Research Article

pH-Potentiometric Investigation towards Chelating Tendencies of $p$-Hydroquinone and Phenol Iminodiacetate Copper(II) Complexes

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Copper ions in the active sites of several proteins/enzymes interact with phenols and quinones, and this interaction is associated to the reactivity of the enzymes. In this study the speciation of the Cu$^{2+}$ with iminodiacetic phenolate/hydroquinonate ligands has been examined by pH-potentiometry. The results reveal that the iminodiacetic phenol ligand forms mononuclear complexes with Cu$^{2+}$ at acidic and alkaline pHs, and a binuclear O phenolate-bridged complex at pH range from 7 to 8.5. The binucleating hydroquinone ligand forms only 2 : 1 metal to ligand complexes in solution. The pK values of the protonation of the phenolate oxygen of the two ligands are reduced about 2 units after complexation with the metal ion and are close to the pK values for the copper-interacting tyrosine phenol oxygen in copper enzymes.

1. Introduction

Copper ions in the active sites of proteins/enzymes mediate a broad scope of chemical processes including electron transfer, dioxygen uptake, storage, and transport and catalytic conversions [1]. When surveying the known copper enzymes and their functions, it is striking that their reactivity is typically linked to dioxygen or compounds directly synthesized from O$_2$-like phenols and quinones [2–7].

For example, copper proteins are involved in reversible dioxygen binding in hemocyanin [8], two-electron reduction to peroxide coupled to oxidation of substrates in amine and galactose oxidases [9], biogenesis of novel metalloenzyme cofactors (e.g., topaquinone in amine oxidases) [10], activation of hydroxylation in tyrosinase [11], and proton pumping in cytochrome c oxidase [12].

Detailed study of the solid and solution chemistry of Cu$^{2+}$ phenolate/hydroquinonate complexes is essential for better understanding of the coordination of the metal ion in the enzymes and the mechanisms of the enzymatic catalysis. Derivatives of phenol or hydroquinone containing nitrogen [13–22] as donor atoms are the vast majority of the ligands used to model the active site of the copper enzymes. Despite the importance of phenolate/hydroquinonate chelating ligands as models of copper enzymes, ligands with other than nitrogen donor atoms such as aminocarboxylate derivatives of phenols, have been much less studied. These ligands exhibit very attractive features for modelling metal enzymes, such as the highly solubility in aqueous solution, forming stable complexes with metal ions and the similarity of the donor groups to those in biological systems. In addition, the one-electron oxidized $p$-semiquinone radical of the ligand 2,5-bis[N,N-bis(carboxymethyl)aminomethyl] hydroquinone (H$_{5}$bicah) has been stabilized in aqueous solution by ligation to metal ions [23] and thus serves as model for the enzymes that operate via a $p$-semiquinone radical, acting in one-electron transfer reactions, including cytochrome c and copper amine oxidases. In previous pH-potentiometric studies [24] of Cu$^{2+}$ with the phen iminodiacetate ligand HBIDA (Scheme 1) the equilibrium calculations have been performed assuming that all the species of Cu$^{2+}$ with HBIDA in solution at various pHs are mononuclear 1 : 1 and 1 : 2.
metal to ligand complexes. A recent detailed crystallographic
study [25] of the Cu2+-phenol iminodiacetate H4cacp, H4bicah
and H4bicah (Scheme 1) complexes isolated at a pH range
2.0–9.0 has shown that binuclear phenolate-bridged Cu2+
complexes (Scheme 2) are also present in solution. It is
apparent that previous pH-potentiometric studies of these
systems should be repeated including also the dinuclear
species in the calculations.

Herein, we describe the pH-potentiometric studies of
Cu2+ with the iminodiacetate phenolate tripod ligands
H4cacp and H4bicah. In contrast to H4cacp, H4bicah
exhibits two metal ion binding sites bridged through the
hydroquinone moiety. The potentiometric study showed that
only the H4cacp ligand forms in solution O phenolate-bridged
binuclear complexes, which is also in agreement with the
previous crystallographic study [25]. The pK values of the
protonation of the phenolate oxygen of the two ligands
reduced about 2 units after complexation with the metal ion
are close to the pK values for the copper-interacting tyrosine
phenol oxygen in copper enzymes, such as glyoxal oxidase
[26].

2. Experimental Section

2.1. Materials. Copper(II) acetate monohydrate, p-hydro-
quinone, 4-hydroxybenzoic acid, iminodiacetic acid, para-
formaldehyde, potassium chloride, and potassium hydrogen
phthalate were obtained from Aldrich. Sodium hydroxide
and hydrogen chloride were purchased from Merck. All
chemicals were reagent grade and used without further
purification.

