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Coordination chemistry of a bis(3-hydroxypyran-4-one) with iron and copper

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The coordination chemistry of a bis(3-hydroxypyran-4-one) containing two bidentate moieties was investigated with iron and copper. The affinity of this ligand for iron was determined by spectrophotometric titration. Using electrospray ionization mass spectrometry, it was established that this bis(hydroxypyranone) derivative does not function as a tetradentate ligand, but rather bis-bidentate, forming multinuclear species, with bridged structures. The major iron species under slightly basic conditions are the multiiron complexes Fe_2L_3 , $[\text{Fe}_3\text{L}_3]^{2+}$, and $[\text{Fe}_3\text{L}_3(\text{LH})]^{2+}$. In contrast speciation with copper is relatively simple, only two species are observed, $\text{Cu}(\text{LH})_2$ and Cu_2L_2 .

Keywords: Speciation; Iron complex; Copper complex; Bis-bidentate chelator; 3-Hydroxypyran-4-one

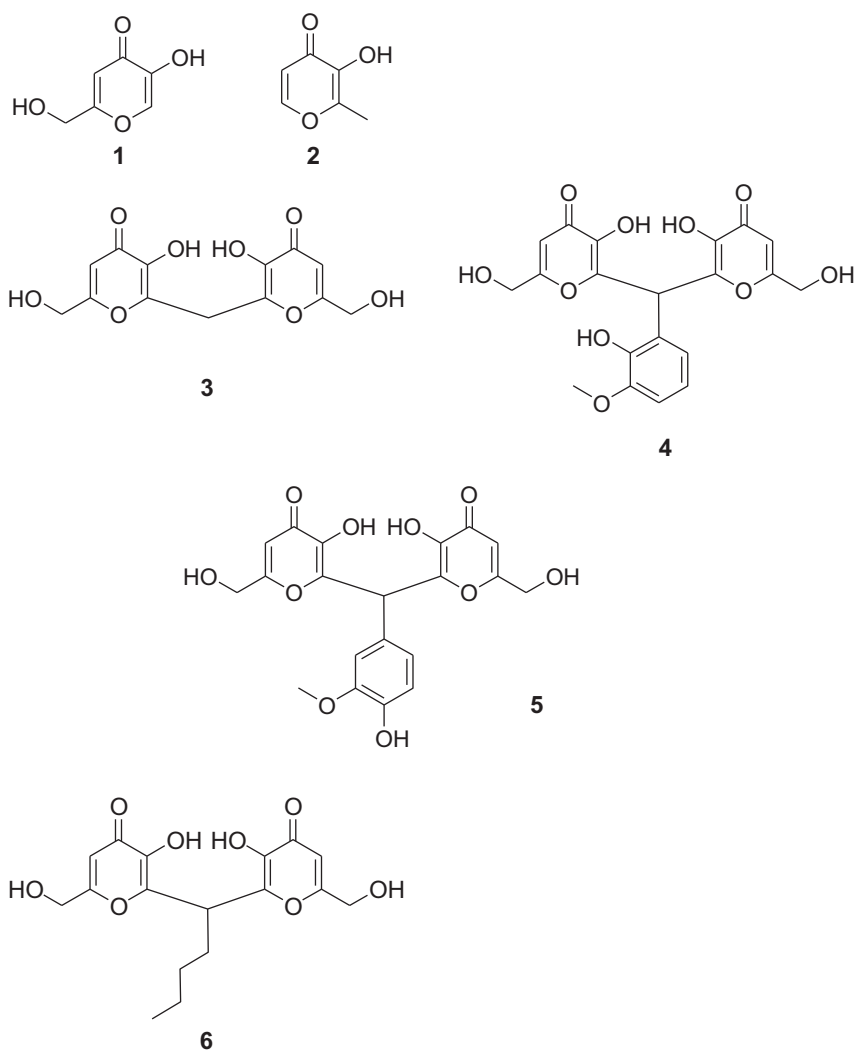
1. Introduction

Coordination chemistry of many molecules containing two bidentate moieties has received attention because typically these molecules are unable to satisfy the octahedral coordination about trivalent ions through formation of a one-to-one metal-to-ligand complex. For instance, rhodotorulic acid (RA), a dihydroxamic acid, was reported to form dimeric complexes with Fe^{3+} , Al^{3+} , and Cr^{3+} with formulas $\text{M}_2(\text{RA})_3$ [1, 2]. A number of dihydroxamate analog of RA have been synthesized and their coordination chemistry with iron explored [3–7]. These molecules exhibit varying metal chelation behavior that is dependent on the length of the link between the two bidentate moieties. For instance, Barclay *et al.* reported a series of dihydroxamic acids derived from simple linear alkane dicarboxylic acids from dimeric complexes with the ferric ion (Fe_2L_3), in which the separation between the octahedrally coordinated Fe (III) ions increases with chain length of the ligand [3]. Iron complexes of dihydroxamates at 1 : 1 Fe/L ratio have been characterized by electrospray ionization mass spectrometry (ESI-

