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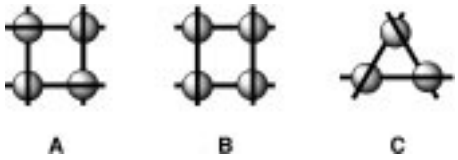
Designed Molecules for Self-Assembly: The Controlled Formation of Two Chiral Self-Assembled Polynuclear Species with Predetermined Configuration**

Thomas Bark, Mathias Düggeli, Helen Stoeckli-Evans, and Alex von Zelewsky*

Self-assembly reactions are not yet as predictable to the same degree as classical reaction sequences. Often, highly interesting structures are obtained through a combination of intuition, conjecture, and serendipity.[1] Herein, we report the formation of two closely related supramolecular structures that were obtained in a programmed way. Our intention is to fabricate supramolecular complexes of the type **A** from octahedrally coordinating metal ions.



Complexes of this type are chiral (D_4 symmetry) as a consequence of the special way the ligand strands enfold the cations. Chirality is the main feature that distinguishes them from the related grid-type complexes **B** investigated by J.-M. Lehn and co-workers,[2a,b] and other recently reported molecular squares.[2c,d]

To achieve such structures we had to design a ligand that fulfils the following demands: 1) it must offer two terpyridine-type binding sites to cover each half of the coordination sphere of an OC-6 cation in a *mer* configuration; 2) it must be geometrically rigid, and define the side of a square in a tetranuclear self-assembled species; and 3) the orientation of the binding vectors of the two terpyridine (terpy) units must be antiparallel, in order to make the ligand coordinate to the metal ions once from "above" and once from "below" the plane defined by the four metal ions. These requirements, and especially the relative orientation of the binding sites, are fulfilled in ligand L^1, in which two 2,2′-bipyridin-6-yl groups are attached to a central pyrazine ring at positions 2 and 5.[3]

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Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

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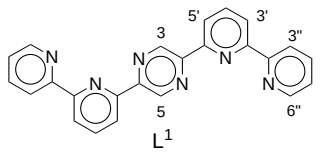
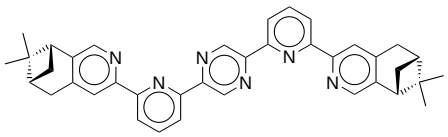


L^1



L^2

This ligand yields the desired tetrameric assembly with Zn^{2+} ions. The solution behavior of $[Zn_4(L^1)_4](PF_6)_8$ (**1**) in MeCN was investigated by electrospray-ionization mass spectrometry (ESI-MS) as well as by ^1H and ^{13}C NMR spectroscopy. The mass spectrum (Figure 1 a) reveals the tetrameric structure of **1** and displays peaks that are attributed unambiguously (from their isotopic distribution pattern) to fragments of the type $[Zn_4(L^1)_4](PF_6)_n$ ($n = 3-6$).

The ^1H NMR spectrum of the complex in CD_3CN displays one half-set of hydrogen atoms that originate from L^1; the symmetry of the ligand is thus not broken upon complexation. All resonances have been identified by 2D experiments ($^1H^1H$-COSY, NOE). The spectrum of **1** is always accompanied by a minor species with the same number of signals and the same coupling patterns. The relative amount of this minor species *increases* at lower overall concentrations of **1** and *decreases* at higher temperatures. Detailed studies revealed the existence of an equilibrium between a trimer[4] of type **C** and a tetramer, with the tetramer being the major species in the concentration range investigated. The thermodynamic parameters of this equilibrium are given in Figure 2.

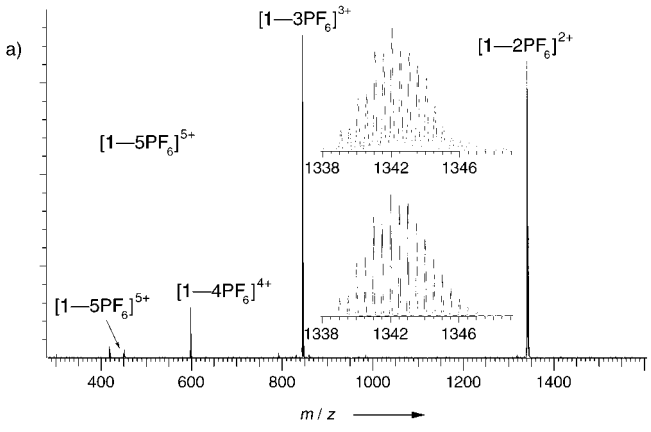


Figure 1. a) ESI mass spectrum of $[Zn_4(L^1)_4](PF_6)_8$ (a) and $[Zn_4(L^2)_4](PF_6)_8$ (b) in MeCN. Inset: found (top in both) and calculated (bottom in both) isotopic distribution for $\{[Zn_4(L^1)_4](PF_6)_6\}^{2+}$ and $\{[Zn_4(L^2)_4](PF_6)_5\}^{3+}$, respectively.

