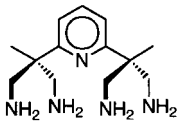
Spontaneous Assembly of a Schiff Base Tetramacrocycle**

Stefan Schmidt, Walter Bauer, Frank W. Heinemann, Harald Lanig, and Andreas Grohmann*

Dedicated to Professor Akio Yamamoto on the occasion of his 70th birthday

Tetrapodal pentadentate ligands, in which a four-legged donor set is supported by a framework containing a central donor atom, are rare.[1] We have set out to explore the potential of such ligands as head groups in functional transition metal complexes, and recently introduced a polyamine of this topology (pyN_4, **1**).[2] Further derivatization aims to append a "pocket" to the tetrapodal ligand, and mono-, di- and tetrafunctionalized derivatives of **1** have been obtained by Schiff base condensation with monocarbonyl compounds.[1] As an extension of this project, we chose to study the reactions of **1** with dialdehydes and selected a classic representative,[3] 2,6-diformyl-4-methylphenol (**2**), as reagent.[4]



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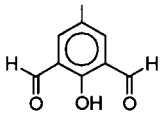

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The condensation of dialdehyde **2** with polyfunctional amines has been used for the synthesis of macrocycles and cryptands[5] having some of the topologies shown schematically in Scheme 1.[4] For good yields, the reactions usually rely on a templating agent (main group, transition metal, or lanthanoid ions; protons), and only a few direct condensations[6] have been reported. Mono- and polymacrocycles whose individual rings each incorporate two molecules of **2** prevail (Scheme 1 a, d); only very few rings containing three[6] (Scheme 1 b) or four[4k] (Scheme 1 c) of these dialdehyde units are known.

a) $n = 1$: [2 + 2]
b) $n = 2$: [3 + 3]
c) $n = 3$: [4 + 4]
d) [2 + 3]
e) [2 + 4]
f) [3 + 6]

Scheme 1. Topologies of documented (a–d, f) and hypothetical (e) macrocycles from the Schiff base condensation of polyamines with the dialdehyde 2,6-diformyl-4-methylphenol (**2**). Only the reactive centers are shown; full circles: polyamine; open circles: dialdehyde. The expressions in brackets refer to the number of polyamine and dialdehyde molecules that combine in each macrocyclization.

One possible condensation reaction between one equivalent of **1** and two equivalents of **2** is the "tetrapode capping"[7] reaction (Scheme 1 e), in which two pyN_4 head groups would be anchored in close proximity. Such a reaction involves six fragments with a total of 16 reactive centers, and hence its probability is very low.[7, 8] There is precedent, however, for the condensation of 1,3-diaminopropane (which is a structural subunit of **1**) with **2** in the presence of acid to yield a [2 + 2] macrocycle (cf. Scheme 1a).[9] We therefore performed the reaction in the presence of protons as a potential templating agent.

The condensation of **1** and **2** in the ratio 1:2 in refluxing methanol, in the presence of two equivalents of HBr, yielded an orange precipitate (**3**) as the only product. Its IR spectrum (KBr) showed strong absorptions in the aldimine region ($\tilde{\nu}$ = 1665, 1643 cm^{-1}), indicating Schiff base formation. No residual aldehyde bands ($\tilde{\nu}$ = 1682, 1666 cm^{-1}; $(C{=}O)_{str}$) were observed. Elemental analysis data of this material indicated a definite 1:2 condensation product, containing two equivalents of HBr. NMR spectra of **3** were broad and badly resolved; however, anion exchange with sodium perchlorate gave a microcrystalline solid (**4**) whose ^1H and ^{13}C NMR spectra showed excellent resolution (see below).

The X-ray structure analysis of a mixed Br^-/PF_6^- salt of the protonated condensation product ($[LH_6]Br_2(PF_6)_4$, **5**; see Experimental Section)[10] revealed a [3 + 6] condensation species (cf. Scheme 1 f) whose molecular structure is shown in Figure 1: three molecules of **1** and six molecules of **2** have combined in the presence of six protons (by inference from the number of anions) to give a macrocycle in which three 20-membered cyclic subunits are strung together into an alternating single and double strand with 42 member atoms along each loop. Each phenolbis(aldimine) unit is planar, suggesting two protons in an N···H···O···H···N hydrogen-bonded arrangement which is unipositive and involves two iminium and one phenoxide group. The molecule is chiral, and crystallizes as a racemic mixture.

