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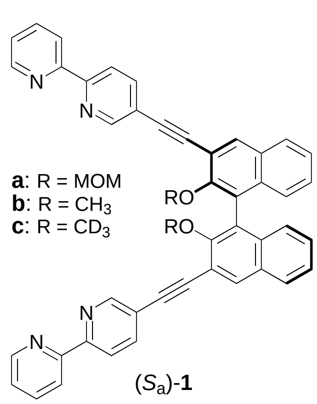
Synthesis and Stereoselective Self-Assembly of Double- and Triple-Stranded Helicates**

Arne Lützen,* Marko Hapke, Jens Griep-Raming, Detlev Haase, and Wolfgang Saak

The last decade has seen a tremendous development in the design and synthesis of self-assembled supramolecular architectures through metal-ion coordination.[1–3] Although examples have been reported in which chiral ligand units[2f,g, 4–11] were used, only a few of these units bear additional inwardly directed functional groups.[10a,c, 11] Therefore, our aim was to design and synthesize a double-branched chelating ligand, held together by a chiral core fragment bearing functional groups.

As part of our approach, the feasibility of the proposed metal–ligand complexes was explored by force-field and semiempirical calculations prior to ligand synthesis.[12] By following this approach we designed ligand **1**, which should self-assemble to form dinuclear coordination complexes with suitable metal ions (Figure 1). 5-ethynyl-2,2′-bipyridine (**4**; Scheme 1) was prepared from 2-bromopyridine (**2**). A modi-



(S_a)-**1**

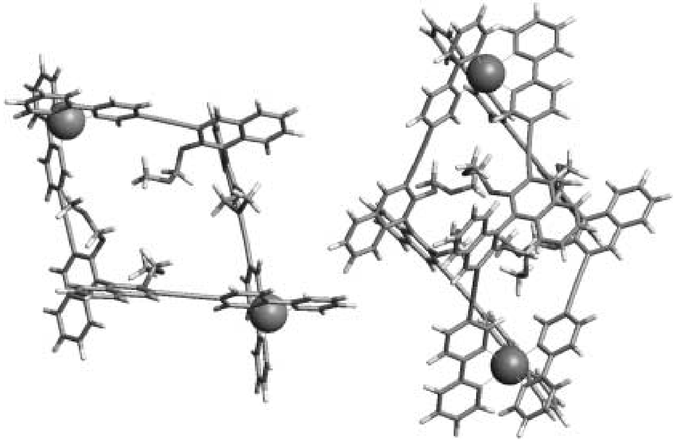
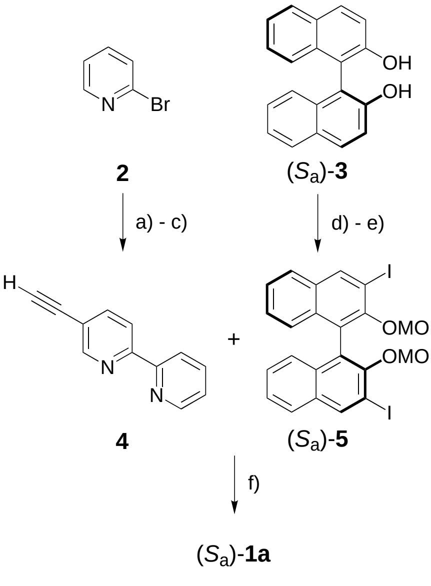


Figure 1. Energy-minimized structures (PM3-TM calculations) of the complexes $[Cu_2\{(S_a)\text{-}\mathbf{1a}\}_2]^{2+}$ (left) and $[Zn_2\{(S_a)\text{-}\mathbf{1a}\}_3]^{4+}$ (right); only one of the three possible stereoisomeric complexes is shown for each.



