Metallamacrocycles

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Self-Assembly of a Cyclic Zn_4O_4 Tetramer by Aerobic Oxidation of a Bisoxazoline: A Molecular "Nest" for Nucleophilic OH^-**

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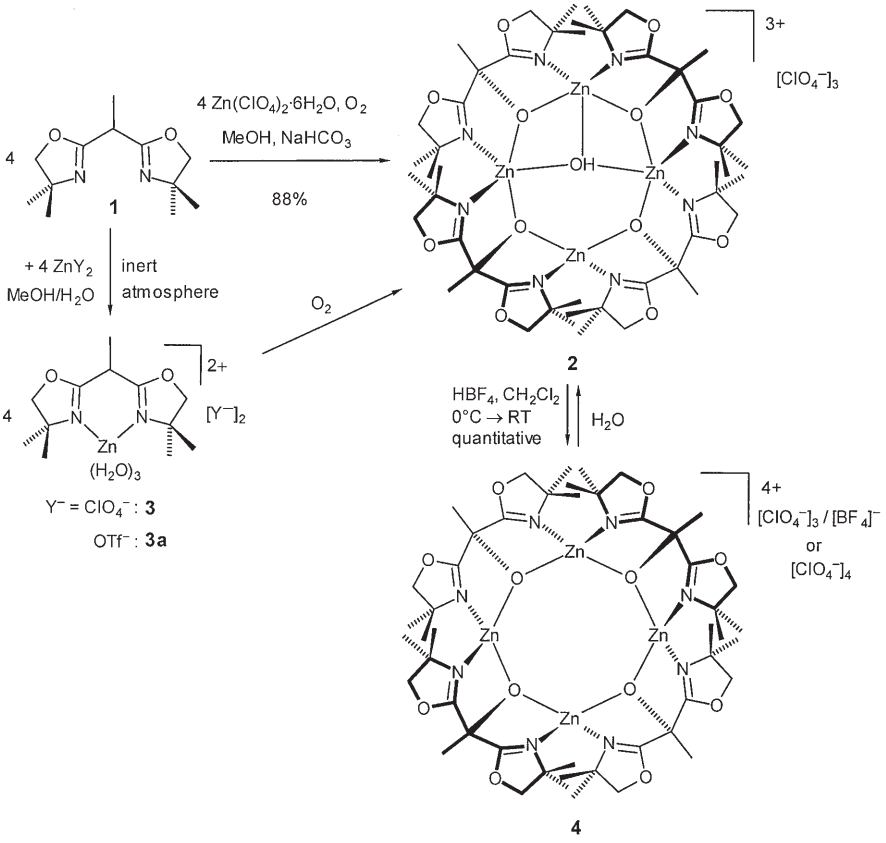
The bewildering complexity of biological structures and functions is based on a limited number of building blocks. Further transformation of these primary structural elements provides the key to the assembly of functional units of great complexity. The oxidative functionalization of biological monomers, in particular amino acids, is an essential step in the generation of the binding sites for metal atoms in the form of catecholates, hydroxamates, and related ligating functions.[1] Their complexation to substitutionally labile metal ions gives rise to stable highly ordered mono or polynuclear coordination units.[2] These may play a role in the sequestering of metal ions, the stabilization of biopolymer structures or as active sites in metalloenzymes.[3]

There is an ever growing number of synthetic host molecules for the binding of charged or neutral molecules which may be employed as catalysts, building blocks for extended solids, and sensors.[4] Many of these are metallamacrocycles[5] or have cage structures based on preconceived ligand architectures which assemble to give the polynuclear aggregate.[6] Herein we report the combination of a selective functionalization step, the aerobic oxidation of a bisoxazoline, with the formation of a highly ordered metallamacrocyclic complex which itself is shown to be a functional catalytic system.



Scheme 1. Synthesis of the tetranuclear complex $[\{(Me_2box)O\}_4Zn_4(OH)][ClO_4]_3$ **2** and its conversion into $[\{(Me_2box)O\}_4Zn_4][ClO_4]_4$ (**4**).

