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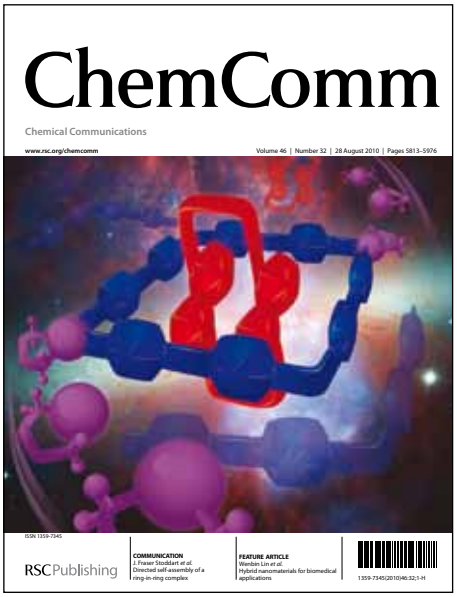

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COMMUNICATION

Self-Promoted Post-Synthetic Modification of Metal-Ligand M_2L_3 Mesocates

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Reactive alcohol functionality has been incorporated into a self-assembled M_2L_3 mesocate. Post-synthetic modification of this complex with suitable isocyanates is not only possible, but is self-catalyzed by multiple internal hydrogen bonds from the self-assembly. As the metal-ligand coordination is reversible at elevated temperature, the isomeric distribution of product changes upon reaction, due to the different steric bulk conferred on the assembly after the modification.

One of the most promising applications of self-assembled metal-ligand cages is their potential as enzyme-mimicking hosts.[1] The molecular recognition properties of these structures have been well-explored, but true biomimicry is not achievable without the introduction of *reactive functionality* to the self-assembled system.[2] Internally derivatized self-assembled species are known, but these display unreactive functional groups.[3] The introduction of reactive functionality to a self-assembled system is extremely challenging. Strongly nucleo- or electrophilic groups on the coordinating ligand can interfere with metal-ligand self-assembly. In addition, most solution-phase self-assembled cages are fragile and are highly sensitive to harsh reaction conditions. Post-synthetic modification of more stable solid state metal organic frameworks is known, allowing the inclusion of more reactive functional groups that are incompatible with the assembly process.[4] Despite this, little attention has been paid to modification of discrete, solution-phase self-assemblies, due to the lower stability of these species, and functionally useful groups have not been attached.[6] Here, we address this issue and describe the selective post-synthetic modification of a reactive, self-assembled Fe-iminopyridine mesocate. The reactivity is not only compatible with the fragile self-assembly: it is *promoted* by the supramolecular environment around the reactive centers.

Incorporation of reactive groups onto a supramolecular metal-ligand complex requires a robust self-assembling motif. To this end, we exploited Fe(II)-iminopyridine-based complex assembly,[6] that employs multicomponent self-assembly from accessible anilines, 2-formylpyridine, and iron(II) salts to give stable assemblies with an intense purple color.[7]

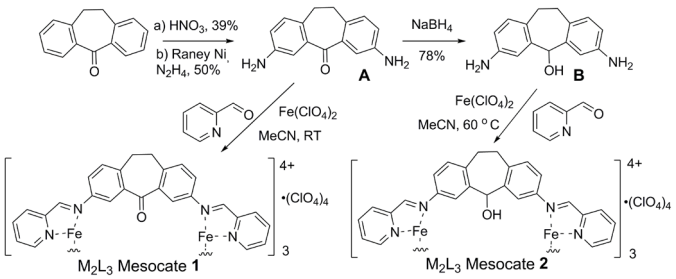

Fig. 1 Synthesis of diaminodibenzosuberone-based iron-iminopyridine mesocates.

