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Stereoselective catalytic oxidations of biomimetic copper complexes with a chiral trinucleating ligand derived from 1,1-binaphthalene

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Dedicated to Professor Renato Ugo on the occasion of his 65th birthday

Abstract

The new octadentate ligand *R*-(−)-*N*,*N*′-dimethyl-*N*,*N*′-bis{3-[bis(1-methyl-2-benzimidazolyl)amino]propyl}1,1′-binaphthalenyl-2,2′-diamine (L) was employed for the synthesis of dinuclear and trinuclear copper(II) complexes. Two terminal binding sites with tridentate aminobis(benzimidazole) linkages (A sites) and one central binding site with the bidentate diamino-binaphthalenyl residue (B site) are used by the ligand to bind divalent metal centres in the trinuclear complex $[Cu_3L][ClO_4]_6$. Spectroscopic measurements suggest that in the dinuclear complex $[Cu_2L][ClO_4]_4$ the copper ions are five-coordinated, with ligation by the aminobis(benzimidazole) residues, one of the tertiary amine donors of the diamino-binaphthalenyl moiety, and one water molecule. The complexes bind azide in the μ-1,3 fashion at low concentration and in the terminal mode at high concentration.

The copper(II) complexes derived from L are catalytically active in the oxidation of 3,5-di-*tert*-butylcatechol (DTBC) by dioxygen. The oxidations are biphasic, with a fast initial stoichiometric phase corresponding to reduction of a pair of copper(II) centres and oxidation of DTBC to quinone, followed by the catalytic reaction, that follows substrate saturation behaviour. The complexes act as stereoselective catalysts in the biomimetic oxidations of the optically active catechol derivatives L- and D-Dopa and their methyl esters. In all the cases, the preferred enantiomeric substrate has the L configuration. This preference is dictated by the chirality of the binaphthalenyl residue.

Keywords: Copper(II) complexes; 1,1-Binaphthalenyl derivative; Catalytic oxidations; Stereoselective catalytic oxidations

1. Introduction

The oxidation of organic substrates with molecular oxygen under mild conditions is of great interest for industrial and synthetic processes both from an economical and environmental point of view [1,2].

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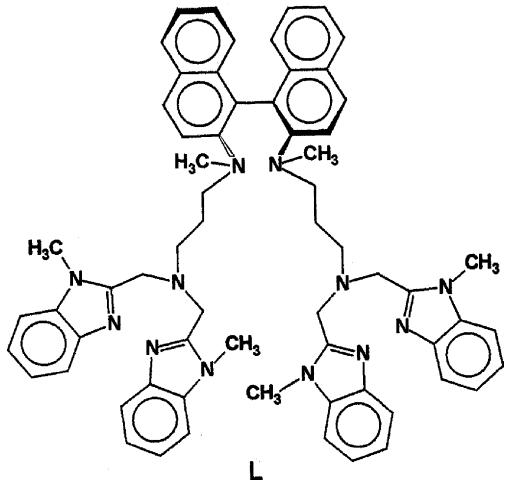
Although the reaction of organic substances with dioxygen is thermodynamically favoured, it is kinetically unfavoured due to the triplet ground state of O_2. In biological systems, this problem is overcome by the use of copper or iron containing metalloproteins which serve as highly efficient oxidation catalysts [3,4]. The synthesis and investigation of functional model complexes for metalloenzymes with oxidase or oxygenase activity is, therefore, of great promise for the development of new and efficient catalysts for oxidation reactions.

