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Coordination compounds in the entatic state

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Contents

Abstract

Much of the selectivity and efficiency of chemical transformations, which involve metalloproteins is due to a modulation of the properties of the metal ions by the protein to which they are bound. Geometric and electronic distortions, enforced by the protein backbone, and specific electrostatic fields and solvation patterns (e.g. hydrophobic pockets) may lead to a destabilization of the catalytically active site (metal center(s) and/or enzyme–substrate complex(es)) and, therefore, to a (selective) activation of certain reaction channels. This is known as the 'energization theory' or, for specific cases, the 'entatic state' principle. Examples, where specifically enforced coordination geometries lead to stresses and enhanced reactivities range from biological systems (metalloproteins and enzymes) to classical coordination compounds and processes of industrial importance (catalytic systems which involve organometallic and transition metal coordination compounds). Hence, entasis is not refined

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to metalloproteins; reactions induced by metal-free enzymes or by small coordination compounds may also involve strained, that is entatic states. Based on few selected examples, which include the classical cases of the blue copper proteins and of electron transfer in general, as well as simple coordination compounds and organometallic catalysis, it is shown that a thorough analysis and interpretation of enhanced reactivities may in general not be assigned exclusively to steric strain. However, specific coordination geometries, enforced by the ligand sphere (protein or simple organic compounds) which may or may not be strained are often of importance. One of the main conclusions is that the understanding, design and synthesis of new compounds with specific and enhanced reactivities may involve similar thoughts, tools and difficulties as the design and study of highly preorganized ligands in areas such as metal ion recognition and host–guest interactions in general.

Keywords: Entatic state; Preorganization; Catalysis; Strain; Energization

1. Introduction

The basic ideas of energized states in proteins, metalloproteins and simple transition metal coordination compounds were developed in the early fifties (see Ref. [1] for a historical overview, Ref. [2] for a comprehensive description of catalysis by metalloproteins in the entatic state, and Refs. [1–4] for arguments on the history and on mechanistic differences between metalloproteins in the entatic state (enforced geometry by a rigid protein) [5], the rack mechanism in metalloproteins (conformational changes of a protein and allosteric effects that may lead to stretching in a rack action) [6,7], the induced fit mechanism (enforced geometry by a locally flexible protein) [8,9], and enforced conformation of the protein by the metal ion [1]). In a less than puristic and somewhat simplistic but scientifically useful view entasis may be defined as the energization due to a misfit between ligands and metal ions (metalloproteins or simple coordination compounds) or between complex fragments and the corresponding substrate–catalyst complexes, and this is the definition on which this review is based.

Simple reaction schemes for single step reactions that visualize the conventional interpretation of a catalyst and that of an enzyme in the entatic state are shown in Fig. 1; similar diagrams may be drawn for the generally more relevant multistep mechanisms of catalytic processes. Note, that in a single step reaction a ligand enforced energization may influence both, the starting materials and the products, and not necessarily in the same way and by the same amount of energy (see Fig. 1(c)); that is, both, the kinetics and thermodynamics of a single step chemical reaction. Therefore, the thermodynamics of the catalyst–substrate complexation and the corresponding decomplexation have also been included in Fig. 1(c), and thermodynamic as well as kinetic aspects of energized (entatic) states of coordination compounds in general will be considered here. A prominent and historical example for the entatic state principle is that involving blue copper proteins, where the oxidized and reduced forms have similar coordination geometries (see, however,

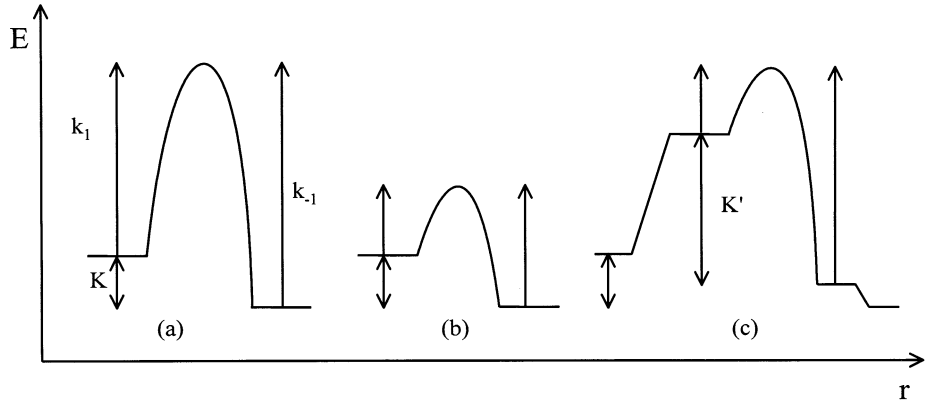


Fig. 1. Kinetics (k_1, k_{-1}) and thermodynamics (K) of a single-step chemical reaction; (a) uncatalyzed; (b) catalyzed (conventional model); (c) catalyzed by entasis, the substrate complexation and decomplexation is also included in this case (K vs. K', see text).

the detailed discussion in Section 2). Therefore, the basic aspects of the entatic state hypothesis will be introduced with cupredoxines, and that section will also include recent results and their interpretations, which started a new controversy with respect to the necessity to involve entatic states in this and in other cases.

Energized states (strained geometries) may involve stresses due to the ligand backbones or the electronic preferences of the metal ion, and, apart from steric strain, electronic and entropic strain, as well as environmental stresses (solvation, crystal lattice effects) may be of importance [10]. These are the same factors that have to be considered in (selective) host–guest interactions, e.g. in the optimization of ligands for metal-ion-selective complexation processes [11]. That is, the ligands (proteins or simple organic molecules) of coordination compounds in the entatic state are highly preorganized [12,13] with respect to the transition state structure (see Fig. 1(c)).

Based on these aspects of entasis I will review recent results from the classical area of the blue copper proteins, followed by the discussion of selected examples of low molecular weight transition metal compounds, relevant to blue copper proteins and other areas of coordination chemistry.

2. Blue copper proteins

Blue copper proteins (cupredoxines, type-1 copper centers in metalloproteins) are generally relatively small proteins (approximately 10 kDa, 100 amino acid residues, 1500 atoms), which have one copper center at the northern pole, close to the periphery of the protein (see Fig. 2). Cupredoxines are involved in fast and efficient

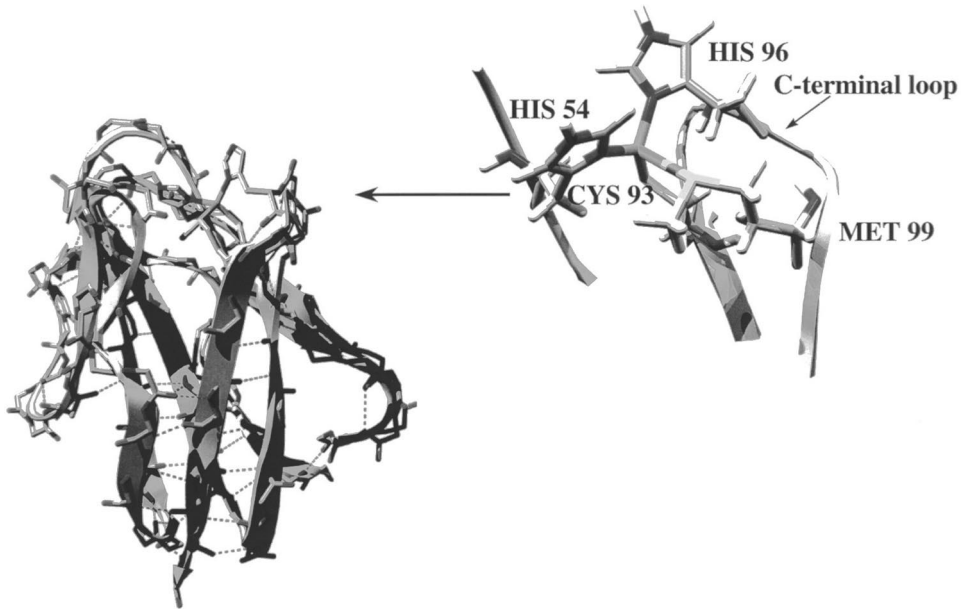


Fig. 2. Representation of the structure of the copper(II) form of amicyanin (*Paracoccus versutus*).

long range electron transfer in plants and in bacteria, such as the plastocyanines, which play a key role in the photosynthetic redox chain of higher plants and algae [14–17].

