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Self-assembly of achiral and chiral macrocyclic ligands: synthesis, protonation constants, conformation and asymmetric catalysis

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New 30-membered achiral and chiral polyaza macrocyclic ligands, **L1** and **L2** were synthesized directly from [3 + 3] condensation of phthalic dicarboxaldehyde with *cis*- and (1*R*,2*R*)-diaminocyclohexane, respectively. The trimeric macrocyclic structures were confirmed by electrospray ionization mass spectrometry (ESI-MS), ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis. Potentiometry was used to determine the protonation constants of the ligands. UV–vis spectrophotometric titration was employed to investigate the coordination and conformational properties of the chiral ligand (**L2**). Direct enantioselective aldol reaction has been successfully performed using 4-nitrobenzaldehyde and acetone in the presence of the chiral macrocycle and its zinc(II) complexes as catalysts.

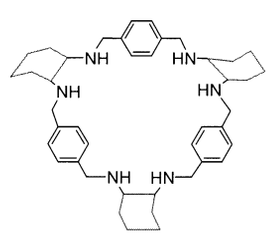
Introduction

Polyaza-crown macrocycles had been reported even before the advent of crown ethers and they continue to be the subject of intense research.[1–5] Metal complexes of polyaza macrocyclic ligands have been utilized as metalloenzyme mimics and catalysts as well.[6–10] In recent years, chiral macrocycles have been reported as host molecules for chiral recognition[11] and asymmetric catalysis.[12–14] However, there are only a handful of chiral polyaza-macrocycles reported to date, mostly in the form of oxaza-macrocycles, which have been derived from naturally occurring oxygen-containing optically active starting materials such as amino alcohols and carbohydrates.[15–18] The reason for this lack is not quite clear, but may be related to the fact that the conventional modular approaches can't be applied to the synthesis of chiral polyazamacrocycles. Herein reported is a concise synthesis of [3 + 3] type chiral and achiral macrocycles and the efficiency of the chiral macrocyclic ligand in the enantioselective catalysis of an asymmetric aldol reaction.

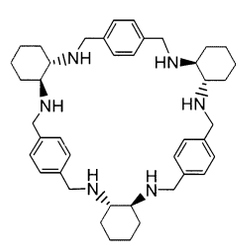
Results and discussion

Synthesis of the macrocyclic ligands

The preparation of the achiral ligand (**L1**) was first attempted by the Schiff base condensation of phthalic dicarboxaldehyde with *cis*-diaminocyclohexane at room temperature and this led to a complex mixture containing the dimeric and trimeric Schiffbase macrocycles, which were identified by ESI-MS spectra as shown in Fig. 1A. Our former investigation indicated that [2 + 2] Schiff bases can be prepared in good yields by condensation of a series of dialdehydes with diethylenetriamines.[6,8] Hydrogenation of the Schiff bases provided the corresponding saturated achiral polyaza ligands. For the synthesis of [3 + 3] hexa-Schiff base macrocycles, different products, such as [2 + 2] tetra-Schiff bases are usually isolated, depending on the reactant and template conditions. In the synthesis of the subject ligand, if the reductive amination approach was utilized, the [2 + 2] type of polyamine was eliminated. As shown in Fig. 1B, positive ESI-MS clearly showed an *m*/*z* peak at 649.4632 (**L1** + H^+), indicating the formation of the trimeric macrocycle. The peak at *m*/*z* = 865.6513 presents the tetrameric byproduct identified by comparison with the theoretical molecular ion peaks. Pure trimeric ligand was isolated by chromatographic purification (CH_2Cl_2–MeOH = 1 : 1). Former investigation indicated that the chiral ligand, **L2** can be prepared with moderate yield by [3 + 3] diamine dialdehyde addition followed by hydrogenation of the Schiff base macrocycle.[19] Our investigation shows that **L2** can be simply synthesized with high yield (> 90%) by reductive amination in the presence of the corresponding diamine and dialdehyde. The ESI-MS spectrum (Fig. 1C) shows that the one-step product is very pure, without any contamination of [2 + 2] or [4 + 4] byproduct. The reaction is believed to proceed through an efficient self-assembly process. Further investigation shows that the product yield can't be improved in the presence of a metal template, indicating that in the synthesis of crown polyazas possessing more than approximately 24 atoms in their macrocyclic chain, the metal ion template is less useful. The ^{1}H NMR spectra of **L1** and **L2** (shown as Fig. 2A and Fig. 2B respectively) are significantly different due to stereoisomeric and conformational reasons. The ^{13}C NMR of **L2** (Fig. 2C), with the numbering system in the inset, clearly shows the purity of this ligand.



