Nanostructures

Combining Metallasupramolecular Chemistry with Dynamic Covalent Chemistry: Synthesis of Large Molecular Cages**

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Molecular cages with large internal voids are best synthesized by assembly of multiple building blocks under thermodynamic control. To connect the building blocks, metal–ligand interactions are commonly employed.[1] The resulting coordination cages have found numerous applications. For example, they can be used as nanoreactors for chemical transformations, as delivery agents for anticancer compounds, or for the stabilization of highly reactive guest molecules.[1]

The assembly of purely organic cages can be achieved using dynamic covalent chemistry.[2–6] Along these lines, imine condensations have been most widely used to date,[3] but the syntheses of cages based on boronic ester condensations,[4] thiol–disulfide exchange reactions,[5] or olefin metathesis[6] have also been described. Metallasupramolecular chemistry has been successfully merged with dynamic covalent chemistry by performing imine condensations in the first coordination sphere of metal ions.[7] This approach has proven extremely robust due to the resulting mutual stabilization of both the metal complex and the imine bond.[8] Fascinating recent results include the stabilization of molecular P_4 within a coordination cage,[9] and the synthesis of a Borromean ring and a Solomon knot.[10]

Our group is interested in synthesizing complex molecular architectures by combining metallasupramolecular chemistry with dynamic covalent chemistry in an orthogonal fashion. Recently, we described a first success in this direction: a 52-membered macrocycle was obtained by the concomitant formation of reversible imine, boronate ester, and rhenium–nitrogen bonds.[11,12] Herein, we describe how the polycondensation of triamines with metallamacrocyclic building blocks, containing pendent aldehyde groups, has enabled the facile synthesis of several new nanoscopic cages.

The reaction of a triamine with a trialdehyde can result in the formation of a [4+4] condensation product, provided that the reactants have complementary shape and rigidity. We hypothesized that it should be possible to make expanded structures by replacing either the triamine or the trialdehyde

with trinuclear metallamacrocycles having appropriate amine or aldehyde functionalities in their ligand peripheries. To implement such a reaction, we synthesized the formyl-substituted 3-hydroxy-2-pyridone ligand **1** (Scheme 1) using
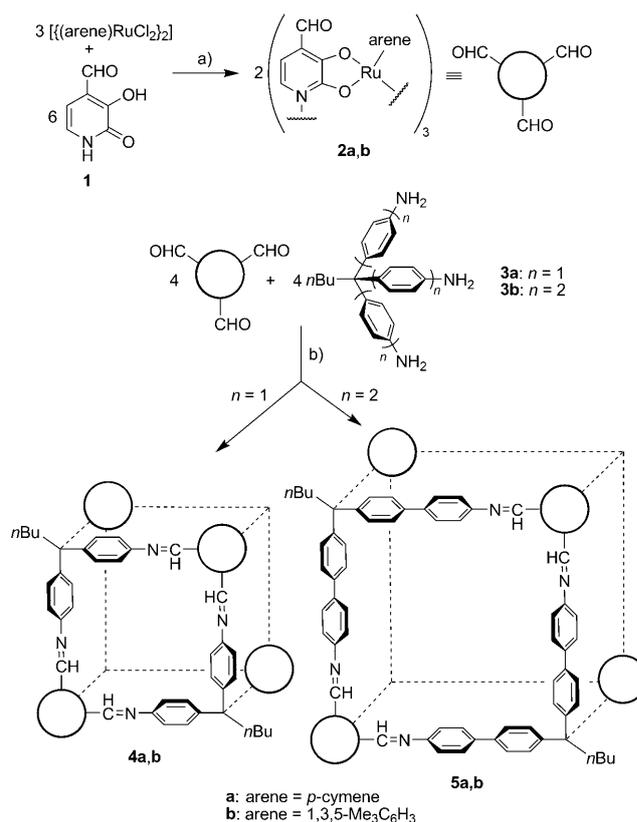
Scheme 1. Synthesis of the cages **4a,b** and **5a,b**. Reagents and conditions: a) Cs_2CO_3, CH_2Cl_2/MeOH (1:1 v/v), room temperature, 70–80%; b) CH_2Cl_2/MeOH (1.75:1 v/v), room temperature, 7–10 days, 18–55%.