The molecule has noncrystallographic threefold rotational symmetry and possesses a central cavity of truncated conical shape, with a wide and a narrow opening. The intermolecular distances do not suggest significant hydrogen-bonding between the cation and any of the counterions. The three cyclic subunits containing the bis(aldimine) bridges have conforma-

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Supporting information for this article (^{13}C data for compound **3**) is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

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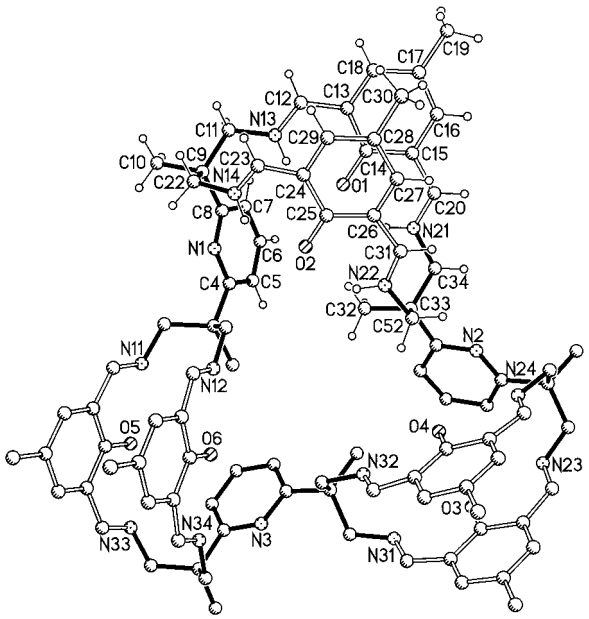

Figure 1. Molecular structure of the tetramacrocyclic cation $[LH_6]^{6+}$ obtained from the condensation of polyamine **1** (solid bonds) and dialdehyde **2** (open bonds) in the presence of acid. See text for the location of charges. For correlation with the NMR data, hydrogen atoms and the numbering scheme are partly shown. The proton numbers follow the numbers of their parent carbon or nitrogen atoms.

tions reminiscent of the conformation of calixarenes, virtually identical to that of the [2 + 2] condensation product of 1,3-diaminopropane and **2**;[9] π – π-stacking interactions induce a parallel orientation of the phenyl rings, with interplanar distances averaging 3.7 Å.

The chiral structure of the cation in $[LH_6]Br_2(PF_6)_4$ (**5**) is completely compatible with the ^{1}H and ^{13}C NMR spectra of the perchlorate salt **4**. A threefold symmetry axis interconverts the three pyridine as well as the three pairs of dialdehyde-derived spacer units. The "inner" and "outer" dialdehyde spacers exhibit different chemical shifts: Owing to the inherent symmetry of the tetramacrocycle, the methine protons and carbon atoms, the NH protons, etc. are pairwise nonequivalent, that means a total of four NH chemical shifts, four methine chemical shifts, etc. are observed. The proton and carbon resonances were assigned by standard 2D NMR methods (COSY, ROESY, HETCOR, COLOC, HMBC), as well as by the newly developed 1D pulse sequence DPFGSE-ROE.[11a] The numbering of the protons follows the numbering of their parent C and N atoms (Figure 1). The starting point for the assignment of the ^{1}H NMR signals is the proton H11g which is *gauche* with respect to its vicinal NH proton (H13): H11g is very close (2.18 Å) to H7 on the adjacent pyridine ring and exhibits, as the only one of all the geminal CH_2 protons, a correspondingly intense cross peak in the ROESY spectrum. The remaining assignment is straightforward (see Figures 1 and 2, and Experimental Section). Of the eight resonances found for the geminal CH_2 protons, four are split into doublets and four are split into triplets (Figure 2a). This is due to the geometry relative to the adjacent NH protons: coupling with NH (^3J(H-C-N-H) ≈ ^2J(H-C-H)) is observed only for the CH_2 proton which is *anti*, not for the one in the *gauche* position (Karplus equation).

