Chirality Transfer

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Effective Chirogenesis in a Bis(metallosalphen) Complex through Host–Guest Binding with Carboxylic Acids**

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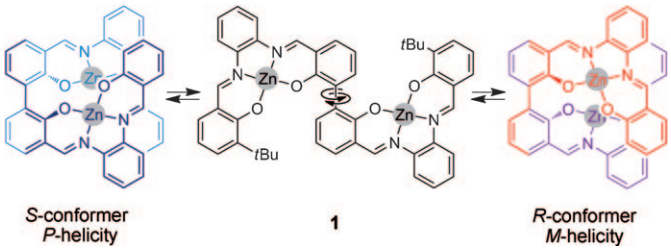
Transfer of chiral information through supramolecular interactions (chirogenesis) has been observed in many natural systems including DNA and proteins,[1] and is nowadays widely used in the development of smart artificial and biomimetic materials.[2] The induction of chirality in bis(metalloporphyrins) for example, has been successfully applied in assigning the absolute configuration of amines,[3] diamines and aminoamides,[4] aminoalcohols and epoxyalcohols,[5] and diols[6] by using a circular dichroism (CD) protocol.[7] Effective chirality transfer with carboxylic acids, however, has proven to be highly difficult, and has only been achieved by using potassium carboxylate salts followed by tedious extractions,[8] or by the addition of a huge excess of substrate to a metal-free host.[9] The low efficiency of chiral induction with these previous methods is mainly due to the relatively weak host–guest interactions with carboxylic acid groups. To overcome this problem, we have designed a bis[Zn^{2+}(salphen)] complex **1** (salphen = *N*,*N*′-phenylenebis(salicylimine)), which, similar to 2,2′-biphenol units,[10] exists in dynamic equilibrium between two chiral conformations (*S* and *R* enantiomers; see Scheme 1). We reasoned that the energy barrier of rotation increases upon binding of a ditopic ligand to the Lewis acidic Zn^{2+} centers.[11,12] Herein, we demonstrate that **1** binds very strongly with acetic acid and that axial chirality can be effectively induced by exchange for chiral α-substituted carboxylic acids, with the practical advantage that substrate derivatization or use of excessive substrate is not required.

Compound **1** was prepared in a single step by reaction of a bis(salicylaldehyde) molecule with two equivalents of a monoimine precursor and $Zn(OAc)_2$ in the presence of pyridine. Subsequent precipitation from MeOH afforded the product in excellent yield (73%) and purity (see the Supporting Information). Characterization by NMR spectroscopy indicated the presence of one equivalent of acetic acid,[13] which had formed as a by-product in the synthesis. Slow evaporation of a solution of the product in toluene/MeCN 1:1 resulted in single crystals suitable for X-ray analysis (Figure 1).[14] The solid-state structure revealed that the two Zn^{2+} centers of **1** are bridged by AcOH (through the oxygen atoms of the carboxylic acid unit) to give a complex with 1:1 stoichiometry (**1**⊃AcOH). As anticipated, both the *S* and the *R* conformer were present in a 1:1 ratio in the unit cell; each conformer has the same dihedral angle (44.9°) and Zn–O(acetate) distance (2.01 Å). This distance is identical to that previously found in a related acetate-bridged complex.[13] Since the exact position of the acidic proton of AcOH could not be resolved by X-ray diffraction, the proton was placed in



Scheme 1. Conformational isomerism of **1**. The *t*Bu groups are omitted for clarity in the line drawings of the conformers. *P* denotes right-handedness and *M* left-handedness.

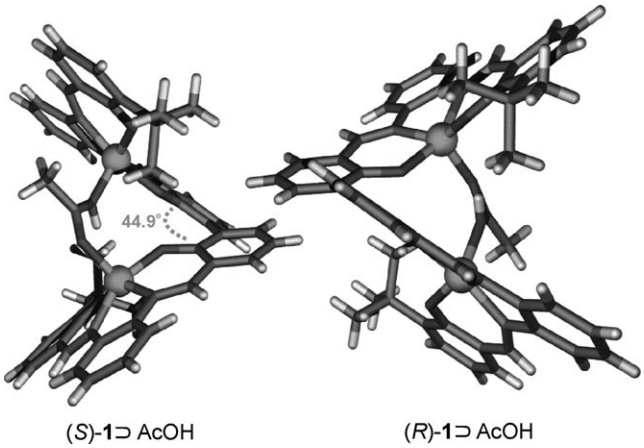


Figure 1. Solid-state structure of **1**⊃AcOH showing the chemically equivalent *S* and *R* conformers. Solvent molecules are omitted for clarity.