standard organic transformations (Supporting Information). Subsequent reaction with $[\{(arene)RuCl_2\}_2]$ complexes in the presence of base gave the trinuclear macrocycles **2a** (arene = *p*-cymene) and **2b** (arene = $1,3,5\text{-Me}_3C_6H_3$; Scheme 1). The spectroscopic features of **2a** and **2b** were similar to what has been reported for other organometallic trimers with bridging 3-hydroxy-2-pyridone ligands;[13] moreover, crystallographic analysis of **2b** confirmed that a trinuclear complex had formed (Supporting Information, Figure S1).[14] The three aldehyde groups are 7.8 Å apart (average O···O distance) and oriented towards the same face of the macrocyclic framework.

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Next, the macrocyclic trialdehydes **2a** and **2b** were allowed to react with the C_3-symmetrical triamine 1,1,1-tris(4-aminophenyl)pentane (**3a**; Scheme 1). The reactions were performed at room temperature without a template or catalyst in a mixture of CH_2Cl_2 and MeOH (1.75:1 v/v) as the solvent. After several days, we observed the formation of one major compound (**4a** and **4b**, respectively), which precipitated in the form of an orange powder upon adiabatic removal of CH_2Cl_2 in vacuum. The products showed remarkably simple ^1H and ^{13}C NMR spectra (Supporting Information, Figure S3, S4), with only one set of signals for the protons of arene π ligands and one signal for the imine protons and carbon atoms. The completeness of condensation was indicated by the lack of aldehyde signals in the $\delta = 10.0$–10.5 ppm region. Although NMR spectroscopy did not allow unambiguous determination of the stoichiometry and topology of the products, formation of the dodecanuclear complexes resulting from a [4+4] condensation was confirmed by low- and high-resolution ESI mass spectrometry (Supporting Information, Figure S7–S9). The complexes **4a** and **4b** were isolated with yields of 55 and 45%, respectively (on a 50 μmol scale), which corresponds to a 93–95% efficiency for each of the 12 imine condensations.[15]

Trimers based on {(arene)Ru} complexes and 3-hydroxy-2-pyridone ligands are known to undergo ligand exchange reactions in polar solvents, such as methanol or water.[16] However, attempted ligand exchange between **2a** and **2b** under the conditions used for the synthesis of **4a** and **4b** (room temperature, CD_2Cl_2/CD_3OH 1.75:1 v/v) did not result in the formation of mixed complexes after two days, as determined by ^1H NMR spectroscopy. Therefore, the trialdehydes **2a** and **2b** should be regarded as inert building blocks on the timescale of the imine condensation process.

Diffusion of Et_2O vapors into solutions of **4a** and **4b** in $CHCl_3$/MeOH (95:5) resulted in the growth of large, well-shaped single crystals, which despite appearances diffracted X-rays rather poorly. A satisfactory data set was nonetheless obtained for a crystal of **4a**[17] whose the structure was solved in $I2/a$, an alternative setting of the monoclinic space group $C2/c$. The solid-state structure of **4a** is shown in Figure 1. The complex displays approximate tetrahedral symmetry (T), which is in line with the simple NMR spectra observed in solution. The trinuclear metallamacrocycles occupy the four vertices, whilst the triphenylmethane units span each of the four faces. Notably, within a given molecule, all four metallamacrocycles have identical relative configuration with respect to rotation about the pseudo threefold axes that connects each vertex with its opposing face (Figure 1a). The crystal as a whole is, however, racemic and thus contains an equal number of opposite stereoisomers.

