Chiral resolution of a racemic macrocyclic complex by recognition of one enantiomer over the other: structures and DFT calculations†

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The enantiopure agents d- and l-leucine, selectively bind RR and SS enantiomers from a racemate [Ni(α-rac-L)]2+ to give ([Ni(RR-L)(d-HLeu)](ClO4)2, (A-1) and ([Ni(SS-L)(l-HLeu)](ClO4)2, (A-1), respectively, and leave the corresponding uninteracted SS and RR enantiomers of [Ni(α-SS-L)](ClO4)2 (S-2) and [Ni(α-RR-L)](ClO4)2 (R-2). Occasionally, a few crystals of ([Ni(RR-L)(l-HLeu)](ClO4)2) (A-3) and ([Ni(SS-L)(d-HLeu)](ClO4)2) (A-3) were found to have accreted with the crystals of A-1/R-2, and A-1/S-2, respectively (the yields are less than 2%). The results of X-ray crystal structural analysis reveal that A-1 and A-1, S-2 and R-2, and A-3 and A-3 are enantiomers, in which A-1 and A-3 possess 1D right-handed helical chains, while A-1 and A-3 exhibit a motif of 1D left-handed helical chains. The results of DFT calculations reveal that the single-point energies of [Ni(RR-L)(d-HLeu)]2+/[Ni(SS-L)(l-HLeu)]2+ in A-1/A-1 are 582 kJ mol−1 lower than those of [Ni(RR-L)(l-HLeu)]2+/[Ni(SS-L)(d-HLeu)]2+ in A-3/A-3, demonstrating the favorable stereo-coordination environments of [Ni(α-RR-L)]2+ and [Ni(α-SS-L)]2+ towards d and l-HLeu, respectively.

Introduction

Chiral resolution is important in both the pharmaceutical industry and material sciences.1,2 Chiral resolution can be performed by spontaneous resolution3 or chiral symmetry breaking.4 Usually, chiral resolution has been achieved by chromatographic techniques, or crystallization of a racemate with an enantiopure reagent, in which the enantiopure reagent forms two diastereomers with a racemate, and the two diastereomers can be separated by the difference in solubility. To our knowledge, this instance of recognition of one enantiomer over the other achieved by an enantiopure reagent has not been reported so far.

The macrocyclic ligand, 5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazaacyclotetradecane (L), was prepared 40 years ago by Curtis.5 Its nickel(ii) complexes exist as two diastereomers of meso and rac (racemic) forms,6 which can be separated by crystallization.5,7 The racemic form of the Ni(ii) complex [Ni(rac-L)]2+ has two isomers of [Ni(α-rac-L)]2+ and [Ni(β-rac-L)]2+, which can be separated conveniently by our previously reported method.8 In addition, the racemic form of [Ni(α-rac-L)]2+ can also be separated into a pair of enantiomers of [Ni(α-SS-L)]2+ and [Ni(α-RR-L)]2+, by the reactions of [Ni(α-rac-L)]2+ with enantiopure reagents such as tartrate9 and phenylalanine.10 We found that [Ni(α-rac-L)]2+ and its two enantiomers of [Ni(α-SS-L)]2+ and [Ni(α-RR-L)]2+ are beneficial for the construction of helical chains.10,11 During our continued efforts to construct helical structures, we found a unique instance in which enantiopure reagents d- and l-leucine selectively bound RR and SS enantiomers only from racemic [Ni(α-rac-L)](ClO4)2, and the racemates could be separated efficiently. The reason for this unique recognition of one enantiomer over the other can be understood from the results of the DFT calculations.

