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Effect of Two Isomeric Tetrapyrazolyl Ligands on the Catalytic Oxidation of 3,5-di-*tert*-Butylcatechol

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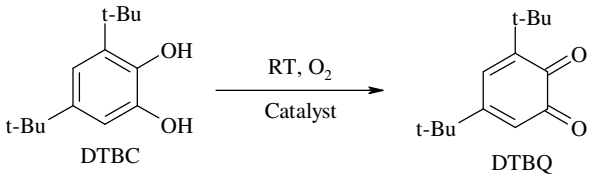
Copper(II) salts were combined with a tetrapyrazolyl ligand ({*N,N,N',N'-tetrakis*-[(3,5-dimethylpyrazol-1-yl)methyl)-1,4-phenylenediamine}**L1** or {*N,N,N',N'-tetrakis*-[(1,5-dimethylpyrazol-3-yl)methyl)-1,4-phenylenediamine}**L2**) and assessed as oxidation catalysts. The corresponding dioxygen complexes were generated *in situ* by mixing the copper salt and the pyrazolyl donor ligand in air. The oxidation of 3,5-di-*tert*-butylcatechol (DTBC), which affords 3,5-di-*tert*-butylquinone (DTBQ), was studied. The reaction rate was found to depend essentially on the nature of the junction linking two pyrazolyl neighbours.

Keywords: Bis-pyrazolyl ligands, Oxidation, 3,5-Di-*tert*-Butylcatechol, Copper(II)

INTRODUCTION

Ubiquitous copper ions in the active sites of proteins/enzymes mediate a broad scope of chemical processes including electron transfer, reversible dioxygen binding and activation, and nitrogen oxide transformations [1-8]. Biological binuclear copper centers involved with dioxygen binding and activation include hemocyanins (Hcs), tyrosinase (Tyr) and catechol oxidase (CO) [3-6]. Notable advances in the understanding of the properties of these proteins have been achieved through the comparison of the biomimetic inorganic model studies [4-5]. The 3,5-di-*tert*-butylcatechol (DTBC) is a common substrate in CO enzyme research [3-6] (Scheme 1), which may be converted in air to the corresponding quinone (DTBQ). The coordination of DTBC to the metal centers has been suggested to favor the intermolecular electron transfer



Scheme 1

reaction that results in the release of DTBQ and the reduction of the copper centers to the dicopper (I) state. This could then react with O_2 to restore the active form of the enzyme [3]. It was observed that the catalytic activities of the complexes are not only dependent on the organic ligand but also on the type of inorganic anion coordinated to the copper center. Generally, complexes containing pyrazol ligands and a fluoroborate anion are more active [9]. Several papers have been published dealing with binuclear copper complexes used as models for CO [10-13]. As part of our studies on pyrazolyl-derived ligands [14], we now decided to associate such ligands with copper(II) salts and study the CO properties of the resulting

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complexes [15-17]. A number of research groups have already focussed on the catechol oxidase activity of various copper complexes [18-26]. It turned out that dinuclear copper complexes are often more efficient than mononuclear complexes, provided the two metal centres lie in close proximity. This favors the binding of the catechol in a bridging mode and therefore facilitates the two-electron transfer step required in the oxidation process.

To the best of our knowledge, no report has described the catecholase activity of copper complexes of *N,N*-bis[(1,5-dimethylpyrazol-3-yl)methyl]arylamine or ligands derived from the latter. In theses amines, each pyrazolyl moiety is linked to the central amino group by a CH_2 spacer. We now describe the catecholase activity of copper complexes obtained from a particular ligand of this class, namely *N,N,N',N'*-tetrakis[(1,5-dimethylpyrazol-3-yl)methyl]-1,4-phenylene-diamine **L2**. Its activity was compared with that of the isomer *N,N,N',N'*-tetrakis[(3,5-dimethylpyrazol-1-yl)methyl]-1,4-phenylenediamine **L1**. In ligand **L1** the pyrazole rings are linked to the aryl unit *via N-C-N* junctions [27], while in **L2** the link is *via N-C-C* junctions [14c]. The study reveals that the rate of the conversion of 3,5-di-*tert*-butylcatechol to 3,5-di-*tert*-butylquinone is dependent on the nature of the junction between the pyrazole ring and the amino group. This study was carried out to model the activity of the copper containing enzyme tyrosinase.

EXPERIMENTAL

Kinetic measurements were made spectrophotometrically using a UV-Vis Cecil CE 292 Digital Spectrophotometer, by monitoring the appearance of 3,5-di-*tert*-butylquinone over time at 25 °C (400 nm absorbance maximum, ε = 1600 M^{-1} cm^{-1} in methanol). A solution of the metal complex (prepared in *situ* from an appropriate copper salt and the ligand; 0.3 ml of a 10^{-3} M methanol solution) [28] and a solution of 3,5-di-*tert*-butylcatechol (2 ml of a 10^{-1} M methanol solution) were mixed in the spectrophotometric cell.