L1



L2

Protonation constants of the ligands

The potentiometric equilibrium curves for **L1**·6HBr and **L2**·6HBr are illustrated in Fig. 3. The pH profiles of these ligands reveal two inflections at $a = 3$ and $a = 6$ (a = moles of base added per mole of the ligand). From $a = 0$ to 3 and $a = 3$ to 6, there are two buffer regions. The first buffered region corresponds to the completion of the neutralization of the three most acidic protons. The buffer region at high a corresponds to the dissociation of the other three substituted ammonium groups on the macrocycle. Indeed, the resulting calculated protonation constants, which are given in Table 1, display the order $pK_1 \sim pK_2 \sim pK_3 > pK_4 \sim pK_5 \sim pK_6$. The overall log protonation constants, $\Sigma \log K_i^H$, for the chiral hexaza macrocycles is 37.91,

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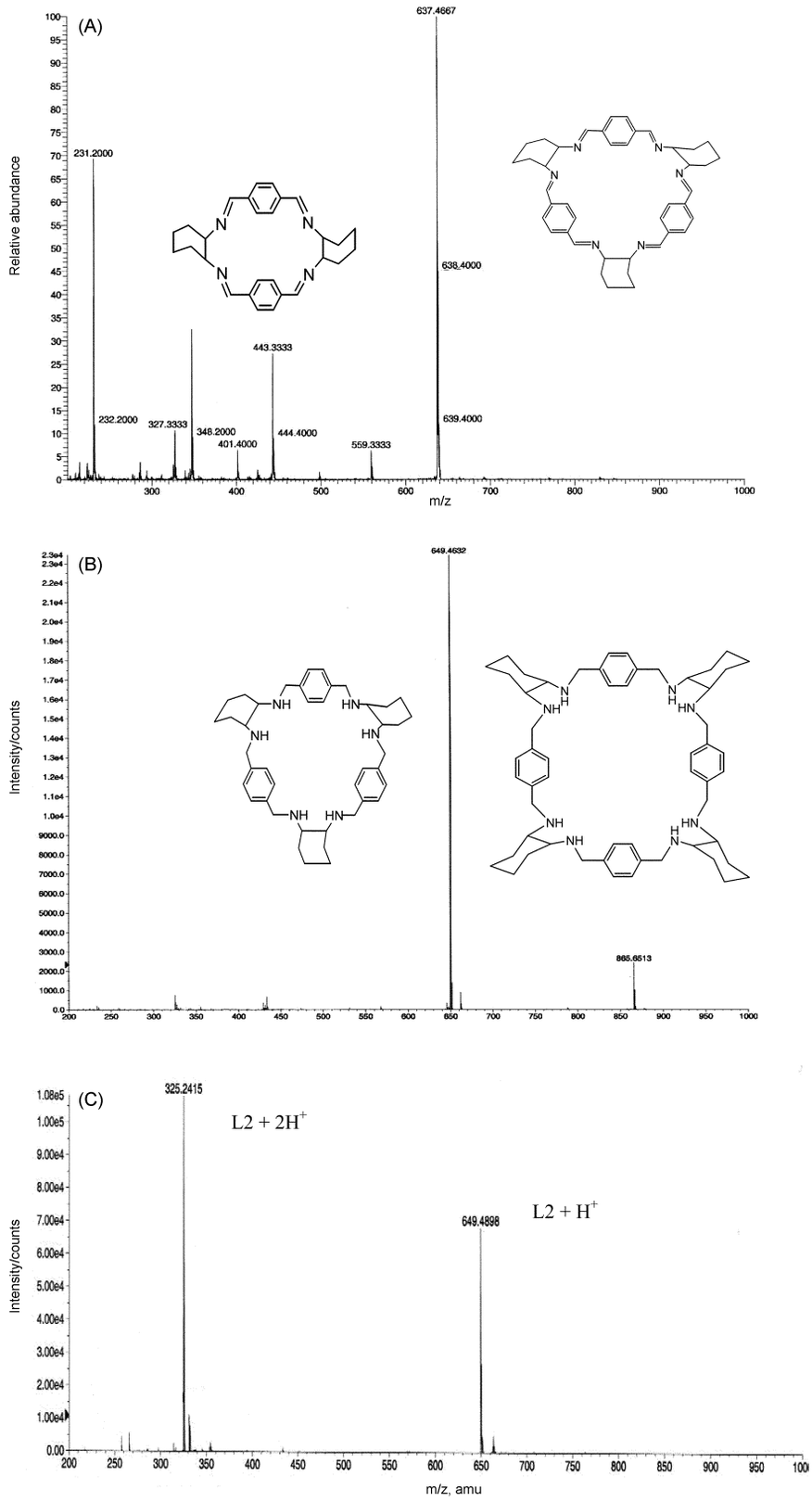


