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Chiroptical Recognition of Carboxylates with Charge-Neutral Double-Stranded Zinc(II) Helicates

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Dedicated to Professor Klaus Jurkschat on occasion of his 70th birthday.

Chirality analysis of small molecules for the determination of their enantiopurity is nowadays ruled by streamlined chromatographic methods which utilize chiral stationary phases. Chiroptical probes which rely on host–guest interactions are so far overshadowed by the latter but have the benefit of depending only on common spectroscopic techniques such as CD spectroscopy to distinguish enantiomers and to quantify their ratio. Interest into this receptor-based approach is constantly rising because non-invasive high-throughput screenings with a minimal waste production can be performed. In this study we investigate the possibility to utilize metal-based containers in form of charge-neutral helicates able to recognize anions for this purpose. Key building block of the helicates are triazole units which show rotational freedom and give rise to either a *meso*-structure or a racemic mixture of the right- and left-handed complex. A chiroptical response of the probe is observed upon recognition of chiral mono- or dicarboxylates and chirality analysis of tartrate is conducted by CD spectroscopy.

Introduction

Chirality as a property is tightly coupled with all biological forms of life and is found in numerous essential biomolecules like amino acids, nucleotides or metabolites. As a result, it is less surprising that pharmaceutical compounds and agrochemicals exhibit also often chirality because their desired biological activity can be limited to, for example, one of the two enantiomers.[1] Thus, analytical methods to measure the ratio of stereoisomers in samples or synthesized bioactive molecules is of utmost importance. A historically prominent approach for determining the enantiomeric excess is the use of Mosher's acid or the corresponding acid chloride, both chiral derivatizing reagents, which readily reacts with, for example, hydroxyl or amino groups of chiral analytes.[2–5] The resulting diastereomers can then be quantified by simple integration of their corresponding individual NMR signals and allow the determination of the enantiomeric ratio/excess of the converted sample. Nowadays, chiral chromatographical methods like chiral HPLC or SFC (high-performance liquid / supercritical fluid chromatography) are the "gold-standard" for analyzing chiral compounds because of their precision.[6–8] Their success is dated back to the development of the first commercially available chiral stationary phases (CSPs) by Pirkle et al. in 1981 and numerous columns with different CSPs are available for a broad versatility today.[9,10]

However, fast spectroscopic methods offer a handle for chirality analysis in a high-throughput manner or even allow real-time monitoring of the enantiomeric excess during stereoselective reactions.[11–13] Measurements of especially charged chiral targets directly in complex mixtures such as biological samples without prior purification processes can benefit from applying widely available spectroscopic techniques like circular dichroism spectroscopy. Chiral molecules bearing carboxylate functions are particularly interesting in this regard because they are important environmental metabolites, they play essential roles in biological processes and several drugs bear carboxylic acid residues which can exist in their deprotonated form in aqueous solutions at physiological pH.[14–17] Unfortunately, most of these target molecules bear no or not enough chromophores which make them suitable for direct chirality analysis by the use of circular dichroism spectroscopy. Thus, a strong focus on various approaches to tackle this issue for spectroscopy-based chirality analysis of especially monocarboxylates like amino and hydroxy acids is observed.[18–24] A straightforward remedy is often based on, for example, the formation of optically active metal complexes with the analyte acting as a chiral ligand or indicator displacement assays are used.[25–29] Alternatively, optically-active racemic stereo-dynamic receptors of which one form preferentially can bind a specific guest enantiomer are an easy to apply solution for this problem because CD effects arise

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due to the enrichment of the favored host enantiomer upon binding charged or neutral chiral guests.[30–59] Similarly, metal-based propeller-shaped complexes, helicates and some cages are also intrinsically chiral receptors and thus, can act as chiroptical hosts for chiral analytes.[60–77] Several examples focus on chiral guests with one carboxylate residue.[30,35,40,42,49,61,62,68,71–75,77] But, probes with two interconvertible enantiomers for chiroptical recognition of biologically relevant chiral dicarboxylates are rare[30,36,42,57,72] and especially stereodynamic metal-based containers as hosts are severely underrepresented.[76]

