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Kit for Unsymmetric Dinucleating Double-Schiff-Base Ligands: Facile Access to a Versatile New Ligand System and Its First Heterobimetallic Copper–Zinc Complex

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The synthetic route toward new unsymmetric compartmental "end-off" Schiff-base ligands in a straightforward two-step reaction of 2,6-diformyl-4-methylphenol and two different amine components is presented. To demonstrate the versatility of this method, we have synthesized two different single-Schiff-base proligands, Hbpahmb and Hphmb, utilizing (2-aminoethyl)bis(2-pyridylmethyl)-amine and (2-aminomethyl)pyridine, respectively. Subsequent reaction with thiosemicarbazide as the second amine component leads to the novel unsymmetric double-Schiff-base ligands {1-[3-[2-[bis(pyridin-2-ylmethyl)amino]ethyliminomethyl]-2-hydroxy-5-methylphenyl]methylidene}hydrazine carbothioamide (H_2bpamptsc) and {1-[3-(pyridin-2-ylmethyliminomethyl)-2-hydroxy-5-methylphenyl]-methylidene}hydrazine carbothioamide (H_2pmptsc). Both ligands provide two distinctly different coordination pockets: a rigid tridentate N,O,S donor set of the hydrazide compartment versus a rather flexible pentadentate (H_2bpamptsc) or tridentate (H_2pmptsc) nitrogen-rich chelating side arm. The reaction of the ligand H_2-bpamptsc with zinc(II) acetate and copper(II) perchlorate yields the heterobinuclear Cu–Zn complex [CuZn(bpamptsc)(μ^2,η^1-OAc)-(MeCN)](ClO_4) (**1**).

For homo- and heterobinuclear active sites found in metalloenzymes, the two metal centers usually reside in chemically distinct binding environments, commonly referred to as site asymmetry at metallobiosites.[1] Differences in the ligand types as well as in the coordination numbers and geometries can contribute to this asymmetry,[2] enabling the two metal centers (even in homobinuclear cases) to perform different tasks in the enzymatic reactions. Therefore, the lack of symmetry of the active center is a very important structural feature of such enzymes and is decisive for the catalytic mechanism. Common examples of unsymmetric binuclear metalloenzymes are the purple acid phosphatases,[3] copper–zinc superoxide dismutase,[4] and the dioxygen carrier hemerythrin.[5]

Therefore, the search for designed unsymmetric binucleating model systems has been an extensive area of research over the last decades. An effective way to obtain such complexes is the application of binucleating ligands providing two chemically different binding compartments.[6] Several approaches have been proposed so far to synthesize such unsymmetric ligands, which utilize multistep synthetic routes usually starting from already unsymmetric bridging units.[7] Probably the most facile route starting from a dicarbonyl-functionalized bridging unit and leading to a double-Schiff-base ligand by successive reaction with two amines is hampered by the fact that this generally results in the formation of considerable amounts of symmetric byproducts, which are usually difficult to separate by conventional chromatography methods utilizing polar silica or alumina gels because of the high polarity of the products. An elegant solution to this problem was suggested by Kahn et al.,[8] where coordinated gadolinium(III) ions are used to protect one of the reactive carbonyl functions. Unfortunately, this approach

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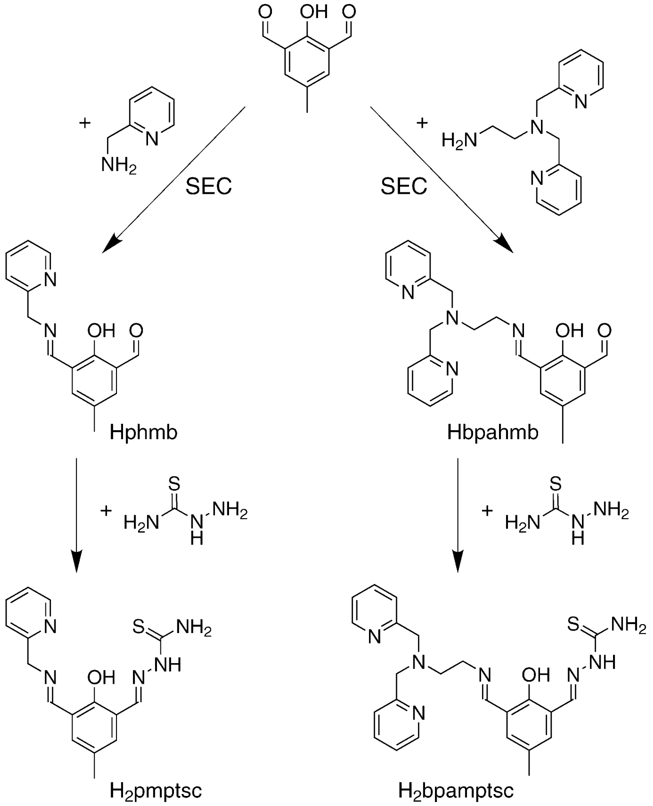
Scheme 1. Synthesis of the Ligands H_2bpamptsc and H_2pmptsc