Experimental

General remarks

The macrocyclic ligand (L) and its nickel(ii) complex were prepared according to the literature methods,6,7 and separated as the racemic form of rac-L. The nickel(ii) complex [Ni(α-rac-L)](ClO4)2, and its two enantiomers [Ni(α-SS-L)](ClO4)2 and [Ni(α-RR-L)](ClO4)2 were prepared according to previously reported methods.8,10 All of the other chemicals are commercially available and used without further purification. Elemental analyses were determined using an Elementar Vario El elemental analyser. The IR spectra were recorded in the 4000 to 400 cm−1 region using KBr pellets and a Bruker EQUINOX 55 spectrometer. The circular dichroism (CD) spectra in water were recorded on a JASCO J-810 spectropolarimeter.

**References**

† Electronic supplementary information (ESI) available: Selected bond distances and angles, the structures for A-1, the XRD patterns, and the results of DFT calculations. CCDC reference numbers 735384 for A-1, and 726187–726191 for A-1, S-2·H2O, R-2·H2O, A-3 and A-3, respectively. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b921141a
prism-shaped crystals of Δ-1 (yield, 34%) and yellow crystals of S-2·H₂O (yield, 39%). Anal. Calc. for C₃₂H₄₆N₆Cl₂O₁₉Ni (Δ-1): C, 39.24; H, 7.33; N, 10.40. Found: C, 39.66; H, 7.23; N, 10.63. IR (KBr, cm⁻¹): 3268(s), 3170(m), 2966(s), 1951(vs), 1507(m), 1457(w), 1392(w), 1369(m), 1340(w), 1271(w), 1170(m), 1091(s), 967(s), 855(m), 821(m), 759(m), 777(w), 623(s), 539(m). Anal. Calc. for C₃₂H₄₆N₆Cl₂O₁₉Ni·S·H₂O (Δ-1): C, 34.31; H, 6.84; N, 10.00. Found: 34.63; H, 6.67; N, 10.15. IR (KBr, cm⁻¹): 3587(m), 3449(m), 3207(s), 2975(m), 1614(m), 1460(s), 1405(w), 1379(m), 1356(w), 1330(w), 1275(w), 1180(w), 1087(s), 1008(w), 930(w), 886(w), 820(w), 777(w), 624(s).

Occasionally (we tried over 6 times, and only once found block-shaped crystals), a few yellow block-shaped crystals of Δ-3 were found to accrete with the crystals of Δ-1 and S-2. Yield, less than 2%. Unfortunately, we could not obtain enough crystals for elemental analysis.

The reaction properties. The reaction of [Ni(α-SS-L)(ClO₄)₂] with l-HLeu (13 mg, 0.1 mmol) in a procedure analogous to that detailed for the preparations of Δ-1 and S-2 gave violet prism-shaped crystals of Δ-1 only. Yield, 89%. Similarly, the reaction of [Ni(α-RR-L)(ClO₄)₂] with d-HLeu afforded Δ-1 only.

The reaction of [Ni(α-RR-L)(ClO₄)₂] with l-HLeu, and the reaction of [Ni(α-SS-L)(ClO₄)₂] with d-HLeu in a procedure analogous to that detailed for the preparations of Δ-1 and S-2 afforded yellow crystals only. The results of elemental analyses and X-ray crystallographic analyses demonstrate that the yellow crystals are R-2·H₂O and S-2·H₂O, respectively, and no violet block-shaped crystals were found. This indicates that it is not favorable for [Ni(α-RR-L)(ClO₄)₂] to interact with l-HLeu, and [Ni(α-SS-L)(ClO₄)₂] with d-HLeu either.

X-ray crystallography

Single-crystal data for Δ-1, S-2·H₂O, R-2·H₂O, Δ-3 and Δ-3 were collected on a Bruker Smart 1000 CCD diffractometer, with Mo-Kα radiation (λ = 0.71073 Å). All empirical absorption corrections were applied using the SADABS program. The structures were solved using direct methods, which yielded the positions of all non-hydrogen atoms. These were refined first isotropically and then anisotropically. All the hydrogen atoms of the ligands were placed in calculated positions with fixed isotropic thermal parameters and included in the structure factor calculations in the final stage of the full-matrix least-squares refinement. The hydrogen atoms of water molecules in S-2·H₂O and R-2·H₂O were not added. All calculations were performed using the SHELXTL system of computer programs. For Δ-3 and Δ-3, one ClO₄⁻ is disordered over two symmetry related sites with 50% occupancy. The crystallographic data are summarized in Table 1. The selected bond lengths and angles are listed in Table S1.†