Compared to those of 'normal' copper coordination compounds type-1 copper sites exhibit unique spectroscopic and electrochemical features [14–20]. In the oxidized form there is an extremely intense electronic absorption band in the visible region, responsible for the intense blue color (~ 600 nm, $\varepsilon_{max} \sim 5000\ M^{-1}\ cm^{-1}$), that is, in the region, where common copper(II) complexes have weak dd transitions with $\varepsilon_{max} \leq 100\ M^{-1}\ cm^{-1}$; a second transition around 450 nm has smaller and variable intensity; the dd transitions appear at the low energy tail of the 600 nm band. Other prominent features are very small parallel copper hyperfine constants in the EPR spectra, with $A_{\parallel} \sim 50 \times 10^{-4}\ cm^{-1}$ or smaller (compared to $A_{\parallel} \sim (150–200) \times 10^{-4}\ cm^{-1}$ for tetragonal copper(II) amine compounds), comparably high redox potentials of approximately 200–500 mV (versus SHE; compared to 150 mV for the aqueous couple) and high electron transfer rates (approximately $(10^3–10^7)\ M^{-1}\ s^{-1}$, compared to $5 \times 10^{-7}\ M^{-1}\ s^{-1}$ for the aqueous couple) [14–20]. These unique properties have generally been attributed to an entatic state, that is, to an unusual coordination geometry, imposed by the protein on the copper(II) site [1]; in particular, the high redox potential was thought to reflect a stabilization of the reduced form of the copper protein (copper(I) is often found in tetrahedral geometries) and/or a destabilization of the copper(II) form (generally found in

Jahn–Teller distorted tetragonal coordination geometries); the fast electron transfer rate suggested little geometric change upon reduction, that is, small reorganization energies. Similar conclusions were drawn from spectroscopic features (including IRCD and XPS spectra) [21,22], leading to a detailed structural model, before the first crystallographic data were available, which essentially confirmed the predictions [23].

The geometric features of the oxidized and reduced forms of the blue copper proteins are very similar [24–26], and similar to those of the apoproteins and of the blue proteins coordinated to other metal ions [15,16,27–34]. The blue copper site has a trigonal pyramidal structure (sometimes called a distorted tetrahedral geometry), with three donors, viz. two histidine nitrogen atoms (at a Cu–N distance of approximately 2.0 Å) and a cysteinate sulfur donor (at a Cu–S distance of approximately 2.1 Å), coordinated to the metal center in a trigonal planar arrangement (out-of-plane distance of the copper center of less than approximately 0.5 Å), and an axial methionine sulfur donor at a rather long distance (Cu–S of approximately 2.7–3.2 Å; see Fig. 2). The largest structural variations of various blue copper sites in the oxidized form of the cupredoxines are found in the out-of-plane distance of the copper center from the trigonal plane, which is loosely correlated to the Cu–S(Met) distance (i.e. the copper center moves from the trigonal plane toward the methionine donor; this may be related to increasing rhombicity of the axial site geometry, see below), and the Cu–S(Met) distance is also loosely correlated to the inverse of the Cu–S(Cys) distance (i.e. the two types of copper–sulfur donation might be partly compensating).

The unique spectroscopic features of the oxidized d^9 site have been studied in detail [18–22,35–42]. The original interpretation of the small $A_{\parallel}$ values involved Cu $4p_z$/Cu $3d_{x^2-y^2}$ orbital mixing due to the distorted tetrahedral coordination geometry as seen in tetrahedral copper(II) compounds of sterically hindered dipyridyl ligands [37]. This idea has been revised on the basis of a series of elegant experiments, involving sophisticated and also new spectroscopic techniques and interpretations supported by SCF-X_α-SW and DFT calculations [20,43,44]. The entire set of experimental data that are related to the electronic structure of the oxidized d^9 and the reduced d^{10} state are now thought to be well understood on the basis of a ground state wavefunction, enforced by the protein, whose basic feature is that the Cu $d_{x^2-y^2}$ orbital is perpendicular to the Cu–S(Met, thioether) and bisected by the Cu–S(Cys, thiolate) bond [18,40,41]. This orbital (SOMO) is responsible for the redox activity and plays an important role in electron transfer processes. The reason for the small $A_{\parallel}$ values is high covalency of the blue copper site, and the two main features in the electronic spectra (the blue 600 nm and the yellow 450 nm transition) are attributed to an S(Cys)$p\pi \rightarrow$ Cu $3d_{x^2-y^2}$ π- and a S(Cys) pseudo-$\sigma \rightarrow$ Cu $3d_{x^2-y^2}$ transition, respectively. Distortions from trigonal pyramidal geometry (out-of-plane movement of the copper center, rotation of the $3d_{x^2-y^2}$ SOMO) lead to perturbed type-1 sites. The rotation of the $3d_{x^2-y^2}$ orbital and an increased ligand field strength (in-plane and/or axial) cause an increase of σ- and a decrease of π-overlap, and a concomitant decrease of the 600 nm and an increase of the 450 nm transition, leading to highly perturbed, green copper sites [43].

A key role in this description of the blue copper site is played by the long S(Met)–Cu bond: A shortening of this bond, that is, an increase of the axial ligand field strength leads to an increase of electron density at the copper center, hence to a weakening of the S(Cys)–Cu bond and a larger out-of-plane distance of the copper center. With the resulting reduction of the splitting between the $d_{x^2-y^2}$ and d_{xy} orbitals the d^9 site becomes Jahn–Teller active. It is the quenching of this distortion in the axial blue copper sites which is believed to be responsible for the small structural changes accompanying the oxidation of the reduced type-1 copper centers. In other words: The entasis is based on a quenching of the Jahn–Teller distortion of the oxidized d^9 copper site, and rhombic blue copper sites are less entatic [20,43].

The fact that the unique spectroscopic as well as thermodynamic and kinetic redox properties of the cupredoxines are correlated with the structural features imposed by the blue proteins, and the determination of many structures of wild type and mutated type-1 copper sites have led to the publication of extensive correlations of structural parameters with parameters emerging from UV–vis, EPR and Raman spectroscopy, as well as with redox potentials and electron self-exchange rates, and correlations of parameters of various properties with each other [45,46]. From the interpretation of the electronic properties (see above) it appears that such correlations are in most cases very approximative, and generally these have not been believed to be more than that. Based on the definition and description of the electronic ground and excited states of the blue copper sites, most properties might be correlated with a weighted sum of structural terms that include the out-of-plane bending of the copper center, the copper–S(Cys) and the copper–S(Met) distances and the rotation of the Cu $3d_{xy}$ orbital away from the Cu–S(Cys) vector.

A slightly different description of the ground state of the d^9 blue copper center was developed in a recent series of papers based on various types of ab-initio calculations, including HF, MP2, various types of DFT calculations and CASPT2 [34,47–52]. These calculations were based on carefully chosen model compounds; combinations of SH, SCH_3, NH_3 and imidazole were used to analyze the coordination geometries of the copper(I) and the copper(II) site, and a challenging result was that the copper(II) geometry is not enforced by the protein [34]; $[Cu(imidazole)_2(SCH_3)(S(CH_3)_2)]^+$ was used as a model for the oxidized plastocyanine site to analyze its electronic spectrum [47]; the influence of the thiolate ligand was modeled by the structure optimization of a series of $[Cu(NH_3)_2(SH)(S(CH_3)_2)]^+$ and $[Cu(NH_3)_3L]^{n+}$ compounds (L = halogenide, O-, S-, Se-, N-, P-donors) [49]. These studies were based on high level and extensive quantum mechanical computations of small model compounds but with the inclusion of electrostatic fields, and a careful comparison of the resulting data with available structural and electronic spectroscopic data. The main results are that the trigonal pyramidal structure of the oxidized blue copper sites with axial symmetry is stabilized by a ground state wave function similar to that described above, that is, a Cu $3d_{x^2-y^2}$/S(Cys) π molecular orbital; that there is a second low lying ground state (within approximately 7 kJ mol^{-1}) with a tetrahedrally distorted tetragonal geometry and significant σ-character in the Cu–S(Cys) bond (rhombic sites); that the 600 and the 450 nm charge

transfer bands are due to π- and σ-overlap, respectively; that electrostatic fields are required to model accurately the electronic transitions; that the structures are not enforced by the protein [34,47–52].

Approximate density functional theory (DFT) methods have also been used to calculate inner-sphere reorganization energies of blue copper proteins, and the conclusion was that soft ligands (Cys, Met) are responsible for the lowering of the reorganization energy because they make the potential energy surfaces rather flat [50]. From free energy perturbation calculation it was concluded that there might only be a minor influence of the protein to enforce the axial Cu–S(Met) bond distance [51], and this is somewhat in contrast to the interpretation of entasis as quending of the Jahn–Teller distortion (see above) [20,43].