seems only to work for small-scale reactions and, to the best of our knowledge, did not find any further application. Therefore, a facile access to unsymmetric double-Schiff-base ligands is still lacking.

In this study, we present a straightforward general synthesis of unsymmetric compartmental "end-off" double-Schiff-base ligands via a two-step reaction of the symmetric bridging unit 2,6-diformyl-4-methylphenol with two different primary amines. We also show how such a ligand system can be utilized for the directed synthesis of its first hetero-bimetallic copper−zinc complex.

In the first reaction step, 2,6-diformyl-4-methylphenol[9] was slowly reacted with a small excess (1.1 equiv, to avoid an unreacted diformyl component) of (2-aminoethyl)bis(2-pyridylmethyl)amine[10] or (2-aminomethyl)pyridine in an alcoholic solution at 0 °C (Scheme 1). Size-exclusion chromatography (SEC) was applied in order to separate the symmetric byproducts, and the proligands 3-{2-[bis(pyridin-2-ylmethyl)amino]ethyliminomethyl}-2-hydroxy-5-methylbenzaldehyde (Hbpahmb) and 3-(pyridin-2-ylmethyliminomethyl)-2-hydroxy-5-methylbenzaldehyde (Hphmb) were obtained sufficiently pure and in good yields (>80% and >60%, respectively). The isolated proligands can be reacted with a second primary amine, providing general access to unsymmetric double-Schiff-base ligands. By reaction with thiosemicarbazide, we obtained the ligands {1-[3-[2-[bis(pyridin-2-ylmethyl)amino]ethyliminomethyl]-2-hydroxy-5-methylphenyl]methylidene}hydrazine carbothioamide (H_2-bpamptsc) and {1-[3-(pyridin-2-ylmethyliminomethyl)-2-hydroxy-5-methylphenyl]methylidene}hydrazine carbothioamide (H_2pmptsc) as red solid materials without any further purification. The subsequent reaction of the ligand H_2-bpamptsc with 1 equiv of zinc(II) acetate and copper(II) perchlorate in the presence of 2 equiv of triethylamine in an acetonitrile solution leads to the formation of the dark-green heterobinuclear complex [CuZn(bpamptsc)(μ^2,η^1-OAc)-(MeCN)](ClO_4) (**1**).[11]