Table 1 The crystallographic data

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<tr>
<th>Compound</th>
<th>Δ-1</th>
<th>S-2·H₂O</th>
<th>R-2·H₂O</th>
<th>Δ-3</th>
<th>Δ-3</th>
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<tr>
<td>Formula</td>
<td>C₃₂H₄₆Cl₆N₆Cl₂O₁₉Ni</td>
<td>C₃₂H₄₆Cl₆N₆Cl₂O₁₉Ni</td>
<td>C₃₂H₄₆Cl₆N₆Cl₂O₁₉Ni</td>
<td>C₃₂H₄₆Cl₆N₆Cl₂O₁₉Ni</td>
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<td>fw</td>
<td>673.27</td>
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<td>Crystal size/mm</td>
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<td>0.35 × 0.25 × 0.21</td>
<td>0.45 × 0.36 × 0.23</td>
<td>0.48 × 0.24 × 0.21</td>
<td>0.36 × 0.30 × 0.13</td>
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<td>Trigonal</td>
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<td>Monoclinic</td>
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<td>P₂₁</td>
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<td>P₂₁</td>
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<tr>
<td>a/Å</td>
<td>13.3805(7)</td>
<td>13.3219(9)</td>
<td>9.0197(16)</td>
<td>9.0136(14)</td>
<td>13.4764(10)</td>
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<tr>
<td>b/Å</td>
<td>13.3805(7)</td>
<td>13.3219(9)</td>
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<td>17.576(2)</td>
<td>10.630(19)</td>
<td>10.5357(16)</td>
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<td>1.434</td>
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<td>1.095</td>
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<td>unique refl. (Rint)</td>
<td>6515 (0.0336)</td>
<td>4955 (0.0563)</td>
<td>4648 (0.0227)</td>
<td>4808 (0.0165)</td>
<td>4735 (0.0668)</td>
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<td>Parameters</td>
<td>350</td>
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<td>295</td>
<td>295</td>
<td>362</td>
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<td>0.1034</td>
<td>1.085</td>
<td>1.025</td>
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<tr>
<td>R₁, wR₁(&gt;2σ(I))</td>
<td>0.0529, 0.1427</td>
<td>0.0443, 0.0823</td>
<td>0.0443, 0.1089</td>
<td>0.0396, 0.1016</td>
<td>0.0532, 0.1105</td>
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<tr>
<td>R₁, wR₁(all data)</td>
<td>0.0747, 0.1616</td>
<td>0.0876, 0.0983</td>
<td>0.0574, 0.1168</td>
<td>0.0450, 0.1060</td>
<td>0.1053, 0.1326</td>
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<tr>
<td>Absolute structure parameter</td>
<td>0.000(18)</td>
<td>0.015(17)</td>
<td>0.021(18)</td>
<td>0.013(15)</td>
<td>0.01(15)</td>
</tr>
</tbody>
</table>

* R₁ = Σ ||Fobs| - |Fcalc|| / Σ |Fobs|, wR₁ = [Σ[w(Fobs² - Fcalc²)]/Σ w(Fcalc²)]¹/², w = 1/[σ²(Fobs)² + (aP)² + bP], where P = [K(Fobs)² + 2Fcalc²]/3.
Computational details