From another quantum mechanical study with the aim to probe the influence of the Cu–S(Met) distance to the reduction potential, it emerged that the large observed variation of reduction potentials could not be modeled accurately. Therefore, this variation was assumed to be due to changes in the solvent accessibility of the copper site [52]. Solvation is an important factor, and it is not generally appreciated that solvation effects are much different in proteins (protection of the active site) and small molecular weight model compounds (see next section), and solvation very often is neglected in computational studies related to metalloproteins and model compounds.

As a whole, the published experimental data (structures and properties) are in agreement with a ground state wave function that is primarily based on Cu $3d_{x^2-y^2}$/S(Cys) π-overlap [34,38–49,53]. The fact that excitation in the 450 and the 600 nm bands leads to close to identical Resonance Raman spectra seems to contradict the idea of two ground states with similar energies [33]. The modulation of the copper coordination geometry by loop mutations that involve the C-terminus, where three of the four donors reside, were thought to contribute to the understanding of the dependence of spectroscopic and redox parameters from subtle structural changes with a conserved donor set [33]. However, a final evaluation of these data might have to wait for the corresponding structural analyses. An intriguing result in this series of experiments was the fact that in at least one case (AmiPse; pseudoazurin loop mutated into the amicyanin protein) the UV–vis spectrum is very much temperature dependent; at room temperature the compound is blue, at low temperature it is green, and this is due to a significant change of the intensities of the 600 (blue) and 450 nm (yellow) band. Both variable temperature Resonance Raman and EPR data were not showing similar dependencies [33,54]. It seems that this behavior is not easily explained by the current proposals of the electronic structure, and some modifications might be needed in future.

The loop mutants might be of importance to probe the entatic state concept and, as expected, there are significant changes of all properties which were considered. However, one has to be careful to correlate these changes with structural parameters, even when structural data are available (see above for various modes of distortion and their influence on the electronic states; for the importance of electrostatic fields, see Ref. [49]; for the importance of solvation see Ref. [52]; for various dependencies with respect to the electron self-exchange rate, see Ref. [33]).

Are blue copper sites entatic? My personal conclusion:

1. The classic idea and common textbook interpretation is at least oversimplified (see Section 3.2 for further features with respect to the preferences of copper(I)).
2. The protein is responsible for the observed reactivity and the electronic properties. This may be primarily due to an environment of the copper site that helps to stabilize the copper(II)/imidazole/thioether/thiolate coordination sphere (see also Section 3.1 for problems in stabilizing Cu(II)–SR bonds), to keep the axial thioether at the required distance and to enforce specific electrostatic fields and solvation patterns.
3. The long and partially controversial discussion on entasis in blue copper proteins has certainly been motivating and lead to a good understanding of the chemistry and biochemistry of copper(II/I) couples. The concept is relevant, the answer to the question whether blue copper sites are entatic is not.

3. Coordination chemistry

In this chapter I will concentrate on selected examples of classical coordination compounds with ligand-enforced coordination geometries and the question of how relevant it is to refer to the entatic state principle in these cases. The first section, on structures and spectroscopy, is primarily devoted to bioinorganic mimics (structural and spectroscopic low molecular weight models of metalloproteins), and I will restrict these entirely to blue copper protein models. The second section is on electron transfer, mainly but not exclusively related to blue copper protein chemistry. The remaining parts are on various subjects and will include systems that may lead to technical applications.

At this point it is useful to summarize the major tools available to coordination chemists for enforcing specific coordination geometries [10,11]: (i) the carbohydrate backbone of multidentate (acyclic, cyclic and polycyclic) ligands is generally more rigid than bonds and angles involving the transition metal center, that is, specific coordination geometries may be enforced by a careful choice of ligand systems; (ii) the only soft modes in ligand backbones are torsions around single bonds, that is, very rigid ligands have ring systems and/or multiple bonds to reinforce the backbone; (iii) substituents at the ligand backbone might also help to enforce a specific conformation (steric hindrance, secondary interactions such as van der Waals and electrostatic interactions, hydrogen bonding and solvation effects); (iv) a very rigid ligand which is preorganized for a specific coordination geometry (note, that this involves the angular distribution of the donors around the metal center and the metal–donor distances) will lead to a strained (unstable and/or reactive) complex when the metal preferences are different; (v) an action that increases the stability of a highly strained complex is dissociation of one or several donors of a polydentate ligand (release of strain) and/or addition of further ligands, that is, an (unwanted) change of the coordination spheres; the denticity of ligands may be controlled by their rigidity, addition of coligands may be prevented by shielding of the chromophore or in non-coordinating solvents and with non-coordinating counter ions.

3.1. Structures and spectroscopy

The main reasons to design, synthesize and study structures and spectroscopy of simple models for metalloproteins are (i) accurate structural parameters (high resolution); (ii) thorough spectroscopic analysis (e.g. single crystal work); (iii) interpretation of structures, electronic properties and reactivities, based on high level quantum mechanical calculations; (iv) correlation of the spectroscopic and thermodynamic properties and reactivities with structural parameters, if a series of species with systematically varied structural features are available. From Section 2 (see also relevant references cited there) it appears that there is not much reason to still try to prepare blue copper model compounds: a variety of wild-type and mutated blue copper protein structures have been solved; very accurate spectroscopic analyses are available; the interpretations are based on high level electronic calculations; site- and loop-selective mutagenesis have produced a wide range of structural variations and these proteins are generally more stable than artificial mimics.

The problems encountered with artificial model compounds are (i) the stabilization of four-coordinate copper(II) in a trigonal pyramidal (tetrahedral) geometry and (ii) thiolate coordination to copper(II), because the copper(II) thiolate bond easily leads to homolysis with reduction of copper(II) and formation of disulfides. The latter fact is a major reason for one of the still missing links which might in fact emerge from classical, preparative coordination chemistry: the assumption, based on quantum mechanical studies [34,47–49], that simple compounds of the type $[Cu(NR)_2)_3(SR')]^+$, with amines that do not enforce a particular geometry, should be trigonal pyramidal, might be supported by preparative coordination chemistry. Anyway, from structural and spectroscopic 'blue copper mimics', a range of interesting new compounds has been isolated and studied and this has lead to significant new insights in the area of copper coordination chemistry, ligand preorganization in general and highly strained compounds. A comprehensive review of this area, with examples up to the early 1990s has been published [55].

One of the early conclusions, based on simple blue copper models, in the mid and late seventies was that various types of sulfur donors (thiolate or thioether), coordinated to copper(II), are able to induce some of the properties that are typical for type-1 copper sites. In particular, electronic spectroscopic properties with charge transfer transitions of high intensity in the region of approximately 600 nm were generally reported in various model compounds with S-donors, and, where measured, relatively high redox potentials (300–700 mV) were observed [55]. These 'blue copper mimics' include mono- and dinuclear copper(II) compounds (and in some cases their reduced forms) with tetra- and pentathiamacrocyclic ligands (Fig. 3(a,b)) [56–58], compounds with peptide ligands and imidazole derivatives (Fig. 3(c–f)) [59–63], dithiolates (Fig. 3(g)) [64] and sterically hindered trispyrazolylborate tripods (Fig. 3(h)), together with sterically demanding thiolate donors [55,65–69]. However, in none of these putative models were all important features simulated; the $A_{\parallel}$ copper hyperfine lines were in most cases as expected for 'normal' copper(II) compounds, that is, larger than observed in the blue copper sites. Of

more concern is the fact that in many examples there were no experimental structural data available and the analysis of the spectroscopic data was by no means as thorough as for the copper proteins (see Section 2). That is, the origin of the blue visible band in the model compounds has not been determined, and in many examples it might be different from that in the proteins. This also applies to the most accurate model compound which has been produced so far (see below) [55,68,69].

From a series of copper(II) compounds with various donor sets, coordination numbers and geometries, which were structurally and spectroscopically characterized, it was concluded that the important spectroscopic features were strongly dependent on the copper–thiolate bond distance and the angular coordination geometry [55,70–76]. This also emerges from studies that involve metal ion substitution in various metalloproteins. Copper(II)–thiolate bonds were for example stabilized in alcohol dehydrogenase [77–79] and in an insulin site [80]. The EPR spectrum in the latter example has an $A_{\|}$ value of 76 G, and in the UV–vis spectrum there are high intensity charge transfer transition at 408 nm and 626 nm. The copper(II) center in an Ag/Cu-substituted superoxidedismutase (SOD) which is in the tetrahedral zinc site exhibits an EPR spectrum which is similar to that of type-1 copper sites ($A_{\|} = 97$ G) [81].