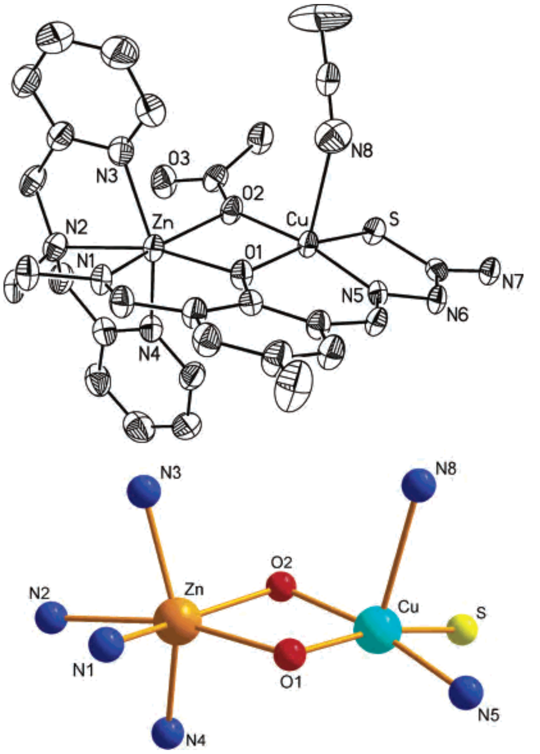


Figure 1. Molecular structure of the complex cation [CuZn(bpamptsc)-(μ^2,η^1-OAc)(MeCN)]$^+$ of **1** (top). Thermal ellipsoids are drawn at the 50% propability level, and hydrogen atoms are omitted. Selected bond distances (pm): Cu−O1 197.0(3), Cu−O2 196.2(3), Cu−N5 194.1(3), Cu−N8 251.3(1), Cu−S 225.2(2), Zn−O1 217.1(3), Zn−O2 210.1(3), Zn−N1 208.4(4), Zn−N2 224.5(3), Zn−N3 215.0(4), Zn−N4 211.1(4). Illustration of the unsymmetric metal coordination environments in **1** (bottom).

The molecular structure of **1** (Figure 1) determined by X-ray diffraction reveals the complexation of two metal ions per ligand molecule.[12] The isotopic pattern of the *m*/*z* 647 signal in the electrospray ionization (ESI) mass spectrum of **1** is in excellent agreement with the calculated pattern of a [CuZn(bpamptsc)(OAc)]$^+$ cation, confirming the heterobimetallic character of **1**. The two ligand compartments provide dissimilar coordination environments and, thereby, induce simultaneously donor set and coordination number asym-

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(11) Analytical data for **1**. Anal. Calcd for $C_{28}H_{33}ClCuN_8O_8SZn$ (M = 806.04): C, 41.72; H, 4.13; N, 13.90; S, 3.98. Found: C, 41.74; H, 4.15; N, 13.85; S, 3.88. IR (KBr, cm^{-1}): 3172 (N−H), 1650 (C=N). UV/vis (MeCN): λ_{max} (ϵ, L mol^{-1} cm^{-3}) 252 (24 200), 321 (14 400), 393 (13 300), 567 (170) nm. MS (micro-ESI in methanol): *m*/*z* 604 (100%, [CuZn(bpamptsc)(μ-OH)]$^+$), 618 ([CuZn(bpamptsc)(μ-OMe)]$^+$), 646 ([CuZn(bpamptsc)(μ-OAc)]$^+$). ***Caution!*** *Perchlorate salts of metal complexes with organic ligands are potentially explosive and should be handled in small quantities and with care.*

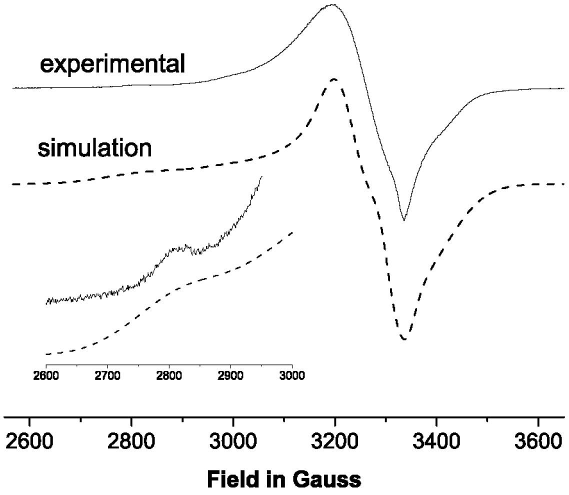

Figure 2. X-band EPR spectrum of **1** in a frozen acetonitrile solution at 3.7 K (solid line) and simulation (dashed line; see the text for parameters). The inset shows the magnified feature at 2800 G.

metry for the two different metal sites in **1**, leading to different coordination geometries for both metal ions (Figure 1). The metal centers are bridged by the phenolate oxygen atom O1 and one μ^2,η^1-bridging acetate ion. The copper(II) ion is placed in the rigid, tridentate pocket generated by the sulfur-rich side arm of the ligand. This assembles a tetragonal [NO_2S] coordination plane with one long Cu−S bond (225 pm). A weekly bound acetonitrile molecule (Cu−N8 251 pm) at the apical position completes the [N_2O_2S] donor set with a distorted square-pyramidal geometry. The zinc(II) ion is coordinated in the more flexible, pentadentate pocket of the supporting ligand given by the nitrogen-rich side arm, leading to a [N_4O_2] donor set with a strongly distorted octahedral coordination environment indicated by trans angles ranging from 151° (N3−Zn−N4) to 163° (O1−Zn−N2). It is important to note here that the structural parameters of the two metal sides are consistent with the assignment of the two different metal ions, not leaving any ambiguity.

