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Stereoselective Recognition of Vicinal Diamines with a Zn(II) Complex

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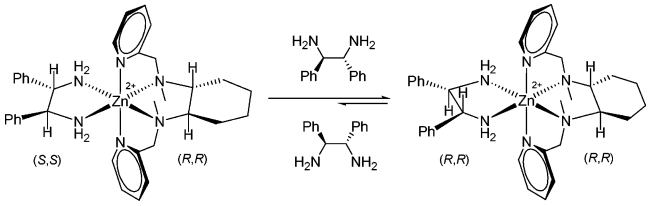
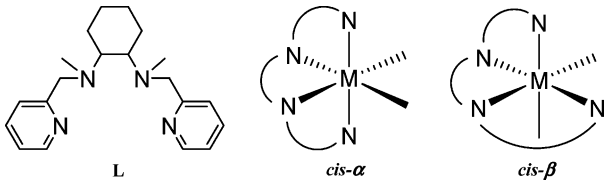


Zn(II) complex of **L** (*N*,*N*′-bis(2-pyridylmethyl)-*N*,*N*′-dimethyl-*trans*-1,2-diaminocyclohexane) binds chiral vicinal diamines (1,2-diphenylethylenediamine (dpen) and 1,2-diaminocyclohexane (dach)) stereoselectively. Crystallographic studies reveal that the ternary complex has the C_2 symmetric *cis*-α topology. ^{1}H NMR shows that the *R*,*R* form of the tetradentate zinc complex binds rapidly and reversibly to the *R*,*R* form of the diamine over the *S*,*S* form with a streoselectivity of about 5:1. Although the diamine exchange rate is rapid it is slower than the NMR time scale, and distinct signals for the diastereomeric complexes are observed when racemic mixtures of the host and guest molecules are mixed. Origin of stereoselectivity is discussed in terms of steric effects.

There has been much interest in developing methods for making chiral 1,2-diamines and determining their enantiopurity since they are important building blocks for a wide variety of stereoselective catalysts and therapeutic agents.[1] We recently reported a highly efficent way of making chiral diamines by using hydrogen-bond directed diaza-Cope rearrangement reactions.[2] Receptors that bind vicinal diamines stereoselectively may be useful for separating their racemic mixtures and for determining their enantiopurity. Here we report a rational and unified approach to stereoselective recognition of C_2 symmetric diamines with a Zn(II) complex of **L**.



Zn(II)**L** complexes are ideal for studying stereoselective recognition processes. Unlike Co(III)**L**[3,4] complexes that are substitutionally inert, Zn(II)**L** complexes are labile and allow rapid and reversible chelation of small molecules. Thus, stereoselectivity of Zn(II)**L** complexes can be studied under thermodynamic control. Although Co(III)**L** complexes can provide valuable insights into stereoselective recognition processes, it would be difficult to use them on a practical basis for separating racemic mixtures of small molecules through reversible chelation.

The tetradentate ligand (**L**) was synthesized according to literature procedures in racemic form as well as in enantiopure form.[4a,5] Figure 1 shows the crystal structure of the ternary complex formed from mixing equimolar amounts of $Zn(OTf)_2$, *rac*-**L**, and *rac*-dpen in methanol.[6] The unit cell consists of two octahedral Zn(II) complexes with one of them chelated by (*R*,*R*)-**L** and (*R*,*R*)-dpen and the other chelated by (*S*,*S*)-**L** and (*S*,*S*)-dpen. It is interesting that only the *cis*-α complexes are found even though vicinal diamines can also chelate to form *cis*-*β* complexes.[7] The two *N*-methyl groups in Figure 1 are in axial position as in previously reported *cis*-α octahedral Fe(II)-**L**,[8] Co(III)**L**,[4a,b] Mn(II)**L**,[9] and Ru(II)**L**[5,10] complexes.

