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Water-Soluble Derivatives of Octanuclear Iron-Oxo-Pyrazolato Complexes; An Experimental and Computational Study

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Abstract

Two water-soluble iron-pyrazolato complexes, [Fe₈], have been prepared by the introduction of twelve hydroxyalkyl groups to the periphery of the approximately spherical octanuclear molecule and they are contrasted with their two organosoluble chloroalkyl analogues. All four new complexes, **1** – **4**, have been characterized in solution by ¹H-NMR and electrospray ionization mass spectroscopy. The one-electron reduction product of the water-soluble **3**, [Fe₈][−], has been structurally characterized by single crystal diffraction methods. In aqueous media, the four terminal Fe-Cl bonds of [Fe₈] are partially hydrolysed and the resulting chloro/aqua/hydroxo species form supramolecular nanoscale aggregates, as determined by dynamic light scattering and electron microscopy. Preliminary computational studies by density functional theory methods have been employed in order to model the H-bonding interactions controlling the competing solvation and aggregation processes.

Keywords

Water-soluble cluster; iron oxide; pyrazolato complexes; TEM; DFT study

Introduction

High nuclearity metal clusters and polynuclear transition metal complexes are rarely studied in aqueous media, limiting their applications in the fields of the “green chemistry” and biomedicine.^[1] The reason behind this scarcity is that, in typical polynuclear complexes, the metal atoms are surrounded by hydrophobic ligands --phosphines, pyridines, thiols, or carboxylic acid-based groups. While rendering metal clusters water soluble can be challenging, there are significant rewards for achieving this goal. For example, the two principal advantages of water as a reaction medium over volatile organic solvents for industrial scale catalytic processes are its obvious environment friendliness and safety.^[2]

Water solubility is of prime importance towards any kind of biological, therapeutic, or medical diagnostic application. It is estimated that for approximately 40% of active substances identified through combinatorial screening programs, difficulties are encountered

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in subsequent efforts to formulate them into pharmaceutical products as a result of their lack of significant water solubility.^[3] Water insolubility can be overcome in some cases by the use of one of a small number of physiologically suitable excipients, an approach which, however, does not eliminate all formulation-related performance issues.^[4] Some of the toxicity of Taxol, for example, is associated with Cremophor-EL, the excipient used to carry the insoluble active ingredient paclitaxel, into aqueous media.^[5] Clearly, whether for simplicity, cost effectiveness, or biological considerations, there are advantages to the preparation of directly water-soluble derivatives of complexes intended for medical applications. Apart from therapeutic applications, water solubility is also a requirement for diagnostic imaging contrast agents, including magnetic resonance imaging (MRI) contrast agents. In contrast agent-assisted MRI, enhanced image contrast is achieved by the intravenous injection of water-soluble, paramagnetic metal complexes, which shorten the magnetization relaxation rate of water protons.^[6–8]

In recent years we have been studying a group of paramagnetic, redox-active, octanuclear iron(III)-pyrazolate clusters of the general formula $[\text{Fe}_8(\mu_4\text{-O})_4(\mu\text{-4-R-pz})_{12}\text{X}_4]$, where R = H, Cl, Br and CH_3 , X = Cl, Br, NCS (Figure 1).^[9–12] The Fe_8O_4 -motif constituting the core of these complexes is the same one encountered in the Fe^{III} minerals maghemite ($\gamma\text{-Fe}_2\text{O}_3$) and ferrihydrite ($\text{Fe}_5\text{HO}_8\cdot 4\text{H}_2\text{O}$), as well as the $\text{Fe}^{\text{III/II}}$ mineral magnetite (Fe_3O_4), all three abundantly available in Nature.^[13–15] This observation implies that there is an inherent stability associated with the iron-oxo motif of $[\text{Fe}_8(\mu_4\text{-O})_4(\mu\text{-4-R-pz})_{12}\text{X}_4]$ complexes. Indeed, they are stable to air and humidity, while they can be safely refluxed in organic solvents and undergo metathetical reactions of their terminal X-ligands. Furthermore, they can be reversibly reduced in four consecutive one-electron steps to the corresponding mixed-valence anions. In one case, the first reduction product, $[\text{Fe}_8(\mu_4\text{-O})_4(\mu\text{-4-Cl-pz})_{12}\text{Cl}_4]^-$, has been isolated and fully characterized: It is readily recognized by its near-IR intravalence charge transfer (IVCT) band and shift of the $\nu_{(\text{Fe-O})}$ stretch in the IR, but is structurally indistinguishable, within experimental error, from its all- Fe^{III} parent compound.^[11] Visual inspection of a three-dimensional model of the $[\text{Fe}_8(\mu_4\text{-O})_4(\mu\text{-pz})_{12}\text{Cl}_4]$ complex, or the space-filling diagram (Figure 1c), shows that its approximately spherical surface is defined by H- and Cl-atoms, rendering it highly hydrophobic. Consequently, $[\text{Fe}_8(\mu_4\text{-O})_4(\mu\text{-4-R-pz})_{12}\text{X}_4]$ complexes with R=H, Cl, Br and CH_3 are all soluble in common organic solvents (methylene chloride, chloroform, tetrahydrofuran, acetone, toluene, acetonitrile, etc.) while remain insoluble in polar protic solvents, like methanol, ethanol and water. In order to explore the rich redox chemistry of these octanuclear complexes as possible electron-transfer agents in aqueous catalysis applications, or their paramagnetism as MRI contrast agents, it is necessary to synthesize water-soluble members of this group of $[\text{Fe}_8]$ compounds.