2.2. Ligand Preparation. The ligands referred to this study
2,5-bis[N,N′-bis(carboxymethyl)aminomethyl]-hydroquinone
(H4bicah) and 2-[[N,N′-bis(carboxymethyl)aminomethyl]-4-
carboxyphenol (H4cacp) were synthesized based
on the Mannich type reaction reported in the literature
[27, 28]. The synthesis of the organic ligands (Scheme 1)
was performed under inert nitrogen atmosphere and
their purity was checked and confirmed by means of 1H-
NMR spectroscopy. 1H-NMR spectra were recorded on a
300.13 MHz Avance Brucker spectrometer.

2.3. Potentiometric Studies and Computational Data Analysis.
The potentiometric equilibrium data determined experimentally,
and conditions of the potentiometric experimental proce-
dure (E°, pKw = 13.78 at 298 K, γ = 0.78). The program sets
up simultaneous mass-balance equations for all components
at each neutralization value involving the concentration of
acid added to the assay and solves for each species present
in the pH region 2.00–10.0. Then, equilibrium constants
are varied in order to minimize the differences between the
calculated and observed values, resulting in the fitting of the
calculated results to the experimental curves. The concen-
tration stability constants, $k_{pyr} = \beta^{-1} \{[M_p][L_q][H_r]\}$,
were considered to be estimated according to the model
proposed by the computational program PSEQUAD [32].
The species considered present in the assays are those
expected to be formed according to established principles of
coordination chemistry including the formation of deproto-
nated and protonated metal chelates, respectively [24, 33–
35]. All potentiometric titrations were performed three times
for each system (about 100 data points each) in the pH range
2.00–10.0 without significant variation.

3. Results and Discussion

3.1. Ligands. Potentiometric titrations of phenol (H4cacp)
and p-hydroquinone (H4bicah) iminodiacetate derivatives
indicate stepwise protonation steps arising from their
characteristic functional groups, amine, carboxylates, and
phenolate, in the measurable pH range. The protonation
constants (overall stability protonation constants log $\beta$) are
listed in Tables 1 and 2, respectively, and their distribution
speciation diagrams are illustrated in Figure 1.

The pH-metric titration curve of H4cacp indicates three
major protonation steps due to the phenolate or the benzoic-
carboxylate oxygen group, the carboxylate oxygen group,
and the amino group with pK values 8.47, 4.84, and 2.42,
respectively (Table 1). The low pK values (2.42) attributed
to the amine nitrogen atom demonstrates intramolecular
hydrogen bonding between the deprotonated amino group
Compositions, overall stability formation constants (log $\beta$) and acidity constants ($pK_a$) for the species formed in $H_4$capc and Cu(II)-$H_4$capc system, over the pH range 2.00–10.0 thus obtained from the potentiometric study (25°C, $I = 0.10$ mol dm$^{-3}$ KCl, $pK_a = 13.78$, and $\gamma = 0.78$).

$\begin{array}{c|c|c|c} \\
(p, q, r) & \text{Species} & \text{log $\beta$} & pK_a \\
\hline \\
(0, 1, 1) & [H_4$\text{capc}$]^2- & 8.40 \pm 0.01 & 8.47^a \\
(0, 1, 2) & [H_3$\text{capc}$]^+ & 13.18 \pm 0.04 & 4.84^b \\
(0, 1, 3) & [H_2$\text{capc}$]^+ & 15.56 \pm 0.02 & 2.42^c \\
(1, 1, -1) & [Cu(H$\text{capc}$)(OH)]^2- & 8.17 \pm 0.01 \\
(2, 2, 0) & [Cu_2(H$\text{capc}$)]^2- & 11.26 \pm 0.02 \\
(1, 1, 0) & [Cu(H$\text{capc}$)(H_2$O$)]^+ & 14.58 \pm 0.02 \\
(1, 2, 2) & [Cu(H_2$\text{capc}$)]^2- & 17.62 \pm 0.02 \\
(1, 1, 1) & [Cu(H_3$\text{capc}$)(H_2$O$)] & 22.94 \pm 0.01 \\
\end{array}$

$^a$Phenolate or aromatic carboxylate oxygen group, $^b$carboxylate oxygen group, $^c$amine nitrogen group.

The process from the deprotonated mononuclear species to the protonated one, which corresponds to the consumption of one H$^+$ per molecule of complex equation (1), is accompanied by a color change from green to blue attributed to the protonation of the phenolic oxygen. The protonation of the phenolic oxygen will result in weakening or non-bonding of the Cu–OH(phenol) bond which is in agreement with the color change (the mononuclear nonphenolic amino acetate complexes of Cu$^{2+}$ at acidic pHs exhibit blue color).

