Orbital analysis of oxo and peroxo dicopper complexes via quantum chemical workflows in MoSGrid

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***Abstract*—**The science gateway MoSGrid (Molecular Simulation Grid) is a valuable tool to submit and process molecular simulation studies on a large scale. An orbital analysis of oxo and peroxo dicopper complexes, which are bioinspired models of tyrosinase, is presented as a real-world chemical example. The orbital analysis is result of a quantum chemical workflow which has been employed on several tyrosinase model complexes as well as on simple $\{Cu_2O_2(NH_3)_x\}$ cores (with x = 4,6). The structures were optimized using Gaussian09 and the orbitals visualized after production of formatted checkpoint files. All meta- and post-processing steps have been performed in this portlet. All workflow features are implemented via WS-PGRADE and submitted to UNICORE.

***Keywords*—**Quantum chemistry, Workflows, Copper complexes, Service Grids, DCIs

I. INTRODUCTION

Molecular Simulation Grid (MoSGrid) [1] is a science gateway for researchers from chemistry and biology which enables the access to high-performance computing (HPC) facilities. MoSGrid aims to enable more researchers to use distributed computing infrastructures (DCIs) by reducing the initial hurdle of using computational chemistry software on DCIs. It provides graphical user interfaces that allow even inexperienced scientists to run molecular simulations of high complexity.

Here, we present a quantum chemical orbital analysis of oxo and peroxo dicopper complexes which is highly relevant for the design of tyrosinase models. This has been achieved using the MoSGrid portal. Tyrosinase is a ubiquitous copper enzyme which selectively hydroxylates phenols to quinones for pigment and hormone production [1]. This bioinorganic study helps a better understanding of the oxygen activation by two copper centers and the subsequent design of environmentally benign oxidation catalysts.

II. BACKGROUND

A. *Workflow-enabled Science Gateways*

Science gateways in general aim to enable users to intuitively access DCIs. This way, users can concentrate on their particular field of research and are thus liberated from installing and maintaining any software with at the same time having the advantage of using well designed user interfaces. These science gateways allow for the easy handling of tools and workflows on DCIs. The MoSGrid science gateway in particular uses the DCI visualization environment gUSE and its graphical interface WS-PGRADE. Both have been extended in the course of the MoSGrid project [2]. It supports the three main molecular simulation domains: quantum chemistry, molecular dynamics and docking. The research presented here takes advantage of the quantum chemistry area. Apart from specific domain support users can also create, manage and submit generic workflows by selecting and concatenating applications and using output from applications as input for subsequent ones. As closely related science gateway Gridchem [3] has to be named: it offers chemists similarly easy access to computing resources but not the option of workflow usage. For building up science gateways further efforts are described in [4].

B. *Application Domain*

A primary goal of bio-inorganic chemistry is the ability to leverage the insights taken from enzymatic systems to create catalytically functional analogs that can affect transformations

and operate in conditions not practicable by the enzyme [5]. Proposing catalytic chemistry based on enzymatic mechanisms, evolved by selection pressures for efficiency, exploits the important fact that a path through the energetic landscape has already been mapped. Reproducing enzymatic transformations and characterizing intermediates are crucial for insights into the reaction mechanism. In metal-based oxidative chemistry, achieving turnover is a substantial challenge, as evidenced by the limited number of good examples in biomimetic chemistry. Catalytic systems must finely balance energetics, minimizing activation barriers and avoiding energetic wells which halt the cycle at products or intermediates. The stability achieved in an enzyme, where tethering site-isolated metals to a peptide matrix discourages destructive decay, opens up thermal regimes favorable to efficient catalysis. In synthetic analogs, stability at kinetically advantageous temperatures often comes at the expense of inherent reactivity. Additionally, undesired side reactions can lead to thermodynamically stable complexes which take catalysts out of the cycle, limiting turnover numbers [6,7].

The most important metals in biological dioxygen activation are iron and copper, and enzymes utilizing these metals are valued sources of inspiration to chemists developing oxidative or oxygen-insertion chemistry. Examples of catalytic oxygen-insertion reactions, in which dioxygen is the sole source of oxygen, are extremely limited, despite the indisputable advantages of using the earth's oxygen reserves.[7-9] Tyrosinase (see Figure 1, upper left and upper right) is a ubiquitous binuclear copper enzyme that catalyzes the hydroxylation of phenols to catechols and the oxidation of catechols to quinones [10,11]. The quinones are then transformed to biologically important molecules, such as the pigment melanin [12] or the neurotransmitter noradrenalin [13]. In the oxygenated form of tyrosinase, a μ-η^2:η^2-peroxodicopper(II) species has been crystallographically identified with an intact O–O bond [14].