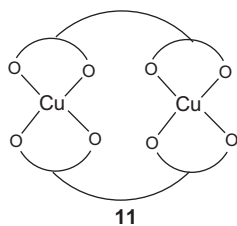
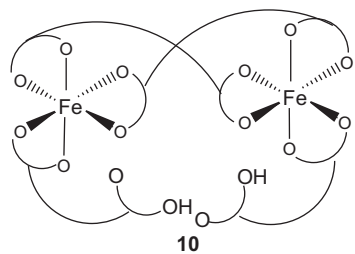
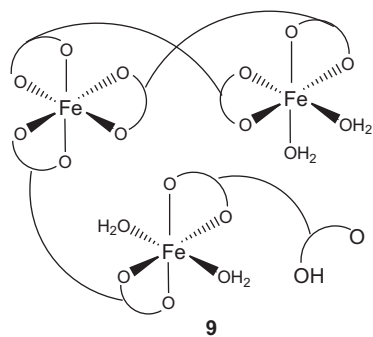
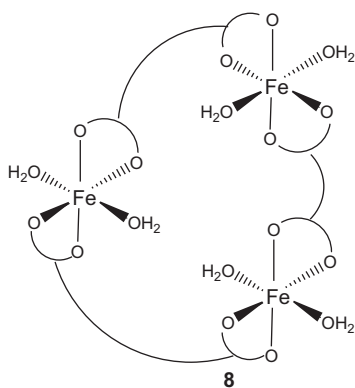
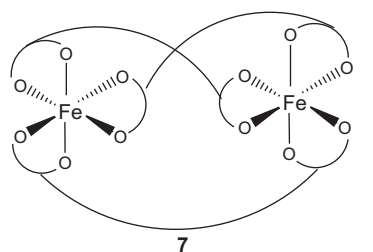
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MS) as FeL^+ and $(\text{FeL}_2\text{Fe})^{2+}$, depending on the chain length between the two hydroxamate groups [8, 9].

3-Hydroxypyran-4-ones, such as kojic acid (**1**) and maltol (**2**), are bidentate ligands (all compound numbers are defined in scheme 1); kojic acid, 5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one, which is isolated from metabolic products of many species of *Aspergillus* and *Penicillium* molds, possesses appreciable inhibitory activity against tyrosinase by chelating copper [10]. As both the chelating atoms are “hard” oxygen, 3-hydroxypyran-4-one derivatives can also form stable 3 : 1 complexes with iron(III) [11]. Thus, kojic acid derivatives find potential application in cosmetics and in the treatment of iron overload disorders; indeed, some bis-(kojic acid) derivatives (**3**, **4**, and **5**) have been investigated for their iron and aluminum chelation behavior [12–14]. Recently, a similar bis-(kojic acid) derivative,



Scheme 1. Structures of hydroxypyranone derivatives (1–6), iron-6 complexes (7–10) and copper-6 complex (11).



Scheme 1. (Continued)