The catecholase activity of copper coordination compounds with different structural features has been investigated for a long time [5–9]. In these studies, mono- or multi-nuclear complexes have been employed and the properties of the chelating ligands, in terms of architecture and number and nature of the donor atoms, have been varied to a large extent. A steric match between substrate and complex is believed to be a key factor: two metal centres have to be located in close proximity to facilitate binding of the two hydroxyl oxygen atoms of catechol prior to the electron transfer. This view is supported by the observation that dinuclear copper complexes are generally more reactive in the oxidation of catechols than are the corresponding mononuclear species [5–9]. Therefore, dinuclear [10–16] and trinuclear [17,18] copper complexes derived from polydentate ligands have received increasing attention in recent years for the challenge of mimicking various aspects of the structure and reactivity that are generally associated with the type 3 or type 2–type 3 copper centres found in several copper proteins, such as hemocyanin [19], the dioxygen carrier for arthropods and mollusks, tyrosinase [20] which catalyzes the hydroxylation of tyrosine to Dopa (cresolase activity) and the oxidation of Dopa to Dopaquinone (catecholase activity), and laccase, ascorbate oxidase and ceruloplasmin [21], which are active in the oxidation of a variety of substrates.

In spite of the complications that usually arise in the synthesis of polyfunctional trinucleating ligand molecules, the resulting metal complexes offer several advantages, in terms of stability and the possibility of keeping the metal centres in relatively close proximity. The original scope of our group is to produce trinuclear complexes with ligands containing eight nitrogen donors which could serve as synthetic models



Scheme 1.

for the as yet incompletely understood type 2–type 3 clusters present in copper proteins, where a total of eight histidine imidazole groups provide the protein ligands for the metal centres. In a previous paper [17], we showed that trinuclear copper complexes derived from an octadentate tetraamine-tetrabenzimidazole ligand show an efficiency greater than the corresponding dinuclear complexes in the catalytic oxidation of 3,5-di-*tert*-butylcatechol. This probably depends on structural factors associated with the spatial relationships between the three catalytic centres, in both their oxidized and reduced states, and the redox potentials of the Cu(II)/Cu(I) couples involved in the electron transfer. More recently [18], we developed new synthetic model compounds containing chiral centres derived from histidine residues, and clearly the presence of these residues has increased the significance of the model complexes. Preliminary results show that these trinuclear complexes are able to induce stereoselectivity in the catalytic oxidation of L- and D-Dopa. In this paper, we report the development of new model systems derived from a ligand, where *R*-(+)-1,1′-binaphthalenyl-2,2′-diamine acts as the spacer between two chelating arms containing tridentate benzimidazole donor residues (Scheme 1). The resulting dinuclear and trinuclear chiral copper(II) complexes represent a new family of potential structural and functional models for the multinuclear sites of copper-enzymes.

2. Experimental

2.1. Materials and physical methods

All reagents and solvents were obtained from commercial sources and used without further purification. *R*-(+)-1,1′-Binaphthalenyl-2,2′-diamine was obtained from Fluka and used as received. D-Dopa methyl ester hydrochloride (D-DopaOMe·HCl) was prepared by dissolving D-Dopa in anhydrous methanol (10 ml), and bubbling into the cooled solution gaseous HCl for 1 h. The resulting solution was refluxed for 1 h and, after cooling, it was concentrated to a small volume under vacuum, yielding a white precipitate, which was crystallised from anhydrous methanol. Elemental analyses were performed at the microanalytical laboratory of the Chemistry Department in Milano. Infrared spectra were recorded on a Jasco FT/IR-5300. Optical spectra were obtained from HP 8452A and 8453 diode array spectrophotometers. Circular dichroism (CD) spectra were recorded with a Jasco J-500 spectropolarimeter using quartz cells of 0.01–2 cm path length.

2.2. Synthesis of the complexes

The multistep synthesis of the ligand *R*-(−)-*N*,*N*′-dimethyl-*N*,*N*′-bis{3-[bis(1-methyl-2-benzimidazolyl) amino]propyl}1,1′-binaphthalenyl-2,2′-diamine, L, starting from commercial *R*-(+)-1,1′-binaphthalenyl-2,2′-diamine is reported elsewhere [22].