The hydroxylation of phenols proceeds through a mechanism consistent with an electrophilic aromatic substitution [11,15,16]. During the last decade, numerous model studies provided insights that the stoichiometric hydroxylation of phenolates can be mediated via synthetic μ-η^2:η^2-dicopper(II) cores [17-20] and bis(μ-oxo) dicopper(III) cores [15,16,21-23] (see Figure 1, below).

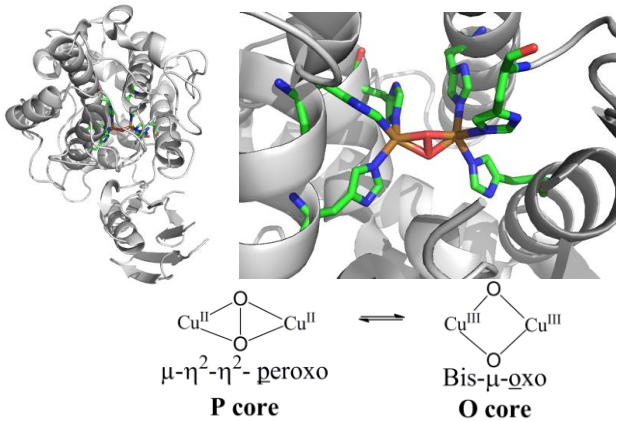

Fig. 1. Tyrosinase (upper left), active site of tyrosinase (upper right) [14] and equilibrium of a P core and an O core (below)

III. Orbital Analysis of Oxo and Peroxo Dicopper Complexes

Understanding of the formation of P and O cores as well as their distinct reactivity relies on comprehensive orbital analyses (Figure 2). However, detailed understanding and computational modeling of these species are still major challenges. In spite of many efforts, the equilibrium between P and O cores is still regarded as a ''torture track'' for computation [24]. Very large variations in the predicted relative stabilities of P and O core motifs have been reported. The situation appears confusing since (i) different levels of theory are used in the calculations and (ii) the chemical equilibrium and properties of the μ-η^2:η^2-peroxo dicopper(II)- and the bis-μ-oxo-dicopper(III) dimers depends sensitively on ligands, solvent, and counterions. Many calculations in this context [15,24-27] use density-functional theory (DFT) with either local (pure) functionals or hybrid functionals such as B3LYP [16,22,28,29] to describe the electron exchange and correlation (XC) energy.

In Figure 2, HOMO is the abbreviation for highest occupied molecular orbital and LUMO for lowest unoccupied molecular orbital. The molecular orbitals are occupied maximal with two electrons. The general frontier orbitals combine contributions of the copper d_{xy} orbitals and the antibonding oxygen orbitals as positive or negative linear combinations, hence constructing delocalized molecular orbitals for the whole Cu_2O_2 core.

Here, we report on orbital analyses of small model systems (Figure 3, left) containing ammonia ligands which are not experimentally accessible and a "real life" system which has been synthesized by us (right).[31] The ammonia complexes deliver a more principle understanding of the orbital contributions of the copper ions, the peroxide/oxido and ammonia ligands.

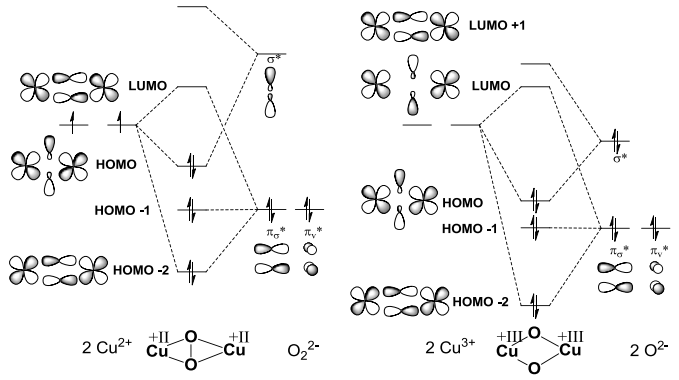

Fig. 2. Molecular orbital diagram of the frontier orbitals of the P core (left) and the O core (right) [30]