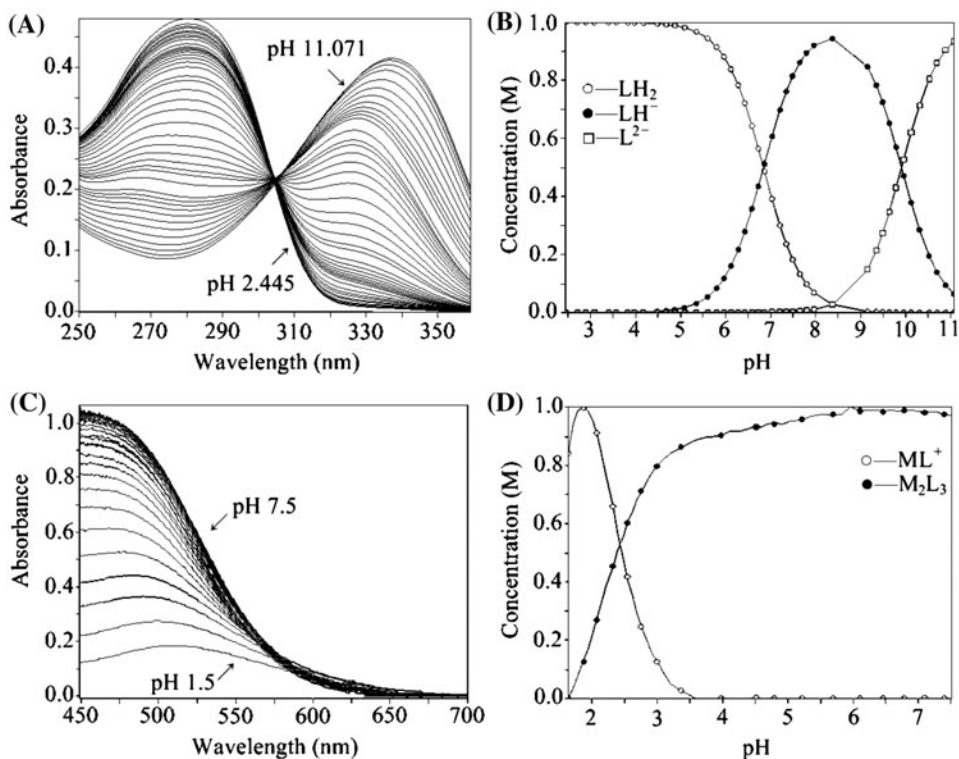


Figure 1. Proton and iron(III) affinity measurements. (A) $[6] = 288.3 \mu\text{M}$ titrated with 0.1 M KOH , pH from 2.445 to 11.071, (B) speciation plots of **6** based on A, (C) overall titration of $[6] = 137.1 \mu\text{M}$ with $[\text{Fe}^{3+}] = 26.7 \mu\text{M}$, ratio of L : M = 5.1, (D) factor analysis of C reveals two species over pH range 1.5–7.5.

3,3'-dihydroxy-6,6'-bis(hydroxymethyl)-2,2'-(pentane-1,1-diyl) di-4*H*-pyran-4-one (**6**), which contains an alkyl chain, was synthesized in our group [15]. The nature of iron(III) and copper(II) complex chemistry with **6** is described in this study and compared with the previously reported complex chemistry of analog compounds, **3** and **4**.

2. Experimental

2.1. *pKa* and iron stability constants

The automatic titration system used in this study comprised of an autoburette (Metrohm Dosimat 765 mL syringe) and Mettler Toledo MP230 pH meter with Metrohm pH electrode (6.0133.100) and a reference electrode (6.0733.100). KCl electrolyte solution (0.1 M) was used to maintain the ionic strength. The temperature of the test solutions was maintained in a thermostatic jacketed titration vessel at $25 \text{ }^\circ\text{C} \pm 0.1 \text{ }^\circ\text{C}$ using a Techne TE-8J temperature controller. The solution under investigation was stirred vigorously during the experiment. A Gilson Mini-plus#3 pump with speed capability (20 mL min^{-1}) was used to circulate the test solution through a Hellm quartz flow cuvette. For the stability constant determinations, a 50 mm path length cuvette was

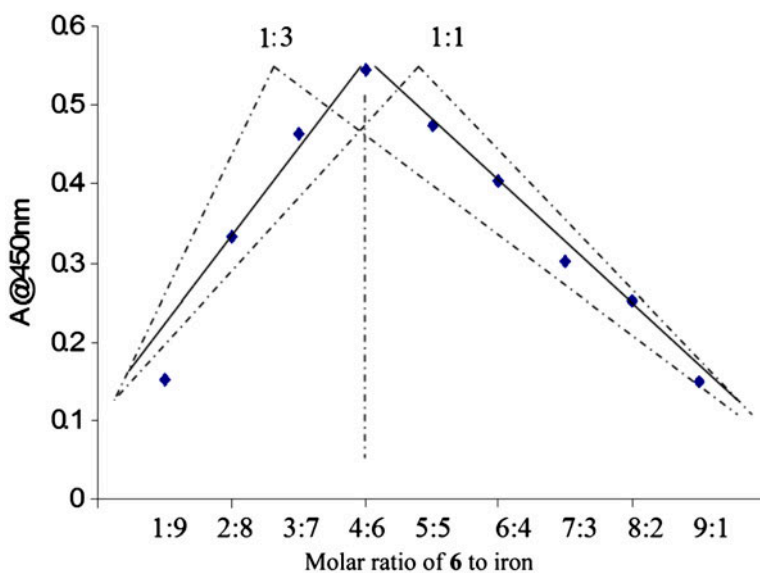


Figure 2. Job plot of Fe:6 solutions monitored at 410 nm. Total concentration of iron plus 6 is 0.4 mM.

used, and for pKa determinations, a cuvette path length of 10 mm was used. The flow cuvette was mounted on an HP 8453 UV-visible spectrophotometer. All instruments were interfaced to a computer and controlled by a Visual Basic program. Automatic titration and spectral scans adopted the following strategy: the pH of a solution was