^{1}H NMR was used to investigate the stereoselectivity of the complexation reaction (Figure 2). Mixing equimolar amounts of $Zn(OTf)_2$ (20 mM) and (*R*,*R*)-**L** (host) with 4 equiv of (*R*,*R*)-dpen (guest) in methanol gives predominantly a single ternary complex in solution (Figures 2a and S1). The proton NMR indicates that this is a *cis*-α complex in agreement with the crystal structure (Figure 1). The most downfield shifted signal

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(6) Crystal structure for [((*S*,*S*)-**L**)Zn(II)((*S*,*S*)-dpen)] : C36H44F6N6−O6.S2Zn, T = 150(1) K, orthorhombic, Pbca, Z = 8, a = 21.4654(4)Å, b = 17.0244(3)Å, c = 21.6341(5)Å, α = 90°, β = 90°, γ = 90°, V = 7905.9(3)Å^3, R1 = 0.0472, wR2 = 0.1041 for $I > 2\sigma(I)$, GOF on F^2 = 1.014.

(7) In principle, the stereoselectivity may be due to counter anion or solvent effects or due to crystal packing. However, we find that the stereoselectivity does not change significantly when the solvent (methanol to dmso) or the counter anion (triflate to chloride or bromide) is changed. Since the sense of stereoselectivity in solution and in solid state is the same, crystal packing is unlikely to be a major factor in determining the stereoselectivity.

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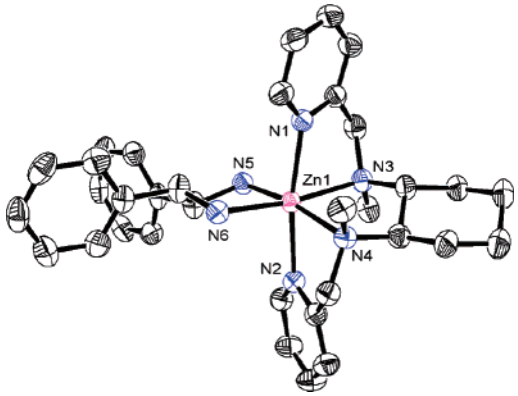
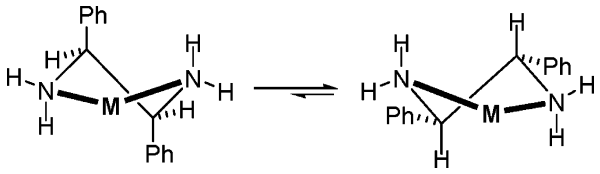
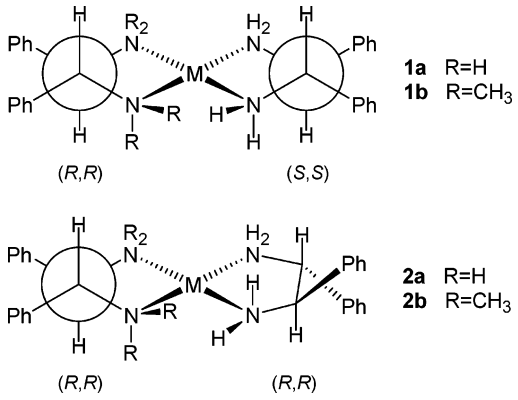


FIGURE 1. ORTEP representation (50% probability) of the crystal structure of [((*R*,*R*)-**L**)Zn(II)((*R*,*R*)-dpen)] (triflate counteranion not shown). Selected bond distances (Å): Zn−N1 = 2.217(2), Zn−N2 = 2.217(2), Zn−N3 = 2.202(2), Zn−N4 = 2.200(2), Zn−N5 = 2.151-(2), Zn−N6 = 2.138(2).

SCHEME 1



SCHEME 2



(δ8.93, Figure 2a) belongs to the proton at the ortho position in the host pyridine group. This signal is further downfield shifted (δ9.15, Figure 2b) when the ternary complex is formed between $Zn(OTf)_2$, (*R*,*R*)-**L**, and (*S*,*S*)-dpen.[11] When racemic host and guest molecules are mixed with $Zn(OTf)_2$, the homochiral ternary complex ((*R*,*R*)host−(*R*,*R*)guest or (*S*,*S*)-host−(*S*,*S*)guest) is the major product and the heterochiral ternary complex ((*R*,*R*)host−(*S*,*S*)guest or (*S*,*S*)host−(*R*,*R*)guest) is the minor product (Figure 2c). Integration of the signals due to the homochiral complex and the heterochiral complex reveals that the stereoselectivity is about 5:1 in favor of the homochiral complex.[12] It is interesting that the guest diamine exchange rate is slower than the NMR time-scale and distinct signals rather than averaged signals are observed for the two diastereomeric complexes (Figures 2c). The guest diamine can be easily displaced with ethylenediamine without affecting the host.