Stirring equimolar amounts of the bisoxazoline Me_2box[7] (**1**) and $Zn(ClO_4)_2{\cdot}6H_2O$ in methanol for 24 h led to the precipitation of a white crystalline solid, which was characterized as the tetranuclear complex $[\{(Me_2box)O\}_4Zn_4(OH)][ClO_4]_3$ (**2**; Scheme 1).

The mass balance in Equation (1) implies the generation

$$4\,Me_2box\ (\mathbf{1}) + 4\,Zn(ClO_4)_2 + 2\,O_2 + H_2O \rightarrow [\{(Me_2box)O\}_4Zn_4(OH)][ClO_4]_3\ (\mathbf{2}) + 5\,HClO_4 \quad (1)$$

of perchloric acid during the course of the oxygenation, which in turn explains the formation of protonated bisoxazoline as a by-product and the incomplete conversion (isolated yield of

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2 ≤ 40 %). Carrying out the reaction in the presence of $NaHCO_3$ gave the tetranuclear complex $[\{(Me_2box)O\}_4Zn_4(OH)][ClO_4]_3$ (**2**) in 88 % yield with respect to $Zn(ClO_4)_2$.

A single-crystal X-ray structure analysis of **2**[8] established the eight-membered ring core consisting of four zinc and four oxygen atoms (Figure 1).[9] Each zinc atom is coordinated by two nitrogen atoms from two different oxazoline ligands as well as two alkoxy oxygen atoms in a μ_2-O mode. The hydroxide ion bridges three of the four zinc atoms [Zn(1)-O(15) 2.144(1), Zn(3)-O(15) 2.170(1), and Zn(4)-O(15) 2.113(1) Å].[10]

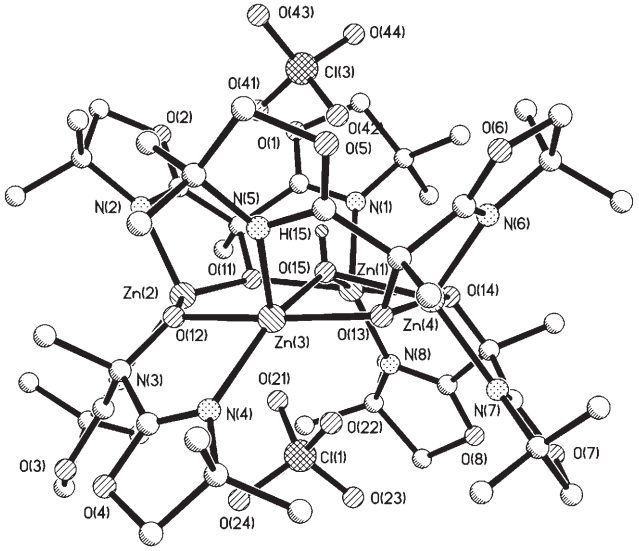

Figure 1. Side view of the molecular structure of the {Zn_4–OH} complex **2**. Two of the three perchlorate ions are shown. All hydrogen atoms (except for the OH hydrogen atom) are omitted for clarity. Principal bond lengths [Å] and angles [°]: O(15)–Zn(4) 2.113(1), O(15)–Zn(1) 2.144(1), O(15)–Zn(3) 2.170(1), O(15)–Zn(2) 3.020(1), O(15)–H(15) 0.77(3); O(14)-Zn(4)-O(13) 163.57(5), O(13)-Zn(3)-O(12) 171.77(5), O(11)-Zn(2)-O(12) 139.76(5), O(14)-Zn(1)-O(11) 173.40(5), Zn(2)-O(11)-Zn(1) 113.82(5), Zn(2)-O(12)-Zn(3) 118.67(6), Zn(3)-O(13)-Zn(4) 96.19(5), Zn(4)-O(14)-Zn(1) 99.70(5).