The reactive functionality was supplied by using suberone derivatives as the core ligands. Dibenzosuberone **1** is a flexible scaffold for studying reactive self-assembled species:[8] amine functions can be introduced at the termini to allow self-assembly, and the internal ketone group provides a reactive internal function. The ligand and complex syntheses are shown in Figure 1. Bis-nitration of **1** followed by reduction of the added nitro groups via transfer hydrogenation gave 3,7-diaminodibenzosuberone **A** in moderate yield.[9] Reduction of the ketone **A** with $NaBH_4$ smoothly yielded the 3,7-diamino-dibenzosuberol product **B**. Both **A** and **B** were suitable substrates for multicomponent self-assembly. Alcohol precursor **B** required heating to reach a stable assembly, however: disordered aggregates were formed at room temperature.

The solid state structures formed by assembly of both ligands **A** and **B** are shown in Figure 2. At first glance, the structures are similar: both ligands form M_2L_3 structures upon assembly, and the stereochemistry at the metal centers is the same. X-Ray crystallographic analysis of ketone derivative **1** (CCDC# 951758) and alcohol **2** (CCDC# 951759) show that ΔΛ mesocate structures are observed in these cases (as opposed

to previously published Fe_2L_3 structures that favour the matched ΔΔ/ΛΛ isomer).[6b] The suberone ligand in **1** is relatively planar, and the carbonyl oxygen points directly at the ethylene backbone of the adjacent ligand. Whereas ketone **A** is almost completely planar, reduction of the ketone to form **B** confers an sp^3 geometry on the backbone carbon, causing an extensive structural change to the ligand geometry. The Ar-C-Ar angle at the central backbone carbon of mesocate **2** is 108.7º. Both ligand **B** and self-assembled complex **2** are significantly more flexible than the suberone counterparts, and as a result the X-Ray crystal structure of **2** shows extensive disorder, most notably in the ethylene backbone. This increased flexibility is presumably the reason that elevated temperature is required to complete the self-assembly process.

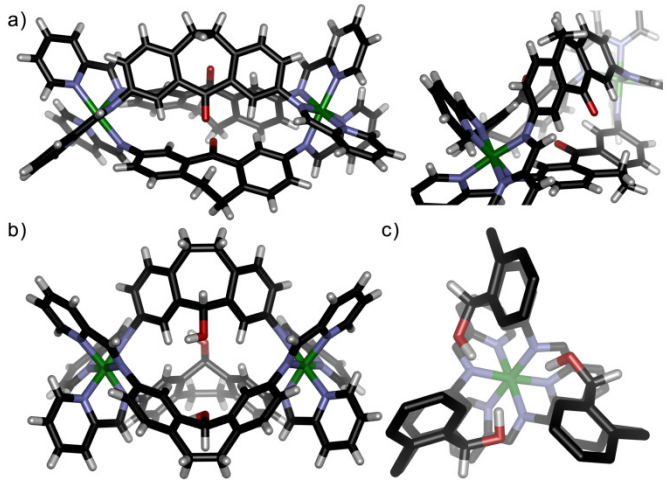

Fig. 2 X-ray crystal structures of a) M_2L_3 ketone **1** and a partially-cropped side-perspective showing how the ketone points at the adjacent ethylene bridge; b) M_2L_3 alcohol **2**; c) cropped view of **2**, indicating OH orientation.

As expected, the ketone mesocate **1** gave a sharp ^{1}H NMR spectrum with only one set of peaks, suggesting that the mesocate is the only species present in solution (see ESI). The ^{1}H NMR spectrum of the alcohol mesocate **2** is not quite as clean (Figure 3a), but the major product does indeed display a simple coupling pattern. Diffusion NMR analysis shows that the minor species has an identical diffusion constant (within error) as the major product, suggesting the minor species also has M_2L_3 stoichiometry. When crystalline **2** was redissolved in CD_3CN, it still showed these minor peaks in the ^{1}H NMR spectrum. The most likely identity of the minor product is an alternate diastereomer at the OH group (i.e. with the alcohol pointed outside the mesocate). Analysis by VT-NMR showed little change in the NMR spectrum: the isomer ratio is not dependent on temperature.