We recently developed double-stranded charge-neutral zinc(II) helicates as potent receptors for dicarboxylates showing very tight binding with association constants in the range of $10^5\ M^{-1}$ to $10^8\ M^{-1}$.[78] Our hypothesis is that the receptor qualifies to be an ideal chiroptical probe for mono- and dicarboxylates because of the following two reasons: 1) The strong anion recognition properties and high binding affinities guarantee a more or less quantitative host–guest complex formation which maximizes the enrichment of one of the two enantiomers even without large excess of added guests. This should result in an enhancement of the sensitivity. 2) Binding occurs by coordinative binding events between the carboxylates and the zinc(II) centers which should allow an optimal chiral information transfer from the guest to the optically-active complex units. But, only the *meso*-form, a so called "*meso*-helicate" with opposite complex configurations and an inversion center, was observed in the crystal structure with a dicarboxylate guest so far (Figure 1).[78] If the host–guest complex with dicarboxylates forms only *meso*-structures our aim would be jeopardized because the working hypothesis depends on the existence of a racemic helicate and the enrichment of one enantiomer upon chiral carboxylate binding. However, guest dependent formation of the *meso* as well as the racemic form of a single helicate with different encapsulated anions is reported.[79] We envisioned that the same is true for our system because the ligand backbone of the zinc(II)-based receptor bears triazole units which can rotate. The *anti-anti* conformation gives rise to the *meso*-form found in the crystal structure for the host–guest complex with naphthalene-2,6-dicarboxylate[78] but also the *syn-syn* conformation can exist. The latter results in a less linear backbone which is necessary for the formation of a racemic helicate. Especially, smaller guests are expected to favor the *syn-syn* conformation because of the resulting shorter zinc-zinc distance in case of twisted ligand strands.

In the present work, we successfully demonstrate that charge-neutral zinc(II) complexes involving quinolinate ligand units connected by an aryl-triazole backbone can be applied as probes for chiroptical recognition of carboxylates with the possibility to perform a chirality analysis by CD spectroscopy (Figure 1) because the *syn-syn* conformation indeed gives rise to a helicate with right- and left-handed helicity. Computational investigations of the triazole rotation and the host–guest structure with tartrate as model guest support the experimental findings in solution.

Results and Discussion

Investigation of chiroptical recognition properties

At first, we concentrated our focus on one model guest to investigate the viability of our hypothesis. Tartrate ($\mathbf{TA}^{2-}$) seems to be an ideal guest for this cause because a high binding affinity is expected and a strong enrichment of one of the helicate enantiomers is suggested as a result of the two stereogenic centers.

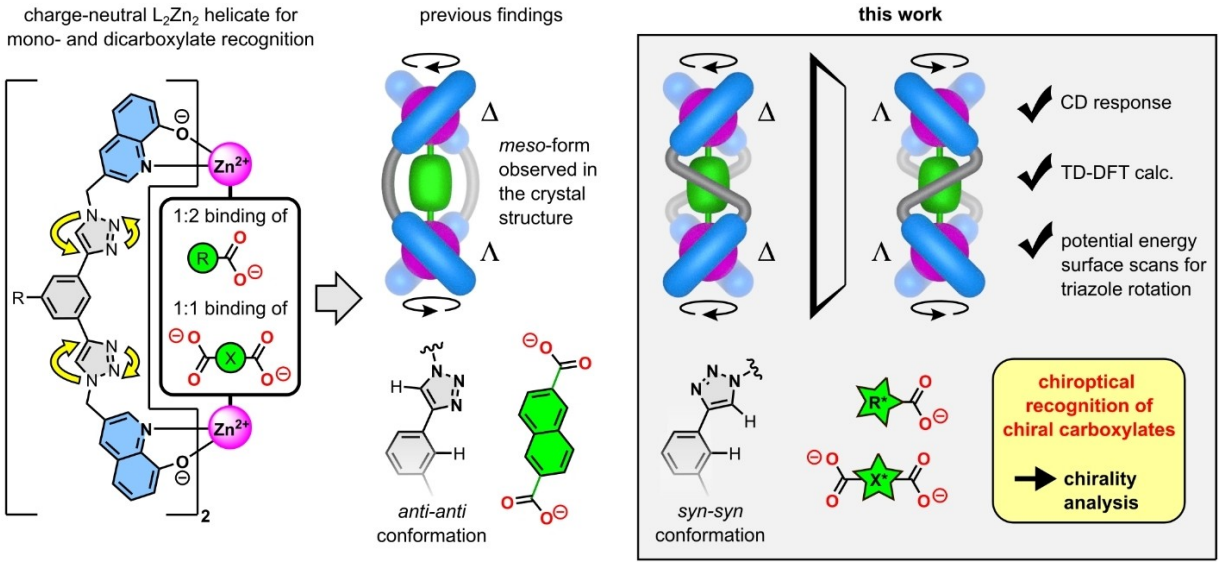


Figure 1. Mono- and dicarboxylate binding with a charge-neutral zinc(II) receptor bearing triazole units in the ligand backbone which can adopt two conformations (*anti-anti* or *syn-syn*). The formation of a *meso*-helicate with an *anti-anti* triazole conformation was found in the crystal structure of the host–guest complex with naphthalene-2,6-dicarboxylate.[78] The *syn-syn* conformation results in the formation of a racemic helicate which was proven by arising CD effects upon binding chiral carboxylates.