The same pyridine proton signal of the host ligand used to monitor the stereoselective recognition of dpen may be used to study the stereoselective recognition of dach. As in the previous case, mixing equimolar amounts of $Zn(OTf)_2$ (20 mM) and (*R*,*R*)-**L** (host) with 4 equiv of (*R*,*R*)-dach (guest) in methanol gives predominantly a single ternary complex in solution (Figures 2d and S2). The homochiral ternary complex (Figure 2d) is more stable than the heterochiral ternary complex (Figure 2e). Thus, the Zn(II)**L** complex binds dach with the same sense of stereoselectivity as for binding dpen (Figure 2c,f). The magnitude of the stereoselectivity is slightly higher for dach (6:1) than for dpen. Even though the two diamines are very different in structure, the NMR patterns in Figure 2 (a, b, c vs d, e, f) are remarkably similar. This is a useful feature for detecting the stereoselective recognition of C_2 symmetric diamines in general.

The Zn(II) complex binds dach and dpen and other C_2 symmetric 1,2-diaryl-1,2-diaminoethanes (e.g., 1,2-bis(*p*-nitrophenyl)-1,2-diaminoethane (pnpen) and 1,2-bis(*p*-methoxyphenyl)-1,2-diaminoethane (pmpen)) with the same sense of stereoselectivity. The same pyridine proton signal of the host ligand used to monitor the stereoselective recognition of dpen and dach may be used to study the stereoselective recognition of other C_2 symmetric 1,2-diaryl-1,2-diamines. Thus a unified approach to detecting the stereoselective recognition of C_2 symmetric vicinal diamines has been found. The stereoselectivity for pnpen recognition (5:1) and pmpen recognition (5:1) is comparable to that for dpen recognition.

It is interesting to examine the possible origin of the stereoselective diamine recognition. Vicinal diamines form puckered five-membered rings upon chelation to metal ions.[13] The direction of this puckering may be made to favor one side since the substituents in the diamine backbone prefer to occupy the equatorial positions rather than the axial ones (Scheme 1). This preference is due to steric effects as in the case of the substitutents in the chair form of the cyclohexane ring.[14] Puckering of the five-membered ring in the diamine chelate allows the formation of staggered conformations about the C−C bond and the C−N bonds as shown in Scheme 1.

If two molecules of dpen were to chelate opposite each other in a square planar complex, the "side-views" of the heterochiral ternary complex and the homochiral ternary complex should look like **1a** and **2a**, respectively (three-dimensional representation of only the "front" amines are shown in Scheme 2). In **1a**, two of the amine equatorial hydrogens are pointing directly at each other. This should result in unfavorable steric and dipole interactions. In contrast, the two amine equatorial hydrogens in **2a** do not point directly to each other. DFT computation at the B3LYP/6-31G* level shows that **2a** is more stable than **1a** by about 0.2 kcal/mol.[15] If one of the diamines is tetramethylated, the homochiral complex (**2b**) is more stable than the heterochiral complex (**1b**) by about 0.5 kcal/mol. This increased

(11) A small amount of the homochiral complex is visible in Figure 2b. This is because commercial (*S*,*S*)-dpen is contaminated with its enantiomer and the homochiral complex is more stable than the heterochiral complex. Although commercial (*R*,*R*)-dpen is also contaminated with its enantiomer, the heterochiral complex is not visible in Figure 2a because it is less stable than the homochiral complex. Figure 2c can also be generated with enantiopure host and racemic guest.

(12) Comparable selectivity is found when dmso is used as solvent instead of methanol.

