Super-exchange mechanism and quantum many body excitations in the archetypal hemocyanin/tyrosinase di-Cu oxo-bridge

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We perform first-principles quantum mechanical studies of dioxygen ligand binding to the hemocyanin protein. Electronic correlation effects in the functional site of hemocyanin are investigated using a state-of-the-art approach, treating the localized copper 3d electrons with cluster dynamical mean field theory (DMFT) for the first time. This approach has enabled
us to account for dynamical and multi-reference quantum mechanics, capturing valence and spin fluctuations of the 3$d$ electrons. Our approach predicts the stabilization of a quantum entangled di-Cu singlet in the London-Heitler limit, with localized charge and incoherent scattering processes across the oxo-bridge, that prevent long-lived charge excitations. This suggests that the magnetic structure of hemocyanin is largely influenced by the many-body corrections. Our computational model is supported by remarkable agreement with experimental optical absorption data, and provides a revised understanding of the bonding of the peroxide to the di-Cu system.

Copper-based metalloproteins play a major role in biology as electron or dioxygen (O$_2$) transporters. Hemocyanin (Hc) is one of three oxygen transporting proteins found in nature, alongside the iron-based hemerythrin and hemoglobin, and is common to a number of invertebrates, such as molluscs and arthropods. Deoxy-Hc employs two half-spin copper (I) cations, each coordinated by the imidazole rings of three histidine residues, to reversibly bind O$_2$. An accurate understanding of the electronic structure (spin and charge) of the Cu$_2$O$_2$ core is essential to clarifying the operation of dioxygen transport as well as the catalytic mechanisms of type 3 copper-based enzymes such as tyrosinase and catechol oxidase, or multicopper oxidases.$^{1,2}$ A theoretical understanding of this mechanism would advance the design of synthetic catalysts that employ dioxygen as a terminal oxidant. There is significant interest in the biomimetic application of naturally occurring metal complexes for the use in metallodrug design, with Cu(II) complexes recently employed in cancer therapeutics as artificial DNA metallonucleases.$^3$ and tyrosinase mimics.$^4$
However, the formation of oxygenated hemocyanin (oxyHc) via the binding of O\textsubscript{2} to deoxygenated hemocyanin (Hc) remains a challenging problem, and key questions remain unresolved. In particular, the binding of O\textsubscript{2} falls into the category of a spin-forbidden transition. Molecular O\textsubscript{2} is in a spin triplet configuration, and the Cu ions in deoxyHc are known to be in the Cu(I) d\textsuperscript{10} singlet configuration. The combination of triplet O\textsubscript{2} and singlet deoxyHc, to produce the Cu\textsubscript{2}O\textsubscript{2} antiferromagnetic singlet in oxyHc, is believed to occur via a simultaneous charge transfer of one electron from each Cu(I) ion to O\textsubscript{2} forming a hybrid Cu(II)-peroxy-Cu(II) configuration. Hence a super-exchange pathway is hypothesized to form across the two Cu atoms\textsuperscript{5}. This mechanism is supported by SQUID measurements that report a large super-exchange coupling\textsuperscript{6} between the two Cu centers, and a diamagnetic ground state.\textsuperscript{7}

Despite intensive theoretical studies on the nature of the side-on coordinated Cu\textsubscript{2}O\textsubscript{2} core, theoretical analysis has so far proved to be challenging for many electronic structure methods including \textit{ab initio} quantum chemistry, density functional theory (DFT) and mixed quantum/classical (QM/MM) methods due to the complex simultaneous interplay of both the charge and spin, and to the multi-reference character of oxyHc. In particular, DFT and hybrid-DFT do not predict the correct singlet ground state\textsuperscript{8,9,10} due to the multi-reference nature of the ground state that is not accessible in DFT-based approaches. To overcome the limitation of DFT techniques, a spin-projection method (also called spin-mixing) has been applied, wherein the different spin-polarized ground states are calculated individually\textsuperscript{11} and the entangled singlet is reconstructed by linear combination of the respective Slater determinants (essentially a combination of the spin-broken symmetry state in the up-down, up-up, down-down configurations to extract an effective singlet.
state). Although this construction yields insights into the energetics, it does not allow for the study of excitations, and limits the scope of comparison with experimental data, such as the optical absorption, that is a stringent test of any theory. Furthermore, the spin-contamination present in spin-polarized hybrid DFT remains an issue and typically the broken symmetry state becomes asymmetric in the oxyHc Cu\textsubscript{2}O\textsubscript{2} core, which is an artefact of the method used. Finally, experiments have also alluded to the necessity of characterizing the oxyHc ground state as a mixed valence state, which cannot be accessed in the ground state DFT approach.

