Emergent properties from dynamic in biomimetic coordination complexes

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Many biological metallocofactors exist in dynamic equilibria of electronic and/or structural isomeric forms. Developing metal complexes that mimic this type of dynamicity, we repeatedly observe the emergence of new properties beyond an average of those of the two isomeric forms. These findings suggest that intrinsic conformational dynamicity within metalloprotein active sites may play functional roles in mediating catalysis.

Metallocofactor dynamicity in biology

Many metalloprotein active sites access multiple electronic and structural forms which rapidly equilibrate with each other during intermediate stages of catalysis. For example, the Mn2O3Ca oxygen-evolving complex of photosystem II exhibits temperature-dependent structural interconversions in the S2 state of its catalytic cycle that coincide with an electronic redistribution thought to be critical for catalysis [1]. In class II ribonucleotide reductase, rapid cleavage and re-formation of the adenosoxylobalamin Co–C bond are believed to enable safe storage of the catalytic radical equivalent when substrates are unavailable [2], and dynamic sulfide exchange processes in nitrogenase enable access to catalytically competent intermediate states during biological nitrogen fixation [3]. These examples (which are but a few of many) suggest that the on-demand production of reactive intermediates may be aided by their transient, reversible formation according to Le Chatelier’s principle. However, the complexity of these proteins and cofactors makes testing this hypothesis, and defining clear correlations between structural dynamicity and catalytic activity, extremely challenging. The study of simpler model complexes can be helpful in clarifying the roles that metallocofactor dynamics may play in effecting catalysis. To these ends, we describe select examples of such model complexes and the emergence of novel properties arising directly from their conformational dynamicity. The cumulative results of these studies, which are highlighted in Figure 1, suggest that metallocofactor dynamics may play key functional roles in mediating enzyme catalysis.

Conformationally dynamic coordination complexes

Oxidation state changes at the Cu(II/I) redox couple are generally associated with coordination geometry changes, where d10 Cu(I) cations have no ligand field stabilization and d0 Cu(II) cations favor tetragonal coordination geometries. These structural differences often lead to large inner sphere reorganization energies and slow electron transfer (ET) rates in molecular copper complexes (self-exchange rate constants, k11, primarily range from 10^3 to 10^4 M⁻¹ s⁻¹) [4]. It is thought that type 1 blue copper proteins avoid this inherent kinetic challenge and mediate fast ET (k11, primarily range from 10^5 to 10^11 M⁻¹ s⁻¹) by binding the copper ion in an intermediate geometry between those which most stabilize Cu(I) and Cu(II). With compensated stabilization via highly covalent cysteine ligation, this so-called entatic (strained) state is thought to be responsible for minimizing the inner sphere reorganization energy associated with ET and result in rapid reaction rates in blue copper proteins.

Researchers have taken advantage of these oxidation state-dependent geometric interconversions by photochemically populating metal-to-ligand charge transfer excited states of copper(I)bis(diamine) complexes [5,6], where the resultant excited state Jahn–Teller distortions can be captured as solvent exciplexes (short-lived excited state intermolecular adducts) or through changes in ligand-binding mode. In general, imposing structural rigidity on these systems increases the lifetimes of the desired charge separated states, but decreases the stability of the complexes to withstand multiple rounds of photoexcitation. Inspired by these studies, we developed a series of dynamic copper coordination complexes that provide the changes in the coordination environment associated with the Cu(II/I) couple [7,8], where in addition to changes in coordination geometry, the two oxidation states also exhibit distinct ‘hard-soft-acid-base’ properties. The ligands developed for these complexes are abbreviated dpaR (where R = OMe, or SMe in the ortho-position of dpa, dipicolyaniline; Figure 2) and exhibit conformational fluxionality enabled by weak Cu–Naniline interactions.

The copper complexes prepared with dpaR ligands are conformationally dynamic and both sets (i.e., R = OMe and SMe) exhibited unexpectedly large k11 of 2.48(6) × 10^5 and 2.21(9) × 10^6 M⁻¹ s⁻¹, respectively. Among the fastest reported for molecular copper coordination complexes, that of [CuO(dpa)_{2}]^{2+} exceeds all others by over an order of magnitude and compares only with those observed in type 1 blue copper proteins [9]. The dynamicity of these complexes establishes presteady state conformational equilibria that minimize the inner sphere reorganization energies to 0.71 and 0.62 eV for R = OMe and SMe, respectively. Notably, copper complexes prepared with rigid ligand frameworks exhibit low k11, ranging from 10^13 to 10^14 M⁻¹ s⁻¹ [4]. Moreover, among the hundreds of published examples of mononuclear blue copper model complexes, only those that exhibit...
dynamicity rather than rigidity appear to achieve $k_{11}$ on par with those of blue copper proteins ($>10^5 \text{M}^{-1} \text{s}^{-1}$) [10]. Our recent studies directly addressed this discrepancy; producing a series of dynamic copper complexes and interrogating their conformational flexibility allowed us to propose a direct correlation between ET rates and structural dynamicity [9]. The relevance of this dynamicity to blue copper proteins remains to be established, however the correlations we have highlighted bring to bear new questions regarding the nature of their entatic states.