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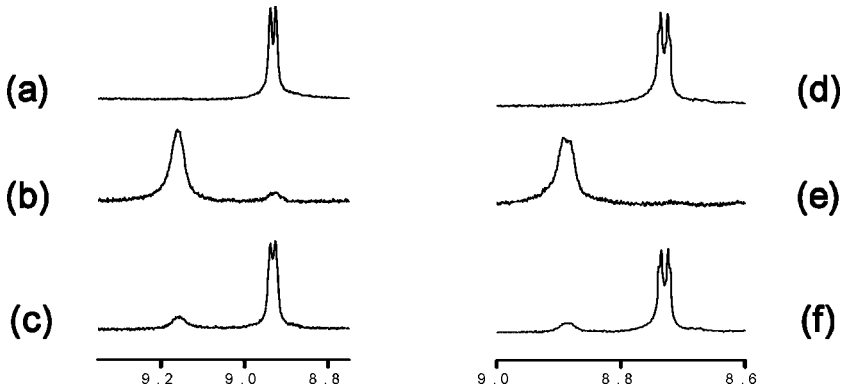

FIGURE 2. ^{1}H NMR signal (in CD_3OD) of the proton at the ortho position in the host pyridine group: (a) (*R*,*R*)-**L**-Zn-(*R*,*R*)-dpen, (b) (*R*,*R*)-**L**-Zn-(*S*,*S*)-dpen, (c) *rac*-**L**-Zn-*rac*-dpen, (d) (*R*,*R*)-L-Zn-(*R*,*R*)-dach, (e) (*R*,*R*)-**L**-Zn-(*S*,*S*)-dach, (f) *rac*-**L**-Zn-*rac*-dach.

stereoselectivity (0.2 to 0.5 kcal/mol) appears to be due to the increase in the steric effect. Computation shows that the stereoselectivity does not change significantly when one or both of the dpen in **1** and **2** are exchanged with dach. In case of the ternary complex formed between **L**, Zn(II), and dpen (Figure 1), the homochiral complex is computed to be about 1.2 kcal/mol more stable than the heterochiral complex. The additional stereoselectivity (1.2−0.5 = 0.2 kcal/mol) appears to be due to steric interaction between the host pyridine hydrogen at the ortho position and the N−H of the guest amine.[16]

There are two levels of stereoselectivity in formation of the ternary complex between **L**, $Zn(OTf)_2$, and vicinal diamines (Figure 1). The first is the selective formation of the *cis*-α form over the *cis*-*β* form and the second is the selective formation of the homochiral complex over the heterochiral complex.[17] Computation, solution-phase NMR, and X-ray crystallography all indicate that the homochiral complex is more stable than the heterochiral complex. Thus, a unified approach to detecting and understanding stereoselective recognition of C_2 symmetric vicinal diamines has been developed.

(16) Although the computations are used here for qualitative trends, the observed stereoselectivity (1.0 kcal/mol) for formation of the ternary complex in Figure 1 is in good agreement with the computed stereoselectivity (1.2 kcal/mol). Molecular mechanics and PM3 semiempirical computations also show the same trend (Supporting Information).

(17) The two methyl groups in **L** play an important role in increasing the stereoselectivity. Without the two methyl groups, the complexity of the ^{1}H NMR increases dramatically from the lowering of both levels of stereoselectivity.

Experimental Section

One equiv of $Zn(OTf)_2$ was added to the *R*,*R* form of the tetradentate ligand (**L**) (10 μmol) in CD_3OD (0.5 mL) and sonicated for 5 min. Initially, mixtures of the *cis*-α and *cis*-*β* complexes were formed. The mixtures were converted to the *cis*-α form by heating at 60 °C for 2 h. The *R*,*R* form of the guest diamines (20 μmol of dpen for Figure S1 and dach for Figure S2) were added to the solution. Equilibrium was established in less than 10 min, and the NMR spectrum did not change for several days (NMR experiments were performed on a 400 MHz spectrometer). Distinct signals appear for the bound and free diamine (Figure S1, δ 3.95 and 3.97) indicating that the diamine exchange rate is slow compared to the NMR time scale. The ternary complex in each of the two figures has the *cis*-α topology.

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Supporting Information Available: Experimental data including crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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