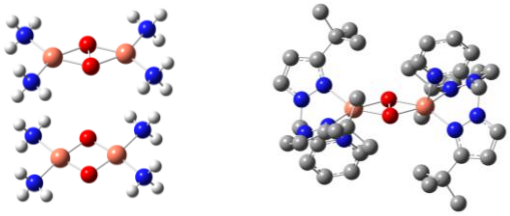

Fig. 3. Complex containing the ammonia ligands (left) and the "real life" system (right, H atoms are omitted for clarity)

IV. METHODS

A. MoSGrid Science Gateway

The orbital analyses on N donor copper complexes were carried out using the MoSGrid science gateway [2], which uses the open-source, commonly used, and very flexible portal framework Liferay [32] as its basis. The science gateway enables scientists from the wide field of molecular simulations to design and compose workflows for simple and complex tasks to be computed in a distributed computing infrastructure (DCI). MoSGrid was designed and implemented to relieve scientists from the necessity to have detailed knowledge about (i) program specific input- and output files and (ii) detailed knowledge of how to access and utilize high performance computing infrastructures (remote access and security aspects, use of remote command line interfaces). The science gateway supports every step in an intuitive way from the generation of a task within a predefined workflow, the submission, and monitoring of a running workflow to the point of accessing output files as well as automatically generated visualizations.

To allow this the MoSGrid science gateway comprises of several sections. First, a public area with general project information, help texts and tutorials about how to conduct simulations is offered. The user is pointed to writing a mail to get activated and getting used to run workflows. Secondly, an area for activated users is presented. It includes a certificate portlet to easily and seamlessly enable the access to the underlying computing clusters. A security token is almost automatically generated from the users certificate to allow the science gateway to act on behalf of the user. gUSE, the underlying middleware to enable submission of jobs to a wide range of DCI systems, is transparently made available to the user. WS-PGRADE as the graphical user interface to gUSE is completely hidden from users by the use of specific graphical interface for the three chemical domains, quantum chemistry, molecular dynamics, and docking. The security token is automatically used for to access several key aspects of the MoSGrid science gateway; first it is used to access the grid middleware UNICORE [33] for the submission and handling of jobs. Secondly the MoSGrid repository can be accessed which includes the distributed cloud file system XtreemFS [34] for raw file storage and UNICORE for enabling the use of metadata and search functionality. Thirdly advanced users can utilize WS-PGRADE to create and manage customized workflows. The token is subsequently used by a so called submitter which enables the communication between gUSE [35] and UNICORE. Jobs and workflows are managed and applications installed on HPC systems can be selected and used. This allows for an efficient jobs submission, since applications don't have to be re-transferred with each job. This is especially important for software packages like Gaussian which has to be installed on HPC resources due to its license scheme.

The third area includes the domain specific user interfaces for the chemical applications. These were developed to just show necessary information to the user to make the use experience as intuitive as possible. The Quantum Chemistry user interface, used for the research presented in this paper, offers user-friendly access to the Gaussian application. To make the workflow submission as easy and quick as possible default values are offered. On the other hand workflows can be fine-tuned to ones specific simulation needs by adjusting a multitude of parameters. These include job type (optimization, job type, energy, or a combination of these), method (DFT, TD-DFT, Hartree-Fock), basis set (3-21G, 6-31G(d), cc-pVQZ), resource specifications (main memory, number of cores, job length), and other options. Another aspect of the interface allows for the monitoring of the currently running workflows and the related results. In addition, MoSGrid administrators have an extra area which enables the easy management of the whole science gateway and user related tasks.

