complex with a fixed stoechiometry.

Same computations performed on the neutral form of the [Fe

Computations performed at the TD-PBE0 level of theory on the acid



Fig. 4. Experimental absorption spectra function of the pH (2.0 and 7.4) and the corresponding vertical electronic transitions function of the acid (LH_2^+) and neutral (LH) form of HQ in case of the (left) free ligand and (right) iron(III) complex. Vertical excitations are computed with the 6-31 + G^{*} basis set at PCM-TD-PBE0 and PCM-TD-CAM-B3LYP levels of theory for the free ligand and iron(III) complex, respectively. Both insets depict the absorption spectra Gaussian convolution of the vertical excitations.

and neutral forms of the complex ($[Fe(HQ)_3]^{3+}$ and $[Fe(HQ)_3]$, respectively) show the raising of 2 new low energy vertical transitions within the visible region of the spectrum (Table 4). Both of them are quasi-degenerated due to the quasi-symmetry of the complex and present a charge-transfer character depicted by a D_{CT} index value varying between 1.3 and 2.6 Å according to the transition type and protonation state.

The analysis of the density difference between the first excited and ground states depicts a strong metal-to-ligand-charge-transfer (MLCT) character characterized by a strong density depletion on the metal and one of its surrounding ligand, compensated by a density increase mainly located on the other ligands (Fig. 5). The D_{CT} index value is here computed as 2.6 and 1.9 Å for the cationic and neutral forms of the complex, respectively. In this specific case, the PBE0 global hybrid is expected to suffer from spurious SIE and to strongly underestimate the energy of the MLCT transitions. Indeed, it models the first low-lying excitation at 1297 nm and 773 nm (0.96 and 1.60 eV) for the acid and neutral forms of the complex, respectively, while the experimental determination of the position of the first absorption band lies at 653 and 582 nm (1.90 and 2.13 eV), namely an error larger than 0.9 and 0.5 eV, respectively (Table 4). Switching to the CAM-B3LYP range-separated density functional partially corrects SIE and models the first low-lying band at 633 and 680 nm (1.96 and 1.82 eV), respectively, thus reducing the error to 0.2 eV (Table 4). Moreover, TDDFT confirms here that the increase of the pH, increases the absorbance of the first absorption band with an oscillator strength going from 0.02 for the protonated [Fe $(HQ)_3]^{3+}$ complex to 0.06 for its neutral form.

The second absorption band is prone to a ligand-to-ligand-charge transfer (LLCT) character which is ruled by a through space charge transfer between 2 ligands with a D_{CT} index value estimated to 1.7 and 1.3 Å for the cationic and neutral forms of the complex (Fig. 5). In this specific case, PBE0 is expected to be particularly prone to SIE because of the through space character of the transition. Indeed, PBE0 overestimates the energy of the transition with an error larger than 0.3 eV. It computes it at 472 and 509 nm (2.63 and 2.44 eV) for the acid and neutral form of the complex, respectively (Table 4). CAM-B3LYP corrects this spurious behavior and models it at 429 and 487 nm (2.89 and 2.55 eV), thus lowering the error to 0.2 eV.

The last intense absorption band observed as the maximum of absorption is pH independent. It is experimentally measured at 369 nm (3.36 eV), and modeled as quasi-degenerated at 379 nm (3.27 eV) with the PBE0 global hybrid (Table 4). The good agreement between experiment and theory points here the character change of the transition. Fig. 5 shows that it is characterized by a local $\pi \rightarrow \pi^*$ excitation located on the ligand itself. CAM-B3LYP confirms this trend and estimates it with a slightly larger error at 336 and 347 nm (3.68 and 3.57 eV) for the acid and neutral form of the complex.

The absorption spectra of NHQ- and OHQ-based complexes in acid and neutral media present similar spectroscopic features with respect to $[Fe(HQ)_3]^{3+}$ and $[Fe(HQ)_3]$, respectively (Fig. 6). Within the visible region, the absorption bands of the OHQ-based complexes are however largely blue-shifted and lie around 560 and 462 nm (2.21 and 2.68 eV) for the acid form, and 525 and 425 nm (2.36 and 2.92 eV) for the neutral form.

