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Water-Soluble Derivatives of Octanuclear Iron–Oxido–Pyrazolato Complexes – an Experimental and Computational Study

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Two water-soluble iron-pyrazolato complexes (compounds **3** and **4**), [Fe₈], have been prepared by introducing twelve hydroxyalkyl groups to the periphery of the approximately spherical octanuclear molecule. They are contrasted with their two organosoluble chloroalkyl analogues (compounds **1** and **2**). All four complexes were characterized in solution by ¹H NMR and electrospray ionization mass spectrometry. The one-electron-reduction product of water-soluble **3**, [Fe₈]⁻, was structurally characterized by single-crystal X-ray diffrac-

tion analysis. In aqueous media, the four terminal Fe–Cl bonds of $[Fe_8]$ are partially hydrolyzed, and the resulting chlorido–aqua–hydroxido species form supramolecular nanoscale aggregates, as determined by dynamic light scattering and electron microscopy. Preliminary computational studies with DFT methods were employed to model the H-bonding interactions controlling the competing solvation and aggregation processes.

Introduction

High-nuclearity metal clusters and polynuclear transition-metal complexes are rarely studied in aqueous media, which limits their applications in the fields of "green chemistry" and biomedicine.^[1] The reason for this scarcity of examples is that, in typical polynuclear complexes, the metal atoms are surrounded by hydrophobic ligands, such as phosphanes, pyridines, thiols, or groups based on carboxylic acids. Although 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 environmental friendliness and safety.^[2]

Solubility in water is of prime importance for compounds intended for any kind of biological, therapeutic, or medical, diagnostic application. For approximately 40% of active substances identified through combinatorial screening programs, difficulties are encountered in subsequent efforts to formulate pharmaceutical products based on these substances, as a result of their lack of significant solubility

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in water.^[3] Insolubility in water 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] For example, some of the toxicity of Taxol is associated with Cremophor-EL, the excipient used to carry the insoluble active ingredient paclitaxel in 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, solubility in water is also a requirement for contrast agents in diagnostic imaging, which includes contrast agents for magnetic resonance imaging (MRI). In contrast-agent-assisted MRI, an enhanced image contrast is achieved by the intravenous injection of water-soluble, paramagnetic metal complexes, which shorten the magnetic relaxation rate of water protons.^[6-8]

Recently, we studied a group of paramagnetic, redoxactive, octanuclear iron(III)–pyrazolate clusters of the general formula [Fe₈(μ_4 -O)₄(μ -4-R-pz)₁₂X₄], where pz is pyrazolate, R is H, Cl, Br, or CH₃, and X is Cl, Br, or NCS (Figure 1).^[9–12] The Fe₈O₄ motif constituting the core of these complexes is the same one found in the Fe^{III} minerals maghemite (γ -Fe₂O₃) and ferrihydrite (Fe₅HO₈·4H₂O) as well as in the Fe^{III/II} mineral magnetite (Fe₃O₄), all of which are abundantly available in nature.^[13–15] This observation implies that there is an inherent stability associated with the iron–oxido motif of [Fe₈(μ_4 -O)₄(μ -4-R-pz)₁₂X₄] complexes. Indeed, they are stable toward air and humidity, they can be safely refluxed in organic solvents, and their terminal

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ligands X can be substituted through metathesis. Furthermore, they can be reversibly reduced in four consecutive one-electron steps to afford the corresponding mixed-valent anions. In one case, the first reduction product, $[Fe_8(\mu_4-O)_4 (\mu$ -4-Cl-pz)₁₂Cl₄, was isolated and fully characterized: it is readily recognized by its near-infrared (NIR) intervalencecharge-transfer (IVCT) band and by a shift of the Fe-O stretching frequency $v_{(Fe-O)}$ in the IR, but it is structurally indistinguishable, within the experimental margin of error, from its all-Fe^{III} parent compound.^[11] The three-dimensional model of $[Fe_8(\mu_4-O)_4(\mu-pz)_{12}Cl_4]$ and its space-filling model (Figure 1c) show that the approximately spherical surface of the complex is defined by H and Cl atoms, which render it highly hydrophobic. Consequently, $[Fe_8(\mu_4-O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_4(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O)_5(\mu_5+O$ $4\text{-R-pz}_{12}X_4$ complexes with R = H, Cl, Br, or CH₃ are all soluble in common organic solvents (dichloromethane, chloroform, tetrahydrofuran, acetone, toluene, acetonitrile, etc.), while they remain insoluble in polar protic solvents, like methanol, ethanol, and water. To explore the rich redox chemistry of these octanuclear complexes, or to use them as possible electron-transfer agents in aqueous catalysis applications to study their paramagnetism, and to employ them as MRI contrast agents, it is necessary to synthesize water-soluble members of this group of [Fe₈] compounds.