RESULTS AND DISCUSSION

Synthesis

The tetrapyrazolyl derivative **L1**, which contains N-C-N junctions (Fig. 1), was prepared according to a literature procedure by condensation of four equivalents of 1-(hydroxymethyl)-3,5-dimethylpyrazole [29] with one equivalent of *p*-phenylenediamine (solvent-free reaction, 3 h reaction time) [14b,27]. Its isomer **L2** [14c], containing N-C-C junctions, was prepared by reacting four equivalents of 3-chloromethyl-1,5-dimethylpyrazol [30] with one equivalent of the *p*-phenylenediamine in refluxing acetonitrile, using sodium carbonate as base (reaction time: 3 h).

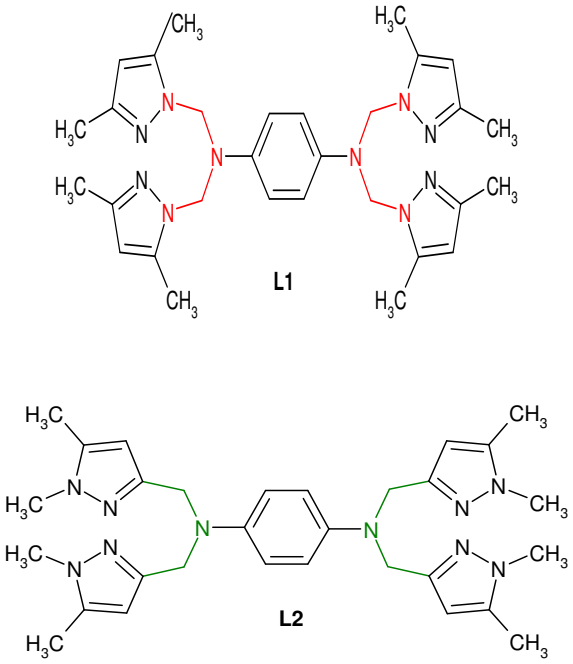


Fig. 1. Structures of ligands **L1** and **L2**.

Effect of the Nature of the Junction on the Catecholase Activity

The catechol oxidation reaction was conveniently followed by monitoring the strong absorbance peak of the quinone with a UV-Vis spectrophotometer. The metal complex (prepared in *situ* from a copper salt and the ligand) [28] and a solution of 3,5-di-*tert*-butylcatechol were mixed together in the spectrophotometric cell at 25 °C. Formation of 3,5-di-*tert*-butylquinone was monitored by following the increase in absorbance at 400 nm as a function of time. In all cases,

catecholase activity was noted. Figures 2 and 3 show the absorbance *vs.* time spectra for the first 70 min of the reaction, while the activities are shown in Table 1.

We have previously reported that the nature of the junctions (*N-C-C* or *N-C-N*) between the aniline N-atom and the pyrazole rings of such ligands affects considerably the molecular geometry of the resulting complexes [14c], but also the inhibition properties of the ligands towards corrosion [31], as well as their liquid-liquid extraction [32] and cytotoxic properties [33].

As can be inferred from Table 1, all the Cu systems based on the tetrapyrazolyl ligand **L1** (characterized by *N-C-N* links) catalyze the oxidation reaction of 3,5-di-*tert*-butylcatechol to 3,5-di-*tert*-butylquinone, the oxidation rate varying from 0.0876 (μmol substrate) (mg catalyst)$^{-1}$ min^{-1} for the **L1[CuCl$_2$]** complex (highest value) to 0.0688 (μmol substrate) (mg catalyst)$^{-1}$ min^{-1} for **L1[Cu(BF$_4$)$_2$]** (lowest value). These rates are weaker than those reported for the same substrate by Malachowski *et al*. [10] (ranging from 0.136 to 0.467 (μmol substrate) (mg catalyst)$^{-1}$ min^{-1}) with complexes containing *N,N,N',N'*-tetrakis(3,5-dimethylpyrazol-1-ylmethyl)-α,α'-di-amino-*m*-xylene as ligand. One factor which may explain the higher activity of the latter complexes is that unlike **L1**, the Malachowski ligands are suited for the synthesis of complexes in which two metal centers lie in close proximity. Such complexes obviously allow the binding of the catechol in a bridging mode, a situation which should favor the two-electron transfer step required in the oxidation process. The reactivity of complexes obtained with ligand **L2** (characterized by *N-C-C* junctions) varies in the order $CH_3CO_2^-$ (0.1054) > NO_3^- (0.0755) > BF_4^- (0.0579) > Cl^- (0.0250).