Water solubility is usually achieved by the introduction of polar groups, including sulfonates, carboxylates, ammonium, phosphonium, and hydroxyl groups.^[16] We have chosen to tackle the hydrophobicity problem of $[\text{Fe}_8]$ compounds by the introduction of hydroxyalkyl 4-R-groups to the twelve pyrazole ligands, based on the following thoughts: The solvation of alcohols, such as methanol and ethanol, in water is an exergonic process. Imperfect dissolution and clustering of the alkyl groups in free solution result in a net entropy decrease, countering the large exothermic term. For EtOH, $\Delta G_{\text{hydr}} \approx -5 \text{ kcal mol}^{-1}$, $\Delta H_{\text{hydr}} \approx -12 \text{ kcal mol}^{-1}$ and $-\text{T}\Delta S_{\text{hydr}} \approx +7 \text{ kcal mol}^{-1}$.^[17] In the case of hydroxyalkyl-modified $[\text{Fe}_8]$ compound, in which the aliphatic part of the alcohol groups will be pre-organized by the octanuclear complex, the entropic contribution of clustering will be null and the exothermic hydration enthalpy term will dominate the energetics of dissolution.

Here, we report the synthesis and characterization of four new $[\text{Fe}_8(\mu_4\text{-O})_4(\mu\text{-4-R-pz})_{12}\text{Cl}_4]$ complexes, two organo-soluble -- R = $\text{CH}_2\text{CH}_2\text{Cl}$ (**1**) and $\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl}$ (**2**) -- and two

water-soluble -- R = CH₂CH₂OH (**3**) and CH₂CH₂CH₂OH (**4**) -- and demonstrate that the introduction of alcohol functionalities on the twelve pyrazole ligands is sufficient in order to carry the intact [Fe₈] complex into water.

Results and Discussion

The four ligands, HL¹ – HL⁴, used for the synthesis of **1** – **4**, were synthesized by optimized literature procedures^[18] and were characterized by ¹H- and ¹³C-NMR. The organosoluble iron complexes **1** and **2** were prepared in one-pot reactions in CH₂Cl₂, while **3** and **4** in EtOH. All four new compounds were characterized in solution by ¹H-NMR and ESI-MS, and in the solid state by IR spectroscopy. In addition, **3**[–], the one-electron reduction product of complex **3**, was crystallographically characterized by single crystal X-ray diffraction. Substitution of the twelve peripheral chlorines of the pendant alkyl groups of **1** and **2** with the hydroxyls of **3** and **4** renders the latter two complexes soluble in polar protic solvents, resulting in intensely red-colored solutions. The solubility of **3** in distilled water is >36 mM, while it is also decreasingly soluble in MeOH, EtOH, PrOH and BuOH (sparingly), but insoluble in octanol. The solubility of **4** in the same solvents is slightly inferior to that of **3**. Complexes **3** and **4** can be recovered from their aqueous solutions, after solvent removal under reduced pressure. ESI-mass spectra of ethanolic solutions of the recovered materials are identical with those of the as prepared complexes. Because the four terminal Fe-Cl bonds of **1** – **4** can undergo solvolysis in H₂O and/or ROH media employed in their synthesis, these complexes are prepared as mixtures of [Fe₈Cl_{4-n}(OH/OR)_n], where the n = 0 product is the major component.

ESI-MS

Mass spectra were obtained in the ES⁺ mode from acetone solutions of **1** and **2**, or EtOH solutions of **3** and **4**. The nebulization gas flow was set to 500 L/h at a temperature of 300 °C, the cone gas was set to 50 L/h, and the source temperature to 150 °C. The capillary and cone voltages were set to 3000 (positive ion) and 60 V, respectively. The time-of-flight data were collected between m/z 500–3000, with a low collision energy of 6 eV. Data were collected in the continuum mode, with a scan accumulation time of 0.5 s. All analyses were acquired using an independent reference spray via the Lockspray interference to assure accuracy and reproducibility. The molecular weights of **1** – **4** were determined from the [M + Na]⁺ ions corresponding to a neutral molecule plus an adventitious sodium ion. The simulated isotopic distribution of this peak for each of the four compounds matches faithfully the experimental one (Fig. 2 and S1). In methanolic solutions of **3** and **4**, the molecular ion attributed to [Fe₈O₄L^{3,4}₁₂Cl₂(OMe)(HOEt)]⁺ was detected, indicating that the terminal chloride ligands are exchangeable in solution(S1).

¹H NMR

The ¹H NMR spectra of the organosoluble compounds **1** and **2** were recorded in CD₂Cl₂, while those of the water-soluble **3** and **4** in CD₃OD, using 5–6 mM concentrations for each compound. The spectra of all **1** – **4** are paramagnetically shifted and broadened, as expected (Fig. 3). The paramagnetism of these octanuclear Fe^{III}-complexes at ambient temperature arises from the population of a few excited states, besides their diamagnetic ground state. A detailed magnetic analysis for the [Fe₈(μ₄-O)₄(μ-pz)₁₂Cl₄]-motif has been published earlier.^[10] The assignment of resonances of **1** – **4** is summarized in Table 1.