Scheme 1. Synthesis of (S_a)-**1a**. a) *t*BuLi, THF, −78 °C, then $ZnCl_2$, −78 °C → RT, 2 h; b) 2-chloro-5-trimethylsilylethynylpyridine, $[Pd_2(dba)_3] \cdot CHCl_3$, tBu_3P, THF, 83 %; c) KF, MeOH, 97 %; d) NaH, DMF, MOMCl, 80 %; e) *n*BuLi, TMEDA, RT, 6.5 h, I_2, −78 °C, 65 %; f) Et_3N, CuI, $[Pd_2(dba)_3] \cdot CHCl_3$, dppf, 50 °C, 78 %. dba = *trans,trans*-dibenzylideneacetone; TMEDA = *N,N,N′N′*-tetramethylethylenediamine; dppf = 1,1′-bis(diphenylphosphanyl)ferrocene.

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[*] Dr. A. Lützen, Dipl.-Chem. M. Hapke, Dr. J. Griep-Raming, Dipl.-Ing. D. Haase, Dipl.-Chem. W. Saak
University of Oldenburg
Department of Chemistry
P.O. Box 2503, 26111 Oldenburg (Germany)
Fax: (+49) 441-798-3329
E-mail: arne.luetzen@uni-oldenburg.de

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

fied Negishi cross-coupling reaction of **2** with 2-chloro-5-trimethylsilylethynyl-pyridine[13] furnished trimethylsilyl-protected 2,2′-bipyridine,[14] which was subsequently desilylated by use of potassium fluoride to give **4** in 81 % overall yield.[15]

Enantiomerically pure (S_a)- and (R_a)-2,2′-dihydroxy-1,1′-binaphthyl (BINOL, **3**) were obtained after clathrate formation of racemic BINOL with *N*-benzylcinchonidinium chloride.[16] Standard methoxymethyl ether (MOM) protection of the hydroxy groups afforded the 2,2′-bis-*O*-MOM protected intermediates, which were converted into *ortho*-diiodinated BINOL-derivatives **5**.[17] Finally, the Sonogashira coupling reaction of building blocks **4** and **5** using Et_3N, CuI, $[Pd_2(dba)_3]\cdot CHCl_3$, and dppf gave **1a** in a good yield of 78 %.[18]

Addition of previously prepared and thoroughly dried $[Cu(CH_3CN)_4]BF_4$, $[Ag(CH_3CN)_2]BF_4$, or $Zn(BF_4)_2$, or commercially available hydrated $Zn(ClO_4)_2\cdot 6H_2O$ or $FeSO_4\cdot 7H_2O$ to solutions of (S_a)-**1a** or (R_a)-**1a** in dichloromethane/acetonitrile resulted in instant color changes from almost colorless to intense red–brown in the case of the copper(I) and the iron(II) salts or pale yellow in the case of the silver(I) and the zinc(II) salts, which indicates the formation of metal complexes. This result was confirmed by NMR spectroscopic experiments on solutions in deuterated solvents, in which significant shifts of the signals in the ^1H and ^{13}C NMR spectra were observed.[19] The signals were very sharp, especially in the case of the silver and the zinc complexes (Figure 2), which indicates the formation of discrete, dinuclear metal complexes rather than higher oligomeric species.

Furthermore, the spectra also indicate that the zinc and iron complexes, as expected, have a different structure to the silver and copper complexes, which are very similar to each other. This structural difference is caused by the change from a tetrahedral coordination of the metal centers by two ligands in the latter cases, to an octahedral coordination of the zinc or iron cation by three ligands.