In this work, we apply for the first time an extension of DFT, dynamical mean-field theory (DMFT), that accounts for all the limitations discussed above, and treats non-perturbatively the many-body effects and the super-exchange of the di-Cu bridge. DMFT is a sophisticated method that includes quantum dynamical effects, and takes into account both valence and spin fluctuations, and thermal excitations. Although DMFT is routinely used to describe materials, it was also recently extended to molecular systems and combined with the linear-scaling DFT software, ONETEP, to extend the applicability of DFT+DMFT to systems of unprecedented size. Here, we systematically study how the Coulomb repulsion term $U$, which is absent from DFT, corrects the magnetic properties of oxyHc. We report the quantum entangled low energy states and analyze the dominant contributions to the charge and magnetic properties of Cu\textsubscript{2}O\textsubscript{2}. This enables the identification of the regime of parameters where the singlet is stabilized ($U = 6 - 8$ eV), and the renormalization of the diamagnetism induced by quantum fluctuations. We show that a dominant spin singlet state is maximized at $U = 8$ eV and discuss the validation of the model by optical experiments. The obtained singlet is in the Heitler-London regime (entangled quantum superposition...
Results

In the present work, we perform the first DFT + DMFT simulations on a 58-atom model of the oxyHc functional complex (Fig. 1). Although previous DFT-based approaches have reported that a di-Cu singlet is obtained across the oxo-brige, these approaches invoke artificial constructions to overcome the single-Slater determinant approach of DFT. Instead, we hereby treat the multi-reference, finite-temperature and explicit on-site Coulomb interaction effects associated with the Cu 3d binding site, in single, self-consistent calculations, and systematically investigate how the Hubbard Coulomb potential $U$ alters the electronic structure at the Cu$_2$O$_2$ site.

As this problem involves direct exchange across two correlated atoms, we use the non-local
DMFT implementation (cluster DMFT), needed to characterize the superexchange mechanism between the Cu\textsubscript{2} \textit{d}-orbitals and intermediate \textit{p}-orbitals, as single site DMFT can only treat the multiplet structure of each Cu atom separately. In its simplest form, DMFT invokes a mean-field approximation across the multiple correlated sites, which is not the case in our approach, as all correlated sites are directly treated in the multi-site Anderson impurity model (AIM). Hence our approach might be denoted as DFT+AIM. Note however that we do carry out a self-consistency cycle over the charge density, as we work at fixed total number of electrons, and this produces a feedback to the solution of the model that is similar in its nature to the mean-field approximation used in DMFT. We consider the the Hubbard \textit{U} coupling in the range \textit{U} = 0 to 10 eV. The Hubbard \textit{U} correction is known to be paramount to describe many-body effects responsible for the superexchange process across Cu atoms. Several competing effects stem from the local Hubbard \textit{U} physics: charge localization, exchange of electrons, charge-transfer excitations, and stabilization of magnetic multiplets. Although typical values for \textit{U} can be obtained by linear response or constrained RPA\textsuperscript{24}, these predictions are typically dependent on the choice of local orbitals and basis representation. We instead consider a range of values; by artificially manipulating the magnitude of the local many-body effects, we can investigate their influence on the electronic spectral weight and magnetic properties. A typical value of \textit{U} for the 3\textit{d} electrons of Cu is 8–8.5 eV\textsuperscript{25,26}.