The ketone complex **1** was not tolerant to post-synthetic modification. To our delight, however, alcohol **2** was amenable to reaction with mild electrophiles. Upon treatment with butyl isocyanate under reflux in acetonitrile, derivatization of the internal alcohol groups occurred, yielding the tris-butyl urethane complex **3**. Reaction was also possible with other unhindered isocyanates: octyl, α-methylbenzyl and isopropyl isocyanates reacted smoothly (see ESI for spectra). The iminopyridine ligands remain intact during the reaction: it is conceivable that hydrolysis could occur to regenerate **B** during the reaction, but this does not happen, as no **B**-urea byproduct was observed. This reaction is remarkable, considering that dibenzosuberol itself is incapable of reacting with isocyanates under the same conditions. Even when dibutyl urea or $Fe(ClO_4)_2$ were added to the mixture of dibenzosuberol and isocyanate, no conversion occurred. This suggests the reactivity is unique to the self-assembled environment.

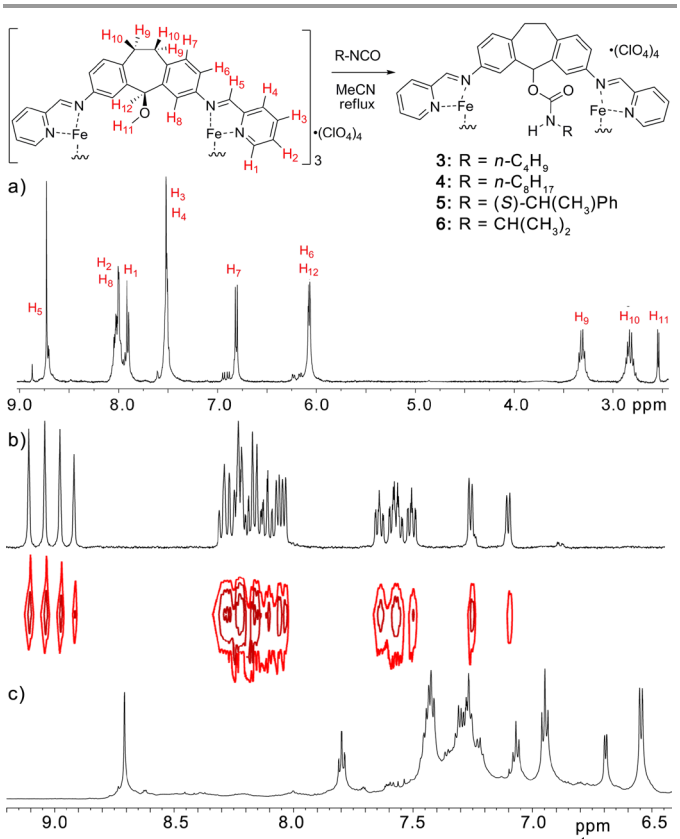

Fig. 3 Post-synthetic modification of mesocate **2**: ^{1}H NMR spectrum of a) M_2L_3 alcohol **2**; b) tris-butylurethane **3**, including the downfield portion of DOSY spectrum (Δ = 100 ms, δ = 2.6 μs, Diffusion coefficient = 7.76 x10^{-10} m^2/s); c) urethane **5**, (CD_3CN, 600 MHz, 298K).

While alkylisocyanates are well precedented to react with hydroxyl groups, the reaction is extremely slow without additional catalysts, especially in solvents such as acetonitrile.[10] The reaction of alcohols with isocyanates is generally promoted by hydrogen-bonding with a second equivalent of alcohol reactant, but the sterically-hindered dibenzosuberol is an ineffective intermolecular H-bond donor. Self-assembly of the complex **2** brings these alcohols into close proximity (Figure 2c), and allows *internal catalysis* of the reaction. To substantiate this, the reaction rate was measured with and without a competitive hydrogen bonding solvent. In CD_3CN, 70% completion was observed after 4 h. With dimethyl-acetamide added as co-solvent, conversion was reduced to almost 50% in the same time period. In addition, bulkier t-

butyl, phenyl, and 1-naphthyl isocyanates gave no conversion to self-assembled urethane products.