Fig. 1 ESI-MS spectrum of: the Schiff base precursor of **L1** synthesized by Schiff base condensation (1A); **L1** synthesized by reductive amination (1B); **L2** synthesized by reductive amination (1C).

which is much higher than the component 1*R*,2*R*-diaminocyclohexane of 16.32.[20] The $\Sigma\log K_i^H$ value for **L1** is 38.86, indicating that the overall basicity of the ligand is influenced by the conformational and the local stereomeric properties. The species distribution diagram for **L2** (Fig. 4) shows that the tri-deprotonated form prevails at pH = 6.6 and the free ligand dominates at above pH 9.0.

Conformational investigation

Preliminary conformational studies of the chiral ligand have been conducted by UV–vis spectrophotometric titration experiments using Cu^{2+} as a probing cation. In the absence of the ligand, the MeOH solution of $Cu(ClO_4)_2$ exhibits a broad d–d absorption at 710 nm. Addition of **L2** causes the λ_{max} to

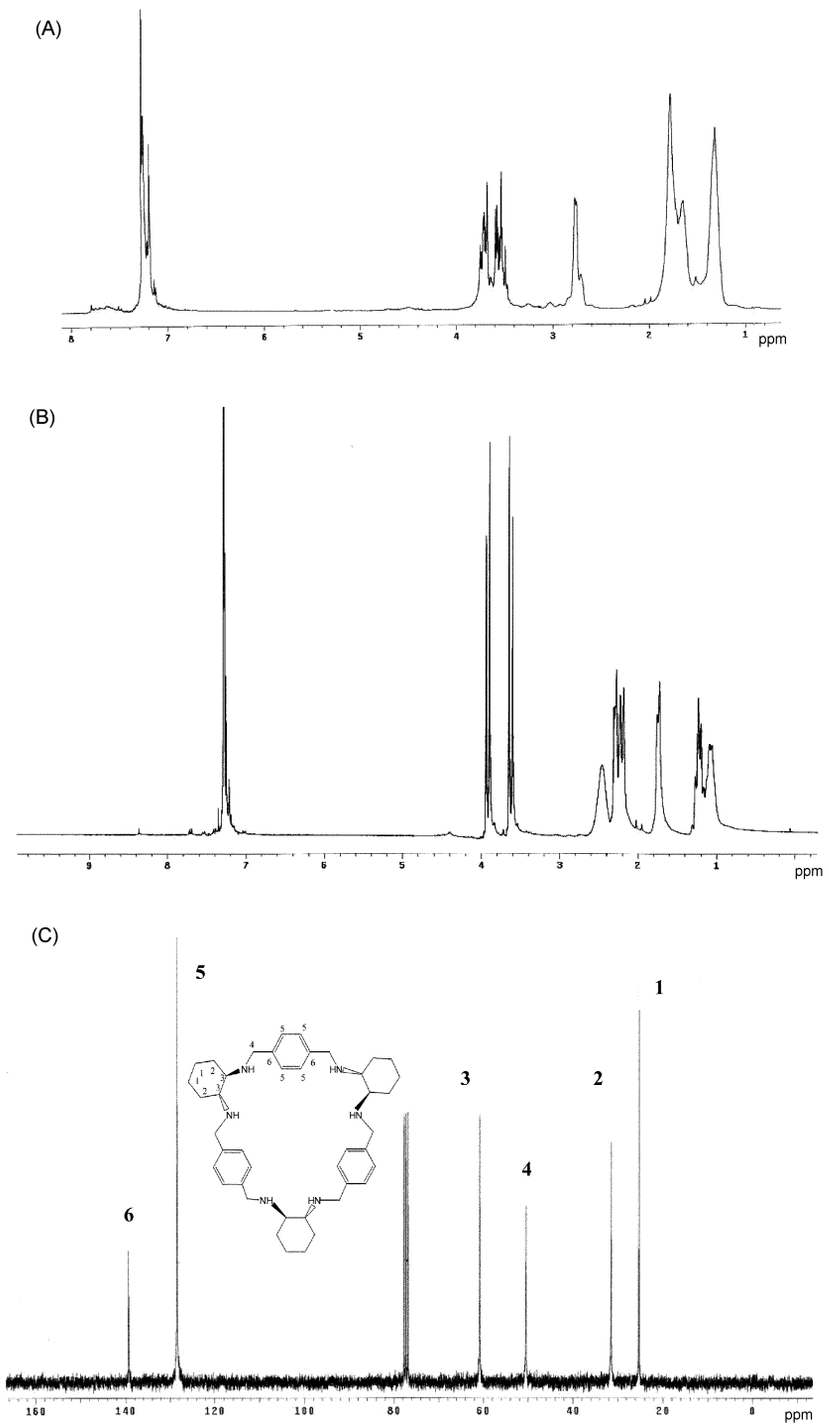


Fig. 2 ^{1}H NMR spectrum of **L1** (2A) and **L2** (2B) in CD_3Cl; ^{13}C NMR spectrum of **L2** (2C).

Table 1 Logarithms of the protonation constants of **L1** and **L2**. (μ = 0.100 M KCl, T = 25.0 °C, under argon)

Symbol	Equilibrium quotient	LogK^{H}_{i} of **L1**	LogK^{H}_{i} of **L2**
K^{H}_{6}	$[H_6L]/[H_5L][H]$	3.66	2.83
K^{H}_{5}	$[H_5L]/[H_4L][H]$	3.85	3.60
K^{H}_{4}	$[H_4L]/[H_3L][H]$	4.95	4.65