\textbf{Charge and spin fluctuations.} We first turn to the study of the charge and spin fluctuations induced by the Coulomb repulsion \textit{U}. We calculated the reduced density matrix of the di-Cu system, and the weight of the obtained eigenvectors, which correspond to the possible excitations of the system (Fig. [2]). This provides a detailed picture of the electronic structure of the 3\textit{d} subspace.
Figure 2: Decomposition of the reduced density matrix of the Cu$_2$ dimer in the different quantum sectors. The colors correspond to the respective weights of the different contributions for each value of the Coulomb repulsion $U$ (if a color occupies all the vertical axis, for example, it means that all eigenvectors of the density matrix are in the same quantum sector). Note that the d occupation is the sum of both Cu sites (for example, d$^{30}$ means the two Cu atoms are respectively in the d$^{10}$ configuration).
of the Cu atoms. Within DMFT, the density matrix is obtained by tracing the Anderson impurity model over the bath degrees of freedom, and gives an effective representation of the quantum states of the two Cu atoms. Note that in our approach, the ground-state wave-function is not a pure state with a single allowed value for the spin states (singlet, doublet, triplet, etc.), yet we can describe the fluctuating spin states of the Cu atom by analyzing the spin distribution obtained from the dominant configurations. In the weakly correlated regime \( U < 2 \text{ eV} \), we obtain a large contribution from the \( d^{20} \) and \( d^{19} \) configurations, indicating that the average charge transfer from the Cu to O\(_2\) involves less than 1\( e \) per Cu, thus preventing the formation of a singlet (as the Cu 3\( d \) orbitals are nearly full).

**Diamagnetism.** As \( U \) increases the total electronic occupation of the Cu dimer decreases (Fig. 2 and Table 1). In the range \( U = 6 – 8 \text{ eV} \), the \( d^{18} \) singlet component is maximized, beyond which \( d^{18} \) triplet excitations begin to contribute. For physical values of the Coulomb repulsion of Cu 3\( d \) orbitals \( (U \approx 6 – 8 \text{ eV} \text{ in the case of both molecules}^{27} \text{ and solids}^{28}) \), we find that oxyHc is in a dominant \( d^{18} \) singlet state \( (\approx 50\% \text{ weight in the singlet multiplet}) \), with \( d^{19} \) charge excitations.

This is further corroborated by the measurement of the spin correlator \( K = 2\langle S_1 \cdot S_2 \rangle \) (Fig. 3), which reaches half the saturation value for \( U = 6 – 8 \text{ eV} \). Note that the saturation value would only be obtained for a diatomic system in vacuum, which is not hybridized to the rest of the molecule. As the local Cu 3\( d \) orbital charge and spin are not true quantum numbers in the molecule, as the two atoms are hybridized, quantum fluctuations reduce the amplitude of the spin correlator to half the full value. This is consistent with the presence of \( \approx 50\% \) combined \( d^{19} \) and \( d^{20} \) excitations (Fig. 2).
Figure 3: The effective magnetic moment $M = \sqrt{\langle S_1^2 \rangle}/3$ (normalized by saturation value) and the spin-correlation $K = 2\langle S_1 \cdot S_2 \rangle$ for varying values of the Hubbard $U$. For a pure two orbital singlet, $K = -1.5$. In our calculations, as the rest of the molecule hybridizes with the Cu orbitals, the spin-correlation is re-normalized to half its saturation value for $U = 6 - 8$ eV.

**Von Neumann entropy.** The accumulation of possible excitations can be quantified by the Von Neumann entropy. This provides a measure to identify whether the system is actually in a highly mixed quantum state with a multitude of other significant components. The Von Neumann entropy, obtained in the di-Cu $3d$ subspace, reads as: $\Lambda = \text{Tr} [\hat{\rho}_d \log \hat{\rho}_d]$, where $\hat{\rho}_d$ is the di-Cu reduced finite-temperature density matrix, traced over the states of the AIM bath environment (Fig. 4). Interestingly, we find that the entanglement entropy increases monotonically in the range $U = 0 - 10$ eV. We report the presence of two plateaus, for $U = 4 - 6$ eV and $U = 7 - 8$ eV, that coincide with the formation of the singlet and triplet configurations in the histogram in Fig. 2.