Figure 1. Ball-and-stick diagram (a), $Fe_8(\mu_4-O)_4$ -core and numbering of pyrazolate C-atoms (b), and space-filling model (c) of complex [Fe_8(\mu_4-O)_4(\mu-pz)_{12}Cl_4]. Color coding: Fe (golden yellow), C (grey), N (blue), O (red), Cl (green).

Solubility in water is usually achieved by the introduction of polar groups, such as sulfonyl, carboxyl, ammonium, phosphonium, and hydroxy groups.^[16] We chose to tackle the hydrophobicity problem of the [Fe₈] compounds by introducing hydroxyalkyl groups at the 4-positions of the twelve pyrazole ligands (residues denoted as 4-R in the molecular formula), because of the following considerations: 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 decrease in entropy, which counters 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 $-T\Delta S_{\text{hydr}} \approx +7 \text{ kcal mol}^{-1}$.^[17] In the case of a hydroxyalkyl-modified [Fe₈] compound, in which the aliphatic part of the alcohol groups will be preorganized by the octanuclear complex, the entropic contribution of clustering will be null, and the exothermic hydration enthalpy term will dominate the energetics of the dissolution.

Here, we report the synthesis and characterization of four new $[Fe_8(\mu_4-O)_4(\mu-4-R-pz)_{12}Cl_4]$ complexes, two organosoluble $[R = CH_2CH_2Cl (1)$ and $CH_2CH_2CH_2Cl (2)]$ and two water-soluble $[R = CH_2CH_2OH (3)]$ and $CH_2CH_2CH_2OH (4)$] and demonstrate that the introduction of alcohol functionalities on the twelve pyrazole ligands is sufficient to render the intact $[Fe_8]$ complex water-soluble.

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 spectroscopy. The organosoluble iron complexes 1 and 2 were prepared in one-pot reactions in CH₂Cl₂, while 3 and 4 were prepared in EtOH. All four new complexes were characterized in solution by ¹H NMR spectroscopy 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. Replacing the twelve peripheral chlorine atoms of the pendant alkyl groups of 1 and 2 with hydroxy groups leads to the complexes 3 and 4, which are soluble in polar protic solvents and give intensely red-colored solutions. The solubility of 3 in distilled water is > 36 mM, it decreases in alcohols in the order MeOH > EtOH > PrOH > BuOH (sparingly) soluble), and the compound is insoluble in octanol. The solubility of 4 in the same solvents is always slightly lower than that of 3. The complexes 3 and 4 can be recovered from their aqueous solutions after solvent removal under reduced pressure. ESI mass spectra of ethanol solutions of the recovered materials are identical to those of the as-prepared complexes. Because the four terminal Fe-Cl bonds of 1–4 can undergo solvolysis in H₂O and in the polar protic solvents (R-OH) employed in their synthesis, these complexes are prepared as mixtures of species $[Fe_8Cl_{4-n}(OH)_n]$ or $[Fe_8Cl_{4-n}(OR)_n]$, where the product with n = 0 is the major component.

ESI-MS

Mass spectra were obtained in the ESI+ mode from acetone solutions of 1 and 2 and from ethanol solutions of 3 and 4. The nebulization gas flow was set to $500 \text{ L} \text{ h}^{-1}$ at a temperature of 300 °C, the cone gas was set to 50 Lh^{-1} , and the source temperature was set 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 in the range 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 performed by using an independent reference spray through the Lockpray interference to assure accuracy and reproducibility. The molecular weights of 1-4 were determined from the [M + Na]⁺ ions, which correspond to a neutral molecule plus an adventitious sodium ion. For each of the four compounds, the simulated isotopic distribution of this peak matches faithfully the experimental one (Figure 2 and Supporting Information S1). In methanol solutions of 3 and 4, the mo-

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lecular ion attributed to $[Fe_8O_4L_{12}Cl_2(OMe)(HOEt)]^+$ was detected, which indicates that the terminal chlorido ligands are exchangeable in solution (Supporting Information S1).