The DFT calculations were performed with the Gaussian03 suite of programs\textsuperscript{44} based on the structural equations of $\Delta$-I/$\Delta$-1 and $\Delta$-3/$\Delta$-3 using the hybrid gradient corrected exchange functional of Lee, Yang, and Parr.\textsuperscript{15,16} This functional is commonly known as B3LYP and has been shown to be quite reliable for computing geometries. The 6-31G\textsuperscript{d} basis set with polarization (d) were selected for all atoms save the Ni atom which was described by the LANL2DZ valence basis set in combination with the corresponding effective core potential.\textsuperscript{14} The single-point energy calculations were achieved at the B3LYP/6-31G(d) (LANL2DZ for Ni) level of theory using the geometries based on the crystal structures. The obtained energies are shown in Table S2.\textsuperscript{†} An attempt to optimize the geometry of $\Delta$-I/$\Delta$-1 and $\Delta$-3/$\Delta$-3 failed, using the B3LYP functional, the 6-31G(d), 3-21G or the ECP LANL2DZ basis set. The original crystal structures did not survive after the optimization, and either planar four-coordinated or five-coordinated structures were obtained.

The numbers of Imaginary Frequencies were calculated using the geometries of the crystal structures based on the B3LYP/6-31G(d) (LANL2DZ for Ni) level of theory. The obtained numbers and their values are given in Table S3,\textsuperscript{†} indicating the numbers of Imaginary Frequencies and their values are close to each other for all four isomers.

Results and discussion

Synthesis

The reaction of racemic $[\text{Ni}(\alpha\text{-rac-L})](\text{ClO}_4)_2$ with $d$-leucine in a 1:1 molar ratio in acetonitrile–water gave violet prism-shaped crystals of $[\text{Ni}(\text{RR-L})(d\text{-HLeu})](\text{ClO}_4)_2$ ($\Delta$-1), together with unreacted yellow crystals of $[\text{Ni}(\alpha\text{-SS-L})](\text{ClO}_4)_2$ ($\Delta$-2) (Fig. 1a), while the reaction of $[\text{Ni}(\alpha\text{-rac-L})](\text{ClO}_4)_2$ with $l$-leucine ($l\text{-HLeu}$) gave violet prism-shaped crystals of $[\text{Ni}(\text{SS-S-L})(l\text{-HLeu})](\text{ClO}_4)_2$ ($\Delta$-1) and unreacted yellow crystals of $[\text{Ni}(\alpha\text{-RR-L})](\text{ClO}_4)_2$ ($\Delta$-2) (Fig. 1b). Under the same reaction conditions, the reactions of $[\text{Ni}(\alpha\text{-RR-L})](\text{ClO}_4)_2$ and $[\text{Ni}(\alpha\text{-SS-L})](\text{ClO}_4)_2$ with $d$- and $l$-HLeu gave the enantiopure compounds of $\Delta$-1 and $\Delta$-1, respectively (Fig. 1c), while there is no reaction between $[\text{Ni}(\alpha\text{-RR-L})](\text{ClO}_4)_2$ and $l$-HLeu (Fig. 1d), as well as $[\text{Ni}(\alpha\text{-SS-L})](\text{ClO}_4)_2$ and $d$-HLeu, indicating $d$- and $l$-HLeu selectively bind $RR$ and $SS$ enantiomers, respectively.