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an idealized position before refinement. Further DFT optimization using the B3P86 level of theory demonstrated that the most favorable location of this proton is between the biphenolic oxygen atoms of **1** (see the Supporting Information).[15] This binding motif is therefore able to assist in the stabilization of **1**⊃AcOH and hence the host–guest complexation of acetic acid with **1** resembles the binding of an acetate molecule.

A range of 1D and 2D ^{1}H NMR experiments (COSY, NOESY, ROESY, GOESY) in a noncoordinating solvent (CD_2Cl_2) confirmed that the structure of **1**⊃AcOH is retained in solution. The most significant NOE correlations are that between the *t*Bu group of **1** and the methyl group of AcOH, and those between the *t*Bu group and opposing aryl and imine protons (see the Supporting Information). When an excess of pyridine was added to the sample, competition with AcOH binding results in disruption of the **1**⊃AcOH complex. This disruption is accompanied by a large bathochromic shift of the absorption maximum (λ_{max}: 390→420 nm), and this change allowed the stability constant to be calculated by competitive titration experiments. Even though pyridine is known to bind very strongly to the Zn^{2+} ion in salphen complexes,[11] complete dissociation could only be realized beyond the addition of approximately 1000 equivalents of pyridine. Multivariate analysis of this titration data provided a very high association constant for **1**⊃AcOH ($K_a = 3.8 \times 10^{10}\,M^{-1}$; see the Supporting Information).

When one equivalent of a competing carboxylic acid (propionic acid) was added to a sample of **1**⊃AcOH in CD_2Cl_2, fast exchange was noted on the NMR timescale, without significant alterations in the chemical shifts of **1**. At lower temperatures, the exchange rate was reduced, and both AcOH and propionic acid containing complexes were observed individually in a 4:1 ratio (see the Supporting Information). We then used optically pure 2-phenylpropionic acid **2** as guest and measured the CD spectra of **1**⊃AcOH in the presence of 0–20 equivalents of **2** (see Figure 2). The CD spectrum of **1**⊃AcOH alone was silent because of the presence of equimolar amounts of (*S*)-**1** and (*R*)-**1**. Addition of (*S*)-**2** however, induced a negative first and second Cotton effect, whereas addition of (*R*)-**2** resulted in mirror-image (that is, positive) signals. A negative first Cotton effect stems from a counterclockwise coupling of electronic transitions and corresponds to *M* helicity.[7,10] It is therefore presumed that host–guest binding with (*S*)-**2** stimulates predominant formation of the *R* conformer of **1** (that is, more (*R*)-**1**⊃(*S*)-**2** than (*S*)-**1**⊃(*S*)-**2**) and the inverse for (*R*)-**2**. After the addition of 10 equivalents of substrate, virtually no further increase in molar ellipticity ($\Delta\varepsilon$) was noted, which indicates full replacement of AcOH by **2**. The corresponding UV/Vis spectra remained unchanged.

Single crystals of **1**⊃(*S*)-**2** were obtained by partial evaporation of a solution of **1**⊃AcOH with 10 equivalents of (*S*)-**2** in CH_2Cl_2/MeCN 1:1, followed by cooling to −30 °C. The molecular structure (see Figure 3)[16] showed the presence of both diastereoisomers in a 1:1 ratio in the unit cell. Comparison of these isomers revealed significant structural differences, such as a smaller dihedral angle and a larger distance of the phenyl substituent to the salphen plane in the