Figure 2. Electrospray mass spectrum of an EtOH solution of compound **3** (a); experimental (curve) and calculated (straight, vertical lines) isotope patterns for the $[Fe_8O_4L_{12}^3Cl_4]Na^+$ ion (b).

¹H NMR

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

A single set of two resonances assigned to the pyrazolato ligands is present in each case, which is consistent with twelve magnetically equivalent 4-R-pz groups and the persistence of the solid-state structure in solution. The assignment of the H³ and H⁵ resonances of the pyrazole rings is agreement with those of previously published data for related octanuclear complexes.^[10] Of these two resonances, the one assigned to H³ (proximal to the Fe₄O₄ cubane core)





Figure 3. ¹H NMR spectrum (500 MHz) of $[Fe_8O_4$ {4-(1-chloroprop-3-yl)pz}₁₂Cl₄] (2) in CD₂Cl₂. Adventitious impurities are marked with an asterisk.



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

Table 1. ¹H NMR spectroscopic data (500 MHz) for 1–4 at 298 K [chemical shifts δ in ppm (±0.01) and relaxation times T_2^* in ms]. Proton labelling according to Scheme 1.

Proton	X = Cl(1)		X = OH (3)		X = Cl (2)			X = OH (4)	
	δ	T_2^*	δ	T_2^*	δ	T_2^*	T_1	δ	T_2^*
Hª,	21.75,	3.52,	22.59,	3.47,	22.90,	3.57,	7.07,	23.17,	3.20,
$H^{a'}$	19.50	3.52	21.06	3.52	22.20	3.69	6.89	22.39	3.20
H^{b}	4.56	3.89	4.37	4.49	2.58	4.06	9.04	2.27	[a]
Hc	_	_	_	_	3.79	6.90	12.87	3.87	5.20
H^3	8.40	0.69	7.66	0.98	7.45	0.75	2.16	7.27	0.87
H^5	1.63	8.35	1.21	11.72	1.51	7.00	409.80	1.16	7.95

[[]a] Because of an overlap with an adventitious impurity, the full width at half maximum could not be measured.

is downfield of and significantly broader than that of H⁵ (proximal to the outer Fe centers). The methylene resonances were assigned on the basis of 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 maximum. Transverse relaxation times are affected primarily by throughbord spin polarization effects, which become less signifi-

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cant further away from the paramagnetic center – here, the [Fe₈] core of 1–4. Accordingly, the broader resonances, resulting from shorter T_2^* values, are assigned to the methylene groups attached to the pyrazole C⁴ (H^a), whereas the sharper ones are assigned to the terminal methylene groups (H^b or H^c) next to the Cl or O atoms. To corroborate the T_2^* -based assignment of resonances, the longitudinal relaxation times T_1 of complex 2 were also determined by spininversion 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} distance dependence of the interaction, where r is the proton-paramagnetic center distance. The T_1 values corresponding to the three methylene groups of 2 increase in the order $(H^a, H^{a'})$ $< H^{b} < H^{c}$, which is in agreement with their increasing distances from the metal core and the T_2^* -based assignment. Interestingly, there is a large variation (by a factor of approximately 10) between the T_2^* values of the H³ and H⁵ atoms of all four complexes as well as between the corresponding T_1 values (variation by a factor of approximately 200) of 2, which indicates a quite unsymmetrical distribution of spin density 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 H^a and H^{a'} atoms are diastereotopic and anisochronous, whereas the geminal H^b atoms (and H^c atoms for 2 and 4) are magnetically equivalent. This indicates that the rotation around the pz-C^aH₂ single bond is restricted, whereas there are free rotations around the C^aH₂-C^bH₂ and C^bH₂-C^cH₂ bonds under ambient-temperature conditions (vide infra).

Vibrational Spectroscopy

The IR spectra of the four complexes are consistent with those of related [Fe₈] compounds featuring differently substituted 4-R-pz ligands (Supporting Information S2). The diagnostic absorption peak assigned to an Fe–O vibration appears between 468 and 475 cm⁻¹ in all four spectra. The spectra of **3** and **4** additionally show broad bands centered at 3273 and 3293 cm⁻¹, respectively, assigned to the hydroxy groups, which are absent in the organosoluble analogues.