The crystallographic data of the complex isolated at pH 3.2 [25] confirm the weak interaction between the protonated phenol oxygen atom and the metal ion [Cu–OH(phenol), 2.529(2) Å]:

$$\text{Cu} \rightleftharpoons \text{Cu} + \text{OH}^-$$

The estimated $pK_a$ involved in this protonation step is 5.22 ± 0.02 and is comparable to that calculated by UV-vis spectroscopic studies and was found to be 5.91 ± 0.05 [25]. The overall stability formation constants of complexes [Cu(H$\text{capc}$)$^-$] and [Cu(H$_2$$\text{capc}$)(H$_2$O)] are greater than those of the iminodiacetate copper (II) complexes [Cu(ida)] (log $\beta$ 10.42) and [Cu(H(ida))] (log $\beta$ 12.35) [33]. The higher stability is ascribable to the coordination of the phenolate oxygen atom. This is also supported by the X-ray crystallographic studies which show that the deprotonated form, even at low pHs, strongly interacts with the metal ion.
the orientation of the flexible carboxylate groups in positions favorable to chelating, especially in the case of the copper(II) ion which forms stable complexes in an octahedral/or square pyramidal coordination geometry pattern [36].

One very significant result of this potentiometric titration study is the detection of the dimeric species $[\text{Cu}_2(\text{Hcacp})_2]^{2-}$. Previous potentiometric studies have postulated that the dimeric complexes are not favored in solution because of steric effects and electrostatic destabilization which do not allow a dimerization process [35]. Harris et
Scheme 1: Iminodiacetic derivatives of phenol/p-hydroquinone ligands with their abbreviations. The ligands referred to the potentiometric/stability studies are denoted in parentheses.

Scheme 2: Molecular drawings of the structures of the phenol and p-hydroquinone iminodiacetate copper(II) complexes, isolated at a pH range 2.0–9.0 according to a recent detailed crystallographic study [25].
al. had suggested the formation of a mononuclear phenolate complex of Cu^{2+} and the phenol iminodiacetate ligand HBIDA at pH above 6.0 (Scheme 1), but they have not mentioned the possibility of dimeric binuclear species in solution [24]. However, recently Stylianou et al. [25] have isolated and crystallographically characterized the dimeric species [Cu_{2}(Hbicah)(H_{2}O)_{2}]^{2-} from aqueous solution at alkaline pHs 8.0–9.0, indicating that such species are present in solution. In this complex the two Cu^{2+} are bridged through the phenolate oxygen group, b carboxylate oxygen group.

The fact that there is almost 0.5 pK unit difference between the two deprotonation steps indicates that the electronic interaction between the two metal centres through the hydroquinone bridge is significant.

A comparison between the overall stability constants of the two ligands in this study shows that the bifunctional ligand H_{6}bicah forms more stable complexes than H_{4}cacp in solution. This extra stabilization is attributed to the larger increase of entropy expected for the formation of the binuclear Cu^{2+}-H_{6}bicah complexes compared to the mononuclear Cu^{2+}-H_{4}cacp.

### 4. Conclusions

The speciation of Cu^{2+} with the iminodiacetic phenol/hydroquinone ligands H_{4}cacp/H_{6}bicah in aqueous solution was investigated by pH-potentiometry. Ligand H_{4}cacp, at pH below 5.0 forms with Cu^{2+} the mononuclear 1:1 and 1:2 complexes. At higher pH the phenol proton is deprotonated and at pH range 5.0–7.0 the major species is the mononuclear 1:1 complex. However at pH 7.0–8.0 the formation of a binuclear complex takes place and it is attributed to a [Cu_{2}(Hbicah)(H_{2}O)_{2}]^{2-} bridged complex. The binucleating ligand H_{6}bicah forms only 2:1 metal to ligand complexes at higher pH range 5.0 to 7.0. The second phenol is protonated at pH below 5.0 resulting in the formation of the blue neutral [Cu_{2}(H_{2}bicah)(H_{2}O)_{2}] which has been previously characterized by single crystal X-ray crystallography (Scheme 2) [25]. The two pK_{a} values for the two equilibriums of the stepwise protonation of the two phenolate oxygen atoms equation (3) have been calculated as 5.89 ± 0.10 and 6.43 ± 0.10 for pK_{a1} and pK_{a2}, respectively. These values are close to the values 6.25 ± 0.08 and 7.19 ± 0.08 for pK_{a1} and pK_{a2}, respectively, found by spectrophotometric studies [25]. These differences are observed because the model used for the calculations in the spectrophotometric studies was incomplete (only the equilibriums in (3) were taken into account):

\[
\begin{align*}
\text{Cu} + \text{OH}^{-} & \leftrightarrow \text{Cu(OH)}_{2}^{+} \\
\text{Cu(OH)}_{2}^{+} & \leftrightarrow \text{Cu}^{2+} + \text{OH}^{-}
\end{align*}
\]
must also be considered in speciation studies of Cu2+ ions with mononucleating phenolate ligands such as H4capc.

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References


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