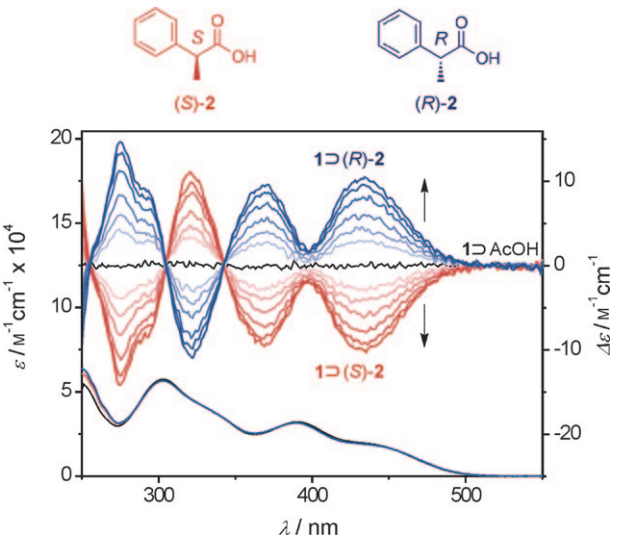


Figure 2. CD spectra (right-hand *y* axis) of **1**⊃AcOH in CH_2Cl_2 (2×10^{-5} M) upon addition of 0.5, 1, 2, 5, 10, and 20 equivalents of (*S*)-**2** and (*R*)-**2**, and corresponding UV/Vis absorption spectra (left-hand *y* axis) before and after addition of 10 equivalents of **2**. Spectra were measured at room temperature.

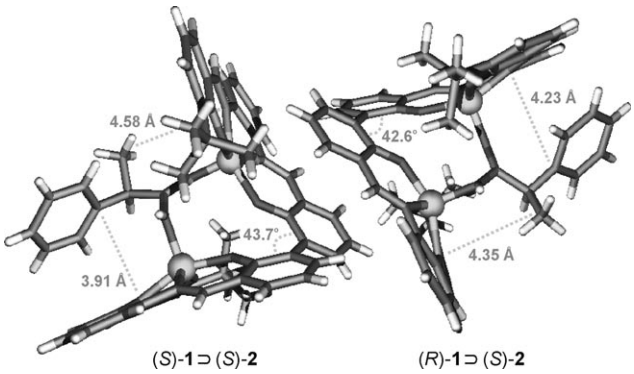


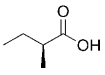
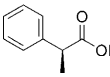
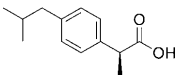
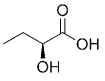
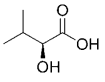
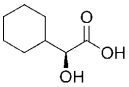
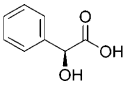
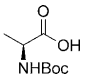
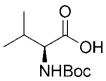
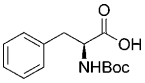
Figure 3. X-ray crystal structure of **1**⊃(*S*)-**2**; the two diastereoisomers are present in the unit cell. Dotted lines denote both the dihedral angles and the distances between the α-carbon and the nearest nitrogen atom. Solvent molecules are omitted for clarity.

case of (*R*)-**1**⊃(*S*)-**2**. This difference results from a more efficient distribution of the α substituents of (*S*)-**2** in the *R* conformer, and leads to less steric crowding compared to (*S*)-**1**⊃(*S*)-**2**. Single-point DFT calculations (single-point B3P86) were then carried out to determine the energy of the structures that were found in the solid state. These calculations clearly showed that host–guest binding of (*S*)-**2** with the *R* conformer is energetically more favorable by 1.88 kcal mol^{-1} than binding with the *S* conformer. Preferential diastereoisomer formation was also observed in solution by ^{1}H NMR spectroscopy (see the Supporting Information) and the 1:1 crystallization of both conformers is therefore ascribed to a preferred pairwise packing arrangement. Based on the negative first Cotton effect in the CD spectrum, it was already expected that (*S*)-**2** induces the *R* conformer of **1**, and the DFT analysis further supports the observation that (*R*)-**1**⊃(*S*)-**2** is indeed the most stable diastereoisomer.