A single set of two resonances assigned to the pyrazolato ligands is present in each case, consistent with twelve magnetically equivalent 4-R-pz groups and persistence of the solid state structure in solution. The assignment of the ³H and ⁵H resonances of the pyrazole rings is in agreement with those of previously published for related octanuclear complexes.^[10] Of

these two resonances, the one assigned to ^3H (proximal to the Fe_4O_4 -cubane) is downfield of and significantly broader than that of ^5H (proximal to the outer Fe-centers). The assignment of the methylene resonances was based on their transverse relaxation time values, T_2^* , calculated as $T_2^* = (\pi w_{1/2})^{-1}$, where $w_{1/2}$ is the spectral width at half-height. Transverse relaxation times are affected primarily by through-bond spin polarization effects, which become less significant further away from the paramagnetic center -- the Fe_8 -core of **1** – **4**, here. Accordingly, the broader resonances, resulting from shorter T_2^* values, are assigned to the methylene groups attached to the pyrazole- ^4C (^aH), while the sharper ones to the terminal methylene groups (^bH , or ^cH) next to the Cl- or O-atoms. In order to corroborate the assignment of resonances based on T_2^* values, the longitudinal relaxation times, T_1 , of complex **2** were also determined by spin-inversion recovery experiments. T_1 values are shortened by a through-space interaction between the protons in question and the paramagnetic center with an r^6 relationship, where r is the proton-paramagnetic center distance. The T_1 values corresponding to the three methylene groups of **2** decrease in the order (^aH , $^a'\text{H}$) < ^bH < ^cH , in agreement with their increasing distances from the metal core and their T_2^* -based assignment. Interestingly, there is a large variation (by a factor of 10, approximately) between the T_2^* values of the ^3H - and ^5H -atoms of all four complexes, as well as between the corresponding T_1 values (by a factor of 200, approximately) of **2**, indicating a quite unsymmetrical distribution of spin densities over the pyrazole rings. An in-depth analysis of electron spin distribution and its effect on nuclear spin relaxation in these octanuclear complexes is beyond the scope of the present manuscript and will be the topic of future work. With regard to the resonances of the aliphatic chains, it is worth noting that for all four compounds the geminal ^aH and $^a'\text{H}$ -atoms are diastereotopic and anisochronous, while the geminal ^bH -atom pair (and ^cH -atom pair, for **2** and **4**) are magnetically equivalent. This indicates that the rotation around the $\text{pz-}^a\text{CH}_2$ single bond is restricted, while there are free rotations around the $^a\text{CH}_2$ - $^b\text{CH}_2$ and $^b\text{CH}_2$ - $^c\text{CH}_2$ bonds in ambient temperature conditions (*vide infra*).

Vibrational Spectroscopy

The infrared spectra of the four new complexes are consistent with those of related $[\text{Fe}_8]$ compounds employing differently substituted 4-R-pz ligands (S2). The diagnostic absorption peak assigned to a Fe-O vibration appears between 468 cm^{-1} and 475 cm^{-1} in all four spectra. The spectra of **3** and **4** show in addition broad bands centered at 3273 cm^{-1} and 3293 cm^{-1} , respectively, assigned to the hydroxy groups, which are absent in the organo-soluble analogues.

Electrochemistry

Electrochemical analyses by cyclic and differential pulse voltammetry were performed in $\text{CH}_2\text{Cl}_2/\text{Bu}_4\text{NPF}_6$ for **2** and $\text{EtOH}/\text{Bu}_4\text{NClO}_4$ for **3**. Both showed reversible reduction processes at -0.49 V (**2**) and -0.46 V (**3**) vs. Fc^+/Fc (S3). The reduction of these $[\text{Fe}_8]$ complexes can, therefore, be readily achieved by mild reducing agents, which has been shown here by the partial reduction of **3** to 3^- observed during the crystallization of the former from an ethanolic solution. The mild reducing ability of ethanol has been reported in the literature.^[19]

UV-vis-NIR Spectroscopy

The electronic absorption spectra of **1** and **2** in CH_2Cl_2 and **3** and **4** in EtOH consist of broad charge transfer (CT) bands in the visible part with $\lambda_{\text{max}} = 26845\text{ cm}^{-1}$ (**1**), 27053 cm^{-1} (**2**), 28680 cm^{-1} (**3**) and 27890 cm^{-1} (**4**). The spectra of **1** – **4** are featureless in the $5,000 - 15,000\text{ cm}^{-1}$ region. However, monitoring the ethanolic solution of **3** over a period of several days revealed the slow emergence of an IVCT band at $6,870\text{ cm}^{-1}$ indicative of a

mixed-valence, $[\text{Fe}_8]^-$ species, formally a $\text{Fe}^{\text{III}}_7\text{Fe}^{\text{II}}$ complex. Slow evaporation of such an ethanolic solution containing the $[\text{Fe}_8]^0/[\text{Fe}_8]^-$ mixture gave a few single crystals of $\mathbf{3}^-$ (*vide infra*) confirming the spectroscopic assignment. A UV-vis-NIR spectrum (Figure 4) obtained from a solution of these single crystals revealed a well defined IVCT band with extinction coefficient $\varepsilon = 4250 \text{ L mol}^{-1} \text{ cm}^{-1}$ and width-at-half height $w_{1/2} = 440 \text{ cm}^{-1}$, whose analysis by the Hush-Sutin method shows $\mathbf{3}^-$ to be a strongly-coupled delocalized, Robin-Day type-III species.^[20–21] We have previously reported the reduction of organosoluble $[\text{Fe}_8]^0$ to $[\text{Fe}_8]^-$ species by electrochemical and chemical means – stoichiometric addition of $[\text{BH}_4]^-$.^[10, 11]