Electrochemistry

Electrochemical analyses by cyclic and differential pulse voltammetry were performed in CH_2Cl_2/Bu_4NPF_6 for **2** and EtOH/Bu₄NClO₄ for **3**. Both compounds showed reversible reduction processes at -0.49 V (**2**) and -0.46 V (**3**) (vs. ferrocene/ferrocinium; Supporting Information S3). The reduction of these [Fe₈] complexes can therefore be readily achieved with mild reducing agents, which was shown here by the partial reduction of **3** to **3**⁻ observed during the

crystallization of the former from an ethanol 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 those of 3 and 4 in EtOH consist of broad chargetransfer (CT) bands in the visible spectral region with λ_{max} values of 26845 (1), 27053 (2), 28680 (3), and 27890 cm⁻¹ (4). The spectra of 1-4 are featureless in the range 5000- 15000 cm^{-1} . However, monitoring the ethanol solution of **3** over a period of several days revealed the slow emergence of an IVCT band at 6870 cm⁻¹, which is indicative of a mixed-valent [Fe₈]⁻ species, formally an Fe^{III}₇Fe^{II} complex. Slow concentration of such an ethanol solution containing the $[Fe_8]^0/[Fe_8]^-$ mixture gave a few single crystals of 3⁻ (vide infra), which confirmed 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 an extinction coefficient $\varepsilon = 4250 \text{ Lmol}^{-1} \text{ cm}^{-1}$ and a full width at half maximum $w_{1/2} = 440 \text{ cm}^{-1}$, which – when analyzed with the Hush-Sutin method – points to 3⁻ being a strongly coupled, delocalized type-III species according to the Robin-Day classification.^[20,21] We previously reported the reduction of organosoluble [Fe₈]⁰ to [Fe₈]⁻ species achieved by electrochemical and chemical means - addition of stoichiometric amounts of [BH₄]^{-.[10,11]}



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

X-ray Crystallography

Complex 3 is quite hydrophilic, and attempts to grow single crystals of it so far failed. Fortunately, however, its anion 3^- crystallized in the trigonal space group $R\bar{3}$ with one third of a molecule per asymmetric unit, and the whole molecule is generated by an improper threefold rotation.

Bond lengths and angles for 3^{-} are summarized in Table 2. The crystal structure of 3^- (Figure 5) consists of an Fe₄O₄ cubane core encapsulated inside a shell of four Fe(4-R-pz)₃-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 a T point group. The variation of substituents at the pyrazole 4-position have no significant effect on the structural parameters of the Fe₈O₄ 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°), which places the methylene C^a atoms within each pair at C^a···C^a distances of 4.81–5.00 Å. Thus, the rotation of the remaining part of the aliphatic chain is hindered, which is consistent with the diastereotopic behavior of the H^a atoms of **3** detected by ¹H NMR spectroscopy. Complex 3⁻ crystallized with the mononuclear counterion [Fe^{II}(HL³)₆]²⁺, which has a trivial octahedral coordination environment, bond lengths, and angles. The ions of 3^- are arranged in hexagonal, Hbonded, honeycomb-like layers, and the consecutive layers show an AB repeat pattern similar to that of the wellknown structure of graphite. The mononuclear Fe^{II} cations occupy the centers of the hexagons (Supporting Information S4). Each cation forms twelve weak H-bonds [O···O distances of 2.89(1) and 2.96(2) Å] between its six alcohol moieties and two pendant alcohol groups of each vicinal 3⁻ and six H bonds [N···O distances of 2.847(8) Å] between its six pyrazole NH groups and one pendant alcohol group of

Table 2. Selected bond lengths [Å] and interatomic angles [°] for $3^{-,[a]}$

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 ^[b]	5.823(2)
O–Fe _c –O	81.7(2)-82.1(2)	Fe _o …Fe _c ^[b]	3.430(2)-3.453(1)
Fe _o –O	1.926(7)-1.936(4)	Fe _o …Fe _c ^[b]	5.457(6)
Fe _o -Cl	2.264(3)-2.273(3)	Fe ^{II} –N	2.180(7)

[a] Fe_c and Fe_o denote cubane- and outer-Fe atoms, respectively. [b] There are three short and one long $Fe_o \cdots Fe_c$ distances per Fe atom between the vertices of the two co-centrical tetrahedra formed by the four Fe_c and four Fe_o atoms, respectively.