2.3. $[Cu_2L][ClO_4]_4·2H_2O$

To a solution of the ligand L (0.085 mmol) in acetonitrile (20 ml) a solution of copper(II) perchlorate hexahydrate (0.170 mmol) in the same solvent was added dropwise, and the resulting green solution was stirred at room temperature for about 5 h. The solution was then evaporated to a small volume (2–4 ml) and the residue was treated with diethyl ether (5–10 ml). The light green precipitate was separated by filtration, washed with a little amount of water, and dried under vacuum at 110 °C. Analytically calculated for $C_{64}H_{66}N_{12}O_{16}Cl_4Cu_2·2H_2O$ (1563.26): C 49.17, H 4.25, N 10.75, Cu 8.13; found: C 49.00, H 4.35, N 10.58, Cu 8.11. IR (NaCl, nujol, $\nu\,cm^{-1}$): 3508 (OH); 1618, 1504, 1485 (ring); 1097, 623 (ClO_4); 939, 750 (CH).

2.4. $[Cu_3L][ClO_4]_6·2H_2O$

The ligand L (0.0846 mmol) dissolved in acetonitrile (20 ml) was treated with a solution of copper perchlorate hexahydrate (0.293 mmol, 15% excess) in the same solvent, and the resulting deep green solution was refluxed under stirring for 24 h. The reaction was followed by TLC (silica gel) using CH_2Cl_2:MeOH (9:1 (v/v)) as eluent, by monitoring the disappearance of the free ligand. The mixture was then cooled to room temperature and evaporated to a small volume (2–5 ml). The blue precipitate thus formed was filtered off, and the residue was treated with diethyl ether (10 ml) under stirring. The deep green precipitate was separated from the solution by filtration, washed several times with water and dried under vacuum at 110 °C. Analytically calculated for $C_{64}H_{66}N_{12}O_{24}Cl_6Cu_3·2H_2O$ (1826.68): C 42.08, H 3.86, N 9.20, Cu 10.43; found: C 42.20, H 4.04, N 9.36, Cu 10.39. IR (NaCl, nujol, $\nu\,cm^{-1}$): 3450 (OH); 1618, 1510, 1485 (ring); 1097, 623 (ClO_4); 939, 819, 752 (CH).

Caution: Perchlorate complexes with organic ligands are potentially explosive and should be handled with great care. Only small amounts of material should be prepared. We did not have problems working with small amounts of the perchlorate complexes described in this paper.

2.5. Ligand-binding studies

Spectrophotometric titrations of azide binding to $[Cu_2L][ClO_4]_4·2H_2O$ and $[Cu_3L][ClO_4]_6·2H_2O$ were performed by adding small amounts of a concentrated solution of the ligand in methanol to solutions of the complexes in methanol or acetonitrile. The data were analysed as previously described [23].

2.6. Kinetics of 3,5-di-tert-butylcatechol oxidation

The efficiency of $[Cu_2L][ClO_4]_4·2H_2O$ and $[Cu_3L][ClO_4]_6·2H_2O$ as catalysts of 3,5-di-*tert*-butylcatechol (DTBC) oxidation was tested by UV-Vis spectroscopy using a magnetically stirred and thermostated 1-cm path length cell. The temperature during the measurements was kept constant at 20 ± 0.1 °C. A mixture of methanol–aqueous phosphate buffer (50 mM, pH 5.0) 30:1 (v/v) saturated with atmospheric oxygen