X-ray Crystallography

Complex $\mathbf{3}$ is quite hydrophilic and attempts to grow it into single crystals have so far failed. Fortunately, however, its anion, $\mathbf{3}^-$, crystallized in the trigonal space group R-3 with one-third molecule per asymmetric unit, the whole molecule generated by an improper three-fold rotation. Bond lengths and angles for $\mathbf{3}^-$ are summarized in Table 2. The crystal structure of $\mathbf{3}^-$ (Figure 5) consist of a Fe_4O_4 -cubane encapsulated inside a shell of four $\text{Fe}(\text{4-R-pz})_3\text{Cl}$ units. The tilting of the pyrazole ligand planes away from the Cl-Fe-O axes reduces the molecular symmetry of these molecules to that of T point group. The variation of substituents at the pyrazole 4-position have no significant effect on the structural parameters of the Fe_8O_4 -core, which remains practically invariant, with bond lengths and angles statistically indistinguishable from those of related compounds in the literature.^[9–12] The twelve pyrazole groups are organized in six approximately parallel pairs (dihedral angles of 22.9° and 28.1°), placing the methylene ^aC -atoms within each pair at $^a\text{C}\cdots^a\text{C}$ distances of $4.81 - 5.00 \text{ \AA}$, thus hindering the rotation of the remaining length of the aliphatic chain, consistent with the diastereotopic behaviour of the ^aH -atoms of $\mathbf{3}$ detected by ^1H -NMR. Complex $\mathbf{3}^-$ crystallized with the mononuclear counter ion $[\text{Fe}^{\text{II}}(\text{HL}^3)_6]^{2+}$ of trivial octahedral coordination, bond lengths and angles. The ions of $\mathbf{3}^-$ are arranged in hexagonal, H-bonded, honeycomb-like layers, with consecutive layers showing an AB-repeat pattern, similar to that of the well-known structure of graphite. The mononuclear Fe^{II} -cations occupy the centres of the hexagons (S4). Each cation forms twelve weak H-bonds -- $\text{O}\cdots\text{O}$ distances of $2.89(1)$ and $2.96(2) \text{ \AA}$ -- between its six alcohol moieties and two alcohol pendant chains of each vicinal $\mathbf{3}^-$, and six H-bonds -- $\text{N}\cdots\text{O}$ distances of $2.847(8)$ between its six pyrazole–NH and one pendant alcohol of each vicinal $\mathbf{3}^-$. Six additional H-bonds exist between $\mathbf{3}^-$ and six interstitial H_2O molecules (refined at 50% site occupancy)-- $\text{O}\cdots\text{O} = 2.83(3) \text{ \AA}$ --- as well as six more intermolecular H-bonds between each $\mathbf{3}^-$ and six of its immediate neighbours, with $\text{O}\cdots\text{O} = 2.86(2) \text{ \AA}$. Besides the crystallographically determined interstitial H_2O molecules, the presence of additional solvent molecules (EtOH and/or H_2O) was evident by unaccounted for electron density peaks in the difference maps, which could not be modeled and whose electron density was eventually removed by the use of the SQUEEZE routine.^[22]

Solution behaviour

Free-chloride concentration (by a chloride-specific electrode) and pH measurements of aqueous solutions of $\mathbf{3}$ in the range of $0.31 - 0.87 \text{ mM}$ are consistent with partial hydrolysis of the four Fe-Cl bonds according to the multistep equilibria of Equation 1, involving neutral all-chloro and chloro/hydroxo and positively charged chloro/aquo and chloro/aquo/hydroxo species:

A 0.50 mM aqueous solution of **3** results in 0.65 mM of free chloride ions and 0.32 mM of hydronium ions (pH = 3.5). The average formula of all [Fe₈] species present in this aqueous solution is [Fe₈O₄(L₃)₁₂Cl_{2.70}(H₂O)_{0.65}(OH)_{0.65}]^{0.65+}. Raising the pH by addition of a base shifts the equilibria of equation 1 towards the right, eventually resulting in coagulation of **3** at pH > 4.4. The IR spectrum of solid **3**, recovered from an aqueous solution by solvent evaporation under reduced pressure, matches that of the as-prepared material (S2). The recovered solid redissolves readily in EtOH and the ESI-MS spectrum of the latter solution contains the same molecular-ion as the original material, while its UV-vis spectrum matches that of the as-prepared **3** (S5).