Figure 5. Ball-and-stick (a) and space-filling (b) diagrams of $[Fe_8O_4{4-(1-hydroxyeth-2-yl)pz}_{12}Cl_4]^-$ (3⁻) in the same orientation. Color coding: Fe (golden yellow), C (grey), N (blue), O (red), Cl (green).

each vicinal 3⁻. Six additional H-bonds exist between 3⁻ and six interstitial H₂O molecules [refined at 50% site occupancy, O···O distances of 2.83(3) Å], and six more intermo-

and six interstitial H₂O molecules [refined at 50% site occupancy, O···O distances of 2.83(3) Å], and six more intermolecular H-bonds exist between each 3^- and six of its immediate neighbors [O···O distances of 2.86(2) Å]. Besides the crystallographically determined interstitial H₂O molecules, the presence of additional solvent molecules (EtOH or H₂O) 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 Behavior

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Free-chloride concentration (with a chloride-specific electrode) and pH measurements of aqueous solutions of **3** having concentrations in the range of 0.31-0.87 mM are consistent with the partial hydrolysis of the four Fe–Cl bonds, which is described by the multistep equilibria of Equation (1) and involves neutral all-chlorido and chlorido–hydroxido species as well as positively charged chlorido–aqua and chlorido–aqua–hydroxido species.

$$[\operatorname{Fe}_{8}\operatorname{Cl}_{4}] \rightleftharpoons [\operatorname{Fe}_{8}\operatorname{Cl}_{4-n}\operatorname{H}_{2}\operatorname{O}]_{n}]^{n+} + n \operatorname{Cl}^{-} \rightleftharpoons [\operatorname{Fe}_{8}\operatorname{Cl}_{4-n}(\operatorname{OH})_{n}] + n [\operatorname{H}_{3}\operatorname{O}]^{+} (1)$$

In a 0.50 mM aqueous solution of **3**, 0.65 mM of free chloride ions and 0.32 mM of hydronium ions (pH = 3.5) were detected. The average formula of all [Fe₈] species present in this aqueous solution is $[Fe_8O_4(L_3)_{12}Cl_{2.70}-(H_2O)_{0.65}(OH)_{0.65}]^{0.65+}$. 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 (Supporting Information S2). The recovered solid redissolves readily in EtOH, the ESI mass spectrum of the latter solution contains the same molecular ion as the original material, and its UV/Vis spectrum matches that of as-prepared **3** (Supporting Information S5).

The hydrodynamic diameter of **3** in aqueous solution was estimated by dynamic light scattering (DLS) experiments (Supporting Information S6), which showed the presence of two differently sized types of aggregates. The major component consists of particles with a mean diameter of 5.8 nm, whereas the minor component consists of larger aggregates with a mean diameter of 140 nm. The average ζ-potential of these particles is of +39 mV, which is consistent with the presence of charged species, as suggested by Equation (1). To corroborate the DLS results, we imaged the aggregates by TEM and scanning electron microscopy (SEM), using a sample produced by solvent evaporation of a drop of an aqueous solution of 3 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 with dimensions of 40-60 nm. The difference between the Date: 02-07-12 16:11:19

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diameters determined by DLS and TEM is consistent with solvent-impregnated, larger particles in solution, which become desiccated and shrink 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, whereas approximately 90 molecules will fit in a 50 nm spherical particle. The electron diffraction pattern observed on both small and large objects indicates crystallinity (Supporting Information S7).



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

Molecules of **3** in their nonhydrolyzed neutral form, [Fe₈Cl₄], do not aggregate, as the intermolecular Cl···Cl interaction is repulsive (8.2 kcalmol⁻¹ at 3.283 Å) and the intermolecular alcohol–alcohol H-bonds are weaker than alcohol–water H-bonds.^[17] Therefore, only hydrolyzed [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 aggregates, which account for the particles observed in the DLS and electron microscopy experiments. Our preliminary computational study to probe the attractive interactions between [Fe₈] units only took [Fe₈Cl₃(OH)] into consideration.

The solvation of an individual neutral [Fe₈Cl₃(OH)] molecule was modeled with 187 water molecules: after optimization, there are 3 water-alcohol H-bonds per pendant alcohol group, one water-Cl H-bond per chlorido ligand, and 3 H-bonds between the OH- ligand and its three nearest water molecules, which add up to 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 kcalmol⁻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 group. The formation of an [Fe₈]–[Fe₈] dimer through reciprocal donor–acceptor Fe– OH···HO-Fe pairs was also modeled (H···O distance of 1.681 Å, Figure 7a). The two H-bonds between the two OH groups are accompanied by four weaker alcohol-alcohol Hbonds, and this leads to a total enthalpy of dimer formation of 19.8 kcalmol⁻¹. In contrast, the weaker H-bonding Fe-OH…Cl-Fe interaction and its four accompanying, reinforcing intermolecular alcohol-alcohol H-bonds (H···Cl distance 2.144 Å, Figure 7b) collectively account for a binding enthalpy of 11.9 kcalmol⁻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 analyses, including other $[Fe_8Cl_{4-n-m}(H_2O)_n(OH)_m]^{n+}$ species and their combinations as well as the determination of the entropy changes associated with the formation of $[Fe_8]$ aggregates, will be the focus of a future comprehensive study.