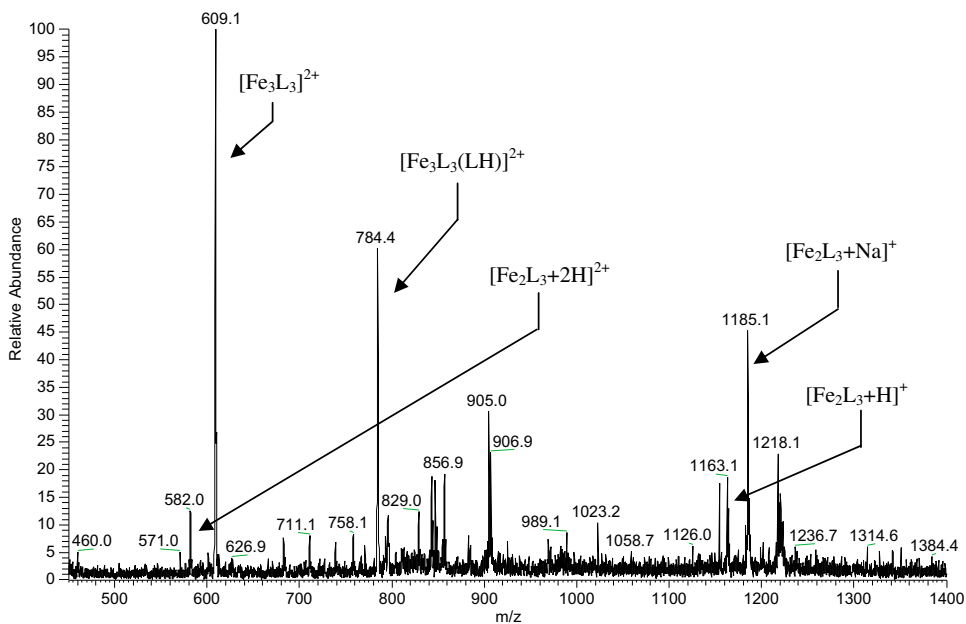


Figure 3. Positive ESI mass spectrum of a solution of a 4:6 M ratio mixture of Fe (0.16 mM) with 6 (0.24 mM) at pH 8.2 (50% aqueous methanol, v/v).

increased by 0.1 pH unit by addition of KOH from the autoburette; when pH readings varied by <0.001 pH unit over a 3 s period, an incubation period was activated. For pKa determinations, a period of 1 min was adopted; for stability constant determinations, a period of 5 min was adopted. At the end of the equilibrium period, the spectrum of the solution was then recorded. The cycle was repeated automatically until the defined end point pH value was achieved. All titration data were analyzed with the pHab program [16]. The species plots were calculated with the HYSS program [17]. Analytical grade reagent materials were used in the preparation of all solutions.

2.2. Job plot of 3,3-dihydroxy-6,6-bis(hydroxymethyl)-2,2-(pentane-1,1-diyl) di-4H-pyran-4-one with iron(III)

Solutions with different ratios of iron(III) and **6** were prepared while keeping the total concentration of iron plus ligand at 0.4 mM. A 50 mM NH_4HCO_3 solution in 50% methanol (v/v) was used to maintain pH in the 8.0–8.4 range. The various solutions were sealed in UV cuvettes. The absorption of each solution was recorded at 410 nm after 4 h. All experiments were carried out at 25 °C.

2.3. Electrospray ionization mass spectrometry

The solutions used in the Job plot study were diluted with 0.1% formic acid in 50% methanol prior to the ESI-MS analysis. All ESI-MS experiments were carried out using a LCQ Deca XP ion trap mass spectrometer (Thermo). The instrument was operated in positive ion mode (full scan, zoom scan) employing the following conditions: spray voltage 4 kV; capillary voltage 10 V; tube lens offset 5 V; capillary temperature 260 °C. The samples were directly infused using a syringe pump at a rate of $5.0 \mu\text{L min}^{-1}$.

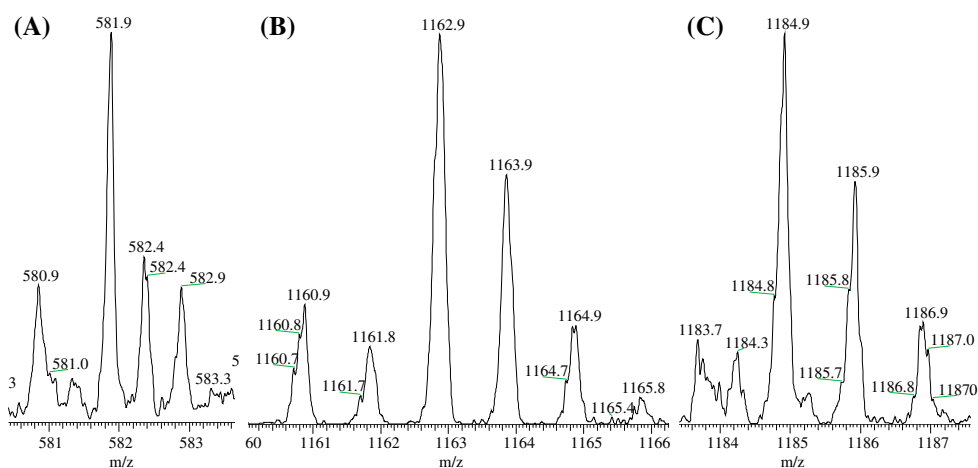


Figure 4. ESI-MS peaks of iron complex Fe_2L_3 . (A) $[\text{Fe}_2\text{L}_3 + 2\text{H}]^{2+}$, (B) $[\text{Fe}_2\text{L}_3 + \text{H}]^+$, (C) $[\text{Fe}_2\text{L}_3 + \text{Na}]^+$.