Binding of tartrate occurs in a 1:1 fashion (Figure 2a) which is distinctly observed in the ^{1}H NMR titration (Figure 2b) between D-(−)-tartrate (**D-TA**$^{2-}$) as tetrabutylammonium (TBA) salt and the host [$\mathbf{L}^{\mathbf{R}}_2Zn_2$] (grey signals) bearing a diphenylamide solubility group in DMSO-d_6. Quantitative complexation towards the host–guest species [(**D-TA**)@$\mathbf{L}^{\mathbf{R}}_2Zn_2$]$^{2-}$ (red signals) is found around 1.2 equiv. to 1.5 equiv. of added D-(−)-tartrate. A binding constant of (174 000 ± 32 000) M^{-1} was determined by ITC measurements and the value fits well to our expectation and into the observed trend[78] for association constants of aliphatic dicarboxylates. A NOESY spectrum of [(**D-TA**)@$\mathbf{L}^{\mathbf{R}}_2Zn_2$]$^{2-}$ measured after the addition of 5 equiv. D-(−)-tartrate to [$\mathbf{L}^{\mathbf{R}}_2Zn_2$] shows only a through-space coupling signal between the triazole proton (H_g) and the "inner" phenyl proton (H_h) which corresponds to the *syn-syn* triazole conformation. This is indicative for complete transformation of any *meso*-form to a chiral helicate. The triazole units seem not to be able to rotate into the *anti-anti* conformation anymore upon binding tartrate in contrast to the empty helicate [$\mathbf{L}^{\mathbf{R}}_2Zn_2$] which shows both conformations simultaneously in solution. And indeed, a chiroptical response of the system is observed by CD spectroscopy upon addition of D-(−)- or L-(+)-tartrate (Figure 2c) which proves our working hypothesis of this study. **D-TA**$^{2-}$ (Figure 2c, red spectra) gives rise to one negative (308 nm) and two positive cotton effects (350 nm and 420 nm). The latter CD bands match the main absorbance bands of the host–guest complex [(**D-TA**)@$\mathbf{L}^{\mathbf{R}}_2Zn_2$]$^{2-}$ (Figure S34) which originate from the quinolinate zinc complex units. The exact mirror image is obtained by the use of the L-enantiomer **L-TA**$^{2-}$ (Figure 2c, blue spectra), no significant further change of the CD response is observed after the addition of 1 equiv. of guest for both cases which showcases again the high affinity and sensitivity of the receptor.

Unfortunately, we were not able to grow suitable crystals of the host–guest complex with tartrate or any other guest of the study. We know from NMR spectroscopy that the major species

