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[13] X-ray structure analysis: STOE-IPDS ($Mo_{K\alpha}$ radiation); data collection and refinement (SHELXS-97, SHELXL-97); empirical absorption correction (Habitus). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-167634 (**1**), CCDC-167635 (**2**), CCDC-167636 (**3**), and CCDC-167637 (**4**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). **1**: $C_{62}H_{72}Ag_4P_4Se_4$, monoclinic, space group $P2_1$ (no. 4), $Z=4$, cell dimensions (190 K): $a=1340.0(3)$, $b=1646.0(3)$, $c=2969.0(6)$ pm, $\beta=102.4(1)^\circ$, $V=6396\times10^6$ pm^3, $\mu(Mo_{K\alpha})=3.620$ mm^{-1}, $2\Theta_{max}=56.18^\circ$, 52315 reflections, 28623 independent reflections, 23755 reflections with $I>2\sigma(I)$, 1234 parameters (Ag, Se, P, and C anisotropic). Absolute structural parameter 0.50(2). Max. electron density 1.6 e Å^{-3}; $R_1=0.08$; $wR_2=0.20$; GooF = 1.070. **2**: $C_{50}H_{65}Ag_8P_2Se_8$, monoclinic, space group $C2/c$ (no. 15), $Z=8$, cell dimensions (190 K): $a=2616.1(5)$, $b=1804.9(4)$, $c=2728.8(6)$ pm, $\beta=90.59(3)^\circ$, $V=12884\times10^6$ pm^3, $\mu(Mo_{K\alpha})=6.979$ mm^{-1}, $2\Theta_{max}=52.04^\circ$, 7177 reflections, 5677 independent reflections, 4883 reflections with $I>2\sigma(I)$, 488 parameters (Ag, Se, P, and C anisotropic). Max. electron density 1.0 e Å^{-3}; $R_1=0.08$; $wR_2=0.19$; GooF = 0.991. **3**: $C_{172}H_{248}Ag_{28}P_8Se_{22}\cdot5CH_2Cl_2$, monoclinic, space group $C2/c$ (no. 15), $Z=4$, cell dimensions (190 K): $a=3355.0(7)$, $b=3016.0(6)$, $c=2473.0(5)$ pm, $\beta=90.33(3)^\circ$, $V=25023\times10^6$ pm^3, $\mu(Mo_{K\alpha})=7.935$ mm^{-1}, $2\Theta_{max}=52.12^\circ$, 49340 reflections, 23253 independent reflections, 19051 reflections with $I>2\sigma(I)$, 1179 parameters (Ag, Se, P, anisotropic, C, Cl isotropic). Max. electron density 3.1 e Å^{-3}; $R_1=0.05$; $wR_2=0.15$; GooF = 1.047. **4**: $C_{260}H_{576}Ag_{124}Cl_6P_{28}Se_{61}$, monoclinic, space group $P2_1/c$ (no. 14), $Z=4$, cell dimensions (190 K): $a=3746.3(7)$, $b=4662.6(11)$, $c=3361.8(10)$ pm, $\beta=90.28(2)^\circ$, $V=58721\times10^6$ pm^3, $\mu(Mo_{K\alpha})=7.935$ mm^{-1}, $2\Theta_{max}=41.62^\circ$, 89967 reflections, 53085 independent reflections, 32780 reflections with $I>2\sigma(I)$, 3180 parameters (Ag, Se, P, Cl anisotropic, C isotropic). Max. electron density 5.0 e Å^{-3}; $R_1=0.08$; $wR_2=0.22$; GooF = 1.047.
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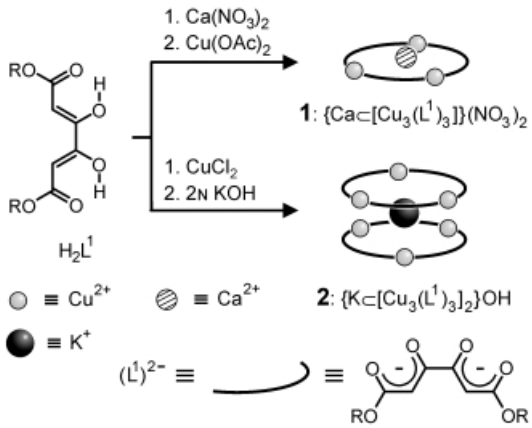
Hybrid Metallacoronates or One-Dimensional Oxo-Bridged Metal Strings by Self-Assembly—Coordination Number Controlled Product Formation**