The formation of the tetranuclear complex **2**, in which the bisoxazolines are oxygenated to give alkoxy ligands,[11] occurred upon conducting this transformation in the presence of air. Under a rigorous anaerobic atmosphere of purified argon, the reaction did not give a similar oxygenation of the ligand and self-assembly of tetrameric aggregates, but afforded the mononuclear complex $[(Me_2box)Zn(H_2O)_3](ClO_4)_2$ (**3**), the triflate salt **3a** of which has been structurally characterized.[8,12] Performing the reaction under an atmosphere of $^{18}O_2$ provided further proof for a clean and selective aerobic oxidation of the ligand [Eq. (2)].

$$4\,Me_2box\ (\mathbf{1}) + 4\,Zn(ClO_4)_2 + 2\,{}^{18}O_2 + H_2O \rightarrow [\{(Me_2box)^{18}O\}_4Zn_4(OH)][ClO_4]_3\ (\mathbf{2a}) + 5\,HClO_4 \quad (2)$$

The formation of the ^{18}O-labeled complex **2a** was confirmed by the ESI mass spectrum, which indicates, at *m*/*z* 1435.1918, the presence of a tetranuclear complex cation corresponding to the formula $[\{(Me_2box)^{18}O\}_4Zn_4(OH)][ClO_4]_2^+$ (Figure 2). IR spectroscopic data are also consistent with the introduction of an ^{18}O atom on the bridging carbon of the bisoxazoline: the C–O stretching mode observed at 1151 cm^{-1} in complex **2** is shifted to a lower frequency at 1144 cm^{-1} in ^{18}O-labeled **2a** (see the Supporting Information).

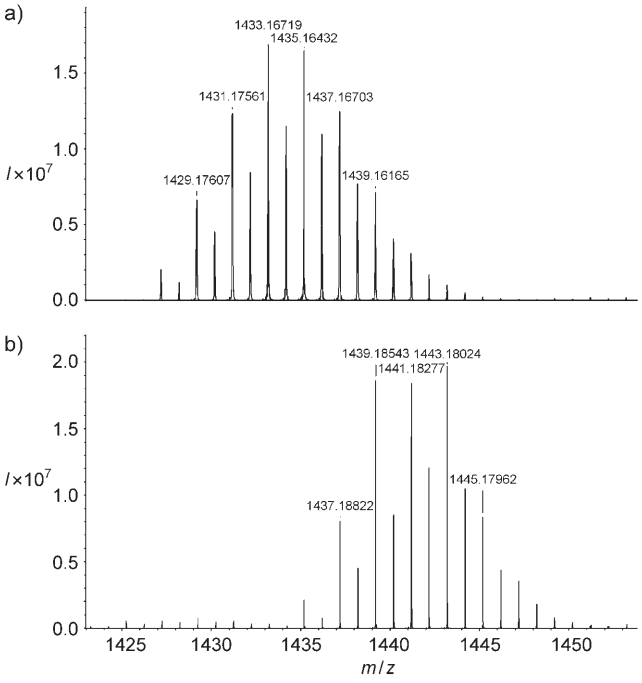

Figure 2. ESI mass spectra of: a) the complex $[\{(Me_2box)O\}_4Zn_4(OH)][ClO_4]_3$ **2** and b) the complex $[\{(Me_2box)^{18}O\}_4Zn_4(OH)][ClO_4]_3$ **2a**.

Whereas the slow aerobic autoxidation of uncoordinated bisbenzoxazoles has previously been noted,[13] in the case at hand, no oxidation of the Me_2box ligand occurred in the absence of the metal salt,[14] suggesting a significant role of the metal in this selective oxidation of a box derivative.[15] Zinc is thought to activate the neutral box, which is deprotonated giving the bisoxazolinato species.[16] In turn, this anionic bisoxazolinate will react with oxygen[17] (acting as an electrophilic diradical) in a similar way as observed by Itoh and coworkers for β-ketiminates.[18] In the presence of radical scavengers, such as TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxide) and BHT (2,6-di-*tert*-butyl-4-methylphenol), the formation of **2**/**2a** was not observed.