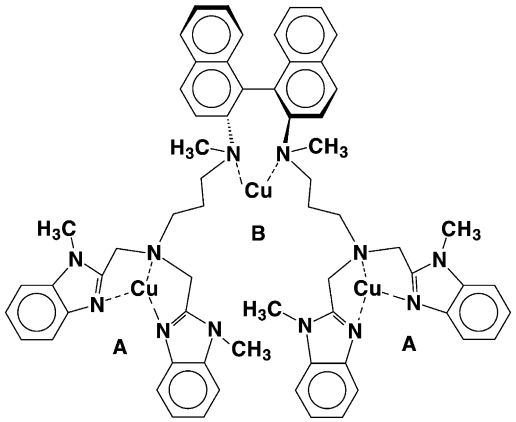
was used as solvent. Studying the dependence of the oxidation rate on DTBC concentration the catalyst concentration was kept at 16 μM, while the substrate concentration was varied between 0.4 and 8 mM. The formation of 3,5-di-*tert*-butylquinone (DTBQ) was followed through the development of the corresponding moderately intense absorption band at $\lambda_{max} = 400$ nm ($\varepsilon_{400} = 1550\,(M\,cm)^{-1}$, in methanol). The noise during the measurements was reduced by reading the absorbance difference between 400 and 800 nm (where the absorbance variation is only due to noise). The initial rate of the oxidations was obtained by fitting the plots of absorbance versus time in the first few seconds of the reactions.

2.7. Kinetics of L- and D-Dopa and L- and D-DopaOMe HCl oxidation

The kinetic experiments were performed in a magnetically stirred and thermostated 1-cm path length cell at 20 ± 0.1 °C. A mixture of methanol–aqueous phosphate buffer (50 mM, pH 8.5) 1:15 (v/v) was used as solvent. The copper catalyst concentration was kept at 5 μM by adding 10 μl of a 10^{-3} M solution of the complex in CH_3CN/MeOH 1/15 (v/v) in the reaction cuvette, while the substrate concentration was varied from 6 μM to 0.7 mM (final volume 2 ml). To prevent further reactions of the Dopa-*o*-quinones and DopaOMe-*o*-quinones initially formed, an excess amount of 3-methyl-2-benzothiazoline hydrazone (MBTH, 1 mM final concentration) was added. The formation of the stable Dopa-*o*-quinone–MBTH and DopaOMe-*o*-quinone–MBTH adducts was followed through the developing strong absorption band at $\lambda_{max} = 500$ nm ($\varepsilon_{500} = 13{,}400\,(M\,cm)^{-1}$ for the adduct with Dopa-*o*-quinone, and $\varepsilon_{500} = 11{,}600\,(M\,cm)^{-1}$ for the adduct with DopaOMe-*o*-quinone). As before, the noise during the measurements was reduced by reading the absorbance difference between 500 and 800 nm. The initial rate of the oxidation was obtained by fitting the absorbance versus time curves in the first few seconds of the reactions.

3. Results and discussion

The distribution of nitrogen donors of the ligand should enable to obtain two equivalent metal coordination sites (A) within the symmetric tridentate units, each containing the two aminobis(benzimidazole) residues with relatively rigid, fused five-membered rings, and a third bidentate coordination site (B) at the chiral 1,1′-binaphthalenyl residue (Scheme 2). The reactivity of L towards copper(II) and other ions can be anticipated on the basis of this assumption. The binuclear complex $[Cu_2L][ClO_4]_4{\cdot}2H_2O$ was easily obtained by reacting at room temperature the acetonitrile solutions of the ligand L with the corresponding amount of copper(II) perchlorate hexahydrate. Though, the binding of a third ion at site B, to form the trinuclear complex is extremely difficult; to obtain the compound $[Cu_3L][ClO_4]_6{\cdot}2H_2O$ requires an excess metal ion and heating at reflux temperature for 1 day. In the present trinuclear system, the ligand chiral centres are in the coordination sphere of CuB, while in the previously reported histidine-containing trinuclear complex the chiral residues were bound at the CuA centres [18].



Scheme 2.

The UV-Vis and CD spectral data of the ligand L, the copper(II) complexes and their azide adducts, in acetonitrile solution, are summarised in Table 1.