The X-ray diffraction analysis also revealed a remarkable feature: crystals of **4a** are perforated by large solvent-accessible voids; less that 30% of the total unit cell volume is accounted for by the complex alone. This is partly due to the relatively large internal volume of the cage, which we estimate as being approximately 500 $Å^3$ (the volume of a polyhedron which fits inside the cage; see Supporting Information, Figure S14). The main contributing factor is, however, the highly inefficient manner in which the cages
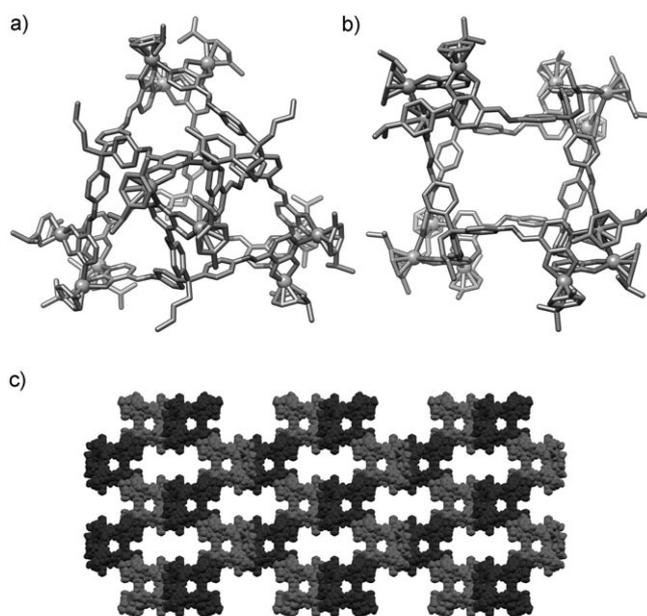

Figure 1. Molecular structure of complex **4a** in the solid state. a) View along the pseudo C_3 axis, b) view along the crystallographic C_2 axis (Ru: spheres), and c) packing diagram as viewed down the crystallographic a axis (opposite enantiomers are shown in different shades of gray). All hydrogen atoms have been omitted for clarity.

pack. The shortest points of contact between any two nearest neighbors are localized on the metallamacrocycles and this gives rise to large pores of up to 45 Å in the cross-section, which propagate along the crystallographic a axis (Figure 1c). The presence of highly disordered solvent molecules in these regions of the structure is most likely the reason why the crystal does not diffract much beyond 1.2 Å in resolution.

The high percentage of solvent-accessible volume in crystalline **4a** prompted us to investigate whether a material with permanent porosity could be generated.[3a] N_2 sorption measurements were performed at 77 K with a sample of crude amorphous **4a**, and also with a sample of an X-ray-quality crystalline product, after prolonged drying in vacuum. The calculated Brunauer–Emmett–Teller surface areas were 30 and 15 $m^2 g^{-1}$ for the amorphous and dried crystalline products, respectively, which indicates that larger voids between the cages are no longer present, presumably because of a structural collapse during the drying process. This conclusion is further supported by the poor match between the powder X-ray diffraction pattern of dried crystalline **4a** with that calculated from the single-crystal diffraction data (Supporting Information, Figure S2).

The synthetic concept described above can be used to create even larger cages. This was demonstrated by the synthesis of complexes **5a** and **5b** from metallamacrocycles **2a** and **2b** and an expanded triamine, the trixenylmethane derivative **3b** (Scheme 1). Indeed, products of the [4+4] condensation were obtained, albeit in lower yields than **4a** and **4b** (20% and 18% for **5a** and **5b**, respectively). The lower yields of the isolated products may indicate that the geometry of the expanded triamine **3b** is less favorable for reaction with metallamacrocyclic trialdehydes. At the same

time, ^{1}H NMR spectra of the reaction mixtures indicated that **5a** and **5b** were the major components (each about 50 %) of complex imine library. Notably, product **5b** precipitated from the reaction mixture after 6 days in an analytically pure form as long (2–3 mm), thin, soft needles that could be bent without breaking and which diffracted X-rays very poorly.