In a separate application, we extended our use of dynamic dpaR ligands to prepare a series of valence tautomeric (VT; undergoing reversible intramolecular ET) cobalt dioxolene complexes. Mononuclear monodioxolene cobalt complexes typically exist in their low spin CoIII(cat$_2^{-}$) and high spin CoII(sq$^{•-}$) forms (cat$_2^{-}$ = catecholato, and sq$^{•-}$ = semiquinonato forms of 3,5-di-tBu-1,2-dioxolene) that reversibly interconvert via temperature-dependent intramolecular ET. Through these studies we reported that, unlike all other complexes of this type, our dynamic ligands enabled two-step magnetic switching to access a low spin CoII(sq$^{•-}$) intermediate between $\sim$115 and 255 K both in solution and in the solid state (Figure 2) [11]. We hypothesize that the Jahn–Teller distortion required in the intermediate state is uniquely accessible with our dynamic ligands. In line with this hypothesis, Krüger et al. [12] have reported each of the two separate one-step transitions in this series. In solution, they observe the VT transition from low spin CoIII(cat$^{2-}$) to low spin CoIII(sq$^{•-}$), whereas in the solid state, they observe the spin crossover transition from low spin to high spin CoII(sq$^{•-}$). Notably, they used pyridinophane supporting ligands in both of these studies, ligands that are well known to exhibit conformational fluxionality. Although VT cobalt complexes are not structural models for any specific metalloenzyme, they serve as functional models for the electronic redistributions operative in iron–sulfur, manganese and iron–oxo, pterin, and heme-containing enzyme active sites.

In a third example aimed at exploring the impacts of conformational dynamicity in coordination complexes, we prepared a series of dinuclear cobalt complexes that feature mono- and bidentate carboxylate ligands (Figure 2). These ligands are held in place by intramolecular hydrogen-bonding interactions about a Co$_2$(μ-OH)$_2$′ diamond core and mimic nonheme dinuclear metalloenzyme active sites. The substitutional versatility of carboxylate ligands is known to modulate enzyme function through ‘carboxylate shift’ reactions, wherein changes in aspartate- and glutamate-binding modes facilitate changes in protonation state, oxidation state, and coordination number during catalysis. Modeling these carboxylate shift reactivity patterns, we were able to induce ligand substitution chemistry not otherwise possible at substitutionally inert octahedral Co(III) centers [13]. Similar carboxylate shift dynamics...
have also been leveraged in metal–organic frameworks, where the ‘breathing modes’ of metal–carboxylate bonds suggest room temperature dynamics, impacting the identity and uptake of guest molecules [14].

**Concluding remarks**

Several metallocofactors in biology are known to access dynamic conformational states. These dynamic states can range from ‘simple’ changes in coordination mode needed for substrate binding, as exemplified by the carboxylate shift reactivity discussed above, to structure-correlated electronic redistributions, exemplified by the VT cobalt complexes discussed above.

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**Figure 2.** In multiple examples, incorporating conformational dynamicity into coordination complexes has resulted in the emergence of new properties that represent more than just the average of the properties of the two separate conformers. (A) In dinuclear cobalt complexes, carboxylate shift reactivity enables facile ligand exchange at coordinatively saturated octahedral Co(III) centers; (B) in mononuclear copper complexes, conformational fluxionality in one oxidation state gives rise to extremely rapid electron transfer kinetics; and (C) in valence tautomeric cobalt catecholato complexes, ligand dynamicity facilitates access to a Jahn–Teller distorted intermediate not observed in rigid systems.
In each case, the active site must access, even if transiently, an activated, destabilized state that does not generally predominate at room temperature. The model studies presented here suggest there may be functional relevance for these dynamics, where perhaps rapid conformational pre-equilibria serve to maintain a small fraction of the less stable states needed for catalysis.

In contrast to this intrinsic dynamicity, many biological systems also undergo specific, triggered structural rearrangements as their rate-determining step of catalysis. In metalloenzymes, these conformational changes often regulate downstream electron and proton transfer steps [15]. This type of mechanism is referred to as conformational gating, and when the conformational gate is triggered, the metallocofactor active site must be able to spring into action.

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A \xrightarrow{\text{trigger}} A' \xrightarrow{\text{conformational change}} B
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Putting these two types of dynamics (intrinsic and triggered) together into one model, we envision that metallocofactor equilibria of conformational/electronic isomers (in the enzyme resting state or an intermediate state in a multistep catalytic cycle) could establish access to a more reactive form, say A', according to Equation 1. Subsequently, when the conformational gate is triggered (via protein–protein interactions, substrate binding, etc.), the reaction can proceed rapidly forward to generate some subsequent state B. The extent to which any of these aspects may come into play for a given system will vary, but the general model presented in Equation 1 provides a framework for the studies discussed above, within the context of metalloenzyme catalysis. The role that dynamics play (enzyme) catalysis remains a potent area of study. Here, we summarize our results by taking a reverse approach to this topic and examining catalytically inactive yet conformationally fluxional systems. We repeatedly observe the emergence of new properties arising from the conformational dynamicity of these systems and suggest that similar phenomena may be operative in other (biocatalytic) systems that may play key functional roles therein.

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Declarations of interest
The authors have no interests to declare.

References

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