Addition of other *S*-configured carboxylic acids to **1**⊃AcOH gave CD signals identical to those observed with (*S*)-**2** (the main absorptions are given in Table 1). In general, the signal amplitude could be directly related to the size of substituents at the α position. In addition to steric effects, the signal amplitude also can depend on the acid-exchange equilibrium, which is reflected in the relatively low $\Delta\varepsilon$ value of mandelic acid and Boc-protected phenylalanine. This low value is assumed to result from a lower binding affinity for **1**, although the larger distance between the steric bulk and the chiral center in phenylalanine may also play a role. Furthermore, the first Cotton effect for the methyl-substituted acids was larger than the second Cotton effect, whereas the reverse effect was observed for the hydroxy-substituted acids and the Boc-protected amino acids. It is possible that the latter two acids have a different binding mode because of hydrogen bonding with the phenolic oxygen atoms of **1**.

In summary, we have presented an accessible biphenol-based bis[Zn^{2+}(salphen)] complex, which exists in an equilibrium between two chiral conformations that interconvert by axial rotation, and forms strong host–guest complexes with carboxylic acids. One of the conformations could be effectively induced at ambient temperature and micromolar concentrations by addition of a chiral acid; no further derivatization of the substrate was required. The resulting CD signal of the complexes relates to the chirality of the substrate, thus allowing for a practical use of this system in assignments of absolute configurations. Further work on this and other applications in areas such as supramolecular enantioselective catalysis, chiral recognition, and molecular devices (switches) is currently in progress.

Table 1: Acid-induced CD effects.[a]

Acid	Structure	λ [nm]	Δε [$M^{-1}cm^{-1}$]
(*S*)-methylbutyric acid		437	−2.9
		366	−2.1
		320	+3.0
(*S*)-2-phenylpropionic acid **2**		439	−7.2
		371	−6.6
		323	+7.3
(*S*)-ibuprofen		433	−7.3
		371	−6.5
		322	+7.4
(*S*)-2-hydroxybutyric acid		429	−5.4
		369	−6.4
		319	+6.0
(*S*)-2-hydroxy-3-methylbutyric acid		432	−6.8
		370	−8.0
		321	+7.5
(*S*)-hexahydromandelic acid		436	−10.7
		370	−12.7
		322	+12.3
(*S*)-mandelic acid		428	−2.6
		369	−3.3
		318	+2.7
Boc-L-alanine		425	−3.7
		368	−5.2
		323	+3.8
Boc-L-valine		424	−4.7
		367	−6.9
		321	+5.4
Boc-L-phenylalanine		432	−3.4
		369	−3.4
		322	+4.2

[a] Measured after addition 10 equivalents of acid to **1**⊃AcOH (2×10^{-5} M) in CH_2Cl_2 containing 0.1% diisopropylethylamine (v/v).[17] Boc = *tert*-butoxycarbonyl.

Experimental Section

Synthesis of bis[Zn^{2+}(salphen)] 1⊃AcOH: 3,3′-diformyl-2,2′-dihydroxy-1,1′-biphenyl (41 mg, 0.17 mmol) and the monoimine precursor (98 mg, 0.37 mmol) based on 3-*tert*-butylsalicylaldehyde and 1,2-phenylenediamine were dissolved in CH_2Cl_2 (4 mL) and the resulting yellow solution was stirred at room temperature. A solution of $Zn(OAc)_2{\cdot}2H_2O$ in MeOH (2 mL) and pyridine (1 mL) was then added dropwise to the stirred solution. The color of the solution slowly turned orange and the solvent was removed in vacuo after 2 h. After five repetitive dissolution/evaporation sequences using MeOH to remove residual pyridine, an orange precipitate was obtained, which was filtered, washed thoroughly with MeOH, and air-dried to give an orange solid; yield: 115 mg (73%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 11.93$ (br, 1H, CO_2H), 9.00 (s, 2H, CHN), 8.91 (s, 2H, CHN), 7.97 (dd, $J = 1.78$, 7.14 Hz, 2H, ArH), 7.85 (m, 4H, ArH), 7.36 (m, 6H, ArH), 7.24 (dd, $J = 1.36$, 7.80 Hz, 2H, ArH), 7.20 (dd, $J = 1.32$, 7.32 Hz, 2H, ArH), 6.61 (t, $J = 7.50$ Hz, 2H, ArH), 6.42 (t, $J = 7.52$ Hz, 2H, ArH), 1.90 (s, 3H, CH_3), 1.44 ppm (s, 18H, *t*Bu), see the Supporting Information for full assignment; ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 171.8$, 170.2 (CO), 162.9 (two overlapping peaks) (CHN), 141.5, 139.7 (two overlapping peaks), 137.3, 134.5, 134.4, 130.2, 130.2, 126.9, 126.8, 119.5, 119.4, 116.3, 116.2, 112.5, 112.1 (ArC), 34.9 ($C(CH_3)_3$), 29.6 ($C(CH_3)_3$), 21.1 ppm (CH_3CO_2H), no signal observed for CH_3CO_2H; MALDI(+)-MS: *m*/*z* 868.0 [M^+−AcOH]; elemental analysis calcd (%) for $C_{50}H_{46}N_4O_6Zn_2$: C 64.60, H 4.99, N 6.03; found: C 64.26, H 4.98, N 6.01.