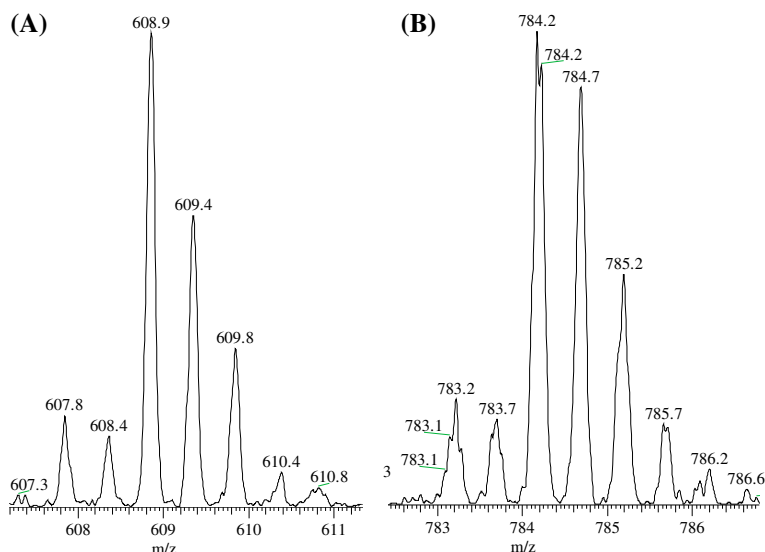


Figure 5. ESI-MS peaks of iron complexes. (A) $[\text{Fe}_3\text{L}_3]^{2+}$, (B) $[\text{Fe}_3\text{L}_3(\text{LH})]^{2+}$.

3. Results and discussion

In order to characterize the iron(III) and copper(II) complexes of the bis(hydroxypyranone) **6**, the pK_a values of the free ligand and the affinity constants for iron were determined. Speciation of the complexes was investigated using Job plots and ESI-MS.

3.1. pK_a values

Titration of **6** ($\text{LH}_2 = \mathbf{6}$) over the pH range 2.445–11.071 disclosed 2 pK_a values (figure 1(A)). The speciation plots of LH_2 , LH^- , and L^{2-} are presented in figure 1(B). The values, 6.84 ± 0.02 and 9.91 ± 0.04 , are similar to those of reported bis(kojic acid) analogues **3** and **4** [14]. The peak of LH^- is shifted from 285 to 340 nm when L^{2-} is fully formed. The fully protonated form of **6** possesses a peak at 278 nm with a lower molar extinction coefficient (figure 1(B)).

3.2. Iron(III)/bis(3-hydroxypyran-4-one) complexes

Bis(3-hydroxypyran-4-one) derivatives contain two bidentate groups and their chelating behavior in solution is affected by chain length between the two hydroxypyranone moieties, the metal, pH, and metal/ligand ratio. Compound **6** is unlikely to bind metal ions in tetradentate mode by virtue of its short linking chain, and thus, it was anticipated to function as a bis-bidentate ligand, leading to the formation of multimetal species.

On interaction with iron(III), solutions of **6** turn red instantly. The overall spectral change over the pH range 1.5–7.5 displays a peak at 510 nm which gradually shifts to 450 nm as the pH is increased (figure 1(C)). Factor analysis revealed that only two species exist over the entire pH range under the titration conditions employed (figure 1(D)). In contrast, a typical bidentate ligand (such as kojic acid) will produce three species.

Table 1. ESI-MS data for iron-6 complexes at different Fe:6 ratios.

Species	Calcd m/z	1:9		2:8		3:7		4:6		5:5		6:4		7:3		8:2		
		Found m/z	Found m/z	Found m/z	Found m/z	Found m/z	Found m/z	Found m/z	Found m/z	Found m/z	Found m/z	Found m/z	Found m/z	Found m/z	Found m/z	Found m/z	Found m/z	
Fe_2L_3	$[\text{Fe}_2\text{L}_3 + \text{Na}]^+$	1185.2	1185.1	1185.1	1185.1	1185.1	1185.1	1186.0	1185.1	1185.1	1185.1	1185.1	1185.1	1185.1	1185.1	1185.1	1185.1	
	$[\text{Fe}_2\text{L}_3 + \text{H}]^+$	1163.2	1163.1	1163.1	1163.1	1163.1	1163.1	1163.1	1163.1	1163.1	1163.1	1163.1	1163.1	1163.1	1163.1	1163.1	1163.1	1163.1
	$[\text{Fe}_2\text{L}_3 + 2\text{H}]^{2+}$	582.1	—	582.7	582.7	582.4	582.0	582.0	582.0	582.0	582.0	582.0	582.0	582.0	582.0	582.0	582.0	582.0
$[\text{Fe}_3\text{L}_3]^{2+}$	$[\text{Fe}_3\text{L}_3]^{2+}$	609.1	609.1	609.0	609.0	609.1	609.1	609.1	609.1	609.0	609.0	609.1	609.1	609.1	609.1	609.1	609.1	609.1
	$[\text{Fe}_3\text{L}_3(\text{LH})]^{2+}$	784.6	784.4	784.4	784.4	784.4	784.4	784.4	784.4	784.3	784.3	784.3	784.3	784.3	784.4	784.4	784.4	784.4
$[\text{Fe}_3\text{L}_3(\text{LH})]^{2+}$	$[\text{Fe}_3\text{L}_3(\text{LH})]^{2+}$	1537.3	—	—	—	1538.7	1538.7	1538.7	1538.7	1538.7	1538.7	1538.7	1538.7	1538.7	1538.7	1538.7	1538.7	1538.7
	$[\text{Fe}_2\text{L}_2(\text{LH})_2]^{2+}$	758.2	—	—	—	758.0	758.0	758.1	758.1	758.0	758.0	758.0	758.0	758.0	758.0	758.0	758.0	758.0
$\text{Fe}(\text{LH})_3$	$[\text{Fe}_2\text{L}_2(\text{LH})_2 + 2\text{H}]^{2+}$	1132.3	1132.1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	$[\text{Fe}(\text{LH})_3 + \text{Na}]^+$	1132.3	1132.1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