Rolf W. Saalfrank,* Harald Maid, Nicolai Mooren, and Frank Hampel

Dedicated to Professor Kenneth N. Raymond on the occasion of his 60th birthday

Recent developments in the field of design and synthesis of supramolecular inorganic structures that exhibit novel properties have provided exciting new prospects.[1] We have reported on the template-mediated self-assembly of three-membered copper coronate **1** and sandwich complex **2**, starting from dialkyl ketipinates H_2L^1 (Scheme 1).[2] A common feature of these complexes is that the incapsulated



Scheme 1. Synthesis and schematic representation (without coordinating solvent molecules) of metallacoronate **1** and metallasandwich complex **2**.

alkali or alkaline-earth metal ions are coordinated to the inner carbonyl oxygen donors. Compared to the ketipinate dianions $(L^1)^{2-}$, the hybrid dianions $(L^2)^{2-}$ or $(L^3)^{2-}$ of the glycolate- or catecholate-bridged bis-1,3-diketones, owing to their extra oxygen donors, should be even better ligands[3–6] for the design of metallacoronates. To test this hypothesis, we prepared a solution of bis-1,3-diketone H_2L^2 and a twentyfold excess of alkali metal acetates (M = K, Rb, Cs) in methanol, and added this mixture dropwise to a solution of copper(II)acetate in methanol. Green crystals were obtained in each case

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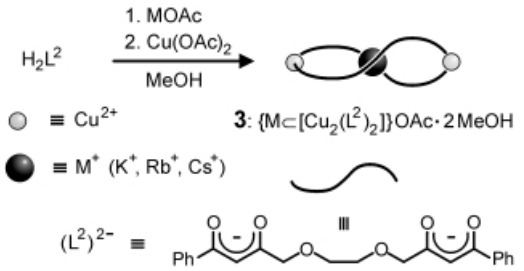
(Scheme 2). The microanalytical data and FAB-MS spectra provided indications that the products were the dinuclear copper chelate compounds **3**.[7, 8]



Scheme 2. Synthesis and schematic representation of the hybrid metallacoronates **3**.

To obtain an unambiguous characterization of the molecular structure of the metallacoronates **3**, we carried out a single-crystal X-ray structure analysis of the potassium complex **3**, M = K[9–11] (Figure 1). According to this analysis, in

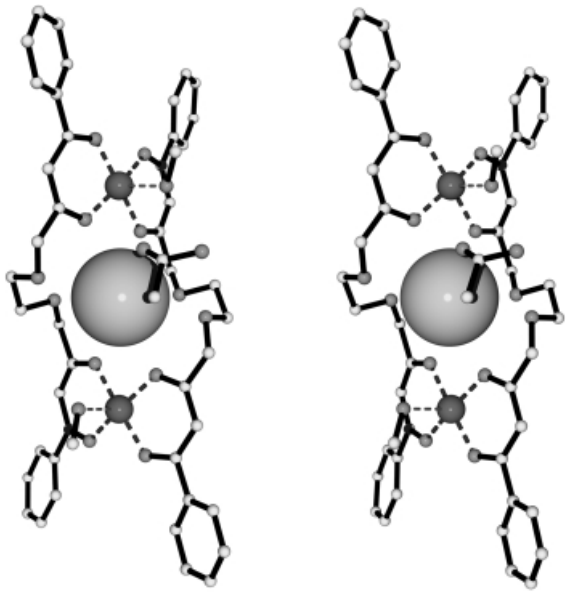
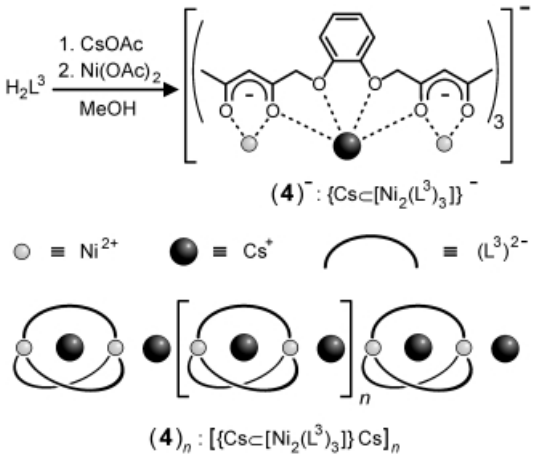


Figure 1. Stereoview of hybrid metallacoronate **3**, M = K, in the crystal. Selected bond lengths [Å] (mean values): Cu-O^{o} 1.918, Cu-O^{i} 1.924, K-O^{i} 2.923, K-O^{e} 2.986 (O^{o} = outer O, O^{i} = inner O, O^{e} = ether-O). The dihedral angle of the tetragonal pyramid bases at copper is 84°.