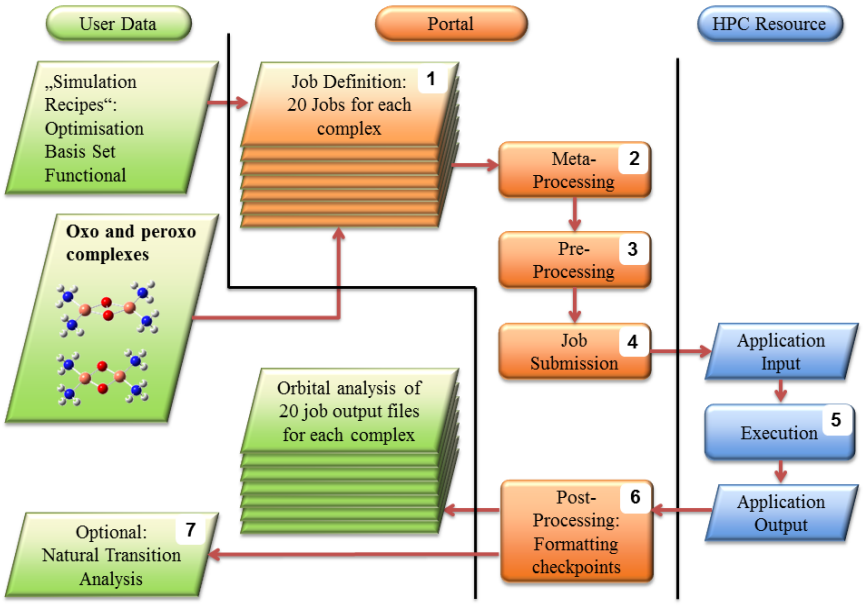

Fig. 4. Workflow of the orbital analysis

B. *Workflows with oxo/peroxo complexes*

The orbital analysis can be mapped to a multi-step workflow (Figure 4) which consists of the following tasks: The first step is the job definition (**1**). Here, the user uploads predefined files containing all necessary information about the copper complex simulation. In particular, the starting structures of the oxo and peroxo complexes are given by the user and a file which functional and basis sets shall be used. A generator port builds the input files stack (20 jobs for each complex). As typical functionals, B3LYP, BLYP, BP86 and TPSSh have been applied, 6-31g(d), cc-pvdz, def2-TZVP were used as basis sets. Meta-processing (**2**) as second step checks the user input for consistency and, if necessary, completes the configuration. A complete set of job-meta-information contains the molecule structure, application, method, temperature and basis set. If not all information is given, the user is guided through the configuration by providing sensible default values that the user can accept or overwrite. The last step of the configuration is the definition of the length of the simulation and the amount of needed resources (20000 MB). The definition of the simulation length is a tricky task, because quantum calculations tend to be non-deterministic. Therefore, the length of the simulation should be guessed long enough. Afterwards, this molecular simulation meta-description is translated to the simulation specific format by a preprocessing step (**3**). For this process adapters are developed for several quantum codes.

Following, the job submission is initiated (**4**). The submitter translates the job information into the UNICORE job format and transfers the job through the UNICORE middleware to the target cluster environment, where it is executed in Gaussian09 [36] (**5**). The job information includes the user credentials, structure format, and input file staging information. Post-processing is performed after the successful execution of the workflow to extract the application independent information from the result files (**6**) and to generate checkpoint files which enable visualization of the orbitals. Optionally, afterwards an NTO analysis can be accomplished (**7**, see Results section). Further, the MoSGrid portal allows annotating the simulation results with MSML and storing them in the MoSGrid data repository for reuse.

V. RESULTS

The workflows give a large number of output files and orbitals. Here, the most important results are summarised. Optical benchmarking of calculated orbitals can be performed via comparison to experimental electronic spectra. Typically, a P core exhibits two absorption bands at 350 and 550 nm whereas an O core possesses two bands at 300 and 400 nm [30]. These features must be predicted correctly. The frontier orbitals for the small model systems are shown in Figure 5 and those of the real system in Figure 6. In the P core, we obtained a UV/Vis spectrum with the two characteristic bands at 350 nm (HOMO→LUMO) and the band at 550 nm (HOMO-1→LUMO) with minor intensity. The HOMO is the linear combination of the d_{xy} atom orbital of the copper with the σ^* atom orbital of the peroxide and the LUMO is the linear combination of the d_{xy} atom orbital of the copper and the π_σ^* atom orbital of the peroxide, whereas the HOMO-1 is the linear combination of the d_{xy} atom orbital of the copper and the π_v^* atom orbital of the peroxide. The transition at 350 nm is an in-plane transition, so there is more overlap between the orbitals, resulting in a higher intensity than in the out-of-plane transition at 550 nm. In the O core, the first transition is the interaction between the HOMO-2 and the LUMO. The HOMO-2 is a linear combination of the d_{xy} atom orbital of the copper and the π_σ^* atom orbital of the oxido bridges, whereas the LUMO is a linear combination of the d_{xy} atom orbital of the copper and the σ_u^* atom orbital of the oxido bridges. The second UV band arises from a transition of the HOMO (a linear combination of the d_{xy} copper orbital and the σ_u^* oxygen orbital) into the LUMO+1 (a linear combination of the d_{xy} copper orbital and the π_σ^* oxygen orbital).