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[13] Although we recently reported that acetate anions can bind through their oxygen atoms as a ditopic ligand between two mono[Zn^{2+}(salphen)] complexes, interaction with formally neutral AcOH ligands has not been observed to date. See: S. J. Wezenberg, E. C. Escudero-Adán, J. Benet-Buchholz, A. W. Kleij, *Chem. Eur. J.* **2009**, *15*, 5695.

[14] Crystallographic data for **1**⊃AcOH·2 CH_3CN·C_7H_8: $C_{61}H_{60}N_6O_6Zn_2$; $M_r = 1103.89$; crystal size $0.40 \times 0.30 \times 0.10\ mm^3$; monoclinic; space group $P2_1/c$; $a = 12.695$, $b = 32.852$, $c = 13.299$ Å; $\alpha = 90°$, $\beta = 110.20°$, $\gamma = 90°$; $V = 5205.286$ Å^3; $Z = 4$; $\rho_{calcd} = 1.409\ mg\,M^{-13}$; $\mu(Mo_{K\alpha}) = 0.981\ mm^{-1}$; $T = 100$ K; $\theta(min/max) = 1.7/36.6°$; 85562 reflections collected; 23651 unique reflections ($R_{int} = 0.080$); refinement method: full-matrix least-squares on F^2; data/restraints/parameters: 23651/1/689; GoF on $F^2 = 1.056$; $R1 = 0.0721$ and $wR2 = 0.1994$ [$I > 2\sigma(I)$]; $R1 = 0.01095$ and $wR2 = 0.2185$ (all data); largest diff. peak and hole: 2.538 and -1.036 e Å^{-3} (CCDC 787737 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.)

[15] Related proton transfer from a 2,2′-biphenol to a chiral diamine to give an anionic biphenol with only one proton between the phenolic oxygen atoms resulted in a significant increase in stability. See reference [10b].

[16] Crystallographic data for **1**⊃(*S*)-**2**·CH_3CN: $C_{59}H_{55}N_5O_6Zn_2$; $M_r = 1060.82$; crystal size $0.10 \times 0.08 \times 0.03\ mm^3$; monoclinic; space group $P2(1)$; $a = 13.1305$ Å, $b = 29.8304$ Å, $c = 13.5930$ Å; $\alpha = 90°$, $\beta = 110.191°$, $\gamma = 90°$; $V = 4997.0$ Å^3; $Z = 4$; $\rho_{calcd} = 1.410\ mg\,M^{-13}$; $\mu(Mo_{K\alpha}) = 1.019\ mm^{-1}$; $T = 100$ K; $\theta(min/max) = 1.60/28.55°$; 85691 reflections collected; 24104 unique reflections ($R_{int} = 0.066$); refinement method: full-matrix least-squares on F^2; data/restraints/parameters: 24104/55/1301; GoF on $F^2 = 1.042$; $R1 = 0.0563$ and $wR2 = 0.1383$ [$I > 2\sigma(I)$]; $R1 = 0.0753$ and $wR2 = 0.1497$ (all data); largest diff. peak and hole: 1.059 and -1.416 e Å^{-3} (CCDC 787738 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.)

[17] In the absence of diisopropylethylamine, slight decomposition of **1** was noted after addition of α-hydroxy-substituted acids. Note that the CD absorption induced by (*S*)-**2** is fairly similar with and without additive.