3, M = K, the two copper(II) centers are linked through two bis-bidentate glycolate-bridged bis-1,3-diketone dianions $(L^2)^{2-}$, affording a [22]metallacrown-8 system (22-MC-8). Formal replacement of the two copper(II) centers in the metallacoronand 22-MC-8 by ethylene bridges gives the topologically equivalent crown ether [24]crown-8. Each copper(II) ion in K-**3** is coordinated in a square-pyramidal fashion to four oxygen atoms of the ligands $(L^2)^{2-}$ and that of a methanol molecule. The resulting metallacoronand 22-MC-8 is wrapped around a central potassium ion with the effect that four carbonyl oxygen and four ethyleneglycol oxygen donors each are coordinated to this center. Charge compensation is achieved through coordination of an extra disordered acetate ion to the potassium ion. Thus **3**, M = K, can be characterized as a double-stranded helicate incapsulating a potassium ion. Viewed ideally, the cationic core of the system $\{K\subset[Cu_2(L^2)_2]\}^+$ has D_2 symmetry, which is reduced for $\{K\subset[Cu_2(L^2)_2]\}^+\cdot 2\,MeOH$ to C_2 and for $\{K\subset[Cu_2(L^2)_2]\}OAc\cdot 2\,MeOH$ to C_1. As a rule, chiral molecules from achiral building blocks yield racemic mixtures.[12] As expected, the crystals of helical **3**, M = K, contain both enantiomers (*P* and *M*) as documented by the space group *C*2/*c*.

The prognosis of the structure of supramolecular coordination complexes is based on the careful selection of matching metal–ligand combinations. However, previous findings prompted us to tackle nonmatching metal–ligand combinations as well.[13] In extension of this strategy, starting with the hybrid dianions $(L^2)^{2-}$ or $(L^3)^{2-}$ and hexacoordinate divalent metal ions, instead of tetra-/pentacoordinate copper(II), bicyclic negatively charged {2}-metallacryptates $\{M^{I}\subset[(M^{II})_2(L^2/L^3)_3]\}^-$ were expected. The formation of a dimetallic triple-stranded helicate (={2}metallacryptand) is associated with the generation of a cavity. The host–guest properties of these self-assembled voids strongly depend on the possible interaction between spacer and guest and the charge of the {2}metallacryptand. Notably, most of the macrobicyclic host cavities remain unoccupied and only recently it was shown that alkyl-bridged biscatecholate ligands or *m*-pyridinediyl-spacered bis-1,3-dicarbonyl dianions yield {2}metallacryptates.[14]

However, despite these achievements, there were only speculations about the final composition of the neutral species, which may be deduced from anionic $\{M^{I}\subset[(M^{II})_2(L^2/L^3)_3]\}^-$. Therefore, we allowed a solution of catecholate-bridged bis-1,3-diketone H_2L^3 in methanol to react with nickel(II) acetate in the presence of a twentyfold excess of cesium ions as template (Scheme 3) and, after work-up, isolated a microcrystalline green solid. Based on the elemental analysis and FAB mass spectrometry, the resulting solid represents a neutral {2}metallacryptate of the composition $[\{Cs\subset[Ni_2(L^3)_3]\}Cs]$, which was unequivocally characterized by an X-ray crystallographic structure determination.[15] According to this analysis the {2}metallacryptand $[Ni_2(L^3)_3]^{2-}$ core is composed of two nickel(II) centers linked through three bis-bidentate catecholate-spacered bis-1,3-diketone dianions



Scheme 3. Synthesis and schematic representation (without methanol molecules) of the one-dimensional oxo-bridged metal string $(\mathbf{4}\cdot 3\,MeOH)_n$.