In the near-UV region, the electronic spectrum of L comprises both 1,1-binaphthalenyl and benzimidazole absorptions. Thus, on the basis of previous studies we can assign to the 2,2′-disubstituted 1,1-binaphthalenyl chromophore four main absorptions at 352, 305, 258, and 210 nm [24,25], and to benzimidazole chromophores the bands at 286, 278, and 271 nm, and overlapping bands at 258 and 352 nm

Table 1
UV-Vis and CD spectral data for copper(II) complexes in acetonitrile solutions

Complex	UV-Vis λ_{max} (nm) (ε (M cm)$^{-1}$)	CD λ_{max} (nm) ($\Delta\varepsilon$ (M cm)$^{-1}$)
L	208 (139000)	214 (+169.8), 225 (124.5)
	257 (71000), 271 sh (54400)	237 sh (−11.3), 248 (+2.7)
	278 sh (43500), 286 (32400)	260 sh (−36.1), 266 (−44.7)
	305 sh (11900), 352 (6300)	301 (+23.2), 368 (−5.9)
$[Cu_2L]^{4+}$	220 sh (95500)	214 (+122.7), 224 (−108.9)
	250 (58000), 262 (48500)	257 (−46.8)
	272 (46600), 280 (41000)	298 (+13.4)
	304 sh (10800), 350 (4750)	352 (+1.4), 400 (+0.085)
		432 (−0.019), 524 (+0.033)
	648 (210)	635 (−0.048)
$[Cu_3L]^{6+}$	227 sh (96600)	212 (+70.5), 222 (−10.3)
		227 (+10.8)
	251 (62400), 264 sh (42000)	251 (−41.9)
	272 (41400), 279 (40300)	270 sh (−8.4),
	290 sh (13350), 300 sh (9900)	300 (+3.7)
	361 (6700)	
	544 (176), 645 (177)	570 (+0.01)
	740 sh (131)	746 (−0.055)
$[Cu_2L(N_3)]^{3+}$	220 sh (135000)	215 (+141.9), 225 (−72.3)
	252 (68500)	258 (−49.7)
	264 sh (56800), 272 (53000)	
	280 (48000), 301 sh (12200)	295 (+19.8), 336 (+1.86)
	360 (5100), 418 sh (2170)	370 (0.0), 395 (+1.0)
	629 (270)	513 (+0.023), 628 (−0.033)
$[Cu_2L(N_3)_2]^{2+}$	220 sh (133000)	214 (+161.0), 225 (−78.1)
	252 (74000), 264 sh (63100)	239 (0.0)
	272 (59900), 280 (54800)	258 (−52.1)
	304 sh (24000)	294 (+20.7)
	620 (426), 740 sh (333)	339 (+2.32), 396 (+1.0)
		540 (−0.027)
$[Cu_3L(N_3)]^{5+}$	225 sh (76500)	211 (+93.0), 223 (−16.4)
		232 (0.0)
	251 (69000), 272 (43000)	257 (−52.0), 296 (+13.2)
	280 (40600), 291 sh (14400)	347 (+3.5), 391 (+1.1)
	301 sh (11800), 360 (7300)	483 (+0.023)
	669 (217), 730 (196)	600 (0.0), 700(−0.01)
$[Cu_3L(N_3)_2]^{4+}$	220 sh (114000)	212 (+98.4), 223 (−19.1)
	251 (73200), 272 (44900)	234 sh (+8.9), 240 (+11.6)
	280 (42300), 300 sh (12400)	257 (−64.4), 296 (+18.6)
	362 (7500)	343 (+4.3), 390 (+1.2)
	634 (288), 754 sh (229)	464 (−0.014), 567 (+0.016)

[14]. The CD spectrum of L displays a relatively weak negative Cotton effect at 368 nm followed, at higher energy, by two strong dichroic bands at 301 nm (positive) and 266 nm (negative). Associated with the intense absorption band at 220 nm, an intense exciton doublet with extreme at 225 nm (negative) and 215 nm (positive) is also observable. The CD pattern closely resembles that observed for the (*R*)-*N*,*N*,*N*′,*N*′-tetramethyl-1,1′-binaphthalenyl-2,2′-diamine [24], showing that the benzimidazoles bonded through an alkyl chain to the 1,1′-binaphthalenyl residue do not alter the chiroptical properties of the chromophore.