The main problem for coordination chemists interested in blue copper mimics is, as indicated above, to stabilize copper–thiolate bonds. In the most successful model, this was achieved by a sterically hindered trispyrazolylborate ligand (see Fig. 3(h)) with isopropyl substituents in 3,5-positions and sterically hindered or acidic thiolates (^{t}ButSH, Ph_3CSH, C_6F_5SH) [68,69]. The spectroscopic and electrochemical properties of these copper(II) compounds are very similar to those of axial blue copper protein sites (e.g. azurin, plastocyanin, see Table 1), and the experimentally determined X-ray structure also confirms a trigonal pyramidal geometry, with the copper center only slightly above the plane defined by two pyrazolyl and the thiolate donors and a significantly elongated bond to the third pyrazolyl donor (see Fig. 4) [55,68,69]. From these results it appears, even without a thorough analysis of the electronic ground state, but in comparison with the data obtained from other, less successful mimics (see above) and with those from the protein type-1 sites (see Section 2), that an important role of the protein is to protect the copper–thiolate bond from homolysis. Clearly, this is not how entasis is traditionally defined. An interesting observation with respect to the trigonal pyramidal coordination geometry observed in this model and in copper protein structures is that in dinuclear copper(I) compounds with a bridging 2,2-bipyrimidine and four phosphine ligands, where each copper center is coordinated to two aromatic nitrogen and to two phosphine donors, the two copper–phosphorous bonds are significantly different and the coordination geometry may be best described as trigonal pyramidal. π-Stacking of a phenyl substituent of one of the phosphorous donors with the bipyrimidine group was assumed to be responsible for the deviation from tetrahedral structure [82]. Apart form this example entasis has only rarely been observed and described in the copper(I) state (see also next section for a

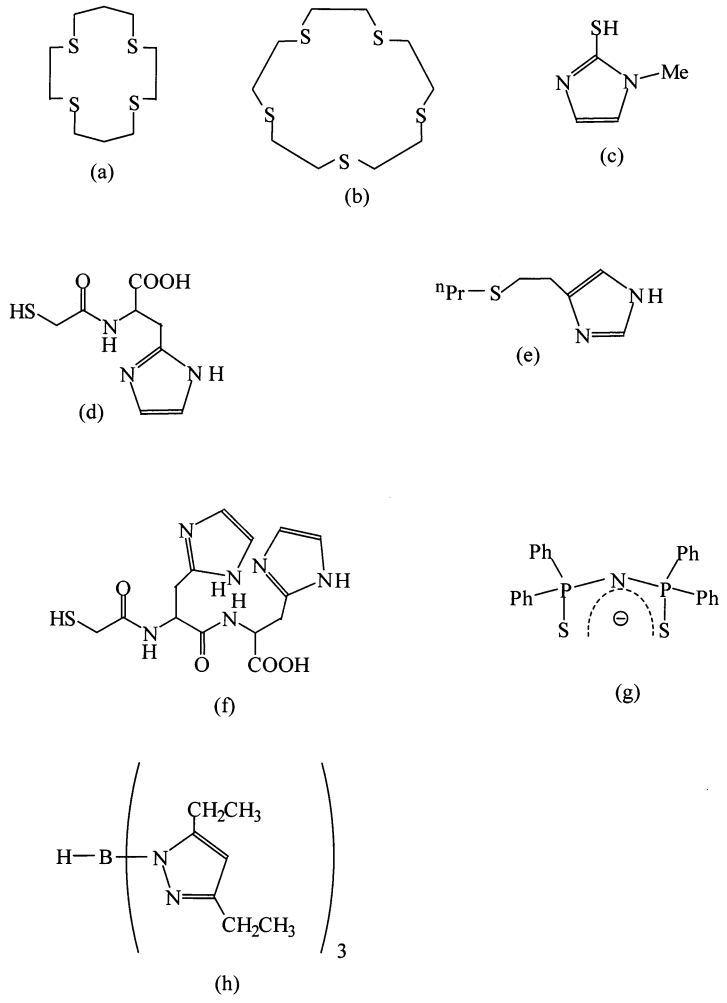


Fig. 3. Ligands for copper complexes used as structural and spectroscopic mimics of blue copper proteins.

detailed discussion on the putative stabilization of copper(I)). Another one of the few examples is that of a 16-membered N_4 macrocycle (four imine donors), where the tetrahedral twist angle $\theta = 57°$ has been reduced significantly from the tetrahedral value ($\theta = 90°$) [83].

Many ligands, the majority of which have four N-donors, have been designed, prepared and coordinated to copper(II), in order to enforce a tetrahedral (or distorted tetrahedral) coordination geometry. Some of these compounds might have been planed as low molecular weight blue copper protein models, and their

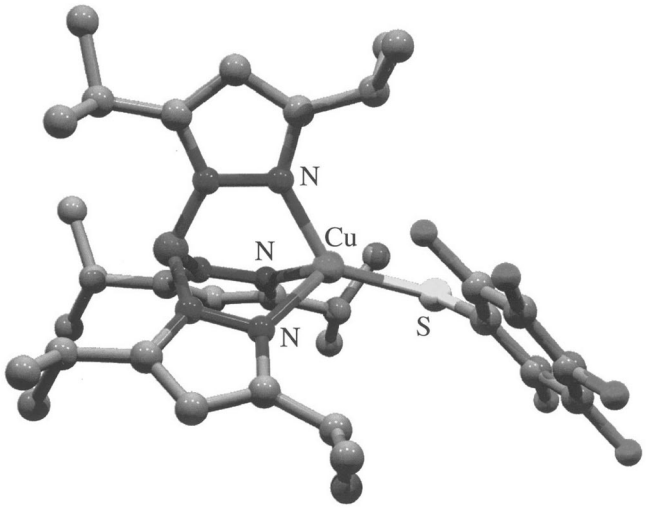


Fig. 4. Representation of the molecular cation of the experimentally determined structure (hydrogen atoms omitted) of a copper(II) compound with a sterically demanding trispyrazolylborate (see Fig. 3(h), isopropyl substituents) and a sterically hindered thiolate ($C_6F_5S^-$) [69].

relevance with respect to blue copper proteins and the entatic state principle has often been pointed out. This is usually based on the meanwhile refuted idea that the small $A_\parallel$ values are due to Cu $4p_z$/Cu $3d_{x^2-y^2}$ orbital mixing, which originates

Table 1
Spectroscopic and redox properties of the trispyrazolylborate blue copper mimics in comparison with those of azurin and plastocyanin [55,68,69]

Compound[a]	Electronic transitions[b]			$g_\parallel$	$g_\perp$	$A_\parallel$[c]	Redox potential[d]
	dd	CT	CT				
Azurin	820 (390)	467(270)	625(3500)	2.26	2.05	58	+300
Plastocyanin	770 (1700)	460(540)	597(4900)	2.24	2.05	63	+370
$[Cu(L)(ScPh_3)]^+$	918 (1200)	440(240)	625(6600)	2.23	2.07	71	−120
$[Cu(L)(SC_6F_6)]^+$	960 (600)	420(200)	665(3600)	2.30	2.10	52	+260
$[Cu(L)(S^tBu)]^+$	900 (450)	–	608(3000)	2.21	2.08	70	−110

[a] L: tris (3,5-propyl) derivative of the tris-pyrazolylborate ligand shown in Fig. 3(h).
[b] In nm, arbitrary assignment; ε-values (in brackets) in M^{-1} cm^{-1}.
[c] In Gauss.
[d] In millivolts vs. SHE.

from distorted tetrahedral coordination geometry [37] (Section 2 and the corresponding references). It has been demonstrated that the ligand field and electrochemical properties can be correlated to the tetrahedral twist [10,84,85], and reports have been published which indicate how the reduced copper(I) state may be stabilized with a careful choice of donors [86–89] (see, however, the next section on electron transfer). This indicates, how entasis in general may be related to ligand preorganization and that the ligands designed for modeling blue copper sites might be of interest in other areas, such as metal ion selectivity [11,90]. In some cases the relevance of various systems for catalytic processes was also noted [89,91]. Some of these examples are now discussed.

A number of ligands have been described that use the non-planarity of the biphenyl moiety to enforce a tetrahedral distortion onto the copper(II) center. Of particular interest is a recent study with such a ligand with a chelating pyridyl/methyltriazolyl substituent on both phenyl rings, because it includes detailed structural data of both the oxidized and reduced forms, as well as electrochemical and electronic spectroscopic data (see Fig. 5) [91]. The two structures are similar with $Cu–N_{py} = 2.01$ and 2.09 Å, $Cu–N_{tz} = 1.96$ and 2.04 Å and a tetrahedral twist angle θ ($\theta = 90°$ for a tetrahedral, 0° for a planar coordination geometry, planes defined by copper and the chelate rings) of 40 and 55°, for the oxidized and reduced forms, respectively.