K^{H}_{3}	$[H_3L]/[H_2L][H]$	8.57	8.63
K^{H}_{2}	$[H_2L]/[HL][H]$	8.71	9.00
K^{H}_{1}	$[HL]/[L][H]$	9.12	9.20
ΣK^{H}_{i}	$[H_6L]/[L][H]^6$	38.86	37.91

undergo a blue shift to 633 nm, which is characteristic of Cu(II) being bound by a diamino moiety. The spectrophotometric titration (Fig. 5) indicates that **L2** bonds Cu(II) in more than one but less than three portions. However, when Cu(en)(1 : 1 Cu(II)–ethylenediamine) was used in the titration process, 3Cu(II) : **L2** solution stoichiometry was achieved (Fig. 6). This phenomenon indicates that in the 1 : 1 Cu(II)–**L2** complex system, the metal cation is coordination unsaturated. Molecular model analysis (Fig. 7) indicated that in the energy minimized-conformation, the three diamino moieties are well separated. The inner cavity is too large to hold a six coordinated Cu(II) complex, reflecting the conformational rigidity of the chiral macrocycle.

Catalysis of asymmetric aldol condensation

The chiral macrocyclic ligand was initially tested as a Lewis base catalyst for the asymmetric aldol reaction of 4-nitrobenzaldehyde and acetone (Scheme 1). As seen from the results in Table 2, the yields and enantioselectivities of the product

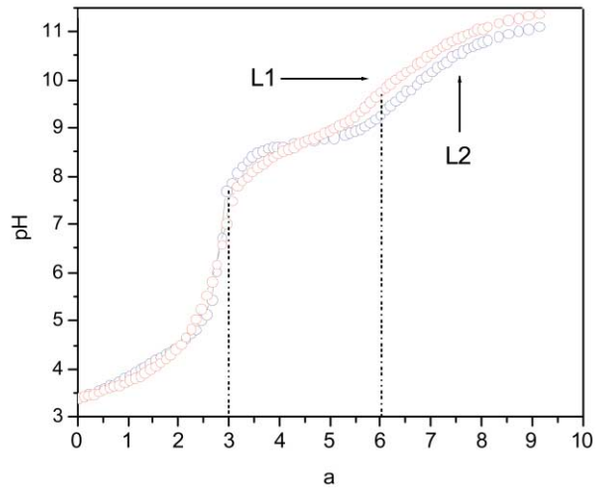


Fig. 3 Potentiometric equilibrium curves for **L1** and **L2** (μ = 0.100 M KCl, T = 25 °C, a = moles of KOH added per mole of L, [L] = 0.001 M).