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$(L^3)^{2-}$. Therefore, each nickel(II) ion is coordinated octahedrally by six oxygen donors. The resulting {2}metallacryptands are homochiral with either (*Δ*,*Δ*)-*fac* or (*Λ*,*Λ*)-*fac* configuration at the nickel centers. They hold a cesium ion in the void, which is coordinated by six carbonyl oxygen and six catecholate oxygen donors, each. Charge compensation of the {2}metallacryptates $(\mathbf{4})^-$ is achieved through extra external cesium ions. Interestingly, the thus accessible neutral (*Δ*,*Δ*)/(*Λ*,*Λ*) building blocks $[\{Cs \subset [Ni_2(L^3)_3]\}Cs]$ **4** are self-complementary and aggregate alternating across the external cesium ions to give the unprecedented one-dimensional oxo-bridged metal string *meso*-$[\{Cs \subset [Ni_2(L^3)_3]\}Cs \cdot 2MeOH]_n$ $(\mathbf{4} \cdot 2MeOH)_n$.[16] In $(\mathbf{4} \cdot 2MeOH)_n$ the coupling external cesium ions are coordinated to two sets of three peripheral carbonyl oxygen donors and two methanol molecules. An additional noncoordinated methanol molecule per monomer unit trapped in the crystal leads to the final overall stoichiometry $(\mathbf{4} \cdot 3MeOH)_n$ for the polymer (Scheme 3, Figure 2). In the crystal, the oxo-bridged metal strings $(\mathbf{4} \cdot 2MeOH)_n$ run parallel to the (*a*,*c*)-plane diagonal of the unit cell (Figure 3).

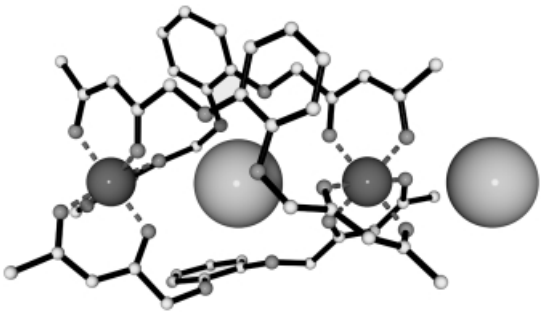

Figure 2. Structure of the self-complementary monomers **4** in the crystal. For reasons of clarity the methanol molecules were omitted. Selected bond lengths [Å] (O^o/Cs^o = outer O/Cs, O^i/Cs^i = inner O/Cs, O^e = ether-O, mean values are labeled with $^+$) of **4**: Ni-O^o 2.044$^+$, Ni-O^i 2.030$^+$, Cs^i-O^i 3.201–3.441, Cs^i-O^e 3.259–3.648, Cs^o-O^o 2.948–3.397.[18]

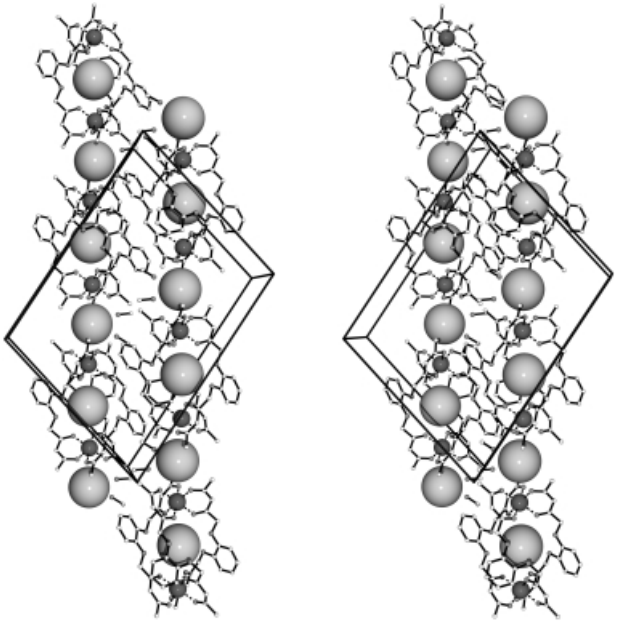

Figure 3. Stereo view of the crystal packing of the oxo-bridged metal strings $(\mathbf{4} \cdot 2MeOH)_n$. View along the *b* axis. For reasons of clarity the noncoordinating methanol molecules are omitted.