Time dependent-DFT calculated spectra predict the experimental optical spectrum with the four LMCT bands at 340 nm, 366 nm, 381 nm and 547 nm. The description of these bands with canonical orbitals shows heavily mixed and complicated transitions. So we describe the transitions with the natural transition orbitals [37]. These transition orbital assigns the most prominent features near 350 nm (340 and 366 nm) to be an in-plane peroxide $\pi_\sigma^* \rightarrow d_{xy}$ transition and the lowest energy feature near 550 nm to an out-of-plane peroxide $\pi_v^* \rightarrow d_{xy}$. The absorbance near 430 nm (calculated at 381 nm) is assigned to a pyrazole/pyridyl $\pi^* \rightarrow d_{xy}$ charge transfer transition, as is positioned for other peroxo complexes with unsaturated, nitrogen-containing ligands [38]. Hence, the difference to the small model systems show the large difference between the frontier orbitals and the significant ligand influence which will be evaluated in further studies.

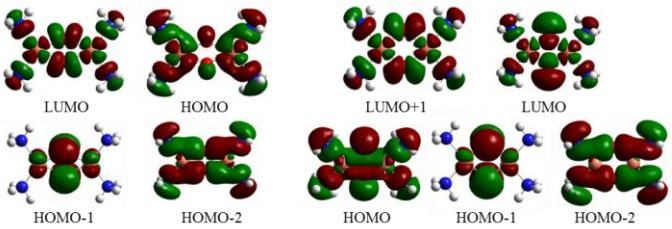

Fig. 5. Molecular orbitals of the frontier orbitals of the small model systems (P core left; O core right)

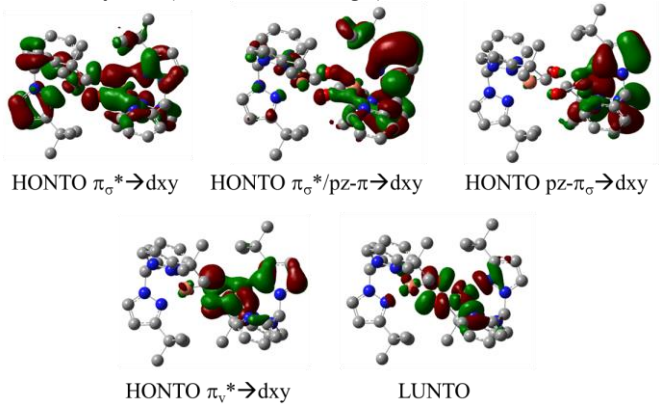

Fig. 8. Natural transitions orbitals (NTOs) of the "real life" system

VI. OUTLOOK

With the results of this computational analysis, a better understanding of oxo and peroxo complexes is possible. In the next steps, we plan to extend the parameter-sweep workflow-driven features of MoSGrid in order to facilitate serial studies even more. Then, benchmarking number can be provided. The functional and basis set dependency of the copper-copper distances has to be studied in detail since it is crucial for the electronic structure.

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REFERENCES

[1] S. Gesing, R. Grunzke, A. Balasko, G. Birkenheuer, D. Blunk, S. Breuers, A. Brinkmann, G. Fels, S. Herres-Pawlis, P. Kacsuk, M. Kozlovszky, J. Krüger, L. Packschies, P. Schäfer, B. Schuller, J. Schuster, T. Steinke, A. SzikszayFabri, M. Wewior, R. Müller-Pfefferkorn and O. Kohlbacher: Granular Security for a Science Gateway in Structural Bioinformatics, *Proceedings of 3rd Workshop IWSG-Life 2011*, London, UK, June 8-10, 2011, CEUR Workshop Proceedings, ISSN 1613-0073, online CEUR-WS.org/Vol-819/paper8.pdf.

[2] S. Gesing, S. Herres-Pawlis, G. Birkenheuer, A. Brinkmann, R. Grunzke, P. Kacsuk, O. Kohlbacher, M. Kozlovszky, J. Krüger, R. Müller-Pfefferkorn, P. Schäfer, T. Steinke, The MoSGrid Community – From National to International Scale. In: EGI Community Forum 2012, Munich, Germany.

[3] http://www.gridchem.org

[4] S. Maddineni, J. Kim, Y. El-Khamra, S. Jha, Dynamic Application Runtime Environment (DARE): A Standards-based Framework For Building Science Gateways, J. Grid Comp., 10 (4), 647 (2012).