Crystal structures

X-ray crystal structural analysis reveals that one asymmetric unit in $\Delta$-1/$\Delta$-1 contains one $[\text{Ni}(\text{RR-L})(d\text{-HLeu})]^+/[\text{Ni}(\text{SS-S-L})(l\text{-HLeu})]^-$, and two ClO\textsuperscript{−} anions. $[\text{Ni}(\text{RR-L})(d\text{-HLeu})]^+$ and $[\text{Ni}(\text{SS-S-L})(l\text{-HLeu})]^-$ are enantiomers (Fig. 2a). In each enantiomer, the nickel(II) ion displays a distorted octahedral coordination geometry by coordination with four nitrogen atoms of L in a folded configuration, and two carbonyl oxygen atoms of $d$- or $l$-HLeu in a cis-position. The macrocyclic ligand L adopts an $RR$ and $SS$ configuration in $\Delta$-1 and $\Delta$-1, respectively (Fig. 2a). In each enantiomer, the Ni–O distances are longer than the Ni–N distances (see Table S1).\textsuperscript{†} In $\Delta$-1, the $[\text{Ni}(\text{RR-L})(d\text{-HLeu})]^+$ monomers are alternately connected by ClO\textsuperscript{−} anions through hydrogen bonding interactions between the protonated nitrogen atom of $d$-HLeu and the oxygen atoms of ClO\textsuperscript{−} anions (Table S1 and Fig. S1†), generating a novel 1D right-handed homochiral helical chain along the 41 axis (Fig. 2b). Each helix within the chain contains four $[\text{Ni}(\text{RR-L})(d\text{-HLeu})]^+$ monomers, with a pitch of 17.6 Å. In $\Delta$-1, the right-handedness is oriented from the chirality of $RR$-L and $d$-HLeu,\textsuperscript{14} and the right-handed helical chains congregate through zipper-like interchain hydrophobic interactions\textsuperscript{10,14} to generate a supramolecular stereoisomer of $\Delta$-1 (Fig. S2†), with a chiral space group of $P4_1$, and an absolute structure parameter of 0.000(18). In contrast to $\Delta$-1, the similar connection of $[\text{Ni}(\text{SS-S-L})(l\text{-HLeu})]^+$ monomers with ClO\textsuperscript{−} in $\Delta$-1 through intermolecular hydrogen bonding interactions generates a 1D left-handed homochiral helical chain along the 43 axis (Fig. 2b). Obviously, the left-handedness is oriented from the opposite chirality of $SS$-L and $l$-HLeu,\textsuperscript{14} and the corresponding supramolecular stereoisomer of $\Delta$-1 is formed through the zipper-like interchain hydrophobic interactions of 1D left-handed helical chains along the 41 axis, with the chiral space group of $P4_1$, and an absolute structure parameter of 0.015(17).

It is very interesting to note that $d$- and $l$-HLeu individually recognize $RR$ and $SS$ enantiomers from a racemic $[\text{Ni}(\alpha\text{-rac-L})](\text{ClO}_4)_2$, and leave the corresponding unreacted yellow $SS$ and $RR$ enantiomers to crystallize from the solution to give $S$-2 and $R$-2, respectively, with the same chiral space group $P2_1$, and absolute structure parameters of 0.021(18) and 0.013(15), respectively, indicating the homochiral nature of $S$-2 and $R$-2.

The chiral recognition of one of the enantiomers from a racemate achieved by a chiral reagent is very unique, and significant for chiral resolution. As shown in Fig. 3, $S$-2 and $R$-2 are enantiomers, in which Ni(II) is four-coordinated to four nitrogen atoms of the ligand L, and the configurations of L in $S$-2 and $R$-2 are $SS$ and $RR$, respectively.

Occasionally, a few block-shaped crystals were found to have accreted with the crystals of $\Delta$-1 and $S$-2, and $\Delta$-1 and $R$-2 (the yield is less than 2%), and the conditions of the formation of these block-shaped crystals are not clear and uncontrolled at present. The results of X-ray crystallographic analyses reveal that the block-shaped crystals are $[\text{Ni}(\text{RR-L})(l\text{-HLeu})](\text{ClO}_4)_2$ ($\Delta$-3) and $[\text{Ni}(\text{SS-S-L})(d\text{-HLeu})](\text{ClO}_4)_2$ ($\Delta$-3), respectively. The coordination environments of Ni(II) in $\Delta$-3 and $\Delta$-3 are similar to those in $\Delta$-1 and $\Delta$-1 (Fig. 4a), and the connections of $[\text{Ni}(\text{RR-L})(l\text{-HLeu})]^+/[\text{Ni}(\text{SS-S-L})(d\text{-HLeu})]^{2+}$ monomers with ClO\textsuperscript{−} through similar intermolecular hydrogen bonding interactions generate 1D right-handed and left-handed homochiral helical chains along the 41 and 43 axes, respectively (Fig. 4b). The helicity of $\Delta$-3 and $\Delta$-3 originate from the chiral macrocyclic ligand rather than the chiral leucine, as both $\Delta$-3 and $\Delta$-3 show the same right-handed helicity, while both $\Delta$-3 and $\Delta$-1 show the same left-handed helicity.