Figure 7. Calculated H-bonding interactions between two molecules of $[Fe_8Cl_3(OH)]$: Fe–OH···HO–Fe (a); Fe–OH···Cl–Fe (b).

Conclusions

We have shown that a hydrophobic, octanuclear ironoxido cluster (1 and 2) can be converted into a hydrophilic one (3 and 4) by the attachment of hydroxyalkyl dangling groups around its periphery. Although the water-soluble compounds are hydrolyzed, their hydrolysis does not lead to uncontrolled polymerization through Fe–O(H)–Fe bond formation, presumably because this process is sterically hindered by the hydroxyalkyl pendant groups.

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

Experimental Section

General: 2-Ethoxy-3-tetrahydrofurancarbaldehyde diethyl acetal, 2ethoxy-3-tetrahydropyrancarbaldehyde diethyl acetal, hydrazine dihydrochloride, triethyl orthoformate, EtOH (anhydrous), thionyl chloride, FeCl₃ (anhydrous), CH₂Cl₂ (anhydrous) were purchased from Sigma-Aldrich and used as received. The CH₂Cl₂ and THF solvents used for washing 3 and 4 were distilled from anhydrous CaCl₂. Spectra/Por CE dialysis membranes with a molecularweight cut-off (MWCO) of 500-1000 Daltons were purchased from Spectrumlabs. Chloride ion concentrations were measured in aqueous media with an Orion 9617BNWP ionplus Sure-Flow chloridespecific electrode by using a Thermo Scientific Orion StarTM 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. Attenuated-total-reflectance (ATR) FTIR spectra were recorded with a Bruker TENSOR 27 FTIR spectrometer with a HELIOS ATR attachment by using a HeliosTM Diamond Cartridge (HLS-CRS-W, Pleasantville, NY). Electrospray ionization mass spectra (ESI-MS) were recorded with a Q-Tof micro mass spectrometer (Waters Corp., Milford, MA, USA) by using ethanol or acetone solutions of 1, 2, 3, or 4. Electrochemical experiments were carried out with a BAS 50 electrochemical analyzer by using Pt-disk or glassy-carbon working electrodes, a Pt-bar counter electrode, and an Ag/AgNO₃ reference electrode. DLS measurements were performed with a Dynapro Titan instrument (Wyatt Technol-

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mission electron microscope (TEM) was used.



Ligand Synthesis: 4-(2-Hydroxyethyl)pyrazole (HL³) and 4-(3-hydroxypropyl)pyrazole (HL⁴) were synthesized by using a literature procedure.^[18] 4-(2-Chloroethyl)pyrazole (HL¹) and 4-(3-chloropropyl)pyrazole (HL²) were synthesized by chlorination of HL³ and HL⁴, respectively, by using thionyl chloride. The chlorination was followed by extraction with hot EtOH and crushing-out by diethyl ether. The (chloroalkyl)pyrazoles were further extracted with CH₂Cl₂ to separate them from the excess starting materials, (hydroxyalkyl)pyrazoles, and they were finally dried under vacuum. All four ligands were characterized by ¹H and ¹³C NMR spectroscopy.

4-(HOCH₂CH₂)pzH (HL³): ¹H NMR (D₂O): δ = 3.56 (t, *J* = 5.0 Hz, 2 H, α-CH₂), 2.54 (t, *J* = 5.0 Hz, 2 H, β-CH₂), 7.37 (s, 2 H, pzH-H^{3,5}) ppm. ¹³C NMR (D₂O): δ = 61.87 (α-C), 25.8 (β-C), 133.63 (pzH-C^{3,5}), 117.3 (pzH-C⁴) ppm.