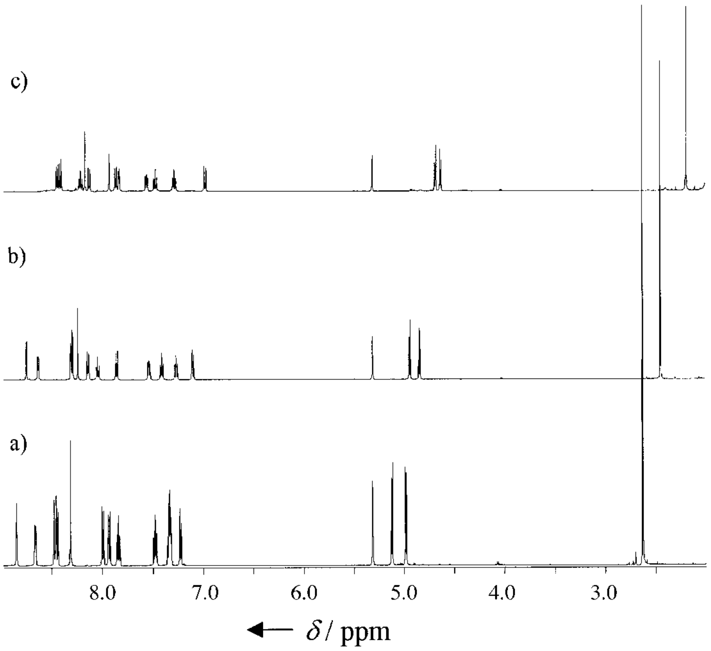

Figure 2. ^1H NMR spectra (500.1 MHz, 300 K, CD_2Cl_2/CD_3CN) of a) (S_a)-**1a**, b) (S_a)-**1a** + 1 equiv $[Ag(CH_3CN)_2]BF_4$, and c) 3 equiv (S_a)-**1a** + 2 equiv $Zn(BF_4)_2$.

In addition, the spectra, which were identical for both enantiomers (R_a)-**1a** and (S_a)-**1a**, clearly reveal that the C_2 symmetry of the ligand remained in the bis- and tris(bipyridine) complexes. Thus, the formation of dinuclear species with two differently configured metal centers can be definitely excluded because the spectra would be more complicated in this case, as the ligand would lose its symmetry.[20] Hence, on the basis of the ^1H and ^{13}C NMR spectroscopic analysis, the number of diastereomers present in solution can be narrowed down to two D_2-symmetric diastereomers with either Λ,Λ- or Δ,Δ-configured metal centers. The spectra even seem to suggest that only one of these diastereomers is present, because it is unlikely that all proton and carbon resonance signals would have the same chemical shift for both diastereomers.

The stoichiometries of the complexes could be demonstrated by ESI–MS, in which we only found signals with the expected isotope patterns for the desired dinuclear complexes and their fragmentation products, as shown in Figure 3 for the zinc complex.[21]

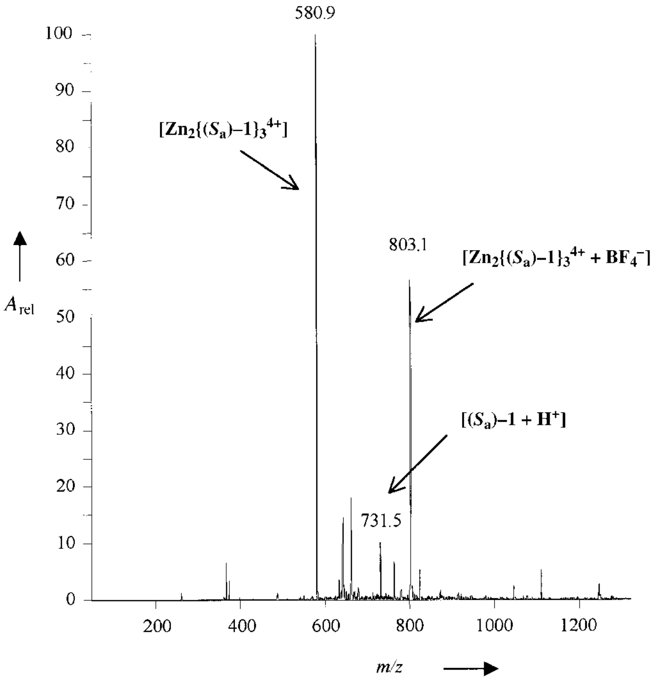

Figure 3. Positive-ion ESI mass spectrum of $[Zn_2\{(S_a)\text{-}\mathbf{1a}\}_3]^{4+}\cdot 4BF_4^-$.