The bond distances are as expected for the corresponding chromophores and the significant twist of the oxidized form towards a less tetrahedral geometry indicates that there is still considerable flexibility in the ligand backbone (the flattening of the

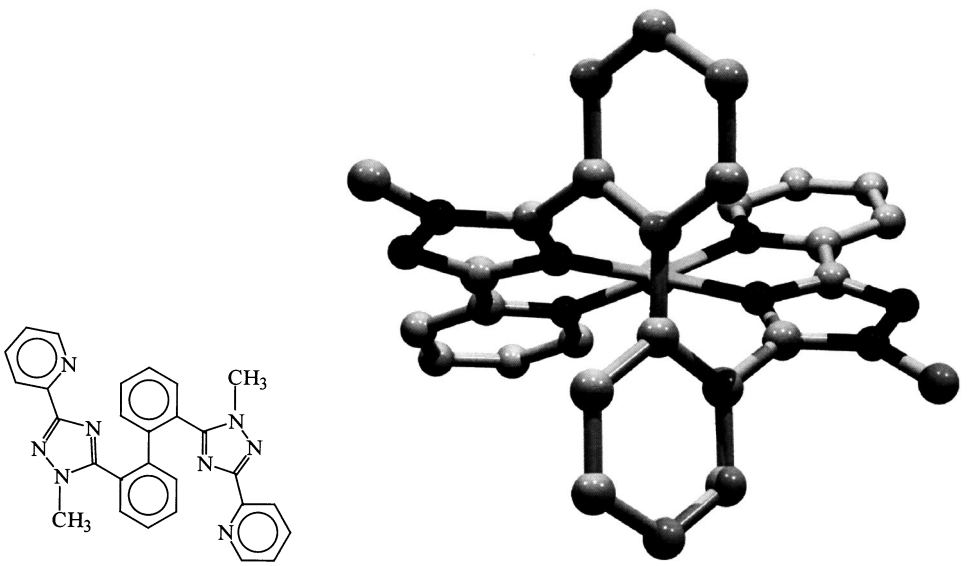


Fig. 5. Plot of the molecular cation of the experimentally determined solid-state structure (hydrogen atoms omitted) of the copper(I) complex with a biphenyl-based tetradentate ligand (the drawing is a representation of the ligand in [91]).

tetrahedral geometry is probably also assisted by the contacts to two axial perchlorate oxygen atoms at 3.0 and 3.1 Å, respectively). The copper(I) compound of a similar ligand with 2,2′-bipyridine instead of the pyridyl/methyltriazolyl chelates is significantly more tetrahedral [92], and this is in agreement with a stronger destabilization of the copper(II) state, that is, a shift of the redox potential towards a more positive value (720 versus 550 mV, SHE, acetonitrile) [91,92].

The tetrahedral twist angle θ in a structure of a similar biphenyl-based ligand with an N_2S_2 donor set (pyridyl/thiaether), coordinated to copper(I), is 67° [93]. Interestingly, this compound forms spontaneously, when copper(II) salts and the ligand are reacted in solution. This is supported by a very high redox potential (1011 mV, SHE, acetonitrile). The influence of the sulfur donors and of the strain imposed by biphenyl groups, have been studied by derivatives, where the sulfur atoms are replaced by nitrogens (N_4 donor set, pyridyl/amine) and where the biphenyl group is replaced by two phenyl groups (N_2S_2 donor set; two bidentate instead of the tetradentate ligand) [93]. The corresponding redox potentials (versus SHE) are 451 mV (N_4/tetradentate) and 771 mV (N_2S_2/bis-bidentate). From these two examples it appears that redox potentials (and electronic properties in general) are, as expected, strongly dependent on both, the donor set and its arrangement around the metal center. The geometric forces have been analyzed by Hückel and by Angular Overlap Model (AOM) calculations and compared with experimental data of the reduced copper(I) state of the biphenyl-type N_4-ligands [91], by the analysis, based on Extended Hückel calculations, of structural, spectroscopic (electronic and EPR) and electrochemical data of a set of copper(II)–N_2S_2 compounds with tetrahedral twists of $3 < \theta < 52°$ [94], as well as by combined force field and ligand field (AOM) calculations and the corresponding experimental data of N_4-macrocyclic ligand copper(II) compounds (see Fig. 6) [10,84,95]

From the second part of this section it follows that ligands which enforce a (distorted) tetrahedral geometry perturb the usual electronic and electrochemical properties of the copper(II/I) couples, leading to compounds with interesting and sometimes unexpected properties. One of the main problems in those of the copper systems discussed here, which were described as bioinorganic models, is, apart from the fact that the well characterized ground state of blue copper sites (see Section 2) still is ignored too often, that the cupredoxines′ most important property, fast electron transfer, has not been investigated in many of these models. Systems where this has been done will be considered in Section 3.2.

3.2. Electron transfer

The thermodynamics and kinetics of electron transfer in cupredoxines, that is, redox potentials and electron transfer (often electron self-exchange) rates have been related to the specific structural and electronic properties of blue copper sites. Very detailed studies of relatively simple coordination compounds have yielded important and exciting new insights and lead to a better understanding of electron transfer and stabilities in copper(II/I) couples and coordination compounds in general, that is, also for blue copper sites. However, a direct comparison of specific

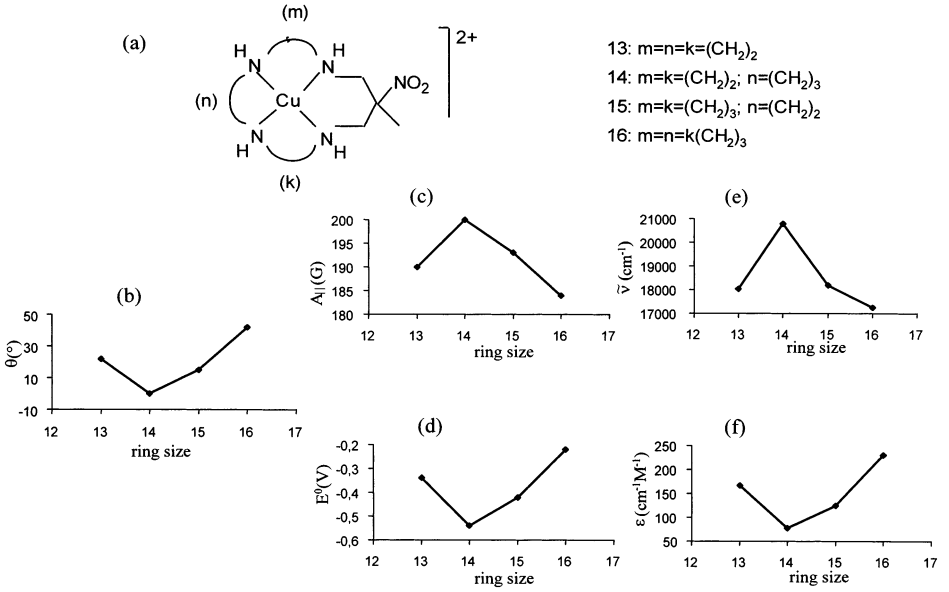


Fig. 6. Correlations of spectroscopic and electrochemical data of a series of copper(II) compounds (a); with the tetrahedral twist ($\theta = 0°$ for planar, $\theta = 90°$ for tetrahedral) (b); EPR parallel hyperfine coupling (c); redox potential (d); dd transition energy (e); dd transition intensity (f); [84].

models with proteins is not appropriate, primarily because there is no internally consistent and general model for all observations, and this has been realized in most publications discussed here. Another point of importance is that electron transfer rates may be influenced by a number of factors (encounter complex formation, electronic coupling, inner-sphere reorganization, outer-sphere reorganization, thermodynamics; the relative importance of these factors on the self-exchange rate constant for copper proteins has been estimated [33]). That is, the inner-sphere reorganization term, related to structural changes and to the entatic state hypothesis, might not be the major factor and could well be offset by other terms. For example is there some consensus that electron transfer in copper proteins might be significantly more nonadiabatic than in some of the model compounds [96,97]. The question of entasis and preorganization has been discussed in detail in some of the relevant publications. Entasis with the meaning of 'by rigid ligands enforced geometry to tune the redox potential' was generally believed to be a more realistic idea than the traditional kinetic interpretation. However, some recent data compilations indicate that some of these ideas might also need to be revised (see below).