4-(HOCH₂CH₂CH₂)pzH (HL⁴): ¹H NMR (D₂O): δ = 3.38 (t, *J* = 7.5 Hz, 2 H, α-CH₂), 1.57 (m, 2 H, β-CH₂), 2.31 (t, *J* = 7.5 Hz, 2 H, γ-CH₂), 7.33 (s, 2 H, pzH-H^{3.5}) ppm. ¹³C NMR (D₂O): δ = 61.89 (α-C), 32.45 (β-C), 19.34 (γ-C), 133.15 (pzH-C^{3.5}), 120.39 (pzH-C⁴) ppm.

4-(ClCH₂CH₂)pzH (HL¹): ¹H NMR (CD₂Cl₂): δ = 3.70 (t, *J* = 7.5 Hz, 2 H, α-CH₂), 3.05 (t, *J* = 5.0 Hz, 2 H, β-CH₂), 7.91 (s, 2 H, pzH-H^{3,5}), 12.40 (s, 1 H, NH) ppm. ¹³C NMR (CD₂Cl₂): δ = 44.07 (α-C), 27.05 (β-C), 131.44 (pzH-C^{3,5}), 119.30 (pzH-C⁴) ppm.

4-(ClCH₂CH₂CH₂)pzH (HL²): ¹H NMR (CD₂Cl₂): δ = 3.54 (t, *J* = 5.0 Hz, 2 H, α-CH₂), 2.05 (m, 2 H, β-CH₂), 2.75 (t, *J* = 5.0 Hz, 2 H, γ-CH₂), 7.88 (s, 2 H, pzH-H^{3,5}), 14.74 (s, 1 H, NH) ppm. ¹³C NMR (CD₂Cl₂): δ = 43.86 (α-C), 32.42 (β-C), 20.57 (γ-C), 131.42 (pzH-C^{3,5}), 121.48 (pzH-C⁴) ppm.

Synthesis of Organosoluble $[Fe_8(\mu_4-O)_4(\mu-L^x)_{12}Cl_4]$ (R = chloroalkyl, x = 1 or 2), Compounds 1 and 2: A conical flask was charged under argon with anhydrous FeCl₃ (1.2 mmol, 0.2 g) and anhydrous CH₂Cl₂ (20 mL). To this suspension was added HL¹ (preparation of 1, 3 mmol, 0.498 g) or HL² (preparation of 2, 3 mmol, 0.54 g), and the color of the solution turned yellow. Upon dropwise addition of triethylamine (500 µL), the color changed to dark red, and dense fumes evolved. The reaction mixture was stirred overnight and then filtered, and the solvent was removed under reduced pressure. The resulting residue was dissolved in a minimal amount of 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, which was followed by vacuum desiccation. The dry compound was then collected and further washed with water (50 mg and 14.5% yield for 1; 120 mg and 32.5% yield for 2).

1:¹H NMR (CD₂Cl₂): δ = 21.75 (s, 1 H, β-CH₂), 19.50 (s, 1 H, β-CH₂), 8.40 (s, 1 H, H³), 4.56 (s, 2 H, α-CH₂), 1.63 (s, 1 H, H⁵) ppm. IR: \tilde{v} = 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) cm⁻¹.

2: ¹H NMR (CD₂Cl₂): δ = 22.89 (s, 1 H, γ -CH₂), 22.20 (s, 1 H, γ -CH₂), 7.44 (s, 1 H, H⁵), 3.79 (s, 2 H, α -CH₂), 2.58 (s, 2 H, β -CH₂), 1.51 (s,1 H, H³) ppm. IR: \tilde{v} = 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) cm⁻¹.

Synthesis of Water-Soluble $[Fe_8(\mu_4-O)_4(\mu-L^x)_{12}Cl_4]$ (R = hydroxyalkyl, x = 3 or 4), Compounds 3 and 4: A conical flask was charged

under argon with HL³ (preparation of 3, 11.1 mmol, 1.242 g) or HL⁴ (preparation of 4, 11.1 mmol, 1.404 g) and anhydrous EtOH (60 mL). To this solution was added anhydrous FeCl₃ (3.6 mmol, 0.6 g), and the color of the solution immediately turned orangered. The reaction flask containing the orange-red solution was then taken out of the glove box, triethylamine (1.5 mL) was added dropwise in the presence of atmospheric moisture, and the color gradually darkened. The reaction afforded the water-soluble octanuclear iron(III) compound 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 with CH₂Cl₂ and then with THF, and it was dried under vacuum. The dark-red solid was then extracted in anhydrous EtOH and filtered, and the solvent was removed under reduced pressure. After the process of extraction and drying was repeated thrice, the resulting dark red oily material was finally crushed out with diethyl ether. A brick-red, solid powder was obtained, which was soluble in methanol, ethanol, propanol, and water. The resulting compound was further dialyzed in *n*-propanol for 5 d by using a Spectra/Por CE dialysis membrane with an MWCO (500-1000 Da), which yielded 3 (170 mg, 18.5%) or 4 (180 mg, 13.0%).