Table 4

Energies (*e*, in eV), wavelengths (λ , in nm), oscillator strengths (*f*, in a.u.) and charge-transfer distance (D_{CT} in Å) of the main vertical electronic transitions computed for the acid ([Fe(HQ)₃]³⁺, pH 2.0) and neutral ([Fe(HQ)₃], pH 7.4) forms of the iron(III) complex chelated by 3 HQ ligands at PCM-TD-PBE0 and PCM-TD-CAM-B3LYP level of theory with the 6-31 + G^{*} basis set. Only transitions with sufficiently large enough oscillator strengths and one among the quasi-generated states are retained. Experimental energies and wavelengths of the main absorption bands are provided as a matter of comparison. $< S^2 >$ values are provided in Table S4 within the SI.

Iron(III) complexes		Exp.		PBE0	PBEO			CAM-B3LYP			
	Туре	e (eV)	λ (nm)	e (eV)	λ (nm)	f (a.u.)	D _{CT} (Å)	<i>e</i> (eV)	λ (nm)	f (a.u.)	D _{CT} (Å)
[Fe(HQ) ₃] ³⁺	MLCT	1.90	653	0.96	1297	0.02	2.6	1.96	633	0.02	3.5
	LLCT	2.76	450	2.63	472	0.05	1.7	2.89	429	0.05	3.9
	$\pi \rightarrow \pi^{\star}$	3.36	369	3.27	379	0.03	2.3	3.68	336	0.05	0.7
[Fe(HQ)3]	MLCT	2.13	582	1.60	773	0.05	1.9	1.82	680	0.06	1.9
	LLCT	2.72	455	2.44	509	0.02	1.3	2.55	487	0.05	1.0
	$\pi \to \pi^{\bigstar}$	3.36	369	3.27	379	0.07	1.4	3.57	347	0.08	1.2



Fig. 5. Computed electronic density variations ($\Delta \rho$, isovalue 0.0004 a.u.) for the main vertical electronic transitions of the neutral form of the [Fe(HQ)₃] complex. The blue and red surfaces represent a density increase and depletion upon excitation, respectively.

CAM-B3LYP provides an accurate estimate of the 3 types of transitions involved in the UV/vis spectrum of $[Fe(NHQ)_3]$ with an error of about 0.2 eV (Table 5). However for $[Fe(OHQ)_3]$, it models the MLCT, LLCT and $\pi \rightarrow \pi^*$ transitions with deviations larger than 0.4, 0.7 and 0.2 eV, respectively. This larger error range lets us suppose that $[Fe(OHQ)_3]$ is not the iron(III) complex formed preferentially in solution, and that the hydroxyl/nitrogen chelation sites of the OHQ is not the one observed. Indeed, the same computations performed on the $[Fe_{oo}(OHQ)_3]$, namely the iron(III) metal chelated by the phenol-like hydroxyl and ester donor sites of the OHQ ligand, provide a better estimate of the three types of transitions with an error of about 0.2 eV (Table 5). More than a structure argument as discussed above, the UV/ vis spectrum of the OHQ-based complex goes in favor to a salicylate chelation of the iron(III) cation.

4.2.4. Determination of the thermodynamic constants

The Specfit analysis of the absorption spectra of HQ-, NHQ-, and OHQ-based iron(III) complexes in acid medium (Fig. 6) allows the determination of an apparent affinity constant K_{13} at pH 2.0:



Fig. 6. Experimental absorption spectra of (top left) HQ $(5 \cdot 10^{-4} \text{ M})$, (top center) NHQ $(5 \cdot 10^{-4} \text{ M})$, and (top right) OHQ $(1 \cdot 10^{-4} \text{ M})$ in presence of an increasing concentration of FeCl₃ at pH 2.0. Same experiments for (bottom left) HQ $(5 \cdot 10^{-4} \text{ M})$, (bottom center) NHQ $(1 \cdot 10^{-4} \text{ M})$, and (bottom right) OHQ $(5 \cdot 10^{-4} \text{ M})$ in presence of an increasing concentration of Fe(III)-NTA at pH 7.4. All the experiments are performed at $25 \pm 0.5^{\circ}$ C. Arrows indicate the direction of spectral changes when the concentration in iron(III) increases.