As the analysis of the NMR spectroscopic experiments suggested that there should be a fast exchange of the ligands on the NMR timescale in the case of the copper(I) and the iron(II) complexes but a slow exchange in the case of the silver(I) and zinc(II) coordination compounds, further ESI–MS experiments were performed to investigate the ligand-exchange behavior. Therefore, we prepared the racemic bis(bipyridine) ligands **1b** and **1c** in which the MOM-groups of **1a** are substituted by methyl (**1b**) or deuterated methyl groups (**1c**). By mixing preformed complexes of **1b** and **1c** we corroborated our assumptions, by observing an almost immediate exchange in the case of the copper(I) complex, as demonstrated by the formation of a mixed $[Cu_2(\mathbf{1b})(\mathbf{1c})]^{2+}$ complex; no ligand exchange was observed in the case of the silver(I) or the zinc(II) complexes, even after longer mixing times.[22]

Unfortunately, CD (circular dichroism) spectroscopic measurements did not allow a definite assignment of the stereochemistry of the newly formed stereogenic metal centers because the most important region of the spectra in this respect[4, 5] (about 320–350 nm) is dominated by signals arising from the BINOL part of **1a** or its complexes. Also, sel-1D-NOESY NMR spectroscopic experiments did not help to reveal the stereochemistry, probably because the complexes are in a mass range in which no NOE contacts can be observed. We therefore performed sel-1D-ROESY NMR spectroscopic experiments on the $[Ag_2\{(S_a)\text{-}\mathbf{1a}\}_2]^{2+}$ and the $[Zn_2\{(S_a)\text{-}\mathbf{1a}\}_3]^{4+}$ complexes. These experiments gave initial indications that the stereogenic metal centers are Δ-configured in these cases, because ROE contacts could be observed between the bipyridine and the BINOL fragments of the ligand, which gave us the relative orientation of these two fragments and hence the stereochemistry of the newly formed tetrahedral or octahedral metal-coordination complexes.[22]

However, as ROESY measurements are more prone to misleading artifacts such as COSY or TOCSY signals, and because the ROE signals were only small—as expected from the minimum distance between these parts of about 4.5 Å—we wanted further evidence for this assignment. We finally obtained suitable crystals of the $[Zn_2\{(S_a)\text{-}\mathbf{1a}\}_3](BF_4)_4$ complex from THF/*n*-hexane/acetonitrile to perform an X-ray structural analysis[23] (Figure 4). This analysis showed unambiguously that the desired discrete dinuclear complex was formed and adopts a structure in which both octahedral metal centers are Δ configured, which thus gives rise to an overall D_3-symmetric *P*-configured triple-stranded helicate.

All these results lead to the conclusion that the configuration of the newly formed stereogenic metal centers is fully controlled by the configuration of the BINOL group. Further evidence for this configuration was obtained from NMR spectroscopic experiments on complexes obtained from racemic **1a**, which gave spectra that were virtually identical to those of the enantiomerically pure compounds; this similarity indicates that each ligand forms only homoleptic, diastereomerically pure complexes.[22] These complexes have well-defined chiral cavities with internal functionalities, which we are attempting to exploit in molecular-recognition studies.

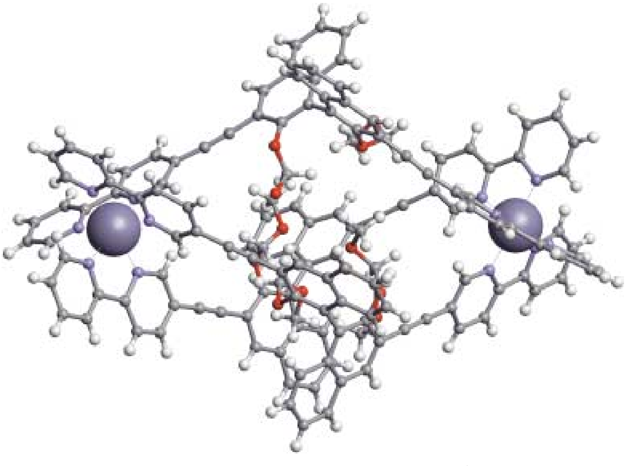

Figure 4. Crystal structure of $(\Delta,\Delta)\text{-}[Zn_2\{(S_a)\text{-}\mathbf{1a}\}_3]^{4+}$ (counterions and solvent molecules omitted).