Apart from ligand preorganization (tetrahedral site geometry) and the stabilization of copper–thiolate (and thioether) bonds there are other possibilities to increase redox potentials. N-methylation of cyclic and open-chained tri- and tetraamine ligands have been used, as well as triamines with terminal alkene groups [86–89]. Electrochemical and spectroscopic properties and the stability constants indicate that the destabilization of the oxidized form by alkenes and by tertiary

amines is very similar while these are significantly smaller than that by thioether groups [89]. A careful analysis of stability constants (copper(II) and the corresponding copper(I) compounds) and of reduction potentials indicates that the stabilities of copper(I) compounds vary only slightly ($\log K_{Cu(I)L} \sim 14 \pm 2$), while the stabilities of the corresponding copper(II) compounds span a large range ($1 \leq \log K_{Cu(II)L} \leq 20$); hence, the variation of the corresponding redox potentials ($-0.66 < E^f < 0.89$ V) is almost entirely due to changes in the stability of the oxidized forms [98]; this already emerges form an earlier study [99], and the data on aminealkylation and alkene donors (see above [89]) fit into this picture. Also, the fact that copper(II/I) redox potentials depend only on the structure of the oxidized form, rather than on those of the copper(II) and the copper(I) states, probably is the main reason for an unexpectedly good correlation of reduction potentials and strain energy differences for a series of copper(II/I) couples [95]. Therefore, the common idea that tetrahedral geometries and sulfur donors, as well as tertiary amines, large cavity sizes and alkene donors stabilize copper(I) has to be reformulated: these factors destabilize copper(II), and this is a statement that is close to the original idea of entasis (if one accepts a thermodynamic rather than a kinetic interpretation).

In an extensive series of kinetic studies on electron transfer of copper(II/I) couples, primarily with tetrathiamacrocyclic ligands of various ring sizes, electron transfer rates, determined by ^{1}H-NMR line-broadening techniques, were compared to apparent self-exchange rates, calculated by the Marcus relationship [100–103] from cross reaction rate constants with the corresponding copper(II) and copper(I) complexes and various reductants and oxidants [99,104–107]. As observed before [108–111], there were significant differences between the calculated self-exchange rates derived from copper(II) reduction and copper(I) oxidation, and the former were up to seven orders of magnitude larger than the latter [104]. To explain these discrepancies, a dual pathway square scheme was proposed, which involves isomerization to activated forms of the reduced and oxidized species, followed by electron transfer (see Fig. 7) [104–106]. Under appropriate conditions either of the two conformational changes might become rate limiting and, in thermodynamically favorable cases, this conformational control is manifested in only one direction [112,113].

Electrochemical and kinetic studies of specific systems allowed to unambiguously identify all four species in the dual pathway square scheme and to deduce all relevant rate constants [114–116]. Fully gated electron transfer was observed in a copper(II/I) couple with a relatively rigid 16-membered N_2S_2 macrocyclic ligand [117]. Structural studies (experimentally determined structures and force field calculations) indicated that donor atom inversion (N- or S-donors) rather than a change of the coordination number (ligand dissociation) may be the major factor that leads to conformational control in the electron transfer kinetics of copper systems [106,107,118]. With ligands which enforce copper(II) structures with the metal center above the plane of the macrocyclic donor atoms (e.g. 12-membered macrocyclic thiaether ligands) the donors are predicted not to invert upon reduction, and indeed this leads to very fast electron self-exchange [107].

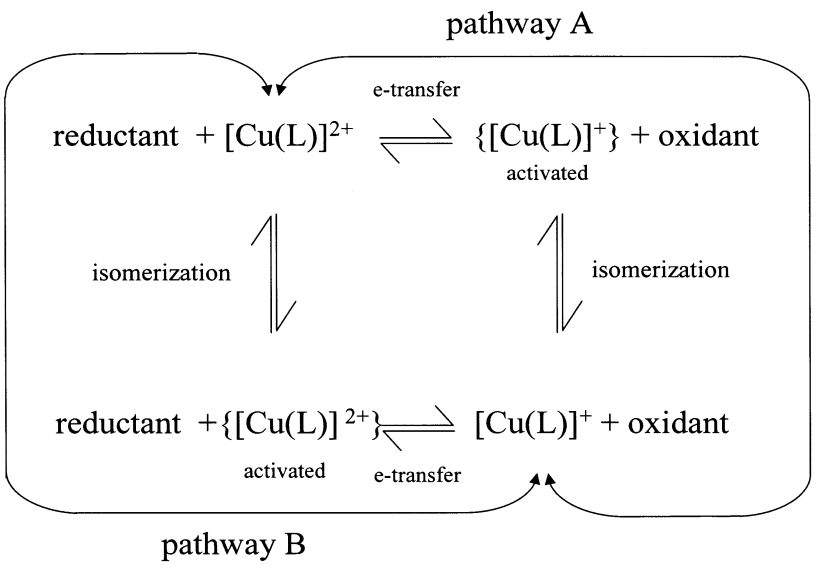


Fig. 7. The dual pathway square scheme for electron transfer in copper(II/I) couples [104–106].

A particularly interesting example is that of $[Cu(L)_2]^{2+/1+}$ where L is a biphenyl-based bidentate ligand with two imidazole donors (Fig. 8) [97,119]: The copper(II) compound has an enforced tetrahedral distortion, the bond length differences between the oxidized and reduced forms are relatively small (≤ 0.07 Å) and, nevertheless, the system has one of the slowest self-exchange rates observed for copper(II/I) couples (0.16 M^{-1} s^{-1}). Based on molecular mechanics calculations the high energy barrier was assumed to be due to significant differences in the angular geometry [97]. It appears that molecular mechanics might be a useful tool to quantify the degree of structural changes (preorganization, entasis). However, inconsistencies in terms of the models that have been used [97,120–122], oversimplifications (e.g. with respect to solvation and entropy differences) and the fact that some of the force fields used have not been validated with respect to thermodynamic properties [11,123] indicate that, in terms of quantitative interpretations, one has to be extremely careful.

In the example of $[Cu(L)_2]^{2+/1+}$ it appears that the simple qualitative idea of the entatic state fails to yield a clear interpretation of the electron transfer reactivity.

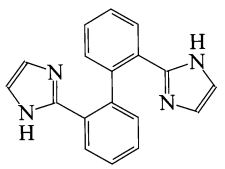


Fig. 8. The biphenyl-based bidentate ligand L, whose $[Cu(L)_2]^{2+/1+}$ couple has an unexpectedly low electron self-exchange rate [97,119].

The ligand strongly enforces a specific coordination geometry, and this leads to very similar chromophores for the oxidized and reduced forms. A number of examples in the last section under the headings of 'copper(II) compounds in the entatic state' and 'structural and spectroscopic blue copper mimics' might fall into the same category, and it might be worthwhile to investigate the electron transfer reactivity and to compute the corresponding inner sphere reorganization energy of some of these systems. It appears that, in the case discussed above, factors other than the inner sphere reorganization term (e.g. factors related to solvation), which is the basis for the entatic state interpretation, might be more important than generally appreciated (see Section 2 [33]).

3.3. Complexation

Complex stability is of importance in many areas, including metal ion separation (metal ion selective complexation, followed by, e.g. solvent extraction or chromatography) [11], the tuning of redox potentials, see above [95,122], the stabilization of specific electronic configurations (e.g. for spectroscopic model compounds, see above [55]) and catalysis (specific catalyst–substrate interactions). The energetics of complexation involves solvation energy changes (desolvation of the metal ion and of the metal-free ligands and solvation of the metal complex), metal–ligand bond formation, entropy changes and steric effects (strain imposed by the metal ion on the ligands and strain imposed by the ligands on the metal ion). The steric energy is at a minimum when the structure of the metal-free and the coordinated ligand are identical, that is, when the ligand is fully preorganized [11–13,124], and this is an important factor in all areas mentioned above. Ligand preorganization may involve enforcing an otherwise less stable conformation by a modification of the ligand backbone [10,11]. Therefore, energization (entasis) of metal-free ligands is an important factor in the area of complexation, and the degree of ligand preorganization has been related to steric energies [124]. This will now be discussed, based on two selected examples.

The coordination of a dinucleating octaazamacrocycle with two bis(pyridine)-bis(tertiary amine) binding sites, linked with two rigid alkine spacer groups, to two copper(II) ions leads to a highly strained dicopper(II) species with five-coordinate copper(II) sites (coordination of an acetonitrile solvent molecule to each of the copper centers, see Fig. 9) [125]. In the presence of potentially bridging ligands (carbonate, cyanide, hydroxide), less strained six-coordinate ligand-bridged dicopper(II) compounds are formed. Release of strain as the driving force has been assumed on the basis of structural data, electronic spectroscopy and qualitative molecular modeling studies, and the bis(five-coordinate) dicopper(II) compound (Fig. 9) was interpreted as an energized precursor of the six-coordinate product with small bridging ligands [125].