The results shown in Table 1 illustrate the effect on the oxidation rate when changing the *N-C-N* junctions to *C-C-N* ones. Thus, while **L2[CuCl$_2$]** displays an activity of only 0.0250 (μmol substrate) (mg catalyst)$^{-1}$ min^{-1}, that of **L1[CuCl$_2$]** reaches a value of 0.0876 (μmol substrate) (mg catalyst)$^{-1}$ min^{-1} under the same conditions. In three cases (Cl^-, NO_3^-, BF_4^-) the catalytic activity is significantly higher for **L1**, which is with the ligand containing the more flexible *N-C-N* links. In contrast, when the anion is $CH_3CO_2^-$, a higher CO rate is observed with the ligand having the *N-C-C* links (0.1054 μmol mg^{-1} min^{-1}). The latter result probably reflects the possible strong influence of the acetate anion on ligand dissociation [9] rather than a particular bonding mode of the ligand.

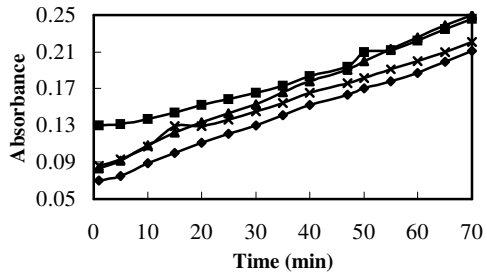


Fig. 2. Oxidation of DTBC by complexes of **L1** (25 °C, 400 nm): (◆) $CuCl_2$, (■) $Cu(CH_3CO_2)_2$, (▲) $Cu(NO_3)_2$, (×) $Cu(BF_4)_2$.

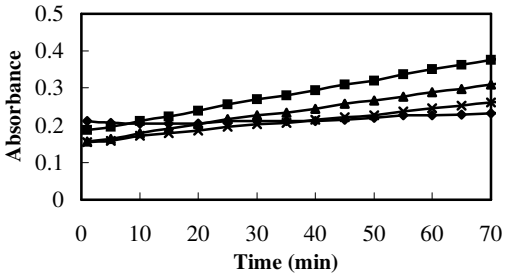


Fig. 3. Oxidation of DTBC by complexes of **L2** (25 °C, 400 nm): (◆) $CuCl_2$, (■) $Cu(CH_3CO_2)_2$, (▲) $Cu(NO_3)_2$, (×) $Cu(BF_4)_2$.

Effect of Copper(II) Concentration on the Catecholase Activity

In solution, the active complex is in equilibrium with the copper salt and the ligand. In order to optimize the oxidation rate, we decided to study the effect of the variation of the copper concentration on the activity. The results of these investigations are summarized in Table 2.

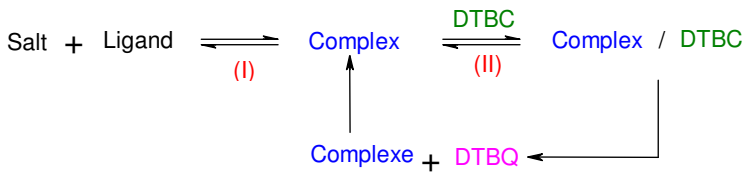
The absorbance measurements were carried out with the following three concentrations of copper salts: 2×10^{-3}, 4×10^{-3}, and 8×10^{-3} M. As can be deduced from Table 2, the catalytic activity increases with increasing copper concentration. These results are in keeping with the mechanism proposed in Scheme 2, based on the existence of a pre-equilibrium involving the free complex. This hypothesis

Table 1. Kinetic Data for the Oxidation of 3,5-Di-*tert*-Butylcatechol [28] Using Copper(II)/**L** Systems (**L** = **L1** or **L2**) [Catalytic Activity (μmol mg^{-1} min^{-1})]

Ligand/Salt	$CuCl_2$	$Cu(CH_3CO_2)_2$	$Cu(NO_3)_2$	$Cu(BF_4)_2$
L1 [*N-C-N*]	0.0876	0.0794	0.0863	0.0688
L2 [*N-C-C*]	0.0250	0.1054	0.0755	0.0579

Table 2. Effect of Copper(II) Concentration on the Catalytic Activity (μmol mg^{-1} min^{-1}) [28]

Ligand	Concentration	$CuCl_2$	$Cu(CH_3CO_2)_2$	$Cu(NO_3)_2$	$Cu(BF_4)_2$
	2×10^{-3}	0.0459	0.0352	0.0467	0.0435
L1 [*N-C-N*]	4×10^{-3}	0.0876	0.0794	0.0863	0.0688
	8×10^{-3}	0.1543	0.1995	0.2193	0.1304
	2×10^{-3}	-	0.0312	0.0289	0.0180
L2 [*C-C-N*]	4×10^{-3}	0.0250	0.1054	0.0755	0.0579
	8×10^{-3}	0.0792	0.2543	0.1474	0.1123



Scheme 2

is supported by the dependence of the reaction rate on both substrate and complex concentrations.

In conclusion, we have studied the catecholase activity of copper complexes of two isomeric pyrazolyl ligands and shown that the oxidation rate of 3,5-di-*tert*-butylcatechol (DTBC) to 3,5-di-*tert*-butylquinone (DTBQ) is strongly dependent on the nature of the junctions between the pyrazolic rings and the arylamino moiety, as well as on complex concentration.

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