$$3\ [Zn_4(L^1)_4](PF_6)_8 \underset{MeCN}{\overset{K}{\rightleftharpoons}} 4\ [Zn_3(L^1)_3](PF_6)_6$$

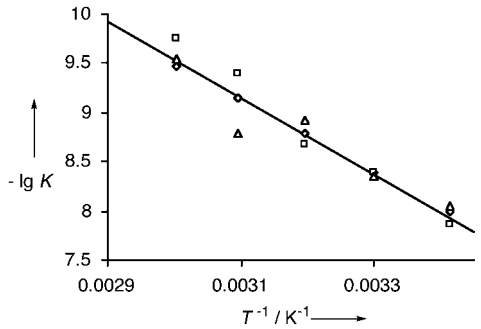


Figure 2. Temperature dependence of the tetramer/trimer equilibrium. The thermodynamic data were obtained by ^1H NMR spectroscopy. The equlibrium constants have been calculated from the integrals over three different protons (◇: H–C(3′); △: H–C(5′); □: H–C(3‴)). The resulting thermodynamic constants are: $\lg K^\circ(303\ K) = -(8.43 \pm 0.02)$; $\Delta H^\circ = -(74.5 \pm 10.0)\ kJ\,mol^{-1}$; $\Delta S^\circ = -(406 \pm 12)\ J\,mol^{-1}\,K^{-1}$.

The formation of the trimeric form from the tetramer is hence exothermic but endotropic. The negative ΔH° value must be the result of a better solvation of the trimeric complexes. The higher "ring strain" in the trimer resulting from a strong deviation from the ideal octahedral coordination geometry at the Zn^{2+} ions can probably be neglected because of the absence of ligand-field stabilization in Zn^{2+} ions. Thus the reduction of "void space" on going from the tetramer to the trimer dominates the reaction enthalpy. The negative reaction entropy is not easily understood, as both the number of complex ions and the configurational diversity increase upon the formation of the trimer. The same counter-intuitive behavior has been reported very recently for the equilibrium between the hexameric and tetrameric form of a silver-containing circular helicate.[5]

Complex **1** crystallizes[6] from $MeNO_2/Et_2O$ as a racemic compound in the centrosymmetrical space group *C*2/*c* (Figure 3). The symmetry of the complex in the crystal is C_2, and the zinc ions define a symmetrical trapezoid which is close to a square ($\alpha = 89.49(0.01)^\circ$, $\beta = 90.51(0.01)^\circ$). The lengths of the coordinative bonds are not unusual: Zn–N(pyridine) varies from 2.050 to 2.126 Å, while the bonds to the pyrazine nitrogen atoms are considerably longer (2.244–2.311 Å), probably as a result of electronic communication through the pyrazine ring. Two of the eight PF_6^- counterions are in close contact with the complex ion and occupy positions

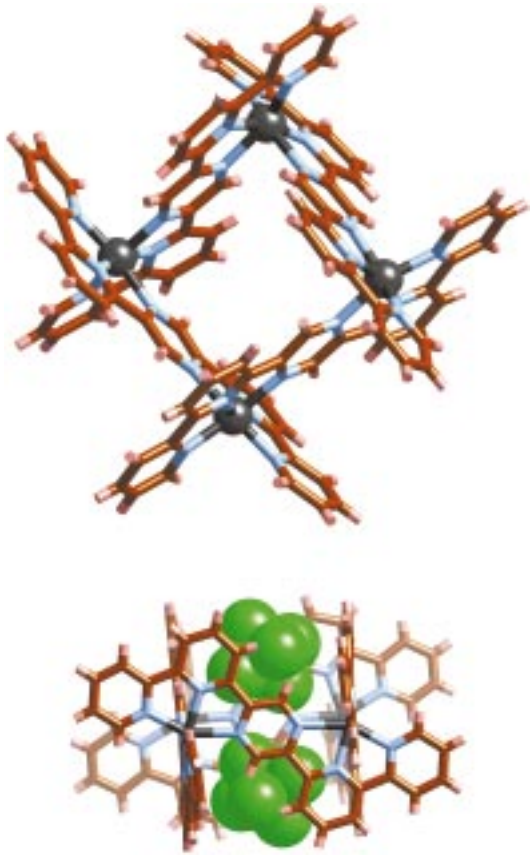
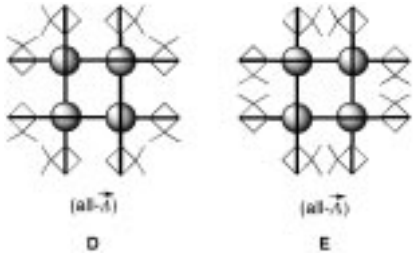