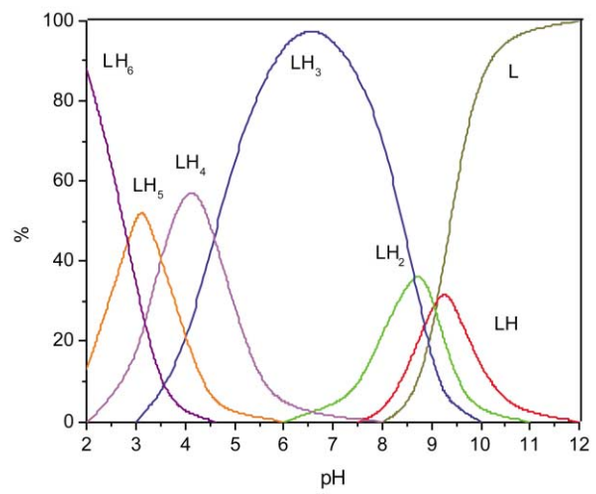


Fig. 4 Species distribution diagram showing the species formed as a function of pH when **L2** = 0.001 M. (μ = 0.100 M KCl, T = 25 °C).

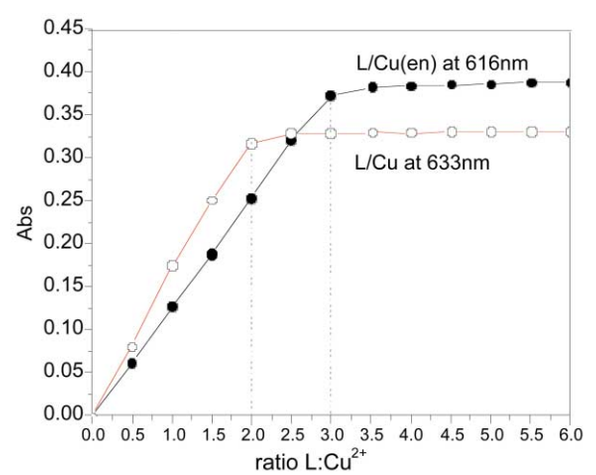
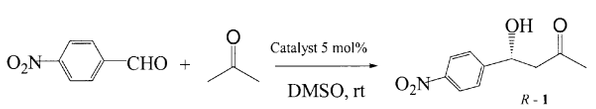


Fig. 5 Absorption variation of spectrophotometric titration of **L2** with Cu^{2+} and $Cu(en)^{2+}$ in MeOH monitored at 633 and 616 nm respectively.



Scheme 1

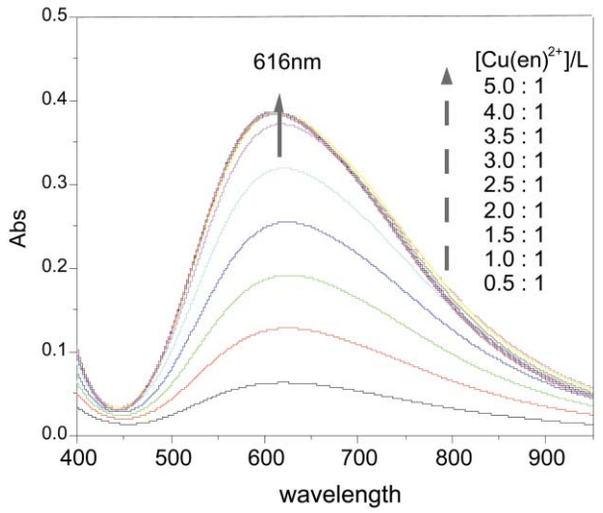


Fig. 6 Spectrophotometric titration of **L2**–Cu(en) system ([**L2**] = 5.0 mM, 25 °C).

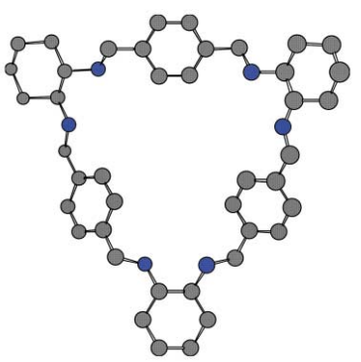


Fig. 7 Molecular model analysis of **L2** indicating the energy-minimized conformation.

increased with increasing deprotonation of the hexahydrobromide. However, adding excessive amounts of Et_3N after the total deprotonation can only slightly increase the product yield and the enantioselectivity of the product remains unchanged. This result can tentatively be ascribed to the very strong basicity of the macrocyclic ligand. We therefore speculate that the stereoselectivity was controlled by a host–guest inter-cavity interaction. The absolute configuration of the product was assigned by comparison to the literature.[21]