The hydrodynamic diameter of **3** in aqueous solution was estimated by DLS experiments (S6), which showed the presence of aggregates of two sizes. The major component consists of particles with a mean diameter of 5.8 nm, while the minor component of larger aggregates with mean diameter of 140 nm. The average ζ-potential of +39 of these particles is consistent with the presence of charged species, as suggested by Equation 1. In order to corroborate the DLS results, we imaged the aggregates by TEM and SEM on a sample produced by evaporation of a drop of **3**/H₂O solution on a copper grid with an ultra thin carbon film (Figure 6). Two types of objects are apparent in the TEM micrograph: several approximately spherical objects with dimensions of 5 – 7 nm and a few larger ones of 40 – 60 nm. The difference between the diameters determined by DLS and TEM is consistent with solvent-impregnated larger particles in solution, which become dessicated and shrunk upon solvent evaporation on the copper grid. Considering both the molecules of **3** and their aggregates as idealized hard spheres, we estimate that approximately 13 molecules of **3** can be accommodated in a 6 nm particle, while approximately 90 molecules will fit in a 50 nm spherical particle. The electron diffraction pattern observed on both small and large objects indicates crystallinity (S7).

Molecules of **3**, in their non-hydrolysed neutral form, [Fe₈Cl₄], do not aggregate, as the intermolecular Cl•••Cl interaction is repulsive (8.2 kcal mol⁻¹ at 3.283 Å) and the intermolecular alcohol-alcohol H-bonds are weaker than alcohol-water ones.^[17] Therefore, only hydrolysed [Fe₈Cl_{4-n}(H₂O)_n]ⁿ⁺, [Fe₈Cl_{4-n-m}(H₂O)_n(OH)_m]ⁿ⁺ and [Fe₈Cl_{4-n}(OH)_n] species, where n + m = 0 – 4, and their combinations can lead to aggregation, accounting for the particles observed in the DLS and electron microscopy experiments. Our preliminary computational study to probe the attractive interactions between [Fe₈] units has only taken [Fe₈Cl₃(OH)] into consideration.

The solvation of an individual neutral [Fe₈Cl₃(OH)] was modeled with 187 water molecules, as follows: after optimization, there are 3 water-alcohol H-bonds per pendant alcohol group, one water-Cl H-bond per chloride ligand, and 3 H-bonds between the OH-ligand and its three nearest water molecules, for a total of 42 water molecules in the first coordination sphere of [Fe₈Cl₃(OH)]. The total hydration enthalpy of this assembly, which includes the H-bonds formed by the remaining 145 water molecules of the outer solvation sphere, is approximately 42 kcal mol⁻¹. Aggregation of [Fe₈] units can occur by intermolecular H-bonding between two Fe-OH groups, or between one Fe-OH and one Cl-Fe. The formation of a [Fe₈]-[Fe₈] dimer via reciprocal donor/acceptor Fe-OH•••HO-Fe pairs was also modeled (H•••O, 1.681 Å, Figure 7a). The two H-bonds between the two OH-groups are accompanied by four weaker alcohol-alcohol H-bonds for a total enthalpy of dimer formation of 19.8 kcal mol⁻¹. In contrast, the weaker H-bonded Fe-OH•••Cl-Fe interaction, along with its four reinforcing intermolecular alcohol-alcohol H-bonds (H•••Cl, 2.144 Å, Figure 7b), collectively account for a binding enthalpy of 11.9 kcal mol⁻¹. The results of the above computational study serve to identify the attractive or repulsive intermolecular interactions responsible for the aqueous chemistry of one of the several possible species resulting from the hydrolysis of **3**. Further analysis including other

$[\text{Fe}_8\text{Cl}_{4-n-m}(\text{H}_2\text{O})_n(\text{OH})_m]^{n+}$ species and their combinations, as well as determination of the entropy changes associated with the formation of $[\text{Fe}_8]$ aggregates, will be the focus of a future comprehensive study.

Conclusions

Here we have shown that a hydrophobic octanuclear iron-oxido cluster can be converted to a hydrophilic one by the attachment of hydroxyalkyl dangling groups around its periphery. While the water soluble compounds do hydrolyse, their hydrolysis does not lead to uncontrolled polymerization via Fe-O(H)-Fe bond formation, presumably because of the steric hindrance to that process by the hydroxyalkyl pendants.

The rich supramolecular chemistry of **3** uncovered in the present work has stimulated further in-depth studies, currently in progress in our laboratory.

Experimental Section

2-Ethoxy-3-tetrahydrofuranaldehyde diethyl acetal, 2-ethoxy-3-tetrahydropyranaldehyde diethyl acetal, hydrazine dihydrochloride, triethylorthoformate, EtOH (anhydrous), thionyl chloride, FeCl_3 (anhydrous), CH_2Cl_2 (anhydrous) were purchased from Sigma-Aldrich and used as received. The CH_2Cl_2 and THF solvents used for washing **3** and **4** were distilled over anhydrous CaCl_2 . Spectra/Por CE dialysis membranes with molecular weight cut-off of 500–1000 Daltons were purchased from Spectrumbios. Chloride ion concentrations were measured in aqueous media by an Orion 9617BNWP ionplus Sure-Flow Chloride-specific electrode using a Thermo Scientific Orion Star™ Series ISE Meter. ^1H -NMR and UV-Vis-NIR spectra were recorded with a Bruker AVANCE DRX-500 and a Varian Cary 500 spectrometer respectively. ATR-FTIR spectra were recorded with a Bruker TENSOR 27 FTIR spectrometer with a HELIOS ATR attachment using a Helios™ Diamond Cartridge (HLS-CRS-W, Pleasantville, NY). Electrospray ionization mass spectra (ESI-MS) were recorded on a Q-TOF- Micro (Waters Corp., Milford, MA, USA) using ethanol or acetone solutions of **1**, **2**, **3** and **4**. Electrochemical experiments were carried out with a BAS 50 electrochemical analyzer, using Pt-disk or glassy carbon working electrodes, Pt-bar counter electrode, and an Ag/AgNO₃ reference. Dynamic light scattering (DLS) measurements were performed with a DynaPro Titan (Wyatt Technology Co.) using a 657 nm diode laser at a 90° scattering angle. For the morphological characterization studies a JEOL JEM-2100F transmission electron microscope (TEM) were used.