The complexes **5a** and **5b** were characterized by NMR spectroscopy and by low- and high-resolution ESI mass spectrometry (Supporting Information, Figure S5–S6, S10–S12). Their ^{1}H and ^{13}C NMR spectra are as simple as those of **4a** and **4b**, with only one set of signals for the π ligand and one singlet for the imine protons. We therefore assume that, like the smaller cages **4a** and **4b**, complexes **5a** and **5b** are formed as single diasteroisomers with the twelve stereogenic metal centers having the same relative configuration. The structure of **5b** was additionally estimated with the help of molecular modeling using force-field (MM3) geometry optimization (Figure 2);[18] it features a larger size (maximal Ru–
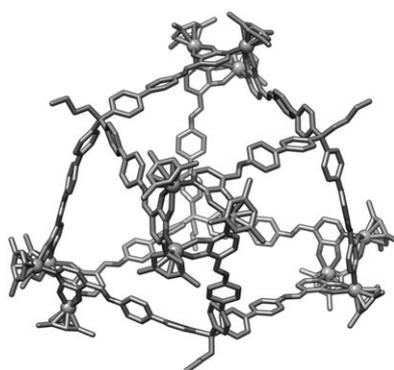

Figure 2. Energy-minimized structure (MM3 force-field) of one of enantiomers of cage **5b** viewed along the pseudo C_3 axis.

Ru distance 29 Å; 23 Å in **4a**) and cavity (approx. 1500 Å^3). The validity of the molecular mechanics calculations was demonstrated by a model of cage **4a**: the calculated structure was found to be reasonably close to the one determined by X-ray diffraction (Supporting Information, Figure S13).

In conclusion, the work described herein provides evidence that remarkably large and complex structures can be obtained by combining metal–ligand bond-forming reactions with imine condensations in an orthogonal fashion (that is, the imine bond is not formed in the coordination sphere of the metal). The approach to connect metallamacrocycles by dynamic covalent chemistry complements existing strategies for the bottom-up assembly of molecular nanostructures, and it should be applicable to a variety of other structures.

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[14] X-ray data for **2b**: Ru$_3$C$_{45}$H$_{45}$N$_3$O$_9$·2 CHCl$_3$, M_r = 1313.79, space group $P2_1/n$, a = 11.9914(8), b = 18.9103(13), c = 23.1709(19) Å, β = 100.073(7)°, V = 5173.3(6) Å^3, Z = 4, ρ = 1.687 g cm^{-1}, μ = 1.230 mm^{-1}, $F(000)$ = 2624, crystal size 0.23 × 0.19 × 0.12 mm^3. A total of 35 234 reflections (2.89° ≤ θ ≤ 26.02°) were collected,

of which 10130 were unique ($R_{int} = 0.0695$). The structure was refined on F^2 to $R_w = 0.2514$, $R = 0.1002$ [8177 reflections with $I > 2\sigma(I)$] and GOF = 1.160 on F^2 for 650 refined parameters, 54 restraints. Largest difference peak and hole 2.896 and -1.536 eÅ^{-3}. CCDC 765892 (**2a**) 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.

[15] On a 300 µmol scale, cage **4a** was obtained in 35% yield.

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[17] X-ray data for **4a**: $Ru_{12}C_{248}H_{288}N_{24}O_{24}$, $M_r = 5634.22$, space group $I2/a$, $a = 29.641(6)$, $b = 68.204(7)$, $c = 36.331(11)$ Å, $\beta = 94.00(3)°$, $V = 73\,268(27)$ Å^3, $Z = 4$, $\rho = 0.511$ g cm^{-1}, $\mu = 0.264$ mm^{-1}, $F(000) = 11\,520$, crystal size $0.2 \times 0.1 \times 0.1$ mm^3. A total of 129695 reflections ($2.82° \leq \theta \leq 17.22°$) were collected, of which 22093 were unique ($R_{int} = 0.2742$). The structure was refined on F^2 to $R_w = 0.3288$, $R = 0.1394$ (5983 reflections with $I > 2\sigma(I)$) and GOF = 1.14 on F^2 for 712 refined parameters, 1056 restraints. Largest difference peak and hole 0.510 and -0.496 eÅ^{-3}. Scattering contributions from diffuse solvent were removed using the SQUEEZE routine in PLATON (see Supporting Information). CCDC 765891 (**4a**) 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.

[18] Molecular mechanics calculations were performed with Scigress Explorer Ultra version 7.7.0.47, **2007**, Fujitsu Ltd.