Upon reaction of $[\{(Me_2box)O\}_4Zn_4(OH)]^{3+}$ (**2**) with one equivalent of HBF_4 in diethyl ether, quantitative conversion into the corresponding OH^--free tetracationic complex $[\{(Me_2box)O\}_4Zn_4]^{4+}$ (**4**) took place immediately (Scheme 1). This complex was obtained in various crystalline forms, invariably cocrystallizing with solvent (dichloromethane and/or methanol, hexane). Its molecular structure, determined by X-ray diffraction of a hexane-containing crystal, is depicted in Figure 3a.[8] The molecular cation has crystallographic C_2 symmetry, and the alternating arrangement of the bisoxazoline ligands confers an overall virtual D_{2d}

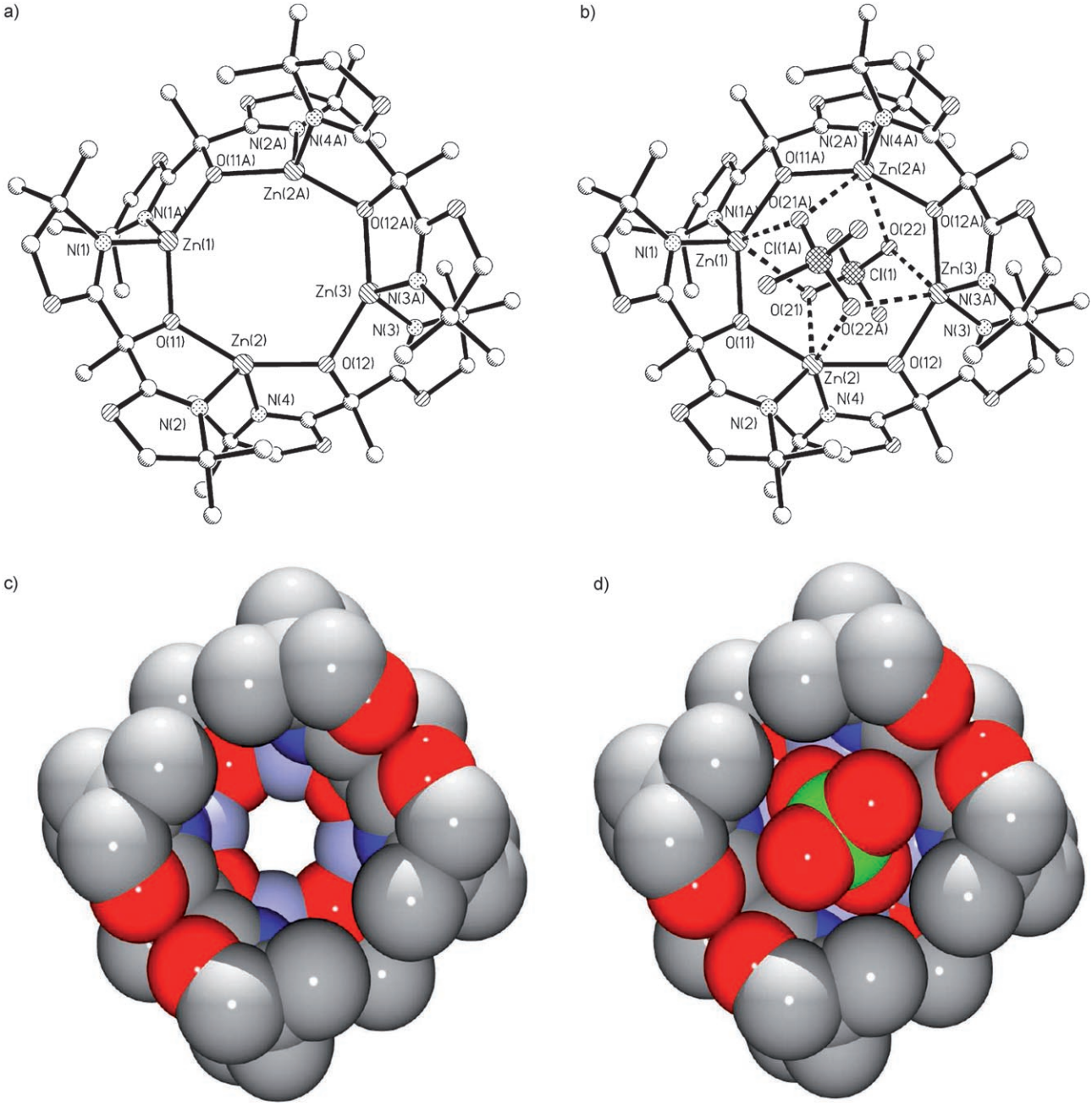

Figure 3. Molecular structure of the complex tetracation in **4**: a) view along the virtual fourfold improper axis, and b) the adduct of the cation with two ClO_4^- counterions occupying the molecular "nest" structure. Space-filling models of: c) the complex cation and d) the ClO_4^- adduct, showing the excellent fit between the $\{Zn_4O_4\}$ host and the guest anions. Zn light blue, N dark blue, O red, C gray, Cl green. Principal bond lengths [Å] and angles [°]: Zn–N 2.038(3)–2.043(3), Zn–O(11,12) 1.982(2)–2.009(2), Cl(1)–O(21)/O(22) 1.445(3)/1.442(3), Cl(1)–O(23)/O(24) 1.429(3)/1.423(3); N-Zn-N 111.9(2)–114.8(2), O-Zn-O 141.7(1)–149.1(1), Zn(1)-O(11)-Zn(2) 124.1(1), Zn(3)-O(12)-Zn(2) 121.1(1).

symmetry to the cationic tetramer, which may be viewed as a molecular "nest" for anionic or Lewis basic guest molecules (Figure 3c). Four perchlorate anions balance the charge of the complex cation. In the crystal, two of them are arranged as molecular guests above and below the $\{Zn_4O_4\}$ core of the molecule, with the eight-membered ring being perfectly suited to accommodate the bridging O–Cl–O moiety of the anions (Figure 3b and d). The $Zn\cdots O_{perchlorate}$ distances are 2.54–2.63 Å, and this bonding interaction is also reflected by the elongation of the Cl–O bond lengths within the perchlorate ions ($Cl–O_{terminal} = 1.42–1.43$ Å vs. 1.45–1.46 Å).[19] The exact fit of anions and cations is apparent in the space-filling model depicted in Figure 3d and consistent with the observation of the mass peaks in the ESI MS spectra corresponding to $\{cation + 2\,ClO_4\}^{+/2+}$.