An X-band electron paramagnetic resonance (EPR) study on a frozen acetonitrile solution of **1** (Figure 2) reveals a rhombic spectrum, which can be simulated[13] quite nicely using the following parameter sets: $g_x = 2.065$, $g_y = 2.130$, and $g_z = 2.228$ and $A_x = 10$, $A_y = 10$, and $A_z = 180 \times 10^{-4}$ cm^{-1}. These values as well as the rhombic symmetry of the spectrum are in excellent agreement with those found for other compounds with a copper(II) ion placed in a distorted square-pyramidal coordination environment with a [$N_{3-n}O_nS$] basal plane and a $d_{x^2-y^2}$ ground state,[14,15] confirming the crystallographic assignment of the metal ions in the present complex. This is corroborated by the electronic spectrum of an acetonitrile solution of **1**, which shows a broad d−d transition band at 567 nm with a shoulder around 720 nm, which is in good agreement with a distorted square-planar copper(II) site with a $d_{x^2-y^2}$ ground state.[15,16]

In conclusion, we presented a simple, straightforward, and versatile synthetic access toward unsymmetric “end-off” double-Schiff-base ligands. The method is based on the stepwise Schiff-base formation utilizing a symmetric dicarbonyl bridge and two primary amines. The key step is the first Schiff-base reaction and the subsequent separation of the resulting monocarbonyl proligand by SEC. The second step, the reaction of the isolated proligand with a second amine, yields the unsymmetric ligand without further purification. In principle, our synthetic approach should be applicable to any combination of dicarbonyl and amine components capable of Schiff-base formation and, therefore, opens a simple way to a large variety of new and interesting ligands and their metal complexes. This variety can be even further extended if the obtained Schiff-base ligands are reduced to their corresponding unsymmetric amine analogues. As a proof of concept, the first heterobimetallic complex **1** of the biorelevant metal combination copper and zinc with the new unsymmetric double-Schiff-base ligand H_2bpamptsc was prepared by a directed synthesis, promising a rich chemistry associated with this system and beyond.

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Supporting Information Available: Experimental details for Hbpahmb, Hphmb, H_2bpamptsc, H_2pmptsc, and **1**; synthesis and ^{1}H NMR data of the symmetric byproducts 2,6-bis{2-[bis(pyridin-2-ylmethyl)amino]ethyliminomethyl}-4-methylphenol and 2,6-bis-[pyridin-2-ylmethyliminomethyl]-4-methylphenol; selected bond angles and electronic spectrum of **1**; measured and calculated MS signal of [CuZn(bpamptsc)(OAc)]$^+$; and experimental details for the crystallographic study in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Crystallographic data for **1**: $C_{28}H_{33}ClCuN_8O_8SZn$, $M = 806.04$ g mol^{-1}, green-brown prism, size $0.5 \times 0.5 \times 0.4$ mm^3, monoclinic, space group $P2_1/n$, $a = 13.1711(3)$ Å, $b = 14.7432(7)$ Å, $c = 17.2400(7)$ Å, $\beta = 93.042(2)°$, $V = 3343.0(2)$ Å^3, $Z = 4$, $T = 183(2)$ K, $\rho_{\mathrm{calcd}} = 1.602$ g cm^{-3}, $\mu = 1.557$ mm^{-1}, 23 395 reflections, $1.90° \leq \theta \leq 27.48°$, 7625 independent reflections, $R_{\mathrm{int}} = 0.052$, 5499 reflections with $I \geq 2\sigma(I)$, 444 parameters, R1 = 0.055 (observed), wR2 = 0.145 (all data), GOF = 1.045. Crystallographic data can be obtained free of charge as CCDC-633833 from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or 12 Union Road, Cambridge CB2 1EZ, U.K.

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