**Lifetime of charge excitations.** We note that the singlet, in oxyHc, is obtained by superexchange processes. Direct hopping between localized d-orbitals is very unlikely due to the large
Figure 4: The Von Neumann entropy $\Lambda$ of the reduced density matrix and its dependence on the on-site interaction $U$.

The super-exchange process is usually pictured in the canonical hydrogen atom dimer system. This system describes a pair of up and down electrons that form a singlet state. In this picture, two different limits are possible: i) when the H atoms form a bond at short distance, and the up and down electron form a delocalized bound singlet (BS) centered on the bond, with a high degree of double occupancy, ii) in the dissociated case, known as the Heitler-London (HL) limit, where the H atoms are far apart and the singlet is a true quantum entangled state of the singly occupied H orbitals. In the latter case, the molecular orbital contains only one electron and double occupancy is zero. Although this transition is known in archetypal systems such as the $\text{H}_2$ molecule, few examples in nature are known to exhibit the BS-HL transition. In the HL limit, the charge is typically localized around the H atoms, and typically occurs in the limit of dissociation. However, this effect may also occur in systems where the local Hubbard Coulomb repulsion $U$
Figure 5: a) Imaginary part of the dynamical mean field local self energy of the Cu-3d empty orbital ($\Sigma''(\omega)$) for Hubbard $U = 2\text{eV}$, $6\text{eV}$, and $8\text{eV}$. At $U = 8\text{eV}$, we obtain incoherent excitations at $\omega = 0\text{eV}$. b) Self energy at $\omega = 0$ and c) double occupancy $D$ as a function of $U$. Note that although the double occupancy is evolving smoothly with the Coulomb interaction $U$, $\Sigma(\omega = 0)$ shows a sharp increase near $U = 8$, that we associate with the stabilization of a localized singlet.
acts as a Coulomb blockage: many-body effects prevent long-lived charge transfer excitations, and the Coulomb repulsion energy is reduced at the expense of the kinetic energy. A signature of the blockage is a large increase in the self energy at the Fermi level (pole structure), indicating charge localization and incoherent scattering associated with a short lifetime of charge excitations.

To investigate the nature of the singlet (BS or HL), we report in Fig. 5(a) the computed self energy of the Cu $3d$ subspace, for various values of $U$. We obtain a qualitative difference between $U = 6 \text{ eV}$ and $U = 8 \text{ eV}$, where at $U = 8 \text{ eV}$ the self energy develops a pole at $\omega = 0$. The formation of the pole is particular to $U = 8 \text{ eV}$ (Fig. 5(b)), and is associated with the regime where excitations are incoherent, which prevents long-lived charge transfer excitations from the Cu $3d$ orbitals to O$_2$. In this limit, the many body effect acts as a Coulomb blockade and the charge is in turn localized, with weak direct coupling (HL limit). For $U = 6 \text{ eV}$, the singlet is in the BS limit, where charge excitations allow a direct electron transfer across the oxo-bridge. Note that the observation of the BS-HL crossover is not apparent in averaged quantities, such as in the double occupancies (Fig. 5(c)), which evolve smoothly with the Coulomb repulsion.

**Optical transitions.** As a further validation of the DFT+DMFT computational model, and to identify the strength of correlations in oxyHc, we extracted the optical absorption spectrum of ligated hemocyanin (Fig. 6). As experiments are performed in the gaseous phase and not in a single crystal, we have calculated the isotropic and anisotropic components of the dielectric tensor. The former involves only pair correlators along the same spatial directions, whereas the latter
Figure 6: Theoretical optical absorption of the Cu$_2$O$_2$ core and imidazole rings obtained by DMFT for values of the Coulomb repulsion $U = 6$eV, 7eV and 8eV. For comparison, we show the experimental optical absorption obtained by UV-Vis$^{[30]}$ in a wide range of wavelengths (infrared to UV).