In the copper(II) complexes of L the overall chiroptical properties of the ligand are maintained, with some significant changes. The intensity of the CD doublet near 214 and 225 nm is progressively reduced in $[Cu_2L]^{4+}$ and $[Cu_3L]^{6+}$. The reduction is likely associated with a change in the dihedral angle within the binaphthalenyl unit [25], which is probably necessary for binding the metal centres. The doublet at lower energy (266 and 301 nm for L) is more markedly perturbed on metal binding. Both components shift to higher energy and that near 300 nm is much weaker in the complexes. That the general reduction in CD intensity observed in the complexes is not due to racemisation during preparation is shown by the fact that CD intensity is gained in the azide adducts of both $[Cu_2L]^{4+}$ and $[Cu_3L]^{6+}$. Additional contributions to the CD spectra of the complexes in the near-UV region result from LMCT transitions. Very weak CD activity is also observed at low energy, in correspondence with the d–d transitions of the Cu(II) centres. The CD pattern is different for the dinuclear and trinuclear complexes in this range, but a detailed analysis is not possible in the present context. Although we have been unable to obtain crystals of the complexes suitable for X-ray analysis so far, some information on the structural features relevant to their catalytic behaviour could be obtained from ligand binding experiments, while the characterization of their magnetic properties will be reported separately.

3.1. Ligand-binding experiments

Small ligand molecules such as azide are probably the most widely used ligand probes for copper protein sites [26,27], but the interpretation of their binding mode has been often controversial. Azide binding to copper(II) centres is generally accompanied by the appearance of LMCT transitions in the near-UV and visible regions that are potentially very useful for empirical correlations between spectra and structure. When a solution of $[Cu_2L]^{4+}$ in methanol or acetonitrile is titrated with azide, the electronic spectrum of the complex undergoes marked changes up to a ratio of $[N_3^-] : [Cu_2] \sim 2 : 1$. The spectrum of the monoazide adduct, in the first half of the titration, shows two resolved components, at 365 and 402 nm that subsequently merge into a symmetrical band at 400 nm as more azide is added. An estimate of the binding constant of the first azide, obtained from the titration data, yields $K_1 = 4500 \pm 240\,M^{-1}$. Binding of the second azide occurs with slightly lower affinity ($K_2 = 2600 \pm 100\,M^{-1}$). On the basis of previous studies [14,23], it is evident that the two-component structure of the first azide-Cu(II) LMCT band indicates the ligand binds in the bridging mode, while the symmetric shape of the LMCT band shows that when the second azide binds the bridge is broken and the adduct contains two terminal azide moieties. Binding of further azide to the bis-adduct occurs with lower affinity and can be followed with additions of the ligand above $[N_3^-] : [Cu_2] \sim 10 : 1$. Isosbestic points are evident at 366 and 570 nm, and rough estimates of the binding constants for these binding steps yielded values of $K_3 \approx K_4 = 2000 \pm 120\,M^{-1}$.

The azide binding experiments on $[Cu_3L]^{6+}$ deserve some more comments because, surprisingly, the spectrum of the complex undergoes no marked changes up to a ratio of $[N_3^-] : [Cu_3] \sim 2 : 1$; only a weak broad band at ~370–380 nm develops in methanol or acetonitrile solutions. This behaviour shows that the trinuclear compound is in a closed conformation that prevents to hold the bridging Cu–N_3–Cu unit. Addition of further azide, up to a ratio of $[N_3^-] : [Cu_3] \sim 4 : 1$, produces the development of a two-components band at 388 and 406 nm, with an isosbestic point at 348 nm, indicating that the azide molecule bind as a μ-1,3 bridge with a binding constant of $K_1 \cong 1600\,M^{-1}$. At a ratio of $[N_3^-] : [Cu_3] \sim 10 : 1$ the two components merge into a single symmetric band at 406 nm with an isosbestic point at 342 nm, which suggests that cleavage of the existing μ-1,3 bridge occurs producing terminally bound azide complex with $K_2 \cong 900\,M^{-1}$.