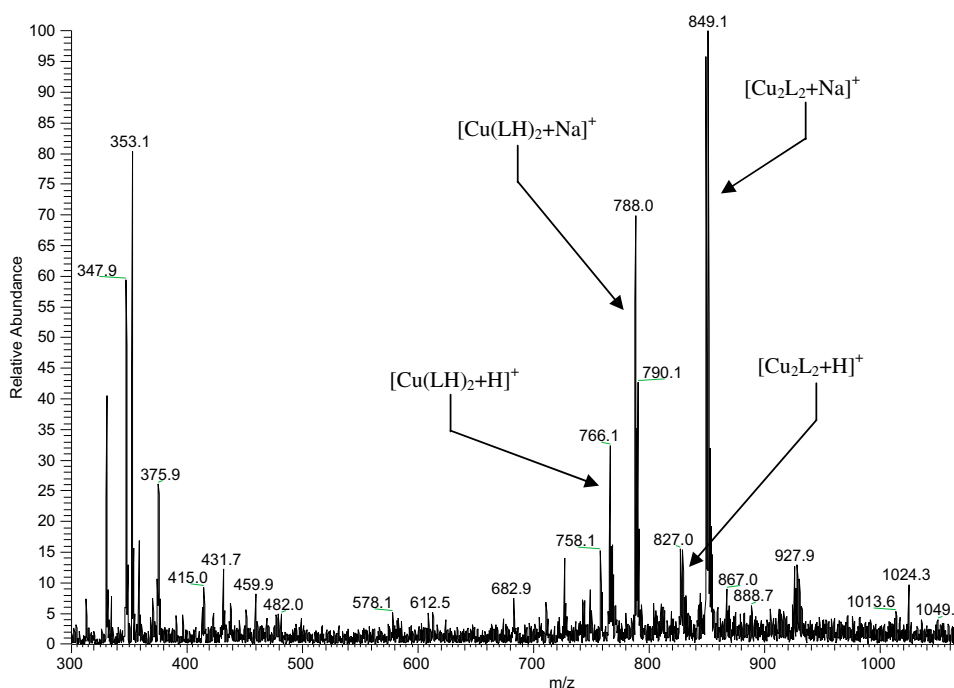


Figure 6. Positive ESI mass spectrum of a solution of a 1:1 M ratio mixture of Cu (1 mM) with **6** (1 mM) at pH 8.0 (50% aqueous methanol, v/v).

To clarify the stoichiometry of the iron(III) complex of **6** and to ascertain the colored species assignment in curve fitting, we carried out a Job plot by varying the concentration of iron(III) and **6** (figure 2). In general, 3-hydroxypyran-4-ones form stable iron complexes in neutral to slightly basic conditions, whereas under acidic and strong basic conditions, the iron complexes become less stable [18]. Thus, the present investigation was carried out in ammonium hydrogen carbonate buffered solution (pH 8.0–8.4). The maximum absorbance was found to occur when the Fe:**6** ratio is 4:6, indicating that the average molar ratio of Fe:**6** of the complex species at slightly basic conditions is likely to be 2:3. On the basis of this result, we concluded that the colored species are ML^+ and M_2L_3 with the corresponding affinity values, $\log K_{11} = 17.15 \pm 0.02$ and $\log \beta_{23} = 54.4 \pm 0.1$.

ESI-MS has proven to be an efficient and relatively simple technique to investigate the speciation of metal–ligand complexes in solution [7, 19, 20]. In this study, direct evidence for the formation of multicentered iron complexes was obtained from ESI mass spectra; an example from a 4:6 iron/**6** molar ratio is presented in figure 3. The isotope distribution pattern was used to determine the stoichiometry of iron complexes (figure 4). As demonstrated in figure 2, the existence of Fe_2L_3 ($LH_2 = \mathbf{6}$), which may have a structure of **7**, was confirmed by the peaks at m/z 582.0, 1163.1, and 1185.1, relating to $[Fe_2L_3 + 2H]^{2+}$, $[Fe_2L_3 + H]^+$, and $[Fe_2L_3 + Na]^+$, respectively (figure 4). The peak at m/z 582 is produced by a doubly charged species, as an apparent half-mass unit signal was observed, whereas peaks at m/z 1163 and 1185 are proton and sodium adducts, respectively, which are singly charged. The strongest peak in the spectrum at m/z 609 (figure 3) is assigned to a doubly charged iron complex $[Fe_3L_3]^{2+}$, that is confirmed by the isotope distribution pattern where