Ligand synthesis

4-Hydroxyethyl pyrazole (**HL**³) and 4-hydroxypropyl pyrazole (**HL**⁴) were synthesized by a literature procedure.^[18] 4-Chloroethyl pyrazole (**HL**¹) and 4-chloropropyl pyrazole (**HL**²) were synthesized by chlorination of 4-HOCH₂CH₂-pzH and 4-HOCH₂CH₂CH₂-pzH using thionyl chloride, followed by extraction in hot EtOH and crushing-out by diethylether. The chloroalkyl pyrazoles were further extracted into CH_2Cl_2 to separate them from the starting hydroxyalkyl pyrazoles excess and finally dried under vacuum. All four ligands were characterized by ^1H - and ^{13}C -NMR. For **4-HOCH₂CH₂-pzH** (**HL**³): ^1H -NMR (D_2O , δ , ppm) 3.56 (t, 2H, α -CH₂), 2.54 (t, 2H, β -CH₂), 7.37 (s, 2H, pzH-H^{3,5}); ^{13}C -NMR (D_2O , δ , ppm) 61.87 (α -C), 25.8 (β -C), 133.63 (pzH-C^{3,5}), 117.3 (pzH-C⁴). For **4-HOCH₂CH₂CH₂-pzH** (**HL**⁴): ^1H -NMR (D_2O , δ , ppm) 3.38 (t, 2H, α -CH₂), 1.57 (m, 2H, β -CH₂), 2.31 (t, 2H, γ -CH₂), 7.33 (s, 2H, pzH-H^{3,5}); ^{13}C -NMR (D_2O , δ , ppm) 61.89 (α -C), 32.45 (β -C), 19.34 (γ -C), 133.15 (pzH-C^{3,5}), 120.39 (pzH-C⁴). For **4-ClCH₂CH₂-pzH** (**HL**¹): ^1H -NMR (CD_2Cl_2 , δ , ppm) 3.70 (t, 2H, α -CH₂), 3.05 (t, 2H, β -CH₂), 7.91 (s, 2H, pzH-H^{3,5}), 12.40 (s, 1H, NH); ^{13}C -NMR (CD_2Cl_2 , δ , ppm) 44.07 (α -C), 27.05 (β -C), 131.44 (pzH-C^{3,5}), 119.30 (pzH-C⁴). For **4-ClCH₂CH₂CH₂-pzH** (**HL**²): ^1H -NMR (CD_2Cl_2 , δ , ppm) 3.54 (t, 2H, α -CH₂),

2.05 (m, 2H, β -CH₂), 2.75 (t, 2H, γ -CH₂), 7.88 (s, 2H, pzH-H^{3,5}), 14.74 (s, 1H, NH); ¹³C-NMR (CD₂Cl₂, δ , ppm) 43.86 (α -C), 32.42 (β -C), 20.57 (γ -C), 131.42 (pzH-C^{3,5}), 121.48 (pzH-C⁴)

Synthesis of organo-soluble [Fe₈(μ_4 -O)₄(μ -L^{1,2})₁₂Cl₄](R = chloroalkyl), **1** and **2**

A conical flask was charged under an argon atmosphere with 1.2 mmol (0.2 g) anhydrous FeCl₃ and 20 mL anhydrous CH₂Cl₂. To this suspension was added 3 mmol (0.498 g 4-ClCH₂CH₂-pzH for **1** and 0.54 g 4-ClCH₂CH₂CH₂-pzH for **2**) and the color of the solution turned yellow. Dropwise addition of 500 μ L triethyl amine changed the color to dark red, with the evolution of dense fumes. The reaction mixture was stirred overnight, then filtered and the solvent was removed under reduced pressure. The resulting residue was dissolved in minimal CH₂Cl₂ and eluted through a chromatographic column packed with silica gel (60–100 Å) and toluene. The bright red eluent was again dried by solvent evaporation under reduced pressure followed by vacuum dessication. The dry compound was then collected and further washed with water (50mg, 14.5% for **1**; 120mg, 32.5% for **2**). For **1**: ¹H-NMR (CD₂Cl₂, δ , ppm): 21.75 (s, 1H, β -CH₂), 19.50 (s, 1H, β -CH₂), 8.40 (s, 1H, H³), 4.56 (s, 2H, α -CH₂), 1.63 (s, 1H, H⁵). IR (cm⁻¹): 1451(w), 1406(w), 1360(m), 1341(m), 1243(w), 1169(w), 1090(w), 1050(vs), 1003(m), 865(w), 771(w), 628(m), 554(w), 474 (vs, br Fe-O). For **2**: ¹H-NMR (CD₂Cl₂, δ , ppm): 22.89 (s, 1H, γ -CH₂), 22.20 (s, 1H, γ -CH₂), 7.44 (s, 1H, H⁵), 3.79 (s, 2H, α -CH₂), 2.58 (s, 2H, β -CH₂), 1.51 (s, 1H, H³). IR (cm⁻¹): 2958(w), 2860 (w), 1441(w), 1404(w), 1354(m), 1260(m), 1163(w), 1092(w), 1047(vs), 1003(m), 850(w), 794(s, br), 626(m), 556(w), 468(vs, br Fe-O), 438(s).