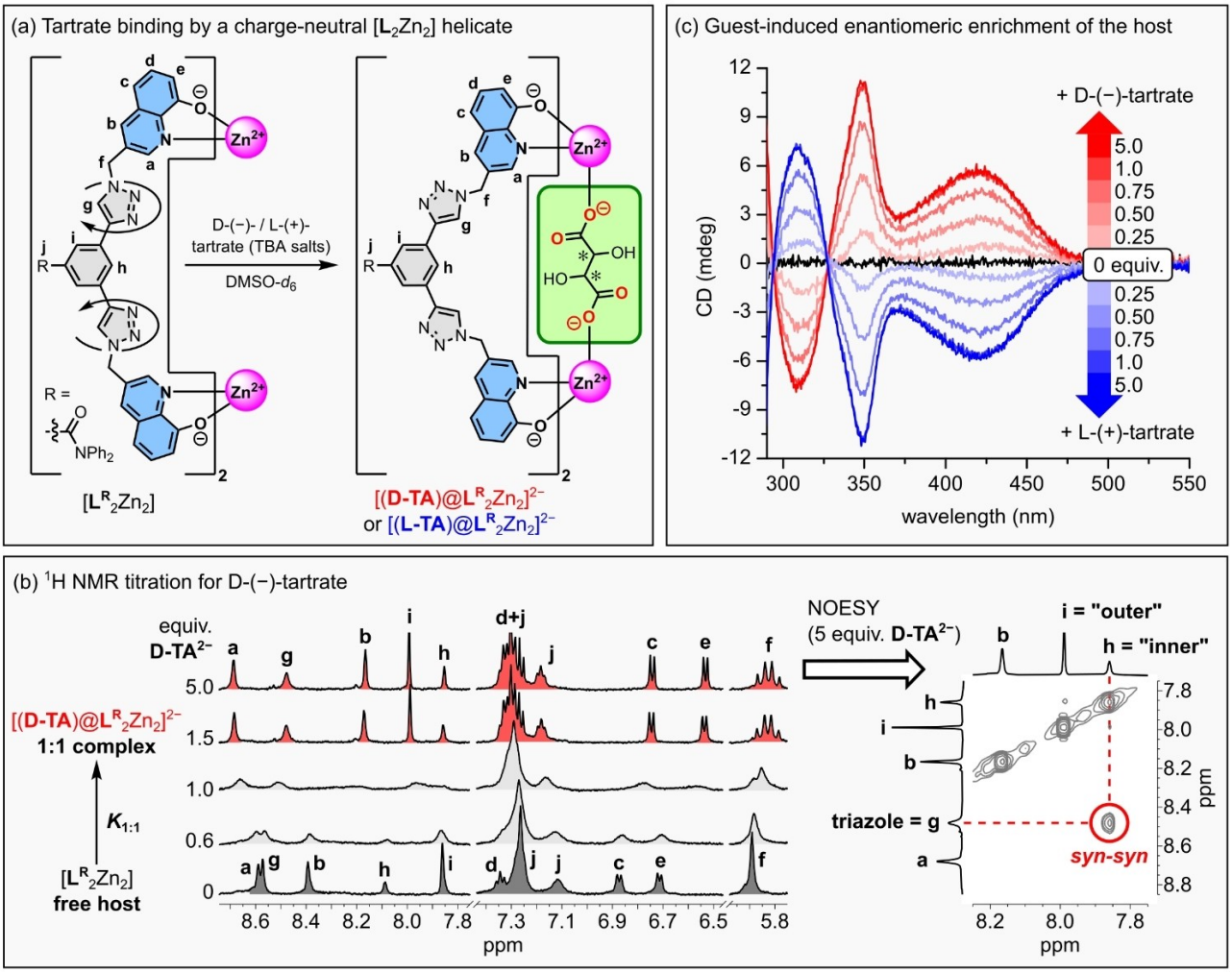


Figure 2. a) Tartrate recognition by the charge-neutral receptor [$\mathbf{L}^{\mathbf{R}}_2Zn_2$]. b) ^{1}H NMR titration (500 MHz, 500 μM, DMSO-d_6, 25 °C) monitoring the recognition event. Binding of D-(−)-tartrate as TBA salt occurs in an intermediate exchange fashion and results in the formation of a 1:1 host–guest complex. NOESY spectrum of the host–guest complex showing exclusively the *syn-syn* triazole conformation. c) CD spectra of [$\mathbf{L}^{\mathbf{R}}_2Zn_2$] (500 μM, l = 2 mm, DMSO-d_6) with varying amounts of D-(−)- and L-(+)-tartrate showing the enrichment of the right- (ΔΔ) and left-handed (ΛΛ) helicate (mirror cotton effects) upon guest binding. The observed cotton effects originate from the quinolinate zinc complex units and match the absorption bands of the host–guest complex [(**D/L-TA**)@$\mathbf{L}^{\mathbf{R}}_2Zn_2$]$^{2-}$ (Figures S34 and S35).

in solution is the helicate with a *syn-syn* conformation of the triazole units in the backbone. Additionally, we can assume that tartrate as a dicarboxylate is bound between the zinc(II) centers of the receptor by forming coordinative bonds which was observed previously for naphthalene-2,6-dicarboxylate in the solid state.[78] With this information in hand we modeled the right- and left-handed enantiomer of the host–guest complex $[(\mathbf{D\text{-}TA})@\mathbf{L^H}_2Zn_2]^{2-}$ and optimized the structures using r^{2}SCAN-3c[80] (ORCA 5.0.2)[81,82] (Figure S45). The choice for using $[\mathbf{L^H}_2Zn_2]$ as host is based on the lower atom count because this complex lacks the diphenylamide solubility groups but still binds D-(−)-tartrate in the same fashion (Figure S25) and shows a comparable CD response (Figure 3a). To verify if the right-handed ΔΔ-$[(\mathbf{D\text{-}TA})@\mathbf{L^H}_2Zn_2]^{2-}$ or left-handed ΛΛ-$[(\mathbf{D\text{-}TA})@\mathbf{L^H}_2Zn_2]^{2-}$ complex is formed with D-(−)-tartrate preferentially we performed TD-DFT calculations (Gaussian16 Rev. B.01)[83] on the optimized structures with BHandHLYP[84]/def2-SVP[85,86] as level of theory and implicit solvation (DMSO) to calculate and compare their respective CD spectrum with the measured one.

The result of the left-handed complex ΛΛ-$[(\mathbf{D\text{-}TA})@\mathbf{L^H}_2Zn_2]^{2-}$ does not fit the experimental observation (Figure S45) and thus, the structure is ruled out. The calculated spectrum of the ΔΔ-$[(\mathbf{D\text{-}TA})@\mathbf{L^H}_2Zn_2]^{2-}$ model (Figure 3a, red) matches clearly the measured spectrum of $[(\mathbf{D\text{-}TA})@\mathbf{L^H}_2Zn_2]^{2-}$ (black) and $[(\mathbf{D\text{-}TA})@\mathbf{L^R}_2Zn_2]^{2-}$ (grey) with an x-axis shift. To clarify this, the calculated spectrum is shifted by 60 nm on the x-axis (red dashes) and the two main positive cotton effects at 350 nm and 420 nm of the measured and calculated spectrum line up perfectly. Additionally, even the relative intensity of the cotton effects are in good agreement so that we can anticipate the formation and enrichment of the right-handed ΔΔ-$[(\mathbf{D\text{-}TA})@\mathbf{L^H}_2Zn_2]^{2-}$ helicate (Figure 3b and c) upon D-(−)-tartrate addition.