Table 5

Energies (*e*, in eV), wavelengths (λ , in nm), oscillator strengths (*f*, in a.u.) and charge-transfer distance (D_{CT} in Å) of the main vertical electronic transitions computed for the neutral [Fe(NHQ)₃], [Fe(OHQ)₃] and [Fe_{oo}(OHQ)₃] forms of the iron(III) complex (pH 7.4) at PCM-TD-PBE0 and PCM-TD-CAM-B3LYP level of theory with the 6-31 + G* basis set. Only transitions with sufficiently large enough oscillator strengths and one among the quasi-generated states are retained. Experimental energies and wavelengths of the main absorption bands are provided as a matter of comparison. $< S^2 >$ values are provided in Table S5 within the SI.

Iron(III) complexes		Exp.		PBE0	PBE0				CAM-B3LYP			
	Туре	e (eV)	λ (nm)	e (eV)	λ (nm)	f (a.u.)	D _{CT} (Å)	e (eV)	λ (nm)	<i>f</i> (a.u.)	D _{CT} (Å)	
[Fe(NHQ)3]	MLCT	2.05	605	1.60	775	0.06	1.5	1.79	692	0.06	1.6	
	LLCT	2.66	465	2.16	573	0.01	1.7	2.35	527	0.03	1.5	
	$\pi \rightarrow \pi^{\star}$	3.28	378	2.81	441	0.04	1.9	3.22	384	0.10	1.8	
[Fe(OHQ) ₃]	MLCT	2.36	525	1.70	729	0.05	1.7	1.95	636	0.06	1.9	
	LLCT	2.92	425	2.51	494	0.03	1.2	2.66	466	0.06	1.3	
	$\pi \rightarrow \pi^{\star}$	3.20	387	3.36	369	0.07	1.8	3.44	360	0.07	1.2	
[Fe _{oo} (OHQ) ₃]	MLCT	2.36	525	1.75	709	0.08	2.1	2.05	604	0.08	1.5	
	LLCT	2.92	425	2.64	470	0.02	0.7	2.75	451	0.03	0.7	
	$\pi \to \pi^{\bigstar}$	3.20	387	3.23	384	0.04	1.5	3.26	380	0.03	1.0	

$$[Fe(LH_2)_3]^{6+} \qquad K_{13}^{-1} = \frac{[LH_2^+]^3[Fe^{3+}]}{[[Fe(LH_2)_3]^{6+}]},$$

$$\Rightarrow 3LH_2^+ + Fe^{3+} \qquad (3)$$

where LH_2^+ and $[Fe(LH_2)_3]^{6+}$ are the cationic forms of the ligand and iron(III) complex predominant at pH 2.0, respectively. The experimental determination of K_{13} at pH 2.0 and the acid-base constants of the free and complexed ligands allow deducing a global stability constant β_{13} , as a combination of the laws of mass action described by Eqs. (1), (2) and (3) such as:

$$[Fe(L)_{3}] \Rightarrow 3L^{-} + Fe^{3+} \quad \beta_{13}^{-1} = \frac{[L^{-}]^{3}[Fe^{3+}]}{[[Fe(L)_{3}]]} = K_{13}^{-1}K_{\rm NH}^{3}K_{\rm OH}^{3}K_{\rm NH}^{\prime}K_{\rm OH}^{\prime-3},$$
(4)

with L^- and [Fe(L)₃] are the deprotonated forms of the ligand and iron (III) complex, respectively.

To extend the comparison with other experimental studies performed in biological media [4,76], pFe of the three different ligands is determined. It is defined as the negative logarithm of the free iron(III) concentration (pFe = $-\log[Fe^{3+}]$) at pH7.4 with an analytical ligand and Fe³⁺ concentration of 10^{-5} and 10^{-6} M, respectively. Table 6 reports both pFe and $\log\beta_{13}$ characteristic constants for the 3 studied ligands and catechol, another well-known chelator in literature (Fig. 1) [8].

Independently on the ligand type, the logarithm of the formation constants of the iron(III) complex is calculated as 3 or 4 times larger at basic than at acid pH. This larger affinity in basic medium is explained by the non-protonation of both chelating sites which facilitates the formation of coordination bonds. The best affinity for the metal cation is found for OHQ and catechol with a log K_{13} and log β_{13} larger than 10.0 and 40.0, respectively. Among them, catechol is by far the best ligand with a log β_{13} of 45.7. Its small size limits the steric hindrance and allows the formation of a very stable hexa-coordinated iron(III) complex by both phenol-like hydroxyl functions [76]. By difference, log β_{13} value of OHQ is about 4 units lower (Table 6). This trend discrepancy depicts a coordination of the metal through the phenol-like hydroxyl and ester

Table 6

Formation constants of the [Fe(L)₃] complex for a selection of ligands L.