CD spectra

The phase purity of $\Delta$-1 and $\Delta$-1 were confirmed by the results of XRD measurements (Fig. S3†). The results of CD measurements are consistent with those of the X-ray crystal structures. As shown in Fig. 5a, the bulk crystals of $\Delta$-1 in water show a positive and a negative Cotton effect at 217 and 245 nm, respectively, while the bulk crystals of $\Delta$-1 in water show the opposite signs at the same wavelengths. The CD spectra of $S$-2 and $R$-2 in water are similar to those of $\Delta$-1 and $\Delta$-1 (Fig. 5b), with the Cotton effects at 217
The pictures of the crystals of (a) Δ-1 and S-2 obtained from the reaction of [Ni(α-rac-L)](ClO₄)₂ with d-HLeu, (b) Λ-1 and R-2 obtained from the reaction of [Ni(α-rac-L)](ClO₄)₂ with l-HLeu, (c) Λ-1 obtained from the reaction of [Ni(α-SS-L)](ClO₄)₂ with l-HLeu, and (d) R-2 obtained from the reaction of [Ni(α-RR-L)](ClO₄)₂ with l-HLeu.
and 245 nm, respectively, demonstrating the Cotton effects of Δ-1 and Λ-1 originate from the chiral macrocyclic ligand rather than the chiral leucine.

**DFT calculations**

To better understand the phenomena of chiral recognition of one enantiomer over the other achieved by chiral leucine, the values of single-point energies are obtained from DFT calculations based on the structural cations of Δ-3/Δ-1 and Λ-3/Λ-1 (Table S2†). From Table S2† it can be found that the single-point energies for [Ni(RR-L)(d-HLeu)]²⁺, [Ni(RR-L)(l-HLeu)]²⁺, [Ni(SS-L)(d-HLeu)]²⁺ and [Ni(SS-L)(l-HLeu)]²⁺ are −1460.4539100, −1460.2308702, −1460.2342387 and −1460.4559491 hartrees, respectively, indicating that the single-point energies of [Ni(RR-L)(d-HLeu)]²⁺/[Ni(SS-L)(l-HLeu)]²⁺ in Δ-1/Λ-1 are 582 kJ mol⁻¹ lower than those of [Ni(RR-L)(l-HLeu)]²⁺/[Ni(SS-L)(d-HLeu)]²⁺ in Δ-3/Λ-3. This demonstrates that [Ni(α-RR-L)]²⁺ and
[Ni(α-SS-L)]^{2+} present stereoselective environments towards d and l-HLeu, respectively, i.e. the coordination of d- and l-HLeu towards [Ni(α-RR-L)]^{2+} and [Ni(α-SS-L)]^{2+} generates more stable complexes of [Ni(RR-L)(d-HLeu)]^{2+} and [Ni(α-SS-L)(l-HLeu)]^{2+}, respectively. As a consequence, d- and l-HLeu selectively bind to [Ni(α-RR-L)]^{2+} and [Ni(α-SS-L)]^{2+} respectively to form stable [Ni(RR-L)(d-HLeu)]^{2+} and [Ni(α-SS-L)(l-HLeu)]^{2+}, and leave the unreacted [Ni(α-SS-L)]^{2+} and [Ni(α-RR-L)]^{2+} in solution. Thus the racemic [Ni(α-rac-L)]^{2+} can be separated efficiently.

**Conclusion**

In conclusion, we demonstrate here a unique instance of chiral resolution of a pair of enantiomers by recognition of one enantiomer over the other using chiral leucine as the resolution reagent. The high chiral selectivity of d-HLeu towards [Ni(α-RR-L)]^{2+} and l-HLeu towards [Ni(α-SS-L)]^{2+} originates from their favorable stereo-coordination environments between HLeu and Ni(II).

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