The model shows the right-handed upper and lower zinc(II) complex units with $\mathbf{D\text{-}TA}^{2-}$ being bound between the zinc centers and a zigzag orientation of the ligand. The triazole-units of the backbone seem to have some room for a slight rotational movement for which the unusual broad triazole signal (Figure 2b, H_g) is also an indication. To investigate this dynamic effect, we performed relaxed potential energy surface scans of the rotations of all the individual triazole rings in implicit solvent[87] (DMSO) at the ωB97X–D3[88]/def2-SVP[85,86] level of theory starting from the optimized ΔΔ-$[(\mathbf{D\text{-}TA})@\mathbf{L^H}_2Zn_2]^{2-}$ model. The potential energy surface has a shallow minimum around the ideal *syn-syn* conformation (dihedral angle approx. +/−25°), while the *anti-syn* conformation is disfavored by at least 2.5 kcal mol^{-1} (Figure S46). In the *syn-syn* minimum, thermal fluctuations at 300 K allow the triazole rings to freely rotate within a broad range of up to 45°, in line with the broadening of the triazole peak in the NMR spectrum.

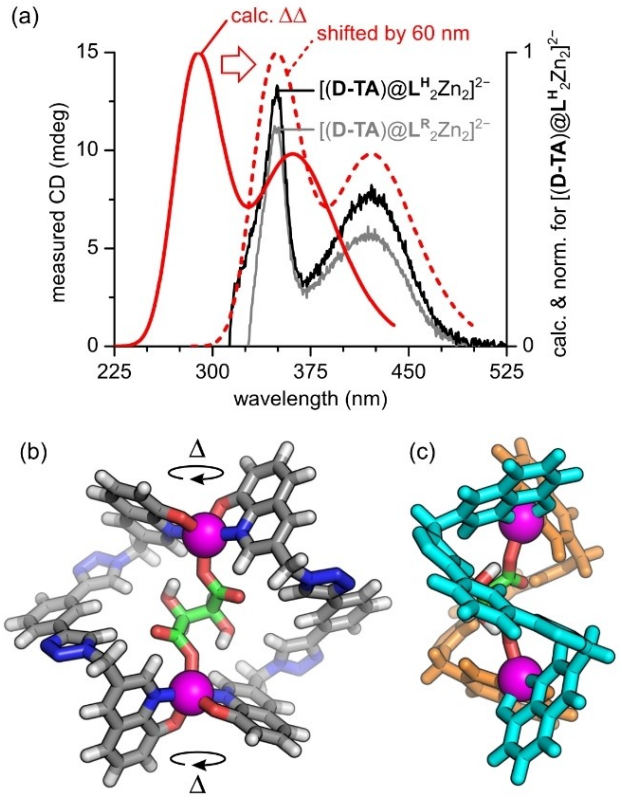
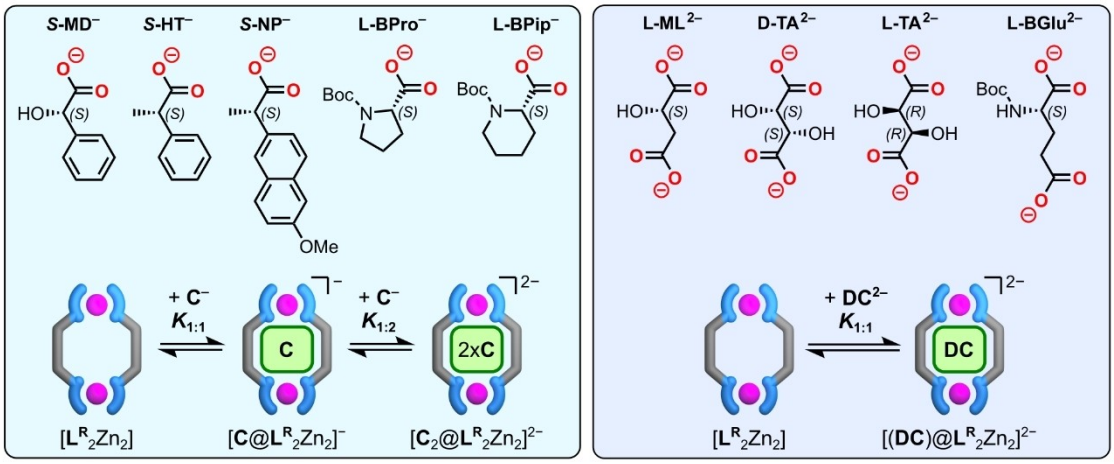