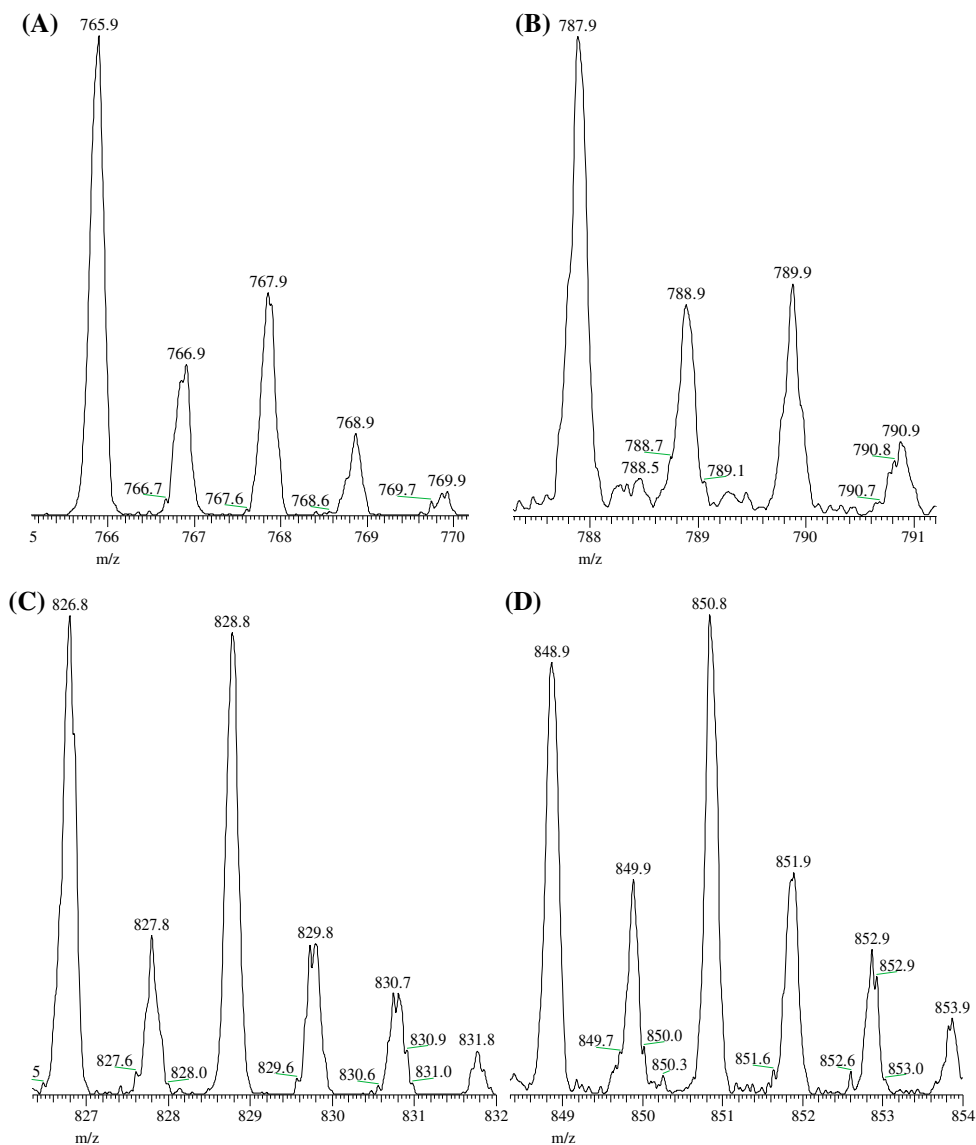


Figure 7. ESI-MS peaks of (A) $[\text{Cu}_2\text{L}_2 + \text{H}]^+$, (B) $[\text{Cu}_2\text{L}_2 + \text{Na}]^+$, (C) $[\text{Cu}(\text{LH})_2 + \text{H}]^+$ and (D) $[\text{Cu}(\text{LH})_2 + \text{Na}]^+$.

an apparent half-mass unit signal was observed (figure 5(A)). Interestingly, in $[\text{Fe}_3\text{L}_3]^{2+}$, with probable structure **8**, there are two ferric irons and one ferrous iron. It is well known that reduction processes may occur in the electrospray ionization chamber when operating at elevated cone voltages. Iron(III) is relatively easy to reduce, yielding a mixture of ferric and ferrous ions in such ESI-MS studies [21]. Indeed, a similar iron complex, $[\text{Fe}(\text{II})\text{Fe}(\text{III})\text{L}_4]^+$, which contains one ferric iron and one ferrous iron, was previously observed in iron/citrate solutions [19]; **3** was reported to form $[\text{Fe}_3\text{L}_3\text{H}_3]^{2+}$ which contains two iron(III) and one iron(II) [14]. The peak at m/z 784 (figure 3) was clarified to be a doubly charged peak by the isotope distribution pattern (figure 5(B)), which refers to