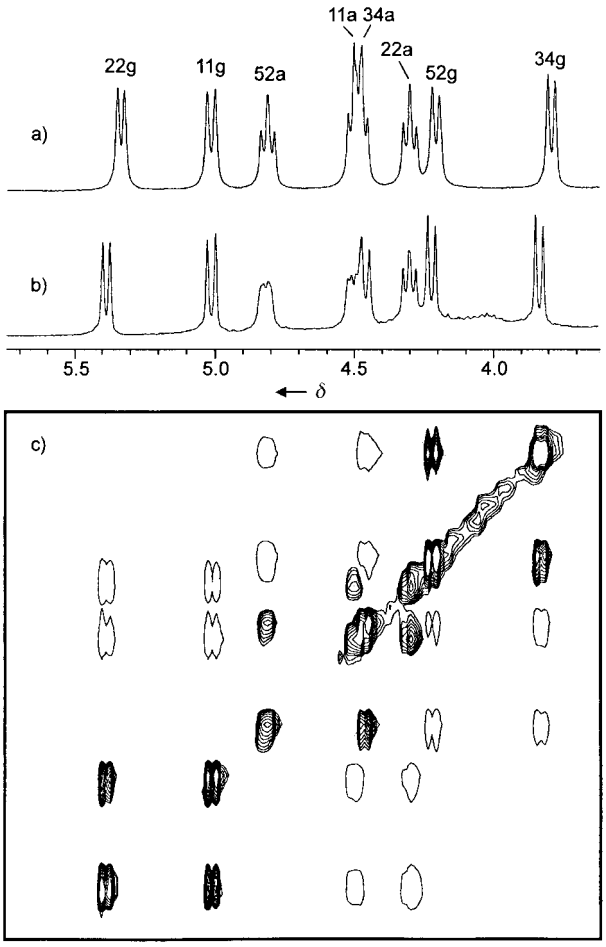

Figure 2. a) ^{1}H NMR spectrum of **4** ([D$_6$]DMSO, +25 °C): Resonance region of the geminal CH_2 protons H11, H22, H34 and H52. The numbering is based on the numbering of the parent carbon atoms in Figure 1. Symbols a and g denote *anti* and *gauche* positions, respectively, relative to the vicinal NH proton. b) Same as a), at +100 °C. c) ROESY spectrum of **4** ([D$_6$]DMSO, +100 °C). Cross peaks with more than one contour are positive (same phase as diagonal peaks) and are due to chemical exchange. Cross peaks with only one contour are negative and originate from NOE.

Unusual dynamic phenomena are observed in the ^{1}H NMR spectra at elevated temperatures. At +70 °C, the ROESY spectrum shows chemical exchange of the NH protons, a quite normal observation for iminium ions. However, at still higher temperatures (≥ 100 °C), there is also pairwise chemical exchange of the methyl groups on the dialdehyde-derived aromatic rings, of the non-aromatic methine protons, and of the geminal CH_2 protons (Figure 2b). Interestingly, no exchange is observed for the protons of the CH_3 groups on the pyridine-derived spacer (C10, C32). Moreover, there is only pairwise exchange (Figure 2c) of the "inner" *gauche*/*anti* CH_2 protons with their "outer" counterparts, for example, $H11_{gauche} \rightleftarrows H22_{gauche}$, $H11_{anti} \rightleftarrows H22_{anti}$. We therefore conclude that the underlying dynamic process must be an inversion of the whole molecule in umbrella-like fashion, leading to its enantiomer. The relative positions of the methyl groups in the pyridine spacers do not change during this process, that is methyl group C10 remains pointing "outward", while C32 remains pointing "inward". As is deduced from the chemical shift separation of corresponding exchanging groups in the

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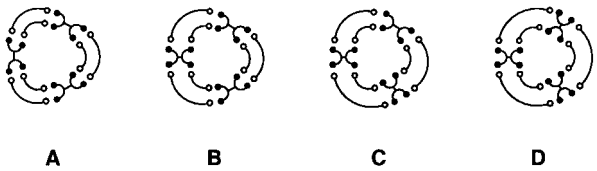
^{1}H NMR spectra, the barrier for the inversion process must be higher than 17 kcal mol^{-1}.[11b]

As shown in Scheme 2, four topologies are conceivable for the macrocyclic product of the condensation reaction at hand: **A**, the topology that is actually found, and **B** – **D**, which differ from **A** and from one another by an increasing number of



Scheme 2. Four topologies are conceivable for the product of the [3+6] condensation of **1** and **2**: **A** – **D** differ from one another by an increasing number of pyN_4 units being oriented "sideways" with respect to the large ring.

pyN_4 units that are oriented "sideways" with respect to the large ring. To estimate the relative stabilities of **A** – **D**, we performed molecular dynamics simulations at constant temperature using the MM3 force field developed by Allinger et al.[12] After the samples had been heated to 300 K, the different topologies were equilibrated for 1 ns. Averaging over the potential energy showed that **A** is by far the most stable. Increasing the ring size of an increasing number of circular subunits by incorporating a progressive number of pyN_4 fragments into the large ring "sideways" results in a stepwise increase of the relative energies. Details of these simulations in combination with NMR spectroscopic results will be reported elsewhere.