3.2. Catalytic oxidations and stereoselective catecholase activity

To clarify whether the model complexes described in this paper show catalytic activity, as do other dinuclear and trinuclear model systems [15–17,28–31], we studied preliminarily the oxidation of 3,5-di-*tert*-butylcatechol (DTBC) since its oxidation product 3,5-di-*tert*-butyl-*o*-quinone (DTBQ), is quite stable at pH 5.0 and can be easily monitored by optical absorption [16,17]. As in other cases [15,16], when the reaction with $[Cu_2L]^{4+}$ or $[Cu_3L]^{6+}$ was carried out in the

Table 2
Kinetic parameters for the catalytic oxidation of DTBC in methanol–aqueous phosphate buffer, pH 5.0, at 20 °C with various copper(II) complexes

Complex	First step			Second step		
	k_{cat} (s^{-1})	K_M (mM)	k_{cat}/K_M $((M\,s)^{-1})$	k_{cat} (s^{-1})	K_M (mM)	k_{cat}/K_M $((M\,s)^{-1})$
$[Cu_2(L\text{-}55)]^{4+}$ [a]	1.40	1.50	900	0.33	2.4	140
$[Cu_2(EBA)]^{4+}$ [b]	0.7	13	60	0.05	7	7
$[Cu_2(LB4)]^{4+}$ [c]				0.05	2.2	23
$[Cu_3(LB4)]^{6+}$ [c]				0.092	2.5	37
$[Cu_2L]^{4+}$ [d]	0.086	0.17	510	0.00056	0.12	5
$[Cu_3L]^{6+}$ [d]	0.042	0.23	180	0.013	0.13	98

[a] Ref. [15].
[b] Ref. [16].
[c] Ref. [17].
[d] This work.

mixed solvent of methanol–aqueous phosphate buffer (50 mM, pH 5.0), saturated with atmospheric oxygen, two phases are observed. The fast initial phase, corresponding to stoichiometric oxidation of one molecule of substrate, is followed by a second, slower catalytic phase. The data can be interpreted according to the following scheme:

$$Cu^{II}\cdots Cu^{II} + DTBC \rightarrow Cu^{I}\cdots Cu^{I} + DTBQ + 2H^{+} \quad (1)$$

$$Cu^{I}\cdots Cu^{I} + O_2 \rightarrow Cu^{II}(O_2)^{2-}Cu^{II} \quad (2)$$

$$Cu^{II}(O_2)^{2-}Cu^{II} + DTBC + 2H^{+} \rightarrow Cu^{II}\cdots Cu^{II} + DTBQ + 2H_2O \quad (3)$$

The rate of both steps depends on the catechol concentration, but they cannot be easily described in terms of a pre-equilibrium, because the observed velocities do not reach a plateau at high substrate concentration. Instead, in the latter conditions, substrate inhibition is observed. Likely, at high concentration, coordination of DTBC occurs as a chelating ligand to each metal centre of the complex [32]. Since coordination of catechol as a bridging ligand between two coppers is a necessary condition for a fast two-electron transfer, the formation of chelating adducts prevents the possibility of the oxidation process. The kinetic constants k_{cat} and K_M, reported in Table 2, in comparison with the values obtained for other dinuclear and trinuclear complexes, were estimated by fitting of the rate versus catechol concentration curve below saturation. In general, the catalytic activity exhibited by the copper complexes of L in the DTBC oxidation is lower than that of the other complexes, but here the steric bulk provided by the catechol substituents may be an important factor in preventing to achieve the correct positioning for efficient electron transfer in the catalyst–substrate adduct. Support to this interpretation comes from the observation that k_{cat} is much smaller for $[Cu_2L]^{4+}$, where the substrate must bind to CuA centres, than for $[Cu_3L]^{6+}$, where bridging of the catechol between the closer CuA and sterically hindered CuB centres is more likely to occur.