The hydroxo complex **2** is formed from **4** under neutral conditions in aqueous solution. This suggests that the pK_a of zinc(II)-bound water is close to physiological pH. A potentiometric titration experiment gave a pK_a value of 8.2. Given this "activation of water", we probed the ability of **2** to

catalyze the hydrolysis of phosphates. The reactivity of phosphotriester substrate tris(4-nitrophenyl)phosphate (TNP) was evaluated in buffered EtOH/H_2O solutions.[20,21] The reaction was found to be first order in both tetranuclear zinc complex and substrate, and the second-order rate constants of hydrolysis were evaluated from pH 7.0 to 9.2. The pH rate profile revealed an inflection point at 8.15 which corresponds to the pK_a obtained in the potentiometric titration. We may therefore conclude that the Zn_3-bridging hydroxide is most likely the base that induces the TNP hydrolysis. The relative reactivity of metal-promoted hydrolysis versus free OH^- provides some insight in the mechanism of the hydrolysis.[22] The second-order rate constant (k'_{max})[23] of the zinc-OH catalyzed hydrolysis was found to be $2.2\,M^{-1}s^{-1}$, and is slightly lower than that observed for the free OH^- ion ($10.7\,M^{-1}s^{-1}$).[23] The nucleophilicity of a metal-bound hydroxide must be lower than free OH^- on the basis of simple steric and charge considerations. Therefore, the fact that the rate hydrolysis with the zinc complex is of approximately the same order of magnitude of free OH^- appears to be consistent with a mechanism involving a nucleophilic attack of the metal-bound hydroxide upon the phosphorus atom aided by a certain degree of zinc–phosphate affinity.

In summary, a simple molecule is activated towards a highly selective aerobic oxygenation by metal complexation. This is relevant for the use of bisoxazolines and bisoxazolinates as stereodirecting ligands in enantioselective catalysis.[24] In the case at hand, the oxidation is followed by the assembly in the form of a highly ordered metallamacrocycle which displays catalytic phosphatase activity. The combination of these different levels of structural assembly and associated function may be viewed as a simple model for the systems of far greater complexity encountered in nature.

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