Synthesis of water-soluble [Fe₈(μ_4 -O)₄(μ -L^{3,4})₁₂Cl₄](R = hydroxyalkyl) **3** and **4**

A conical flask was charged under an argon atmosphere with 11.10 mmol of 4-R-pzH (1.242 g for R = CH₂CH₂OH, or 1.404 g for R = CH₂CH₂CH₂OH) and 60 mL anhydrous EtOH. To this solution was added 3.6 mmol (0.6 g) of anhydrous FeCl₃ and the solution color immediately turned orange-red. The reaction flask containing the orange-red solution was then taken out of the glove box, 1.5 mL of triethyl amine was added dropwise in presence of atmospheric moisture and the color gradually darkened resulting in the water-soluble octanuclear iron(III) compounds **3** or **4**. After 18–20 h, the solution was filtered to remove a small amount of insoluble solids and the filtrate solvent was removed under reduced pressure. The crude reaction product was washed, first with CH₂Cl₂, then with THF, and was dried under vacuum. The dark red solid was then extracted in anhydrous EtOH, filtered and the solvent was removed under reduced pressure. After repeating the process of extraction and drying thrice, the resulting dark red oily material was finally crushed out with ether. A brick red solid powder was obtained, which was found to be soluble in methanol, ethanol, propanol and water. The resulting compound was further dialyzed in n-propanol for 5 days using Spectra/Por CE dialysis membrane with MWCO 500–1000 D, yielding 170 mg of **3** (18.5%). For **3**: ¹H-NMR (CD₂Cl₂, δ , ppm): 22.598 (s, 1H, β -CH₂), 21.063 (s, 1H, β -CH₂), 7.66 (s, 1H, H³), 4.37 (s, 2H, α -CH₂), 1.219 (s, 1H, H⁵). IR (cm⁻¹): 3273(w, br), 2927(w), 2863(w), 1435(w), 1398(w), 1358(m), 1295(m), 1147(w), 1121(w), 1043(vs, br), 100 (s, br), 863(w), 738(w), 675(w), 624(m), 537(m, br), 475(vs, br Fe-O), 416(m, br). For **4**: ¹H-NMR (MeOD, δ , ppm): 23.17 (s, 1H, γ -CH₂), 22.39 (s, 1H, γ -CH₂), 7.27 (s, 1H, H³), 3.87 (s, 2H, α -CH₂), 2.27 (s, 2H, β -CH₂), 1.16 (s, 1H, H⁵). IR (cm⁻¹): 3293(m, br), 2931(w), 2860(w), 1448(w), 1400(w), 1354(m), 1296(w), 1122(w), 1121(w), 1048(vs, br), 1014 (s, br), 849(w), 668(w), 615(m), 552(m, br), 469(vs, br Fe-O). An aliquot of the original ethanolic reaction mixture was withdrawn prior to work-up and was allowed to slowly evaporate, resulting after 20 days in bright red single crystals of [3]₂[Fe^{II}(4-HOCH₂CH₂-pzH)₆²⁺]₃•3H₂O•x(solvent) suitable for X-ray diffraction. The UV-vis-NIR spectrum of these crystals in ethanol shows an IVCT band at 6,870 cm⁻¹ confirming the

mixed-valence nature of 3^- (see results and discussion section). This IVCT band is not present in aliquots freshly withdrawn from the reaction mixture.

X-ray Crystallography

X-ray diffraction data, collected from a single crystals mounted atop glass fibers with a Bruker APEX-2 CCD diffractometer, were corrected for Lorentz and polarization effects.^[23] The structure was solved employing the SHELXS97 program and refined by a least-squares method on F^2 , SHELXL97 incorporated in SHELXTL, Version 5.1.^[23–25] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in calculated positions and refined with their thermal ellipsoids riding on the corresponding carbon or oxygen atoms. Large solvent accessible voids in the crystal structure of 3^- are occupied by interstitial solvent molecules whose crystallographic disorder could not be modeled satisfactorily. Consequently, the diffraction data set of 3^- was modified by the SQUEEZE routine of the PLATON package before final refinement.^[22] An ORTEP diagram and complete tables of bond lengths and angles are given in S6.

Crystal data for $[3^-]_2[Fe(HL3)_6]$ — $C_{150}H_{222}Cl_8Fe_{17}N_{60}O_{41}$; $M_r = 4752.91$, space group Trigonal, R-3 (No. 148), $a = 21.260$ (3), $c = 42.441$ (9) Å; $V = 16613$ (5) Å³; $Z = 3$; $T = 296$ (2) K; λ (MoK α) = 0.71073 Å; $\rho_{calcd} = 1.425$ g cm⁻³; $\mu = 0.832$ mm⁻¹. A total of 64186 reflections were collected, 8464 unique ($R_{int} = 0.0829$); $R_1 = 0.0840$ for 5280 independent reflections with $I > 2\sigma(I)$, $wR_2 = 0.2523$ for all data.