To explore the potential ability of these chiral complexes to perform stereoselective oxidations we used the optically active catechol derivatives L- and D-Dopa and their methyl esters, L- and D-DopaOMe, as substrates. Preliminary studies on the pH dependence of the oxidation showed that at pH 8.5 the rate of quinone formation was highest, probably because in these conditions coordination of the substrates to the Cu(II) centres is easiest. The UV and CD spectra of the complexes in these conditions are very similar to those obtained in acetonitrile solutions, with the only difference that the near-UV dichroic band at 352 nm for the dinuclear complex is shifted to 340 nm, and the ligand field transitions are slightly decreased in intensity. Quinones derived from Dopa and Dopamine derivatives are extremely unstable and spontaneously evolve to complex mixtures of products [33]. To prevent further reactions of the unstable Dopa-*o*-quinones, an excess amount of 3-methyl-2-benzothiazoline hydrazone (MBTH) was added, in order to produce stable

Table 3
Kinetic parameters for the stereoselective catalytic oxidations of L- and D-Dopa; L- and D-DopaOMe in methanol–aqueous phosphate buffer, pH 8.5, with MBTH at 20 °C

Substrate	k_{cat} (s^{-1})	K_M (mM)	k_{cat}/K_M $((M\,s)^{-1})$
$[Cu_2L]^{4+}$			
L-Dopa	0.0041	0.055	75
D-Dopa	0.0033	0.068	49
L-DopaOMe	0.0080	0.023	352
D-DopaOMe	0.0053	0.022	242
$[Cu_3L]^{6+}$			
L-Dopa	0.0041	0.171	24
D-Dopa	0.0039	0.162	24
L-DopaOMe	0.0069	0.010	666
D-DopaOMe	0.0048	0.010	506

Dopa-*o*-quinone–MBTH adducts, as is widespread used in enzymatic studies employing tyrosinase [34]. As shown by the kinetic data in Table 3, the copper complexes derived from L exhibit significant stereoselectivity in the oxidation of Dopa substrates.

Although it has been derived only from kinetic studies, to our knowledge this is the first example of biomimetic stereoselective oxidation of catechols by chiral copper model complexes. It is perhaps surprising that $[Cu_2L]^{4+}$ is more selective than $[Cu_3L]^{6+}$ in these reactions, probably because the binaphthalenyl unit is more free to interact with the substrate in the former case. Clearly, stereoselectivity involves chiral recognition between the catalyst and the amino acid substituents at the α-carbon atom, which are removed from the catechol nucleus undergoing the oxidation reaction. Binding of this nucleus to the CuA sites of the dinuclear complex enables the amino acid portion to interact relatively strongly with the binaphthalenyl residue. By contrast, the catechol residue likely interacts with one CuA site and the CuB site in the trinuclear complex. Thus, in this case, the amino acid portion of the substrate is more likely blocked by interaction with the remaining "nonchiral" CuA site, rather than with the binaphthalenyl residue. This model accounts for the complete lack of stereoselectivity exhibited by $[Cu_3L]^{6+}$ towards L- and D-Dopa, where the amino and carboxylate groups next to the α-carbon atom are likely involved in strong binding to the redox inactive CuA site. With the DopaOMe substrates this interaction is likely weaker and some stereoselectivity is observed.

Assuming the ratio $|(k_{cat}/K_M)_L - (k_{cat}/K_M)_D|/(k_{cat}/K_M)_{max}$ (where max refers to the larger of the two absolute values) as an empirical index of enantioselectivity, the largest value observed here, for the oxidation of L- and D-Dopa by $[Cu_2L]^{4+}$, amounts to 35%, that only slightly decreases to 31% for the oxidation of L- and D-DopaOMe by the same catalyst. The enantioselectivity index exhibited by $[Cu_3L]^{6+}$ in the oxidation of the latter substrates amounts to 24%. In all the cases, the preferred enantiomeric substrate has L configuration. It is likely that this preference is associated with the chirality of the binaphthalenyl residue.

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