Figure 3. a) Comparison of the measured (host $[\mathbf{L^R}_2Zn_2]$ with and $[\mathbf{L^H}_2Zn_2]$ without solubilizing group after the addition of 5 equiv. D-(−)-tartrate, 500 μM, l = 2 mm, DMSO-d_6) and calculated CD spectra (optimized with r^{2}SCAN-3c, TD-DFT with BHandHLYP/def2-SVP and implicit solvation) for ΔΔ-$[(\mathbf{D\text{-}TA})@\mathbf{L^H}_2Zn_2]^{2-}$. b) Obtained model for ΔΔ-$[(\mathbf{D\text{-}TA})@\mathbf{L^H}_2Zn_2]^{2-}$. c) Side view of the structure showing a zigzag ligand orientation.

Binding of other chiral mono- and dicarboxylates

Having established the underlying principles of chiroptical recognition for our $[\mathbf{L}_2Zn_2]$ receptors, we investigated a variety of chiral substrates which bear carboxylic acid units as their respective tetrabutylammonium salts (Table 1). ^{1}H NMR titrations were conducted in DMSO-d_6 (Figure S3, S5, S7, S10, S12, S15, S18, S21, S22 and S26) prior to CD spectroscopic measurements. Recognition of monocarboxylates ($\mathbf{C}^-$) is expected to result in 1:2 host-guest complexes $[\mathbf{C}_2@\mathbf{L^R}_2Zn_2]^{2-}$. (*S*)-(+)-hydratropate ($\mathbf{\textit{S}\text{-}HT}^-$), (*S*)-(+)-2-(6-methoxy-2-naphthyl)propionate (deprotonated naproxen, $\mathbf{\textit{S}\text{-}NP}^-$), *N*-Boc-L-prolinate ($\mathbf{L\text{-}BPro}^-$) and *N*-Boc-L-pipecolinate ($\mathbf{L\text{-}BPip}^-$) show indeed inflection points indicative for 1:2 binding events for at least one proton signal of the central phenyl unit of the ligand backbone (Figures S6, S9, S11, S14, S17 and S20). The 1:1 association constants of (*S*)-(+)-hydratropate and (*S*)-(+)-2-(6-methoxy-2-naphthyl)propionate stand out especially with log $K_{1:1}$ of 4.45 ($\mathbf{\textit{S}\text{-}HT}^-$) and 4.51 ($\mathbf{\textit{S}\text{-}NP}^-$). The corresponding individual constants for the 1:2 binding event are more than one order of magnitude lower which is probably a result of the guest size because it is simply hard to accommodate two of these large guests simultaneously inside the receptor. The same trend with in general lower constants is observed for *N*-Boc-L-prolinate and *N*-Boc-L-pipecolinate. The last monocarboxylate of the study, (*S*)-(+)-mandelate ($\mathbf{\textit{S}\text{-}MD}^-$), behaves in a contradictory way because no inflection point for a 1:2 binding event was found which is probably a result of the much weaker binding tendency with log $K_{1:1}$ = 2.38 compared to its methyl-analogue (*S*)-(+)-hydratropate with log $K_{1:1}$ = 4.45. This significant differ-

Table 1. Binding constants of the investigated anionic guests as TBA salts in DMSO-d_6.



Monocarboxylate (C^-)	$K_{1:1}$ [M^{-1}][a]	$K_{1:2}$ [M^{-1}][a]	Dicarboxylate (DC^{2-})	$K_{1:1}$ [M^{-1}]
(*S*)-(+)-mandelate (***S*-MD**$^-$)	240 ± 20	–	L-(−)-malate (**L-ML**$^{2-}$)	n.d.
(*S*)-(+)-hydratropate (***S*-HT**$^-$)	28 000 ± 2 000	1 700 ± 100	D-(−)-tartrate (**D-TA**$^{2-}$)	174 000[b] ± 32 000
deprotonated naproxen (***S*-NP**$^-$)	32 000 ± 6 000	1 800 ± 100	L-(+)-tartrate (**L-TA**$^{2-}$)	202 000[c] ± 18 000
N-Boc-L-prolinate (**L-BPro**$^-$)	4 700 ± 800	680 ± 40	*N*-Boc-L-glutamate (**L-BGlu**$^{2-}$)	193 000[d] ± 101 000
N-Boc-L-pipecolinate (**L-BPip**$^-$)	1 900 ± 400	700 ± 120		