species $[\text{Fe}_3\text{L}_3(\text{LH})]^{2+}$, having a proposed structure **9**. The existence of $\text{Fe}_2\text{L}_2(\text{LH})_2$, which may have structure **10**, was confirmed by peaks at m/z 1537.7 and 758.1, relating to the sodium adduct $[\text{Fe}_2\text{L}_2(\text{LH})_2 + \text{Na}]^+$, and doubly charged $[\text{Fe}_2\text{L}_2(\text{LH})_2 + 2\text{H}]^{2+}$, respectively. Overall, in a 4:6 Fe:6 ratio, three main iron species are observed, Fe_2L_3 , $[\text{Fe}_3\text{L}_3]^{2+}$, and $[\text{Fe}_3\text{L}_3(\text{LH})]^{2+}$ together with one low abundance species, $(\text{Fe}_2\text{L}_2(\text{LH})_2)$. The most intense peaks correspond to Fe_2L_3 .

The presence of a dimeric iron(III) complex ($\text{Fe}_2\text{L}_2^{2+}$) in iron/dihydroxamate solutions was confirmed by electrospray mass spectrometry [9]. Similarly, fashion-related Fe_2L_2 species were reported for iron/bis-(kojic acid) solutions [13, 14]. Surprisingly, no Fe_2L_2 species were observed in this study. The mass spectral data of the solution with different Fe:6 ratios are summarized in table 1. Fe_2L_3 , $[\text{Fe}_3\text{L}_3]^{2+}$ and $[\text{Fe}_3\text{L}_3(\text{LH})]^{2+}$ were observed under most of the conditions in relatively high abundance, whereas $\text{Fe}_2\text{L}_2(\text{LH})_2$ was only observed in some cases with relatively low abundance, and Fe_2L_2 was not observed under any of the conditions. In the case of the 9:1 solution (Fe:6 ratio), no peaks of the above iron complexes were observed; in the case of the 8:2 solution (Fe:6 ratio), only low abundances of Fe_2L_3 and $\text{Fe}_2\text{L}_2(\text{LH})_2$ were observed. In the 1:9 solution (Fe:6 ratio), a low abundance of FeL_3 was observed, which was not observed at any of the other ratios investigated, suggesting that the 1:3 complex Fe:6 was only formed when 6 was present in large excess.

The clogP of **6** is 0.777 [22]. Clearly, this could be readily modulated by the choice of the joining alkyl function. The molecular weight of this ligand is less than 500, the notional Lipinski cutoff value for membrane penetration. Thus, it is reasonable to predict that **6** will be orally active and will gain access to the liver where it could scavenge excess iron and be excreted into the bile in a similar fashion to that of exjade [23]. We are currently investigating the efficacy of **6** to remove iron from various mammalian iron overload models.

3.3. Copper(II)/bis(3-hydroxypyran-4-one) complexes

ESI-MS was employed to investigate copper(II)/bis(3-hydroxypyran-4-one) complexes. Although **6** contains two 3-hydroxypyran-4-one moieties, it is unlikely to form a CuL complex in a tetradentate mode, as the link between the two chelating moieties is unable to satisfy both square and tetrahedral coordination geometries. Direct evidence for the formation of a Cu_2L_2 was obtained from ESI mass spectra (figures 6 and 7). The peaks at m/z 849 and 827 relate to $[\text{Cu}_2\text{L}_2 + \text{Na}]^+$ and $[\text{Cu}_2\text{L}_2 + \text{H}]^+$, respectively. These two peaks are singly charged (figure 7). The intensity of the peak at 829 is similar to that of the peak at m/z 827; similarly, the peak at 851 is similar to the peak at 849, which is due to the fact that the abundance of isotope ^{65}Cu is nearly half of that of isotope ^{63}Cu . Cu_2L_2 almost certainly adopts structure **11**. The peaks at m/z 766 and 788 refer to $[\text{Cu}(\text{LH})_2 + \text{H}]^+$ and $[\text{Cu}(\text{LH})_2 + \text{Na}]^+$, respectively, which are also singly charged (figure 7(B)). As can be seen in the isotopic distribution, the peaks at m/z 768 and 790 are attributable to the presence of ^{65}Cu isotope. The anticipated linear oligomeric copper complexes were not observed in mass spectra. In solutions with low Cu/6 ratios (1:9 and 2:8), where **6** was present in excess, only $\text{Cu}(\text{LH})_2$ was observed, the 2:2 complex Cu_2L_2 not being detected under these conditions (table 2). With increasing proportions of copper, the formation of Cu_2L_2 gradually increases. These results broadly agree with those of Nurchi *et al.* [13].

4. Conclusions

We have demonstrated a dynamic equilibrium of complexes in the presence of iron and copper with the bis(hydroxypyranone) **6**. Under no conditions does **6** function as a tetradentate ligand, but behaves as a bis-bidentate ligand, forming multinuclear species with bridged structures. With iron(III), the neutral 2:3 complex dominates. As a result of this finding, **6** may find potential as an orally active iron chelator and should be further investigated.

Acknowledgments

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