also incorporates non-diagonal terms (note that both are causal quantities), which are important in oxyHc as the local coordination axes of the Cu atoms are not aligned. The arrows highlight the positions of the resonances reported by experiments. Remarkable agreement is obtained for $U = 8$eV, with however a blue shift at high frequency ($\omega > 4$eV), and a concomitant transfer of optical weight to lower energies ($\omega < 3$eV). Note however that the positions of the peaks at approximately 3.5eV and 4.5eV are in excellent agreement. The experimental features at 3eV (see arrow) are clearly visible in the theoretical calculations. The peaks at 1.8eV and 2.2eV contribute to the long infrared tail of the optical weight down to 1.5eV. We note that the main difference, between
the BS ($U = 6$ eV) and the HL singlet ($U = 8$ eV), is the presence of a peak associated with charge transfer from ligand to Cu $3d$ orbitals at 2 eV, which is absent in experiment. This strongly associates oxyHc with the HL limit, as numerous optical studies have confirmed the absence of this feature. The suppression of the optical weight at 2eV is due to a large increase in incoherent scattering at $\omega = 0$ eV at $U = 8$eV (Fig. 5). This is associated with a localization of the holes in the Cu $3d$ shell at $U = 8$eV. The strong suppression of the optical weight in the near infrared-regime ($\omega < 2$eV), and the consistent agreement with our calculations, shows that the di-Cu singlet is in the HL regime, and is stabilized via scattering processes.

**Characterization of optical transitions.** To identify the features present in the optical absorption spectrum, we now turn to the discussion of the spectral weight (Fig. 7). The absorption spectrum of this protein has been reported experimentally to be qualitatively dependent on its ligation state. In its oxygenated form, a weak peak at 570 nm (approximately 2.2 eV, see arrow) corresponds to ligand-to-metal charge transfer from the $O_2 \, \pi$ anti-bond with lobes oriented perpendicular to the metal atoms. This orbital is denoted “$\pi^*_{\sigma}$”; the $\pi$ anti-bond with lobes directed towards the copper atoms is denoted $\pi^*_{\pi}$ and is responsible for an experimentally observed (much stronger) peak at approximately 3.7 eV. Our calculations associate the 2 eV peak in the optical absorption spectrum with a transition from the weight at -1 eV in the density of states (Fig. 7), which is localized on Cu$_A$/Cu$_B$/imidazole, to the LUMO. In our calculations, the LUMO is a hybridized state between the Cu and the $O_2$, with dominant Cu $3d$ character. We therefore associate the optical weight at 2eV with d-d transitions mediated by charge transfer across the oxo-bridge (although the optical transition from Cu$_A$ to Cu$_A$ is optically dark, that from Cu$_A$ to Cu$_B$ is not). We observe that
Figure 7: (a) The local density of states for $U = 8$ eV and (b) the different total density of states of the system for a range of Hubbard $U$ values from DMFT.
the increasing $U$ disfavors charge transfer into the Cu $3d$ subspace, and this is manifested in the optical absorption by the reduction of the optical weight at 2eV. The comparison with experiments allows us to identify $U$ precisely with $U = 8$ eV. We note also that DFT, without extensions, puts a strong emphasis on the near infrared peak in the optical absorption. This peak corresponds to Cu-Cu charge transfer across the oxo-bridge. However, as the aforementioned scattering processes are absent at this level of theory, it produces coherent resonances across the HOMO-LUMO gap, observed in the optical spectra at 1.5eV, but absent in experiments.