In conclusion, we have developed a convenient route for the template-mediated self-assembly of hybrid metallacoronates $\{K \subset [Cu_2(L^2)_2]\}OAc$. Evaluation of the construction plan of these systems initiated the elaboration of self-complementary monomer $[\{Cs \subset [Ni_2(L^3)_3]\}Cs]$ and finally of the one-dimensional oxo-bridged metal string $[\{Cs \subset [Ni_2(L^3)_3]\}Cs]_n$. There is currently much interest in the fundamental study of oxygen-mediated metal–metal interactions and their potential applications.[17]

Experimental Section

K-**3**: A solution of H_2L^2 (96 mg, 0.25 mmol)[3] and potassium acetate (245 mg, 2.5 mmol) in methanol (64 °C, 5 mL) was added dropwise to a solution of copper(II) acetate monohydrate (50 mg, 0.25 mmol) in methanol (5 mL). The green solution was filtered and layered with diethyl ether (20 mL). Yield: 129 mg (98 %), green crystals; m.p. >134 °C (decomp); IR ($CHBr_3$): $\tilde{\nu}$ = 1592, 1559, 1516 cm^{-1}; FAB-MS (3-nitrobenzyl alcohol matrix): *m*/*z*: 927 $\{K \subset [Cu_2(L^2)_2]\}^+$.[18]

$(\mathbf{4})_n$: A solution of nickel(II) acetate tetrahydrate (166 mg, 0.67 mmol) in methanol (5 mL) was added dropwise to a mixture of H_2L^3 (306 mg, 1.00 mmol)[3] and cesium acetate (1.286 g, 6.70 mmol) in methanol (64 °C, 5 mL). The green solution was filtered and layered with diethyl ether (10 mL). Yield: 116 mg (27 %), emerald green crystals; m.p. >230 °C (decomp); IR ($CHBr_3$): $\tilde{\nu}$ = 1611, 1469 cm^{-1}; FAB-MS (3-nitrobenzyl alcohol matrix): *m*/*z*: 1561 $[Cs\{Cs \subset [Ni_2(L^3)_3]\}Cs]^+$, 1429 $[\{Cs \subset [Ni_2(L^3)_3]\}Cs]^+$.[18]

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[15] Crystal data for (**4** · 3 HOMe)$_n$: $C_{51}H_{60}Cs_2Ni_2O_{21}$, $M_r = 1392.24$; crystal dimensions $0.40 \times 0.35 \times 0.35$ mm^3; monoclinic, space group $P2(1)/n$, $a = 1767.67(5)$, $b = 1459.88(2)$, $c = 2271.77(3)$ pm, $\beta = 103.9790(10)^\circ$, $V = 5688.88(13)$ Å^3; $Z = 4$; $F(000) = 2788$, $\rho_{calcd} = 1.626$ g cm^{-3}. Diffractometer: Nonius KappaCCD, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å); $T = 173(2)$ K; graphite monochromator; θ range [°] $1.32 < \theta < 27.48$; section of the reciprocal lattice: $-22 \le h \le 22$, $-18 \le k \le 14$, $-29 \le l \le 29$; of 19152 measured reflections, 12962 were independent and 9364 with $I > 2\sigma(I)$; linear absorption coefficient 1.997 mm^{-1}. The structure was solved by direct methods using SHELXS-97 and refinement with all data (685 parameters) by full-matrix least-squares on F^2 using SHELXL-97;[10] all non-hydrogen atoms were refined anisotropically; $R1 = 0.0446$ for $I > 2\sigma(I)$ and $wR2 = 0.1396$ (all data); largest peak (1.304 e Å^{-3}) and hole (-1.607 e Å^{-3}).[11]
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Natural Products Are Biologically Validated Starting Points in Structural Space for Compound Library Development: Solid-Phase Synthesis of Dysidiolide-Derived Phosphatase Inhibitors**

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The combinatorial synthesis of compound libraries on polymeric supports is at the heart of protein ligand and inhibitor discovery, in particular in the development of new drugs and chemical tools for the study of biological processes. To achieve high efficiency in this process, powerful and alternative strategies for the design of compound libraries are of paramount importance. Herein, a structure-based approach to this fundamental problem is outlined. The key feature is to employ the structural frameworks of biologically active natural products, which are evolutionarily selected for binding to specific protein domains, as a guiding principle for library development. Furthermore, it is demonstrated that the key synthetic challenge posed by this approach, the multistep solid-phase synthesis of natural products and their analogues, can successfully be met.

Proteins can be regarded as modularly built biomolecules assembled from individual domains as building blocks. Since the total number of all available protein domains appears to be fairly limited,[1] it has to be expected that in newly discovered proteins with widely varying function and activity the same modules (i.e. domains) or close relatives will be found repeatedly in varying combinations and arrangements as structure- and function-determining entities. Thus, a key to the efficient discovery of new ligands and inhibitors for known and, in particular, for newly discovered proteins is to identify compound classes already biologically validated as being

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