The ^{1}H NMR spectrum of butylurethane **3** shows four distinct urethane triplets between 9.1-8.9 ppm. Diffusion analysis (Figure 3b) shows that each signal displays an almost identical diffusion coefficient, suggesting that each peak belongs to an M_2L_3 mesocate rather than larger M_4L_6 complexes formed after addition of the larger urethane groups. ESI-MS analysis of the product (Figure 4a) shows evidence for the tris-butylurethane. Further characterization of the product was hindered by the excellent leaving group ability of the urethane group introduced upon reaction. Attempted recovery of the urethane-containing bis-imine ligand by hydrolysis of **3** in 50/50 D_2O-CD_3CN led to cleavage of the complex, imine, and urethane, and no product was observed.

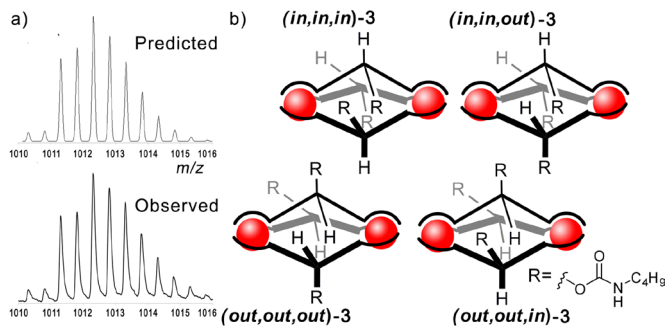

Fig. 4 a) Characterization of **3**: a) Predicted and observed ESI-MS of parent ion **[Fe_2•L_3•$(ClO_4)_3$•Na•CH_3CN]$^{2+}$**; b) Cartoon representation of the observed isomers of **3** in solution.

As all the products of the post-synthetic modification are M_2L_3 mesocates, it must be concluded that introduction of larger groups on the mesocate interior *disfavours* the ***in$_3$*** isomer and a mixture of conformers at C-O (i.e. ***in$_3$***, ***in$_2$•out***, ***in•out$_2$*** and ***out$_3$***, see Figure 4b) is formed. Even though the ***in$_3$*** isomer of **2** was predominant, this is controlled by sterics and packing of the ligand around the metal. After reaction, greater steric bulk is added to the ligand, disfavouring the ***in$_3$*** isomer and causing isomerisation to a statistical mixture of M_2L_3 products. ^{1}H, ^{13}C and DOSY NMR analysis (see ESI) corroborates the assignment: the four urethane NH peaks (~9.0 ppm, Figure 3b) provide the clearest evidence. Integration shows that while the populations of the isomers are similar, they are present in different amounts, and the four peaks do not correspond to diastereotopic protons in a single assembly. Analysis of the ^{1}H spectrum of **3** at temperatures ranging from -40 ºC to +75 ºC shows the populations vary slightly with temperature, corroborating that different isomers are formed. The other alkylisocyanate products **4** and **6** show similar ^{1}H NMR spectra to **3**, and the four possible isomers are observed. For α-methybenzyl derivative **5**, however, the newly added group is so large it completely disfavours formation of any of the ***in*** isomers, giving only the ***out$_3$*** isomer (see ESI for illustrative molecular modeling).

In conclusion, we have shown that self-assembled mesocates can promote their own post-synthetic modification. Activation by multiple internal hydrogen bonds is necessary to catalyze the reaction, and the reversible nature of the Fe-N dative bonds allows self-selection of the most thermodynamically favorable products. While the alcoholic reactant favors a single isomer upon assembly, greater steric bulk is added upon reaction, forcing isomerization to a statistical mixture of M_2L_3 products during the reaction process.

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Notes and references

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