**Molecular bonding.** In order to understand the nature of the bonding in the Cu$_2$O$_2$ complex, natural bond orbital (NBO) analysis was performed on the DFT and DMFT electronic densities. This involves a series of diagonalization and occupancy-weighted orthogonalization procedures on the single-particle density matrix, transforming it into a set of atom-centered orthogonal natural atomic orbitals (NAOs), then natural hybrid orbitals, and finally the natural bond orbitals $\{|\sigma_i\rangle\}$, which are either one- or two-atom centered. By construction, this procedure decomposes the electronic density into terms resembling Lewis-type chemistry (with bonding and lone pairs of electrons). For hemocyanin, this analysis reveals a hole in one $3d$ orbital for each Cu atom (with $3d$ occupancies of 9.11 and 9.07 for $U = 8$ eV), confirming the expected Cu(II) oxidation state $3d^94s^0$ (Figure 8(a)).

A second-order perturbation analysis detects multiple energetically favorable transfers of electronic density from filled to unfilled NBOs, revealing those aspects of the electronic structure that are not well described by Lewis-like chemistry. Early studies of hemocyanin identified
Figure 8: Isosurfaces of several natural bonding orbitals for $U = 8$ eV. (a) Two Cu $3d$ orbitals are identified as half-filled by the NBO analysis. (b) The O$_2$ $\sigma^*$ anti-bond is empty, and does not hybridize with any Cu orbitals. (c) Instead, O $2p$ (blue) to Cu $4s$ (red) charge transfer is favorable.

back-bonding charge transfer from Cu $3d$ to oxygen $\sigma^*$ anti-bonding orbitals (Figure 8(b)) as an important factor in explaining the comparatively low 750 cm$^{-1}$ Raman frequency of the O$_2$ bond.$^{[10]}$

However, our second-order perturbation analyses find that this back-transfer is not present. For $U = 8$ we instead detect favorable charge transfer from O $2p$ orbitals to Cu $4s$ orbitals (Figure 8(c)).

Conclusions

We have presented the application of a DFT + cluster DMFT approach, designed to treat strong electronic interaction and multi-reference effects, to oxyHc, a molecule of important biological function. NBO analysis revealed a hole in one $3d$ orbital for each Cu atom, confirming the expected Cu(II) oxidation state ($3d^94s^0$). The reduced density matrix of the $3d$ subspace of the two Cu atoms revealed the presence of fluctuating spin-states, in which a Cu$_2$ $d^{18}$ singlet component is maximized at $U = 8$eV. When quantifying the highly mixed quantum state, we observed the formation of
singlet and triplet states in the Von Neumann entropy of the reduced density matrix at different $U$.

Our approach reproduced the experimentally-observed peaks in the absorption spectrum at around 2.2 eV, 3.7 eV and 5.2 eV. NBO analysis revealed that the hybridization of the Cu 4$s$ and O 2$p$ orbitals is much more favorable than O$_2$ $\sigma^*$ orbital back-bonding.

We have found that the Hubbard $U$ is necessary to capture the multi-reference character of the ground-state, placing oxyHc in the limit of a true quantum entangled singlet in the limit of the Heitler-London model. We solve a long-standing problem in the density-functional theory based simulations of type-3 copper systems, which depend heavily on the choice of functional and incorrectly describe multi-reference effects. Our approach, which is implemented in linear-scaling DFT software,\textsuperscript{19} is optimized to describe transition metal proteins, and hence supports a large range of applications, for example, to enzymes\textsuperscript{38} or the oxygen-evolving complex (OEC) of photosystem II.\textsuperscript{39}

**Methods**

The geometry of the 58 atom system was obtained from the literature.\textsuperscript{10} This had been optimized using the B3LYP hybrid functional and closely matches the experimentally observed structure.\textsuperscript{10,10}

The DFT ground-state was obtained using ONETEP\textsuperscript{19,41,42}, which is a linear-scaling DFT code that is formally equivalent to a plane-wave method. This is achieved by the \textit{in situ} variational optimization of its atom-centered basis set (spatially-truncated nonorthogonal generalized Wannier functions, or NGWFs).\textsuperscript{42} The total energy is directly minimized with respect to the NGWFs and the
single-particle density matrix. The use of a minimal, optimized Wannier function representation of the density-matrix allows for the DFT ground state to be solved with relative ease in large systems. This is particularly useful in molecules, since explicit truncation of the basis functions ensures that the addition of vacuum does not increase the computational cost.