3: ¹H NMR (CD₂Cl₂): *δ* = 22.598 (s, 1 H, β-CH₂), 21.063 (s, 1 H, β-CH₂), 7.66 (s, 1 H, H³), 4.37 (s, 2 H, *α*-CH₂), 1.219 (s, 1 H, H⁵) ppm. IR: \tilde{v} = 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.) cm⁻¹.

4: ¹H NMR (MeOD): *δ* = 23.17 (s, 1 H, γ-CH₂), 22.39 (s, 1 H, γ-CH₂), 7.27 (s,1 H, H³), 3.87 (s, 2 H, α-CH₂), 2.27 (s, 2 H, β-CH₂), 1.16 (s,1 H, H⁵) ppm. IR: \tilde{v} = 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) cm⁻¹.

An aliquot of the original ethanol reaction mixture was withdrawn prior to the workup and was allowed to slowly concentrate, which resulted after 20 d in bright-red single crystals of $[3^-]_2[Fe^{II}(HL^3)_6^{2+}]$ · $3H_2O \cdot x$ (solvent) suitable for X-ray diffraction. The UV/Vis/NIR spectrum of these crystals in ethanol shows an IVCT band at 6870 cm⁻¹, which confirms the mixed-valent 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 of [3-]2[Fe(HL³)6]: X-ray diffraction data, collected with a Bruker APEX-2 CCD diffractometer from a single crystal mounted atop of a glass fiber, were corrected for Lorentz and polarization effects.^[23] The structure was solved by employing the SHELXS97 program and refined by a least-squares method on F^2 with 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 3are 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 OR-TEP diagram and complete tables of bond lengths and angles are given in Supporting Information S6. $C_{150}H_{222}Cl_8Fe_{17}N_{60}O_{41}$; $M_r =$ 4752.91; space group trigonal; $R\bar{3}$ (No. 148); a = 21.260(3) Å, c =42.441(9) Å; V = 16613(5) Å³; Z = 3; $T = (296\pm 2)$ K; λ (Mo- K_a) = $0.71073 \text{ Å}; \rho_{\text{calcd.}} = 1.425 \text{ g cm}^{-3}; \mu = 0.832 \text{ mm}^{-1}$. A total of 64186 reflections were collected, 8464 unique ($R_{int} = 0.0829$); $R_1 = 0.0840$

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for 5280 independent reflections with $I > 2\sigma(I)$, $wR_2 = 0.2523$ for all data. CCDC-865897 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 the DMol3 program.^[26,27] Perdew–Burke–Ernzerhof (PBE) exchange and correlation functionals were employed.^[28] The Kohn–Sham orbitals were expanded in the double-numerical-plus polarization (DNP) basis set, and the semi-core pseudopotential (DSPP) included in DMol3 program was employed to approximate a large number of core electron density.^[26,27] In a large metal cluster, a number of low-lying unoccupied orbitals lie energetically very close to the ground state (ca. 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.

Supporting Information (see footnote on the first page of this article): Electrospray ionization mass spectra (S1), infrared spectra (S2), differential pulse voltammogram of **3** (S3), ORTEP diagram and packing diagram of a layer of $[3^{-7}]_2$ [Fe(HL³)₆²⁺] (S4), UV/Vis/NIR spectra of **3**, dynamic light scattering intensity distribution of aqueous solution of **3** (S6), electron diffraction pattern of **3** (S7).

Acknowledgments

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Octanuclear Iron-Oxido-Pyrazolato Complexes



Coordination Chemistry

Twelve hydroxyalkyl pendant groups render an octanuclear iron–oxido–pyrazolato complex soluble in water, where partial hydrolysis and extended intermolecular Hbonding interactions result in supramolecular assemblies.

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Water-Soluble Derivatives of Octanuclear Iron–Oxido–Pyrazolato Complexes – an Experimental and Computational Study

Keywords: Cluster compounds / Oxido ligands / Iron oxide / Pyrazolato complexes / Electron microscopy / Density functional calculations