Experimental Section

1a: M.p. 213 °C; (S_a)-**1a**: $[\alpha]_D^{20} = +333°$ ($c = 1.01$, THF); (R_a)-**1a**: $[\alpha]_D^{20} = -327°$ ($c = 0.99$, THF); ^1H and ^{13}C NMR spectroscopic data see Supporting Information; MS (CI, isobutane): *m/z* 731.9 (100 %); UV/Vis: $\lambda_{max}(\varepsilon) = 242$ (65 500), 332 nm (79 000); elemental analysis (%) calcd for $C_{48}H_{34}N_4O_4$: C 78.89, H 4.69, N 7.67; found: C 78.83, H 4.68, N 7.46 ((S_a)-**1a**); C 78.23, H 4.65, N 7.66 ((R_a)-**1a**).

$(\Delta,\Delta)\text{-}[Ag_2\{(S_a)\text{-}\mathbf{1a}\}_2](BF_4)_2$: M.p. 160–163 °C (decomp.); $[\alpha]_D^{20} = +269°$ ($c = 0.9$, CH_2Cl_2/CH_3CN 3/1); ^1H and ^{13}C NMR data see Supporting Information; MS (ESI): *m/z* (%): 839.4 ($[Ag_2(\mathbf{1a})_2]^{2+}$, $[Ag(\mathbf{1a})]^+$, 1/2 ratio, 100), 731.5 ($[\mathbf{1a}+H]^+$, 35), 1764.3 ($[Ag_2(\mathbf{1a})_2{}^{2+}+BF_4{}^-]$, 3); elemental analysis (%) calcd for $C_{96}H_{48}B_2F_8N_8O_8Ag_2$: C 62.29, H 3.70, N 6.05; found: C 62.04, H 3.96, N 6.06.

$(\Delta,\Delta)\text{-}[Zn_2\{(S_a)\text{-}\mathbf{1a}\}_3](BF_4)_4$: M.p. > 300 °C (decomp.); $[\alpha]_D^{20} = -1373°$ ($c = 0.70$, CH_2Cl_2/CH_3CN 3/1); ^1H and ^{13}C NMR data see Supporting Information; MS (ESI): *m/z* (%): 580.9 ($[Zn_2(\mathbf{1a})_3]^{4+}$, 100), 803.1 ($[Zn_2(\mathbf{1a})_3{}^{4+}+BF_4{}^-]$, 55), 731.5 ($[\mathbf{1a}+H]^+$, 10); elemental analysis (%; perchlorate complex $[Zn_2\{(S_a)\text{-}\mathbf{1a}\}_3](ClO_4)_4$) calcd for $C_{144}H_{102}Cl_4N_{12}O_{28}\text{-}Zn_2 \cdot 4H_2O$: C 61.92, H 3.97, N 6.02; found: C 61.87, H 3.88, N 6.04.

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[18] Use of other phosphane ligands in the Sonogashira coupling reaction gave only unsatisfactory yields.

[19] NMR spectra were recorded on a Bruker Avance 500 at 300 K. Signals were assigned according to ^{1}H, ^{13}C, H,H-COSY, HMQC, and HMBC experiments (17 mM initial concentration of **1a**).

[20] This diastereomer can be described as a kind of *meso*-form. However, this description is not quite correct as the complex remains chiral because of the axial chirality of the BINOL. In fact, this complex is less symmetric (C_2) than the other two D_2-symmetric, helical diastereomers.

[21] ESI–MS spectra of dichloromethane/acetonitrile solutions (5×10^{-4} mM concentration of **1a**, **1b**, or **1c**) were recorded on a Thermo Finnigan LCQ.

[22] See Supporting Information for further details.