[5] H. B. Gray, E. I. Stiefel, J. S. Valentine, I. Bertini, Eds., Biological inorganic chemistry: structure and reactivity, University Science Book, Mill Valley (2006).

[6] R. van Eldik, J. Reedijk, Homogeneous Biomimetic Oxidation Catalysis, Academic Press, New York, (2006).

[7] S. Itoh, S. Fukuzumi, Acc. Chem. Res. 40, 592 (2007).

[8] S. Itoh, Comprehensive Coordination Chemistry II, L. Que, Jr.; W. B. Tolman, Eds., Elsevier, Amsterdam (2004), vol. 8, 369.

[9] M. A. Halcrow, P. F. Knowles, S. E. V. Philipps, Handbook on Metalloproteins, I. Bertini, A. Sigel, H. Sigel, Eds., Marcel Dekker, Inc.: New York (2001), 709.

[10] E. I. Solomon, U. M. Sundaram, T. E. Machonkin, Multicopper Oxidases and Oxygenases, Chem. Rev. 96, 2563 (1996).

[11] M. Rolff, J. Schottenheim, H. Decker, F. Tuczek, Copper–O_2 reactivity of tyrosinase models towards external monophenolic substrates: molecular mechanism and comparison with the enzyme Chem. Soc. Rev. 40, 4077 (2011).

[12] K. E. van Holde, K. I. Miller, H. Decker, Hemocyanins and Invertebrate Evolution, J. Biol. Chem. 276, 15563 (2001).

[13] G. Eisenhofer, H. Tian, C. Holmes, J. Matsunaga, S. Roffler-Tarlov, V. J. Hearing. Tyrosinase: a developmentally specific major determinant of peripheral dopamine, FASEB J. 17, 1248 (2003).

[14] Y. Matoba, T. Kumagai, A. Yamamoto, H. Yoshitsu, M. Sugiyama, Crystallographic Evidence That the Dinuclear Copper Center of Tyrosinase Is Flexible during Catalysis, J. Biol. Chem. 281, 8981 (2006).

[15] L. M. Mirica, M. Vance, D. J. Rudd, B. Hedman, K. O. Hodgson, E. I. Solomon, T. D. P. Stack, Tyrosinase Reactivity in a Model Complex: An Alternative Hydroxylation Mechanism, Science 308, 1890 (2005).

[16] B. T. Op't Holt, M. A. Vance, L. M. Mirica, D. E. Heppner, T. D. P. Stack, E. I. Solomon, Reaction Coordinate of a Functional Model of Tyrosinase: Spectroscopic and Computational Characterization, J. Am. Chem. Soc. 131, 6421 (2009).

[17] S. Itoh, H. Kumei, M. Taki, S. Nagatomo, T. Kitagawa, S. Fukuzumi, Oxygenation of Phenols to Catechols by A (μ-η^2:η^2-Peroxo)dicopper(II) Complex: Mechanistic Insight into the Phenolase Activity of Tyrosinase, J. Am. Chem. Soc. 123, 6708 (2001).

[18] L. Santagostini, M. Gullotti, E. Monzani, L. Casella, R. Dillinger, F. Tuczek, Reversible Dioxygen Binding and Phenol Oxygenation in a Tyrosinase Model System, Chem. Eur. J. 6, 519 (2000).

[19] L. M. Mirica, M. Vance, D. Jackson Rudd, B. Hedman, K. O. Hodgson, E. I. Solomon, T. D. P. Stack, A Stabilized μ-η^2:η^2 Peroxodicopper(II) Complex with a Secondary Diamine Ligand and Its Tyrosinase-like Reactivity, J. Am. Chem. Soc. 124, 9332 (2002).

[20] S. Palavicini, A. Granata, E. Monzani, L. Casella, Hydroxylation of Phenolic Compounds by a Peroxodicopper(II) Complex: Further Insight into the Mechanism of Tyrosinase, J. Am. Chem. Soc. 127, 18031 (2005).

[21] A. Company, S. Palavicini, I. Garcia-Bosch, R. Mas-Ballest, L. Que, Jr., E. V. Rybak-Akimova, L. Casella, X. Ribas, M Costas, Tyrosinase-Like Reactivity in a $Cu^{III}_2(\mu\text{-}O)_2$ Species, Chem. Eur. J. 14, 3535 (2008).