[a] Determined by fitting ^{1}H NMR shifts with BindFit.[89–91] Uncertainty estimation by random data exclusion. [b] Average value determined by three ITC titrations. [c] Constant obtained by a single ITC titration with the error representing the goodness of the fit. [d] Average value determined by integration of ^{1}H NMR signals (slow exchange).

ence is the result of the electron withdrawing hydroxyl group of ***S*-MD**$^-$ contrary to the electron donating methyl unit of ***S*-HT**$^-$. The investigated dicarboxylates (**DC**$^{2-}$) show an intermediate to slow exchange characteristic in ^{1}H NMR titrations with [$L^R_2Zn_2$] resulting in 1:1 host–guest complexes [(**DC**)@$L^R_2Zn_2$]$^{2-}$. No data analysis was performed for L-(−)-malate (**L-ML**$^{2-}$) because multiple unknown species are formed at sub-stoichiometric amounts and the exact equilibria are unknown. The 1:1 complex [(**L-ML**)@$L^R_2Zn_2$]$^{2-}$ is the major species between 1.5 and 2 equiv. of guest added but the complex is not stable if the amount of guest is further increased. Association constants for binding of tartrate were measured by isothermal titration calorimetry (ITC) because the observed intermediate exchange behavior does not allow simple determination by integration (Figures S23 and S24). An average binding constant of log $K_{1:1}$ = 5.24 was obtained for D-(−)-tartrate (**D-TA**$^{2-}$) from three measurements with the value being in the expected region for short dicarboxylate guests. L-(+)-tartrate (**L-TA**$^{2-}$) as the other enantiomer shows a very similar binding constant of log $K_{1:1}$ = 5.31 determined by a single experiment. The reasonable matching values are expected because the binding affinity of the two enantiomers with the racemic host [$L^R_2Zn_2$] is theoretically the same. A binding constant of log $K_{1:1}$ = 5.29 was obtained for *N*-Boc-L-glutamate (**L-BGlu**$^{2-}$) by integration of the NMR signals (slow-exchange) of free host and the ones of the host–guest species (Figure S27).

Chiroptical recognition and chirality analysis

The possible enrichment of one helicate enantiomer as seen for tartrate is studied for the various guests (Figure 4a). *N*-Boc-L-prolinate (**L-BPro**$^-$), *N*-Boc-L-pipecolinate (**L-BPip**$^-$), L-(−)-malate (**L-ML**$^{2-}$) and *N*-Boc-L-glutamate (**L-BGlu**$^{2-}$) are also able to enrich the amount of one of the two complex enantiomers (Figures S31–S33 and S41) but the overall CD response is much weaker compared to D-(−)- or L-(+)-tartrate. L-(−)-malate results in the same two positive (350 nm and 420 nm) and one negative cotton effect (308 nm) as D-(−)-tartrate and is expected to favor also the right-handed form of the helicate with regards to the TD-DFT results. L-(+)-tartrate as well as the amino acid derivatives **L-BGlu**$^{2-}$, **L-BPro**$^-$ and **L-BPip**$^-$ show an inverse picture with two negative and one positive cotton effect which is expected to be a result of the enrichment of the left-handed complex enantiomer. The guests bearing aromatic residues, (*S*)-(+)-mandelate (***S*-MD**$^-$), (*S*)-(+)-hydratropate (***S*-HT**$^-$), and (*S*)-(+)-2-(6-methoxy-2-naphthyl)propionate (***S*-NP**$^-$), show no significant cotton effects related to their corresponding host-guest complexes (Figures S28–S30). The individual CD band of the naproxen-based guest ***S*-NP**$^-$ is observed because the guest's absorption bands are within our measurement range. The missing chiroptical response clearly cannot be related to the binding affinity because ***S*-HT**$^-$ and ***S*-NP**$^-$ show much stronger binding than the monocarboxylates **L-BPro**$^-$ and **L-BPip**$^-$ based on amino acid derivatives. Our hypothesis is that