The stabilization of oxo- and peroxo-bridged dicopper compounds (biological oxygen transport and activation) has been studied extensively in recent years [55,126–128]. I will concentrate here on end-on μ-peroxo-bridged dicopper(II) species [126]. These are particularly unstable, and only one experimentally deter-

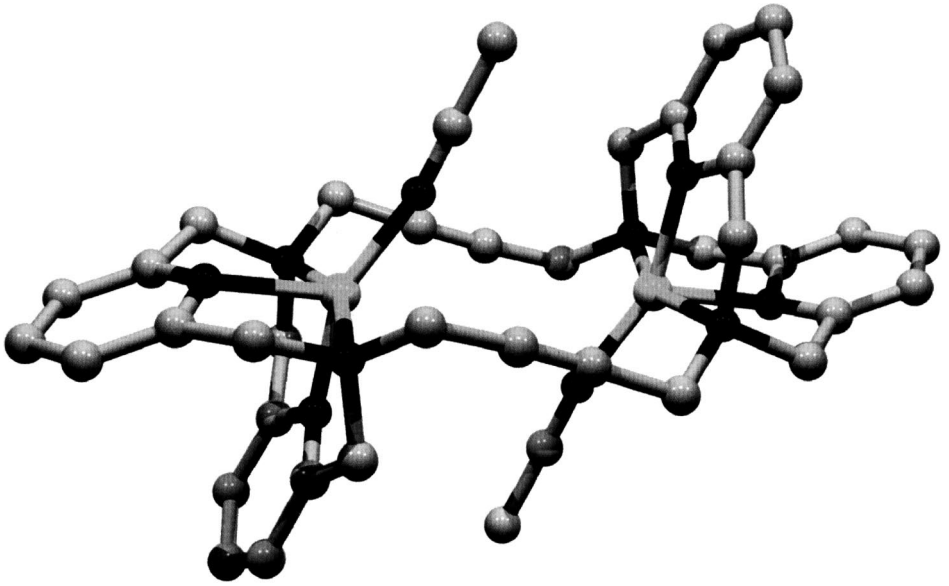


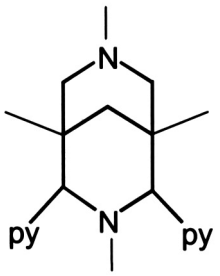
Fig. 9. Representation of the molecular cation of the crystal structure analysis of the bis(five-coordinate) precursor of bridged bis-(six-coordinate) dicopper(II) complexes (hydrogen atoms omitted) [125].

mined solid state X-ray structure has been published so far [129]. Efforts to stabilize these compounds have involved preorganization of the peroxo products with carefully designed dinucleating ligands [130–133], stabilization of the copper–oxygen bond by enforcing a particular coordination geometry [133] and destabilization of the copper(I) precursor (see, however, Section 3.2) [131,134,135]. All these factors may be related to the entatic state principle (i.e. to ligand preorganization, see above), and a combination of the three factors, viz. a preorganized dinucleating ligand, which enforces square pyramidal geometry with strong in-plane copper–oxygen bonding, and which destabilizes the copper(I) precursor has produced a system which has been shown to lead to one of the most stable end-on (μ-peroxo)dicopper(II) compounds (see Fig. 10) [133,135].

The factor which is most related to the classical interpretation of entasis, and a feature which is usually not analyzed with respect to the stabilization of peroxo-dimetal compounds, is the destabilization of the dicopper(I) precursor, that is, ligand preorganization for the dicopper(II) chromophore (note, that this is the inverse situation to that discussed above for blue copper model compounds; note also, that stabilities of copper(I) complexes are in general practically invariant (so far, there are no data available for the copper-bispidine compounds shown in Figs. 10 and 11, see above) [135]. Crystallographic studies of copper(I)-bispidine compounds revealed that two isomeric forms, a four- and a five-coordinate species exist. The cavity, provided by the rigid ligand is not well suited for copper(I) in either case (see Fig. 11) [135]. This is supported by superimposing structures of the copper(II) product with those of the metal-free ligand and of the reduced form of the complex

(a) $2[Cu^{I}L] + O_2 \rightleftharpoons [(Cu^{II}L)_2(O_2)]$

(b) L =



(c)

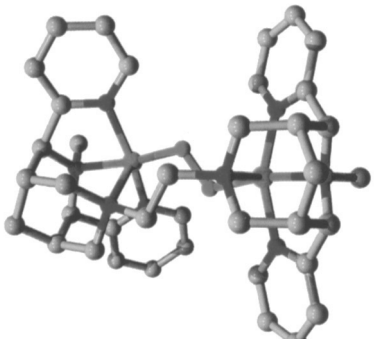


Fig. 10. Stabilization of end-on (μ-peroxo)dicopper(II) compounds: (a) complex formation; (b) bispidine ligand backbone; (c) computed structure of the most stable compound of the series (hydrogen atoms and irrelevant ligand substituents omitted) [133].

(see Fig. 11). Further support for the entasis of this copper(I) state comes from the fact that in solution there is a fast dynamic process. The low temperature ^{1}H-NMR spectrum (frozen isomer) is compatible with the five-coordinate form (two identical pyridine rings), and this suggests that the crystallographic analysis (Fig. 11a) is a good visualization of the dynamic process [135]. This dynamic process involves bond formation and rupture, and these are generally not related to very low energy barriers. The assumption is that changes in bonding energy and steric strain are partially compensating. This preliminary interpretation [133,135] might not be correct in all details and a quantum mechanical analysis could be of interest. Therefore the assumption of a copper(I) precursor in the entatic state might here, as in many other cases, not be entirely warranted.

Nonetheless, this example indicates that highly preorganized ligands are especially efficient when they are very rigid. Since rotations around single bonds are the lowest energy modes in the organic backbone of ligand molecules, highly preorganized ligands generally have fused small ring systems and/or multiple bonds. In the example with the bispidine-type ligands (Figs. 10 and 11) the only low energy

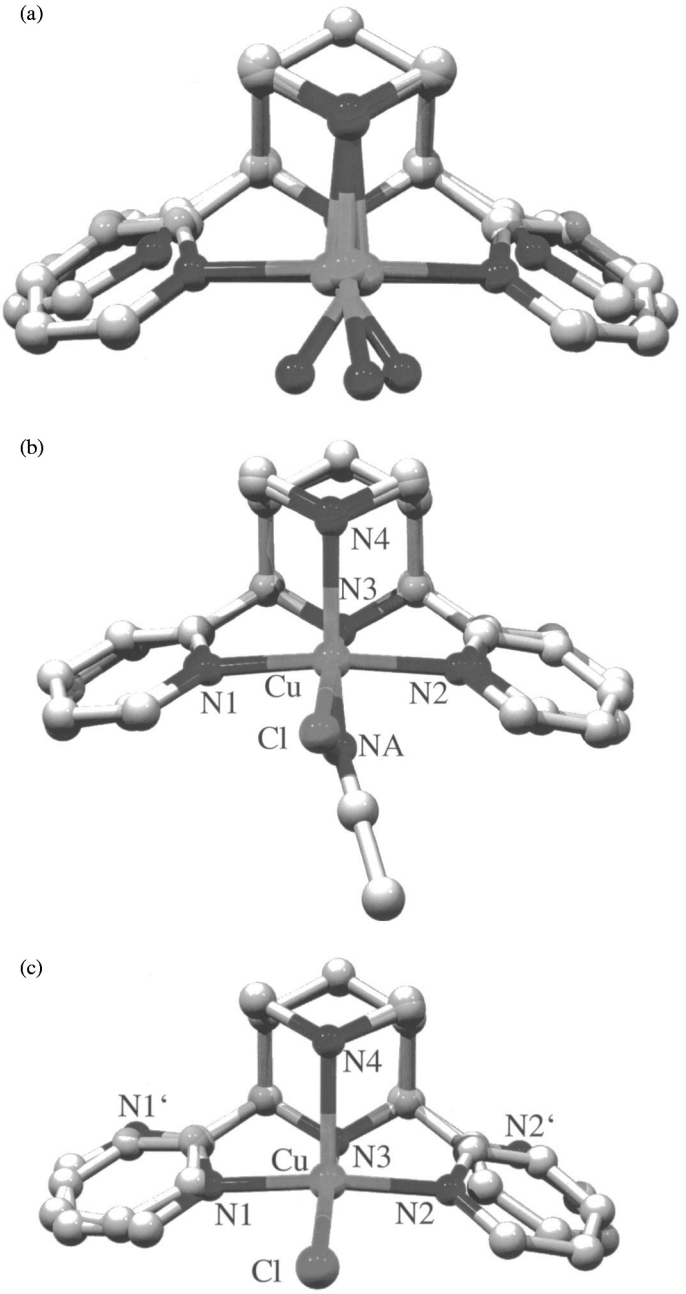


Fig. 11. Visualization of the destabilization of the copper(I) precursor, based on experimentally determined structures (hydrogen atoms and irrelevant ligand substituents omitted): (a) overlay of four- and five-coordinate isomers of the copper(I) structures; (b) overlay of the five-coordinate copper(I) and copper(II) structures; (c), overlay of the structures of the copper(II) compound and of the metal-free bispidine ligand [135].

modes are the rotations around the two single bonds involving the pyridine substituents and the bispidine backbone.