CCDC-865897 (3^-) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

DFT Calculations

All geometric optimizations were carried out using DMol3 program.^[26, 27] Perdew-Burke-Ernzerhof (PBE) exchange and correlation functionals were employed.^[28] The Kohn-Sham orbitals were expanded in double numerical plus polarization (DNP) basis set, and the semi-core pseudo-potential (DSPP) included in DMol3 program was employed to approximate a large number of core electron.^[26, 27] In a large metal cluster, a number of low-lying unoccupied orbitals lie very close energetically to the ground state (~0.1 eV). In the present calculations, the fractional occupation number technique was employed,^[26, 27] where electrons were ‘smeared’ by an energy width of 0.1 eV over the orbitals around the Fermi energy. The resulting total energy may be viewed as an average over the configurations lying energetically close to the ground state of the cluster.

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Figure 1.

Ball-and-stick diagram (a), $\text{Fe}_8(\mu_4\text{-O})_4$ -core and numbering of pyrazole C-atoms (b), and space-filling diagram (c) of complex $[\text{Fe}_8(\mu_4\text{-O})_4(\mu\text{-pz})_{12}\text{Cl}_4]$. Colour coding: Fe, golden yellow; C, grey; N, blue; O, red; Cl, green.

Figure 2. Electrospray mass spectra of EtOH solution of compound **3** (a); the experimental (green) and calculated isotope patterns (red) for the $[\text{Fe}_8\text{O}_4\text{L}^3_2\text{Cl}_4]\text{Na}^+$ ion (b).

Figure 3. 500 MHz 1H -NMR spectrum of $[Fe_8O_4(4-Cl-CH_2CH_2CH_2-pz)_{12}Cl_4](2)$ in CD_2Cl_2 . Adventitious impurities marked with an asterisk.

Figure 4. Solution UV-Vis-NIR spectrum of 3^- . Inset: expanded IVCT band.

Figure 5. Ball-and-stick (a) and space-filling (b) diagrams of $[\text{Fe}_8\text{O}_4(4\text{-OHCH}_2\text{CH}_2\text{-pz})_{12}\text{Cl}_4]^{3-}$ (**3⁻**) in the same orientation. Colour coding: Fe, golden yellow; C, grey; N, blue; O, red; Cl, green.

Figure 6.
TEM images of particles of **3** deposited from an aqueous solution.

Figure 7.
Calculated H-bonded interactions between two molecules of $[\text{Fe}_8\text{Cl}_3(\text{OH})]$: Fe-OH...HO-Fe (a); Fe-OH...Cl-Fe (b)

Scheme 1.

Proton labelling in the pyrazolates of clusters **1–4**; (**a**) corresponds to compounds (**1**) and (**3**), while (**b**) corresponds to (**2**) and (**4**).

500 MHz ^1H -NMR data for **1–4** at 298 K (chemical shifts in ppm, $\pm$ 0.01 and relaxation times in milliseconds), Proton labelling according to Scheme 1.

Table 1

protons	X=Cl (1)		X=OH (3)		X=Cl (2)		X=OH (4)	
	δ	T_2^*	δ	T_2^*	δ	T_2^*	δ	T_2^*
^aH , ^dH	21.75, 19.50	3.52 3.52	22.59, 21.06	3.47, 3.52	22.90, 22.20	3.57, 3.69	23.17, 22.39	3.20, 3.20
^bH	4.56	3.89	4.37	4.49	2.58	4.06	2.27	*
^cH	-	-	-	-	3.79	6.90	12.87	5.20
^3H	8.40	0.69	7.66	0.98	7.45	0.75	7.27	0.87
^5H	1.63	8.35	1.21	11.72	1.51	7.00	409.80	7.95

* Because of overlap with an adventitious impurity, the half-height width could not be measured.

Table 2Selected Bond Lengths (Å) and Interatomic Angles (°) for **3⁻**.

Fe _c – O	2.045(4)–2.052(4)	Fe _o – N	2.018(7)–2.031(6)
Fe _c – N	2.054(6)–2.058(6)	O – Fe _o – Cl	179.9(2)–180.0
Fe _c ...Fe _c	3.074(2)–3.081(2)	N – Fe _o – N	118.6(2)–121.4(2)
Fe _c – O – Fe _c	97.3(2)–98.1(2)	Fe _o ...Fe _o ^a	5.823(2)
O – Fe _c – O	81.7(2)–82.1(2)	Fe _o ...Fe _c ^a	3.430(2)–3.453(1)
Fe _o – O	1.926(7)–1.936(4)	Fe _o ...Fe _c ^a	5.457(6)
Fe _o – Cl	2.264(3)–2.273(3)	Fe ^{II} – N	2.180(7)

^aFe_c and Fe_o denote cubane- and outer-Fe atoms, respectively. There are three short and one long Fe_o...Fe_c distances per Fe-atom, between the vertices of co-central tetrahedra formed by the four Fe_c and four Fe_o atoms, respectively.