The DFT calculations of the oxyHc system were run with an energy cut-off of 897 eV, and with 9 NGWFs on the copper atoms, four on each carbon/nitrogen/oxygen, and one on each hydrogen. Spin symmetry was imposed. All NGWFs employed 7 Å cutoff radii. Open boundary conditions were achieved via a padded cell and a Coulomb cut-off. The Hubbard projectors were constructed from the Kohn-Sham solutions to an isolated copper pseudopotential. The pseudopotentials were generated with the OPIUM pseudopotential generation project.

We refined our DFT calculations using the DFT + DMFT method in order to obtain a more accurate treatment of strong electronic correlation effects. In particular, DMFT introduces both quantum and thermal fluctuations, which are multi-reference effects not captured at the level of Kohn-Sham DFT. The oxyHc model was mapped, within DMFT, to an Anderson impurity model (AIM) Hamiltonian and we used a recently developed extended Lanczos solver to obtain the DMFT self energy.

To identify the best spatial representation of the local $d$-space in the projected Anderson impurity model, we first identified the orthogonal transformation which reduces the off-diagonal elements of the local Green’s function, for respectively the Cu$_A$ and Cu$_B$ sites. Then, we implemented a minimization procedure which finds the closest corresponding real space $SO(3)$ rotation.
of the local Cartesian axis corresponding to the $O(5)$ orthonormal transformation in $d$-space. This provides a unique set of local axes, different on each Cu atoms, which make the local Green’s function nearly diagonal in frequency space. As a result, we observed that the Cu$_A$ and Cu$_B$ holes are of pure orbital character within the local axis representation.

Since only a single impurity site ($3d$ orbital subspace) is present, the system becomes crystal momentum independent in the molecular limit, and since the Kohn-Sham Green’s function is computed in full, by inversion, before projection onto the impurity subspace, the Anderson impurity mapping is effectively exact, and the necessity of invoking the DMFT self-consistency is not required. However, in DFT + DMFT there is also a charge self-consistency cycle, where (i) the chemical potential can be updated to ensure particle conservation and/or (ii) the DFT + DMFT density kernel can be used to generate a new Kohn-Sham Hamiltonian, which in turn provides a new input to the DMFT; the procedure being repeated until convergence is achieved. In this work, we updated the chemical potential but not the Hamiltonian due to computational cost.

Example input and output files for the DFT and DMFT calculations can be found in the supplementary materials.

To obtain the Kohn-Sham Green’s function, we performed the matrix inversion, as well as all matrix multiplications involved in the DMFT algorithm, on graphical processing units (GPUs) using a tailor-made parallel implementation of the Cholesky decomposition written in the CUDA programming language. Electronic correlation effects are described within the localized subspace
by the Slater-Kanamori form of the Anderson impurity Hamiltonian specifically:

\[ H_U = U \sum_{m} n_{m\uparrow} n_{m\downarrow} + \left( U' - \frac{J}{2} \right) \sum_{m>m'} n_{m} n_{m'} - J \sum_{m>m'} \left( 2S_m S_{m'} + \left( d_{m\uparrow}^\dagger d_{m\downarrow} d_{m'\uparrow}^\dagger d_{m'\downarrow} \right) \right), \]

where \( m, m' \) are orbital indices, \( d_{m\sigma} (d_{m\sigma}^\dagger) \) annihilates (creates) an electron with spin \( \sigma \) in the orbital \( m \), and \( n_{m} \) is the orbital occupation operator.

The first term describes the effect of intra-orbital Coulomb repulsion, parametrized by \( U \), and the second term describes the inter-orbital repulsion, proportional to \( U' \), which is renormalized by the Hund’s exchange coupling parameter \( J \) in order to ensure a fully rotationally invariant Hamiltonian (for further information on this topic, we refer the reader to Ref. 55). The third term is the Hund’s rule exchange coupling, described by a spin exchange coupling of amplitude \( J \). \( S_m \) denotes the spin corresponding to orbital \( m \), so that \( S_m = \frac{1}{2} d_{ms}^\dagger \vec{\sigma}_s d_{ms'} \), where \( \vec{\sigma} \) is the vector of Pauli matrices.