The assembly of **3** is remarkable in that it is a high-yielding (>90%) single-batch nine-component condensation that leads to a cyclic oligomer in which 12 new bonds have been formed. The specificity with which the cyclization proceeds is quite extraordinary. Protons can be assumed to play a templating role in the formation of the three smaller macrocyclic rings in much the same way as in the [2 + 2] condensation of 1,3-diaminopropane with 2,6-diformyl-4-methylphenol.[9] While bromide ion acting as an electrostatic template in the closure of the protonated large ring cannot be ruled out, its role is expected to be minor since Br^- can be removed completely by anion exchange. A more decisive factor may be simultaneous or sequential aminal formation between the 1,3-diaminopropane subunits of three molecules of **1** and the carbaldehyde functionalities of three molecules of **2**, leading to the kinetically controlled closure of a single-stranded large ring containing six six-membered cyclic aminals. In the presence of protons, these aminals may open and incorporate three additional dialdehyde molecules to give the more thermodynamically stable macrocycle containing cyclic Schiff base subunits. The intermediacy of aminals in the formation of Schiff base macrocycles is documented in the literature,[13] and a bis(aminal) derivative of **1** obtained from the reaction with two equivalents of ferrocenecarbaldehyde has been isolated and structurally characterized.[14]

The tetramacrocycle described here is compartmental[4b] and contains 21 potential donor atoms (15 N and 6 O atoms). In the solid-state structure of the metal-free macrocycle, the orientation of three of these (the pyridine N atoms) is divergent, but the conformation of the molecule may readjust upon metal coordination. Also, reduction of the imine moieties is expected to make the framework more flexible.

Experimental Section

$[LH_6]Br_6$, **3**: **1**·4HBr·MeOH (2.59 g, 4.26 mmol) was suspended in anhydrous methanol (100 mL) under an atmosphere of dry dinitrogen. Sodium metal (0.20 g, 8.53 mmol) was added with stirring, and the suspension gradually became a clear solution. After the evolution of H_2 had ceased, a solution of 2,6-diformyl-4-methylphenol (1.40 g, 8.53 mmol) in methanol (200 mL) was added in one portion, and the reaction mixture was refluxed for 15 h. During this time the color of the solution changed from yellow through orange to red, and an orange precipitate formed. The mixture was allowed to cool and then filtered under dinitrogen, the solid was washed with methanol, and dried in vacuo (2.59 g, 91%). Elemental analysis data indicated the correct composition, but ^{1}H and ^{13}C NMR spectra were poorly resolved. Anion exchange with ClO_4^- gave an analytically pure compound whose spectra showed excellent resolution at room temperature.

$[LH_6](ClO_4)_6$, **4**: Compound **3** (0.25 g, 0.12 mmol) was suspended in methanol (25 mL), and water (ca. 2 mL) was added to give an almost clear solution. After filtration, $NaClO_4$ (0.18 g, 1.44 mmol) dissolved in the minimum amount of methanol was added in one portion. Compound **4** precipitated immediately, was isolated by filtration, washed with methanol, and dried in vacuo (0.27 g, 95%). Correct elemental analysis for $C_{93}H_{105}N_{15}O_{30}Cl_6 \cdot 3CH_3OH \cdot 3H_2O$; IR (KBr): $\tilde{\nu} = 1665$, 1643 cm^{-1} (C=N)$_{str}$; 1088 (ClO_4); MS (FAB, p-NBA): *m*/*z* (%): 1524, $[LH_3]^+$ (100), 1826 $[(LH_6)(ClO_4)_3]^+$ (40); ^{1}H NMR (500 MHz, [D$_6$]DMSO, +25 °C; the numbering follows the C and N atom-numbering in Figure 1; "*anti*" and "*gauche*" refer to positions relative to vicinal NH protons): $\delta = 14.31$ (t, 3H, 12.0 Hz, H13), 13.51 (t, 3H, 12.2 Hz, H21), 13.13 (t, 3H, 12.5 Hz, H22), 13.07 (t, 3H, 12.5 Hz, H14), 8.80 (d, 3H, 12.0 Hz, H12), 8.79 (d, 3H, 13.0 Hz, H23), 8.74 (d, 3H, 13.6 Hz, H20), 8.67 (d, 3H, 13.6 Hz, H31), 8.37 (t, 3H, 8.6 Hz, H6), 8.19 (d, 3H, 8.6 Hz, H5), 8.00 (d, 3H, 8.6 Hz, H7), 7.45 (d, 3H, 3.1 Hz, H18), 7.30 (d, 3H, 3.1 Hz, H29), 7.29 (d, 3H, 3.1 Hz, H16), 7.11 (d, 3H, 3.1 Hz, H27), 5.33 (d, 3H, 12.0 Hz, H22$_{gauche}$), 5.01 (d, 3H, 14.6 Hz, H11$_{gauche}$), 4.81 (t, 3H, 12.5 Hz, H52$_{anti}$), 4.50 (t, 3H, 10.7 Hz, H11$_{anti}$), 4.48 (t, 3H, 10.1 Hz, H34$_{anti}$), 4.31 (t, 3H, 12.0 Hz, H22$_{anti}$), 4.21 (d, 3H, 13.0 Hz, H52$_{gauche}$), 3.79 (d, 3H, 13.6 Hz, H34$_{gauche}$), 2.16 (s, 9H, H19), 1.98 (s, 9H, H30), 1.72 (s, 9H, H32), 1.46 (s, 9H, H10).