Figure 3. Crystal structure of the racemic compound $[Zn_4(L^1)_4](PF_6)_8$. Only the all-$\vec{\Delta}$ enantiomer is shown.

above and below the center of the square (Figure 3). Large numbers of disordered solvent molecules complicated the refinement of the structure. Related structures have been reported with the commercial ligand bispyridyltetrazine.[7]

After having obtained the racemic complex **1**, we envisaged the *stereoselective synthesis* of similar molecular assemblies. For this purpose we developed L^2, a chiral derivative of L^1. By rendering the ligand chiral, the all-$\vec{\Delta}$ and all-$\vec{\Lambda}$ isomers of the complex, which are enantiomers in the case of achiral L^1, will become diastereomers with L^2 (**D** and **E** in Scheme 1).



Scheme 1. Schematic representation of the two diastereomers of tetranuclear complexes with L^2. The methyl groups of the pinene moieties in **D** point to each other at the "corners" of the square, while in **E** their orientation is along the sides of the quadrangle.

The "chiralization" (that is, chiral derivatization) of the ligand was achieved quite straightforwardly by introducing pinene moieties, a technique used many times before for pyridine-type ligands.[8] The auto-assembly process delivers the tetranuclear Zn^{2+} complex (all-$\vec{\Delta}$)-$[Zn_4((R,R)\text{-}L^2)_4](PF_6)_8$ (**2**) as the major product with a high diastereomeric excess and in high yield.

The ^1H NMR spectrum shows that three minor species are also present; these species are presumably the other diastereomer of the tetramer and the two diastereomers of the trimer. Although further quantitative analysis of the NMR data is difficult because the signals are insufficiently separated, we can confirm that for a concentration suitable for NMR measurement (here 11.7 mmol L^{-1}), over 95% of the mass of complex **2** is present as the dominant diastereomer of the tetrameric complex, which is the same as that found in the solid state.

The crystal[9] contains only one diastereomer of **2** (type **D**, Scheme 1). The asymmetric unit comprises one complex molecule (Figure 4), and all the Zn^{2+} ions are thus crystallographically inequivalent. The parameters of the coordinative

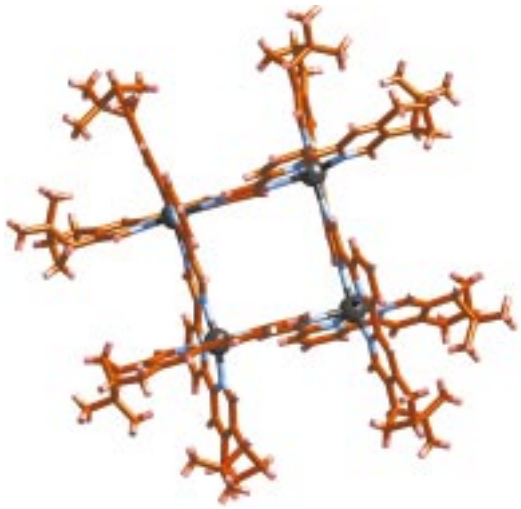


Figure 4. Crystal structure of $[Zn_4(L^2)_4](PF_6)_8$.

bonds are in the usual range (Zn–N(pyridine) 2.077 – 2.171 Å, Zn–N(pyrazine) 2.234 – 2.359 Å). Again, two PF_6^- ions are in close contact with the complex ion (not displayed). The X-ray structure analysis does not only establish the *relative* configuration of the complex (configuration of the ligand ↔ configuration at the metal centers), but it also confirms the *absolute configuration*; the Flack parameter[10] converged to 0.016(13) for the absolute structure containing the $(R,R)/\vec{\Delta}$ isomer of the complex.

In conclusion, we have reported a new type of chiral square complex and presented for the first time the configurational predetermination of the metal centers in such a tetramer by the use of a chiral ligand.

Experimental Section

The syntheses of L^1 and L^2 will be reported, together with isomeric and related pyrazine containing ligands, in a forthcoming publication.

rac-$[Zn_4(L^1)_4](PF_6)_8$ (**1**) was obtained by treating L^1 with a stoichiometric amount of $Zn(ClO_4)_2 \cdot 6H_2O$ in a small volume of MeCN. The ligand dissolved within a few minutes, and after one day at RT, the complex was isolated by precipitation from an aqueous NH_4PF_6 solution.

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$[Zn_4(L^2)_4](PF_6)_8$ (**2**) was prepared similarly, but the reaction mixture needed to be refluxed and the subsequent PF_6^- salt recrystallized from $MeCN/Et_2O$. The yields in both cases exceeded 95%. **ATTENTION**: The intermediate perchlorate salts of the complexes are explosive.