Our DMFT calculations were carried out at room temperature, \( T = 293 \text{ K} \) and the Hubbard \( U \) was varied in the range 0 - 10 eV, with a fixed Hund’s coupling \( J = 0.8 \text{ eV} \). The theoretical optical absorption was obtained in DFT + DMFT within the linear-response regime (Kubo formalism), in the no-vertex-corrections approximation which is given by:

\[ \sigma(\omega) = \frac{2\pi e^2 \hbar}{\Omega} \int d\omega' \frac{f(\omega' - \omega) - f(\omega')}{\omega} \times \left( \rho_{\alpha\beta}(\omega' - \omega) v_{\beta\gamma} \rho_{\gamma\delta}(\omega') \cdot v_{\delta\alpha} \right), \]

and the factor of two accounts for spin-degeneracy, \( \Omega \) is the simulation-cell volume, \( e \) is the elec-
tron charge, $\hbar$ is the reduced Planck constant, $f(\omega)$ is the Fermi-Dirac distribution, and $\rho^{\alpha\beta}$ is the density-matrix given by the frequency-integral of the interacting DFT + DMFT Green’s function. The matrix elements of the velocity operator, $v_{\alpha\beta}$, noting that we do not invoke the Peierls substitution, are given by:

$$v_{\alpha\beta} = -\frac{i\hbar}{m_e} \langle \phi_\alpha | \nabla | \phi_\beta \rangle + \frac{i}{\hbar} \langle \phi_\alpha | [\hat{V}_{nl}, \hat{r}] | \phi_\beta \rangle.$$  \hspace{1cm} (3)

This expression is general to the NGWF representation used in this work, where the contribution to the non-interacting Hamiltonian due to the non-local part of the norm-conserving pseudopotentials, represented by $\hat{V}_{nl}$, is included.

Finally, the double-counting correction $E_{DC}$ must be introduced, since the contribution of interactions between the correlated orbitals to the total energy is already partially included in the exchange-correlation potential derived from DFT. The most commonly used form of the double-counting term is:

$$E_{dc} = \frac{U_{av}}{2} n_d (n_d - 1) - \frac{J}{2} \sum_{\sigma} n_{d\sigma} (n_{d\sigma} - 1).$$ \hspace{1cm} (4)

The natural bonding orbital analysis was performed using the NBO 5 programme. Performing this transformation starting from ONETEP’s basis of NGWFs is non-trivial, and is described in Ref. The NBOs generated from DFT + DMFT densities largely retain the familiar profile of DFT-based NBOs, but their occupancies may be expected to deviate further from integer values due to quantum-mechanical and finite-temperature multi-reference effects captured within DFT + DMFT.
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Table 1: DMFT $3d$ orbital occupations of Cu in our model of ligated hemocyanin for different Hubbard $U$ values.

| Atom    | $d_{x^2-y^2}$ | $d_{3z^2-r^2}$ | $d_{xy}$ | $d_{xz}$ | $d_{yz}$ |
|---------|---------------|----------------|----------|----------|----------|
| Cu1 ($U = 0$ eV) | 2.00          | 2.00          | 1.95     | 1.72     | 1.93     |
| Cu2 ($U = 0$ eV) | **1.68**      | 2.00          | 1.98     | 1.99     | 2.00     |
| Cu1 ($U = 8$ eV) | 2.00          | 2.00          | 1.95     | **1.25** | 1.93     |
| Cu2 ($U = 8$ eV) | **1.21**      | 2.00          | 1.98     | 1.99     | 2.00     |
| Cu1 ($U = 10$ eV)| 2.00          | 2.00          | 1.95     | **1.18** | 1.93     |
| Cu2 ($U = 10$ eV)| **1.14**      | 2.00          | 1.98     | 1.99     | 2.00     |