[23] Crystal structure of (Δ,Δ)-[Zn$_2${(S_a)-**1a**}$_3$](BF$_4$)$_4\cdot$2.5THF$\cdot$5CH$_3$CN: STOE-IPDS-diffractometer (Mo$_{K\alpha}$ radiation), $T = 193$ K. Crystal dimensions $= 0.25 \times 0.24 \times 0.17$ mm^3, $C_{164}H_{137}B_4F_{16}N_{17}O_{14.5}Zn_2$; $M_r =$ 3055.89, orthorhombic, space group $P2_12_12_1$, $a = 28.3103(10)$, $b =$ 33.0824(15), $c = 35.7949(14)$ Å, $V = 33525(2)$ Å^3, $Z = 8$, $\rho_{calcd} =$ 1.211 mg m^{-3}, $F(000) = 12640$, $\theta_{max} = 22.47°$, $-30 < h < 30$; $-35 < k < 35$; $-38 < l < 38$, 180110 measured reflections, 43248 independent reflections ($R_{int} = 0.2759$). All non-hydrogen atoms were anisotropically refined and the H atoms were inserted in the calculated positions. 11548 reflections $I > 2\sigma(I)$ and 1776 refined parameters, GOF(F^2) $= 0.786$, final R indices: $R_1 = 0.1067$, $wR_2 = 0.2483$, Flack parameter $x = 0.01(2)$, max./min. residual electron density 0.980/ -0.539 e Å^{-3}. The structures were solved by the direct method (SHELXS-97)[24] and refined on F^2. CCDC-178150 ((Δ,Δ)-[Zn$_2${(S_a)-**1a**}$_3$](BF$_4$)$_4\cdot$2.5THF$\cdot$5CH$_3$CN) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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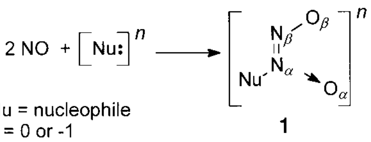
Traube's "Oxazomalonic Acid" is a 3-Hydroxysydnone Carboxylate with an *E*-ONNO Geometry**

Navamoney Arulsamy and D. Scott Bohle*

In his seminal early investigations of the base-mediated condensation of nitric oxide with organic acids,[1–4] Wilhelm Traube prepared an adduct of diethylmalonate, which he formulated as "$ON_2C(CO_2H)_2$" and termed an "oxazomalonic acid".[3] As written, this derivative is formally a conjugated diazotate,[5, 6] and in contrast with the low thermal stability of diazotates, Traube's disodium salt is stable to 343 °C. These observations and much of the organic chemistry of nitric oxide have received scant attention since then, but the discovery of the numerous roles of nitric oxide in biology has renewed interest in this once obscure chemistry.[7] We and others have recently extended many of Traube's original discoveries,[8–12] and one of the universal observations is that the condensation of nitric oxide with nucleophiles returns diazeniumdiolate products **1**, often in high yields and with a *Z* orientation of the two oxygen atoms that flank the newly formed N=N bond (Equation (1)).[9] We have recently reexamined Traube's reaction and his "oxazomalonic" acid product. Herein we report: 1) the product is, in fact, an unusual heterocycle with a five-membered ring and corresponds to the 3-hydroxy-2-carboxysydnone dianion; 2) the synthesis, structure, and spectroscopic analysis of its methyl ester; and 3) theoretical results, which suggest a low-lying transition state for *Z* to *E* isomerization of an initial NO condensation product. Taken together, these results allow the unambiguous characterization of a new diazeniumdiolate with an *E*-ONNO framework.[13]



(1)

The condensation products of nitric oxide and dimethyl malonate depend on the temperature and on the substrate/base stoichiometry (Scheme 1). There are three predominant reactions that account for the observed products: 1) condensation of two nitric oxide molecules, followed by ring closure to give the planar heterocycle 2-carboxy-3-hydroxysydnone (**2**), which was isolated as either a monomethyl ester **2a** or as a dianionic salt **2b,c**; 2) condensation of four nitric oxide molecules and decarboxylation to give the bisdiazeniumdiolate **3**, which was isolated as a tripotassium salt; and 3) one-

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[*] Prof. Dr. D. S. Bohle, Dr. N. Arulsamy
Department of Chemistry, University of Wyoming
Laramie, WY 82071-3838 (USA)
Fax: (+1)307-766-2807
E-mail: Bohle@uwyo.edu

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