3.4. Catalysis

The oxidation of catechole derivatives is known to be catalyzed by a variety of copper(II) compounds (see Fig. 12a). Various complexes have been used to catalyze this reaction, and, dependent on the catalyst, different reaction pathways have been observed [136,137]. Copper(II) compounds with bispidine type ligands (see Section 3.3) have been investigated as potential catalysts for catechol oxidation, and qualitative studies with complexes of the simple mononucleating and various dinucleating ligands with different bridge geometries indicate that cooperative effects, based on a dicopper(II) species, are of importance [138]. From models it emerges that an ethyl bridge (compare Fig. 10) should be ideal and, indeed, that dicopper(II) compound leads to the most efficient catalyst in the series. A catechol-

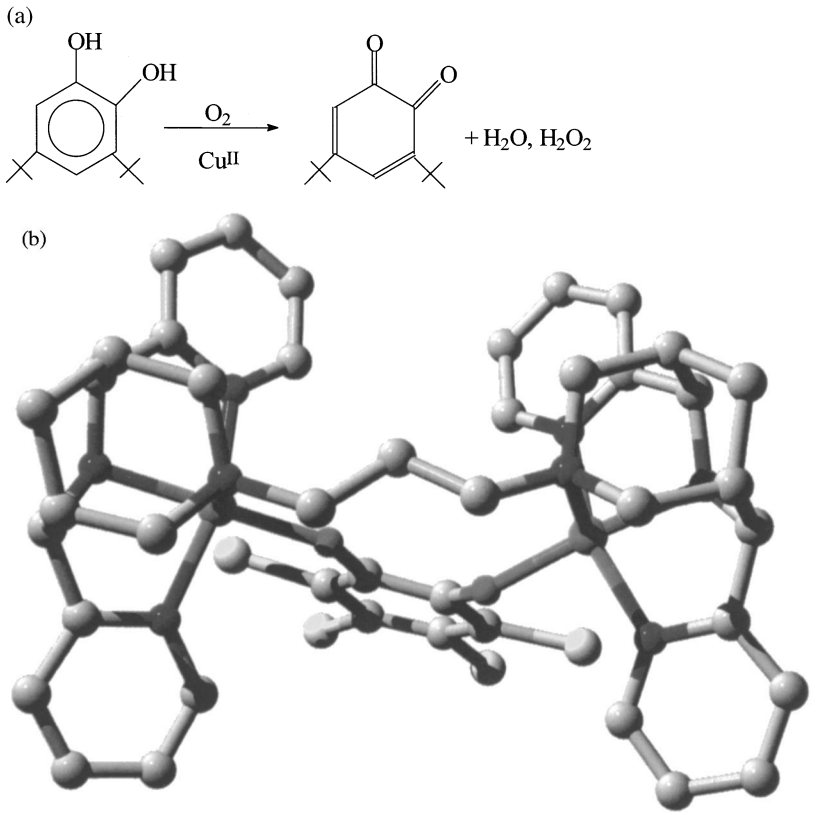


Fig. 12. The copper(II) catalyzed oxidation of bis-*tert*-butyl-catechol (a), and the experimentally determined structure of a catecholate-bridged (tetrachlorosubstituted derivative) dicopper(II) compound with bispidine-type ligands (hydrogen atoms and irrelevant substituents omitted) [138].

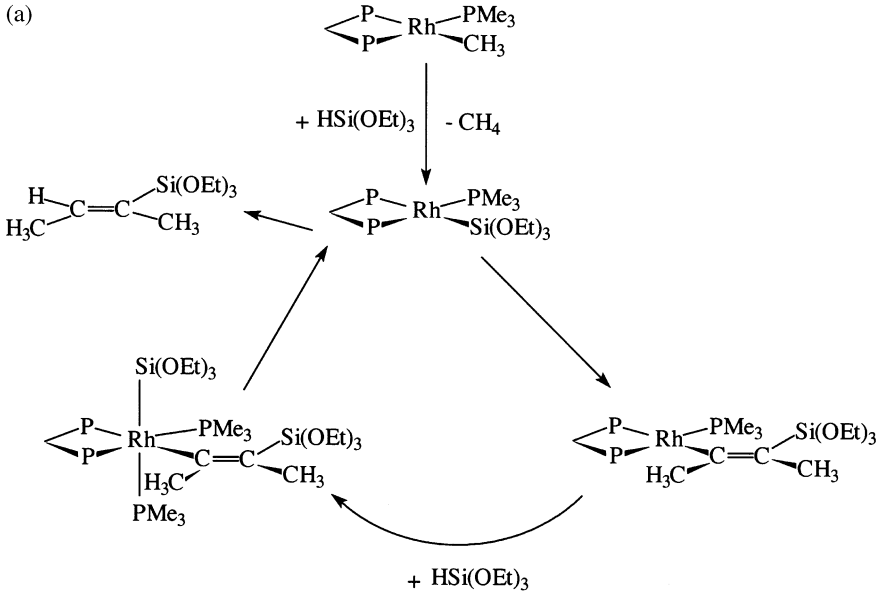


Fig. 13. Proposed catalytic cycle for a Rh-catalyzed hydrosilylation (a) and a representation of the experimentally determined structure of one of a catalyst precursors (hydrogen atoms omitted) (b) [140–143].

derivative-bridged dicopper(II) compound with a dinucleating bispidine-type ligand has been crystallized, and this supports the importance of cooperative effects (see Fig. 12) [138]. This structure is one of the few catechole-bridged dicopper(II) compounds [139], and is similar to that predicted for the corresponding dicopper(II) peroxo species (see Fig. 10 for that with an ethyl instead of a propyl bridge). It is assumed again that the efficiency of catalysis is due to good ligand preorganization.

Among the large number of carefully tailored catalysts late (heavy) transition metal phosphine compounds with enforced *cis*-bisphosphine coordination and highly strained four-membered chelate rings are a particularly appropriate example in relation to the entatic state hypothesis. Bis(di-*tert*-butylphosphenyl)methane compounds of rhodium have been studied extensively [140–143]. A number of experimentally determined solid-state structures have been reported (see Fig. 13 for one of the examples), molecular orbital theory has been used to correlate angular distortions with the electronic structure and homogeneous alkyne hydrosilylation (see Fig. 13) [140,141] and olefin metathesis [142,143] have been studied extensively as examples for very efficient catalytic processes.

Energization in the area of low molecular weight coordination compounds is based on the fact that the geometry of the organic backbone of ligands is generally more rigid than the coordination geometry around transition metal ions. With rigid ligands unusual and strained coordination geometries may be enforced to metal centers. Thermodynamic, kinetic and electronic properties of coordination compounds are related to the geometry of the chromophore, and enforced coordination geometries may therefore be used to tune the properties of metal complexes. These very general ideas are the basis of most of the discussions involving entatic states in coordination compounds.

4. Conclusions

The entatic state hypothesis [5] has inspired a large number of scientists and lead to new and important insights in many areas of coordination and biochemistry. This is particularly true for systems involving copper centers and electron transfer processes. The fact that the label 'entatic state' is used excessively is due to the facts that: (i) there are some ambiguities in terms of the original definition [1–9]; (ii) entasis is related to the tuning of properties by enforced geometries [10,144], and this is a very general principle, which is based on ligand preorganization [12,13], a principle which by itself is rather broad, somewhat diffuse and often misused; (iii) there are kinetic and thermodynamic aspects related to entasis, and this is not generally appreciated (see also Fig. 1 and relevant discussion); (iv) there are too many examples where stabilities, reactivities and spectroscopy are discussed without a thorough understanding of detailed electronic structures and mechanistic pathways; (v) solvation effects are of importance, they are very different in proteins and small molecular weight coordination compounds and often neglected in computational work. One of the more recent features of entasis is the importance of quenched and enforced Jahn–Teller effects (see Sections 2 and 3.3), and it appears

that more information in this area might be of interest. Another feature, related to recent observations is the fact that the large variation of copper(II/I) redox potentials is primarily based on the stabilities of the oxidized form (see Section 3.2), a fact that has not yet been discussed and interpreted in detail. In terms of copper(II/I) electron self-exchange the most interesting examples are those, where the design of unusual copper(II) geometries, leading to 'energized' systems, have produced couples with very slow electron transfer (Section 3.2), and it seems that more examples are needed for a thorough interpretation of these observations.

Acknowledgements

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