[22] S. Herres-Pawlis, P. Verma, R. Haase, P. Kang, C. T. Lyons, E. C. Wasinger, U. Flörke, G. Henkel, T. D. P. Stack, Phenolate Hydroxylation in a Bis(μ-oxo)dicopper(III) Complex: Lessons from the Guanidine/Amine Series, J. Am. Chem. Soc. 131, 1154 (2009).

[23] A. Spada, S. Palavicini, E. Monzani, L. Bubacco, L. Casella, Trapping tyrosinase key active intermediate under turnover, Dalton Trans., 6468 (2009).

[24] C. J. Cramer, M. Wloch, P. Piecuch, C. Puzzarini, L. Gagliardi, Theoretical Models on the Cu_2O_2 Torture Track: Mechanistic Implications for Oxytyrosinase and Small-Molecule Analogues, J. Phys. Chem. A 110, 1991 (2006).

[25] M. J. Henson, P. Mukherjee, D. E. Root, T. D. P. Stack, E. I. Solomon, Spectroscopic and Electronic Structural Studies of the $Cu(III)_2$ Bis-μ-oxo Core and Its Relation to the Side-On Peroxo-Bridged Dimer, J. Am. Chem. Soc. 121, 10332 (1999).

[26] J. L. Lewin, D. E. Heppner, C. J. Cramer, Validation of density functional modeling protocols on experimental bis(μ-oxo)/μ-η^2:η^2-peroxo dicopper equilibria, J. Biol. Inorg. Chem. 12, 1221 (2007).

[27] B. F. Gherman, C. J. Cramer, Quantum chemical studies of molecules incorporating a $Cu_2O_2^{2+}$ core, Coord. Chem. Rev. 253, 723 (2009).

[28] A. Poater, L. Cavallo, Probing the Mechanism of O^2 Activation by a Copper(I) Biomimetic Complex of a C−H Hydroxylating Copper Monooxygenase, Inorg. Chem. 48, 4062 (2009).

[29] P. Kang, E. Bobyr, J. Dustman, K. O. Hodgson, B. Hedman, E. I. Solomon, T. D. P. Stack, Bis(μ-oxo) Dicopper(III) Species of the Simplest Peralkylated Diamine: Enhanced Reactivity toward Exogenous Substrates, Inorg. Chem. 49, 11030 (2010).

[30] L.M. Mirica, X. Ottenwaelder, T.D.P. Stack, Structure and Spectroscopy of Copper−Dioxygen Complexes, Chem. Rev. 104, 1013 (2004)

[31] A. Hoffmann, C. Citek, S. Binder, A. Goos, M. Rübhausen, O. Troeppner, I. Ivanović-Burmazović, E. C. Wasinger, T. D. P. Stack, S. Herres-Pawlis, Catalytic Phenol Hydroxylation with Dioxygen: Extension of the Tyrosinase Mechanism Beyond the Protein Matrix, Angew. Chem. Int. Ed. 52, 5398 (2013).

[32] Inc. Liferay: Liferay. http://www.liferay.com

[33] A. Streit, P.Bala, A. Beck-Ratzka, K. Benedyczak, S. Bergmann, R. Breu, J.M. Daivandy, B. Demuth, A. Eifer, A. Giesler, B. Hagemeier, S. Holl, N. Lamla, D. Mallmann, A.S. Memon, M.S. Memon, M.

Rambadt, M. Riedel, M. Romberg, B. Schuller, T. Schlauch, A. Schreiber, T.Soddemann, W. Ziegler, UNICORE 6 - Recent and Future Advancements. JUEL-4319 (February 2010). http://hdl.handle.net/2128/3695 (2010).

[34] F. Hupfeld, T. Cortes, B.Kolbeck, J. Stender, E. Focht, M. Hess, J. Malo, J. Marti, E. Cesario, The XtreemFS Architecture - A Case for Object-based File Systems in Grids, Concurrency and Computation: Practice and Experience 20(17), 2049-2060 (2008).

[35] MTA SZTAKI: gUSE. http://www.guse.hu/

[36] M.J. Frisch, et al.: Gaussian 09, Revision B.01, (2012). Gaussian, Inc., Wallingford CT.

[37] R. L. Martin, Natural transition orbitals, J. Chem. Phys. 118, 4775 (2003).

[38] C. Citek, C. T. Lyons, E. C. Wasinger, T. D. P. Stack, Self-assembly of the oxy-tyrosinase core and the fundamental components of phenolic hydroxylation, Nat. Chem. 4, 317 (2012).