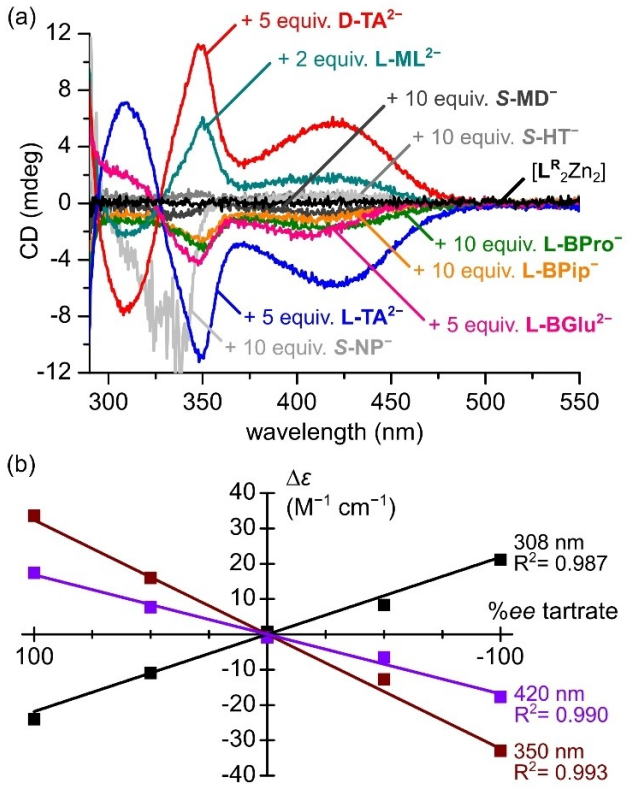


Figure 4. a) Overview of the CD response of the receptor (500 μM, $l = 2$ mm, DMSO-d_6) upon addition of anionic guests. b) Chirality analysis of tartrate (5 equiv. added) with linear regressions of the three main cotton effects. Positive *ee* values correspond to an excess of D-(−)-tartrate and negative values to L-(+)-tartrate.

L-BPro$^-$ and **L-BPip**$^-$ as saturated cyclic compounds with additional Boc-protecting groups have a much larger sterical demand and result in small but observable chiroptical responses. The fact that dicarboxylates show a stronger CD effect can be related to the bridging nature of the guest which reduces the degree of freedom throughout the host–guest structure.

Finally, we tested the possibility to use the chiroptical response of the receptor to perform spectroscopy-based chirality analysis (Figure 4b). Therefore, solutions of enantiopure D-(−)- and L-(+)-tartrate are mixed accordingly to obtain three additional data points (Figure S36) and linear regression of the cotton effect's circular dichroism intensity of all 5 points (±100 %*ee*, ±50 %*ee* and 0 %*ee*) are performed which show very good R^2 values of around 0.99. Measurements of samples possessing 25 %*ee* at different conditions (Figure S37 and Table S6) show that also the analysis of samples with a low enantiomeric excess can be accomplished. However, the host concentration should not fall below 50 μM if common cuvettes up to 1 cm pathlength are used. Thus, the analyte concentration of 250 μM (5 equiv.) is the expected limit of quantification for samples with 25 %*ee* or higher. Samples with an even lower *ee* should be measured at higher concentration for reliable results. The examples prove that the receptor can be used for chirality analysis of chiral carboxylates by CD spectroscopy.

Conclusions

The intrinsic chirality paired with the strong affinity for carboxylates of charge-neutral double-stranded zinc(II) helicate-based anion receptors is utilized for chiroptical recognition of chiral guests by CD spectroscopy. Binding of the chiral guests inside the metal-based containers result in the enrichment of one complex enantiomer of the racemic host upon formation of the host–guest complexes which gives rise to the emergence of three cotton effects. Deeper insights into the underlying process were obtained by 2D NOESY experiments, TD-DFT calculations and relaxed potential energy surface scans. In this respect, we could show that the *syn-syn* conformation of the triazole units is essential for the formation of a helical host–guest complex which is crucial for chiroptical recognition. Binding constants above 10^5 M^{-1} are found for the studied chiral dicarboxylate anions. These affinities guarantee a nearly quantitative guest uptake which is also observed by CD titrations so that the system can be used for chirality analysis of dicarboxylate guests at concentrations above 250 μM in case of enantioselectivities above 25 %*ee*. The latter was shown for tartrate resulting in a linear behavior of the cotton effect's intensity with varying enantiomeric excess.

Experimental Section

The receptor synthesis was accomplished by the reported two synthon approach in which the hydroxyquinoline complexation units are "clicked" onto the ligand backbone by a CuAAC reaction. Complex formation with zinc(II) acetate in DMSO readily results in the desired double-stranded charge-neutral zinc(II) helicates [L_2Zn_2] by stirring the mixture for one day. The complexes are obtained as powders after removal of DMSO and the byproduct, acetic acid, via lyophilization in quantitative fashion (Scheme S1).[78] Additionally, complexation in methanol was performed which leads to the precipitation of the helicate and allows an alternative workup procedure for the removal of acetic acid by filtration. By this way, the complex is obtained with 78 % yield without the need for lyophilization.

Chiral mono- and dicarboxylic acids were deprotonated in methanol with tetrabutylammonium hydroxide added as a solution in methanol. The majority of the solvent was removed with a rotary evaporator after vortexing the mixtures for 30 min and the salts were obtained and directly used after additional lyophilization.

Titrations (NMR, ITC, UV-Vis and CD) were performed in DMSO-d_6 to maintain the same water content throughout the different experiments.

Supporting Information

The authors have cited additional references within the Supporting Information.[78,80–93]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: charge-neutral helicates · chiroptical recognition · chiral anions · chirality analysis · metal-based containers

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