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[6] Crystal data for **1**: $C_{109}H_{100}F_{48}N_{26}O_8P_8Zn_4$, $M_r = 3323.39$; pale yellow block, $0.40 \times 0.40 \times 0.30\ mm^3$, obtained from $MeNO_2$/EtOH/MeOH by the diffusion of Et_2O. $\mu = 0.947\ mm^{-1}$, $F(000) = 6688$. Monoclinic, space group $C2/c$, $a = 19.8633(12)$, $b = 31.1631(17)$, $c = 22.8036(12)$ Å, $\alpha = 90$, $\beta = 110.562(6)$, $\gamma = 90°$, $V = 13216.2(13)$ Å^3, $Z = 4$, $\rho_{calcd} = 1670\ kg\,m^{-3}$. Data collection at 153 K on a Stoe Image Plate Diffraction system, by using graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). Image plate distance: 70 mm, ϕ oscillation scans 0–190°, step $\Delta\phi = 1°$, $2\theta = 3.27–52.1°$, $d_{max}/d_{min} = 12.45/0.81$ Å. A total of 49250 reflections of which 12828 were independent and used to refine 857 parameters. 6968 observed reflections with $I > 2\sigma(I)$. $R = 0.0748$, $wR_2 = 0.2002$ (observed); $R = 0.1216$, $wR_2 = 0.2214$ (all data). The structure was solved by direct methods (SHELXS-97) and refined anisotropically on F^2 (SHELXL-97). Hydrogen atoms were included in calculated positions and treated as riding atoms. Max./min. residual electron density $+1.274/-1.056$ e A^{-3}. One molecule of CH_3NO_2 was located in the asymmetric unit together with a considerable amount of highly disordered, and difficult to identify, solvent. The SQUEEZE routine in PLATON (A. L. Spek, *Acta Crystallogr. Sect. A* **1990**, *46*, C43) was used to modify the HKL data and indicated the presence of the equivalent of 515 electrons per unit cell. This value was equated to one MeOH, one EtOH, and two Et_2O molecules per molecule of complex. b) 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-159770 (**1**) and -159771 (**2**). 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).

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[9] Crystal data for **2**: $C_{169}H_{199}F_{48}N_{31}O_{12}P_8Zn_4$, $M_r = 4277.83$; pale yellow rod, $0.30 \times 0.20 \times 0.15\ mm^3$, from $MeCN/MeOH/Et_2O$. $\mu = 0.605\ mm^{-1}$, $F(000) = 2198$. Triclinic, space group $P1$, $a = 13.7635(10)$, $b = 18.9612(11)$, $c = 21.8334(16)$ Å, $\alpha = 102.476(8)$, $\beta = 106.002(9)$, $\gamma = 90.240(8)°$, $V = 5335.5(6)$ Å^3, $Z = 1$, $\rho_{calcd} = 1331\ kg\,m^{-3}$, data collection (at 153 K) and refinement as for **1**. $2\theta = 3.72–51.82°$, $\phi = 0–200°$, $\Delta\phi = 1°$. In total 42111 reflections were collected of which 34862 were independent and used to refine 1622 parameters. $R = 0.0717$ and $wR_2 = 0.1604$ for 13535 observed reflections ($I > 2\sigma(I)$); $R = 0.1711$ and $wR_2 = 0.1871$ for all data. Disordered solvent was equated to 7 MeCN, 3 MeOH, and 11 H_2O molecules. The PF_6^- ions are disordered and suffer from thermal motion. Flack parameter[10] $x = 0.016(13)$. Max./min. residual electron density $+0.811/-0.441$ e Å^{-3}.[6b]

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By Overexpression in the Yeast *Pichia pastoris* to Enhanced Enantioselectivity: New Aspects in the Application of Pig Liver Esterase**

Anna Musidlowska, Stefan Lange, and Uwe T. Bornscheuer*

Dedicated to Professor Günter Schmidt-Kastner on the occasion of his 75th birthday

Lipases and esterases can be used as efficient biocatalysts for the preparation of a wide variety of optically pure compounds.[1] Whereas a range of lipases—especially of microbial origin—are commercially available, only a few esterases can be obtained for the kinetic resolution of racemates or desymmetrization. In the majority of publications, pig liver esterase[2] (PLE) is used, which is isolated from pig liver by extraction. Although it has been demonstrated that this preparation can convert a broad range of compounds at partially very high stereoselectivity, its application is connected with a number of disadvantages. Besides a variation of the esterase content between different batches, the presence of other hydrolases particularly has to be considered as problematic with respect to stereoselectivity.[3] Furthermore, it has been shown that PLE consists of several isoenzymes,[4] which in part differ considerably in their substrate specificity. Thus, electrophoretic separation by isoelectric focusing enabled access to PLE fractions that,

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