$[LH_6]Br_2(PF_6)_4$, **5**: Single crystals of a methanol solvate of this composition were obtained by slow diffusion of a methanolic solution of $NaPF_6$ into a methanolic solution of **3**.

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[10] X-ray structure data for $[LH_6]Br_2(PF_6)_4 \cdot 7MeOH$: $M_r = 2492.91$, triclinic, space group $P\bar{1}$, $a = 18.071(3)$, $b = 18.184(2)$, $c = 20.081(2)$ Å, $\alpha = 78.67(1)$, $\beta = 81.87(1)$, $\gamma = 62.49(1)^\circ$, $V = 5729(2)$ Å^3, $\lambda = 0.71073$ Å, $T = 200(2)$ K, $Z = 2$, $\rho_{calcd} = 1.445$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 0.867$ mm^{-1}. Red block ($0.84 \times 0.52 \times 0.44$ mm). No absorption correction; number of measured/unique/observed ($F_o \geq 4.0\sigma(F)$) reflections: 22115/20018/7798 ($R_{int} = 0.0535$); $3.5^\circ \leq 2\theta \leq 50.0^\circ$; ω-scan; structure solution/refinement: direct methods, full-matrix least-squares, SHELXTL NT 5.10 (Bruker AXS, 1998); refined parameters: 1502. The crystal deteriorated during measurement, and the intensity of three standard reflections (measured every 100 reflections) decreased 28%. The crystal diffracted poorly despite its size; consequently, the data set was measured only up to an angle $\theta = 25^\circ$. One of the PF_6^- ions shows positional disorder which could be resolved. All H atoms were calculated in geometrically optimized positions. $R1 = 0.1086$, $wR2 = 0.2781$; ρ_{fin} (max./min.): 1.364/ − 1.020 e Å^{-3}. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-135908. 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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Discovery of a New Efficient Chiral Ligand for Copper-Catalyzed Enantioselective Michael Additions by High-Throughput Screening of a Parallel Library**

Isabelle Chataigner, Cesare Gennari,* Umberto Piarulli,* and Simona Ceccarelli

The 1,4-addition of organometallic reagents to α,β-unsaturated carbonyl compounds is an important process for C–C bond formation in organic synthesis.[1] A number of chiral stoichiometric reagents have been described during the last few years which allow enantioselective additions,[2] while the development of chiral catalysts has been comparably slower. A prominent position in this rapidly expanding field is occupied by the copper-catalyzed, chiral-ligand-accelerated, 1,4-addition of organozinc reagents.[3] In particular, chiral phosphoramidites,[3b] phosphites,[3c–f] and aminophosphanes[3g] were used as ligands in the addition to cyclic enones with very good enantioselectivities (up to 98% *ee*).[3b] On the other hand, chiral sulfonamides, which have proved effective in various catalytic asymmetric processes, were reported to catalyze the conjugate addition of organozinc reagents to cyclic enones[4a] only with marginal enantioselectivity (up to 31% *ee*).[4b]

We have developed a new family of chiral Schiff base ligands of general structure **5**, which contain a set of different metal binding sites (a phenol, an imine, and a secondary sulfonamide), with the expectation that such a multidentate array would favor the formation of organometallic complexes with well-organized spatial arrangements, and with the goal of obtaining ligands for asymmetric catalysis capable of broad applicability. Ligands **5** were easily obtained (Scheme 1) by condensation of salicylaldehydes with enantiomerically pure β-amino sulfonamides. Sulfonamides **3** were in turn synthesized by coupling different primary amines with sulfonyl chlorides **1**, prepared in high yields from L-α-amino acids by a straightforward synthetic protocol.[5] At the beginning of this work, a few model ligands **5** were prepared and tested, which proved effective in accelerating the copper-catalyzed (5% $Cu(OTf)_2$; $Tf = F_3CSO_2$) conjugate addition of diethylzinc to

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Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

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