[Fe(L) ₃]	$\log K_{13}^{a}$	$\log \beta_{13}^{b}$	pFe ^c
HQ	$\begin{array}{l} 9.70 \pm 0.05 \\ 7.80 \pm 0.10 \\ 13.40 \pm 0.40 \\ 10.00 \pm 0.40 \end{array}$	31.1	13.5
NHQ		25.3	10.5
OHQ		41.5	17.1
Catechol		45.7	21.0

^a Affinity constant measured at pH 2.0 by spectroscopy.

^b Overall stability constant.

^c pFe = $-\log[Fe^{3+}]$ when $[Fe^{3+}]_{total} = 10^{-6}$ M and $[L]_{total} = 10^{-5}$ at pH 7.4.

groups which allows the formation of a structure very close to the ideal octahedral environment with a less strong coordination binding since the basic character of the ester function is lower than the one of the hydroxylate.

Furthermore, the worse affinity constant is by far determined for NHQ with a $\log \beta_{13}$ of about 25.3. Here, it is drastically decreased due to the strong steric hindrance which leads to a strongly distorted structure of the resulting hexa-coordinated complex.

The iron(III)-HQ complex presents an affinity constant in between both previously reported cases $\log \beta_{13} = 31.1$ since its structure is less prone to steric hindrance than [Fe(NHQ)₃] but is computed as more distorted than [Fe_{oo}(OHQ)₃] in comparison with the ideal octahedral environment.

The pFe values confirm this trend (Table 6). For OHQ and catechol, the values are much closed to the ones of other bidentate ligands reported in literature like 1-hydroxypiridin-2-one (pFe = 16.0), and deferiprone (pFe = 19.0) [4]. Similar conclusions can be drawn for the HQ and NHQ ligands which lead to less stable iron(III) complexes, the pFe value of NHQ being 6.6 units lower than that of OHQ.

Such a trend supports the conclusions drawn by Serratrice and coworkers for the N-TRENSOX and O-TRENSOX ligands [24] and correlates with our previous investigations dealing with tuned ciprofloxacine and D-cycloserine ligands [26,27]. It shows that the ester functionalization in 2-position of their HQ moieties increases the steric hindrance and disfavors the formation of an iron(III) hexa-coordinated complex, while its ester functionalization in 7-position allows the formation of an ideal-like octahedral complex, and thus favors a coordination of iron(III) through the salicylate function.

5. Conclusions

In this paper, we performed a joined experimental and theoretical investigation aiming at understanding the formation of iron(III) complexes chelated by bidentate 8-HydroxyQuinoline-based derivatives, and the relative stability of the resulting complexes with respect to a functionalization of their ligands by electron withdrawing groups in 2or 7-positions. More precisely, we succeeded to raise a protocol able to characterize and follow by UV/vis spectroscopy the formation of the iron(III) complexes.

DFT computations performed with the PBE0 global-hybrid and confirmed with the OPBE semilocal density functional, showed that the hexa-coordinated complex was stabilized in its ground electronic state by adopting a high spin state configuration. They demonstrated that according to the position of the withdrawing group on the heterocyclic skeleton, the steric hindrance can destabilize the iron(III) complex by forcing it to adopt a distorted structure far from the ideal octahedral environment. In this respect, we found that the ester functionalization of HQ in 2-position weakens the iron(III) complex while its functionalization in 7-position allows a salicylate coordination of the metal very close to the ideal octahedral environment.

UV/vis spectroscopic investigations at experimental and theoretical levels confirmed the existence of these complexes by providing matching signatures with an error close to 0.2 eV. TDDFT computations performed with the CAM-B3LYP range-separated hybrid proved that the two degenerated low-lying absorption bands of the experimental spectra correspond to strong charge-transfer excitations with metal-toligand and ligand-to-ligand characters, respectively. Moreover in case of the 7-position functionalization, they confirmed that the ester/hydroxyl chelation prevails over the nitrogen/ester one by modeling similar chemical shifts of the bands.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jinorgbio.2019.110864.

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