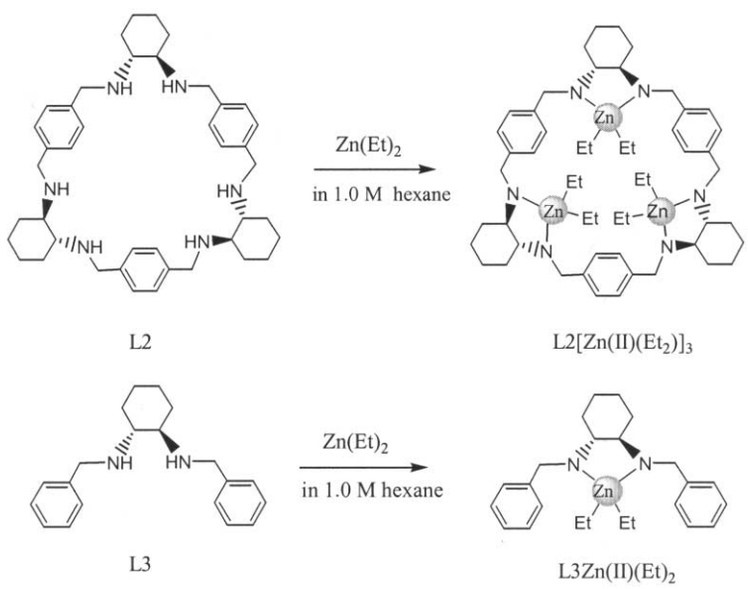
With this result in hand, we tested the effects of Lewis acid on the yield and enantioselectivity by adding $Zn(II)(Et)_2$ *in situ* to the reaction system. The structure of the complex catalyst is shown in Scheme 2.

The trimeric chiral diamino moieties within the macrocycle provide an unique opportunity to observe the cooperative mechanism, which is common to this type of aldol reaction.[21] The trinuclear complex catalyst system displayed substantial improvements in enantioselectivity relative to the mono, di-nuclear analogues and the free ligand, with kinetic behavior consistent with cooperative reactivity within the macrocyclic framework. In the control experiments, chiral segment **L3** and its Zn(II) complex were readily prepared to mimic the local geometry of the trimeric macrocycle and the trinuclear complex respectively (also Scheme 2). Enantiomeric excess of 15.4% and 32.7% were observed for **L3** and **L3**Zn(II) complex respectively. These values are much lower than the corresponding macrocycle and the macrocyclic complex, further indicating the cooperative effects in the trimeric catalysts. Since this ligand proved to be easily prepared and with high tolerance to strong acid and base, the Zn(II)–complex system appears to hold significant promise from both fundamental and practical

Table 2 **L2** and its Zn(II) complexes catalyzed aldol reaction, catalyst concentration is 5 mol%

Entry	Et_3N added (equiv. of **L2**·6HBr)	Dominant form of the catalyst	Yield (%) [a]	ee (%) [b]	Product configuration
1	2	**L2**·4HBr	80.2	18.5	*R*
2	3	**L2**·3HBr	85.7	26.5	*R*
3	4	**L2**·2HBr	88.6	28.8	*R*
4	5	**L2**·HBr	90.1	34.0	*R*
5	6	**L2**	92.5	36.2	*R*
6	7	**L2**	93.1	37.1	*R*
7	6	**L2**-Zn(II)	93.2	42.3	*R*
8	6	**L2**-2Zn(II)	92.2	48.4	*R*
9	6	**L2**-3Zn(II)	94.6	56.7	*R*

[a] Isolated after column chromatography. [b] Enantiomer excess was determined by the comparison of the data obtained from chiral polarimeter and Chiral HPLC (Chiralcel OD column).



Scheme 2

perspectives. We currently are working on further application of this chiral ligand to other catalytic asymmetric reactions.

In summary, we have developed a novel and concise synthetic methodology for the construction of certain achiral and chiral polyaza macrocycles containing rigid aromatic units. We are currently investigating the scope of this synthetic method for the preparation of other classes of chiral polyaza macrocycles and the utilization of them for chiral molecular recognition and catalysis.

Experimental

Material and measurement

All solvents of analytical grades were obtained from the Sigma-Aldrich Chemical Company. Methanol was dried on molecular sieves (3) prior to use. ^{1}H NMR spectra were obtained on a Unix-VMR-300 MHz spectrometer. Analysis for C. H. and N, were carried out on a Perkin-Elmer analyzer, Model 240. Electronic spectra (in methanol) were measured on a Beckman 640B UV–vis spectrophotometer. Positive ion ESI-MS was recorded using LCQ electrospray mass spectrometry. The spectra were recorded over the mass range *m*/*z* 200–1000. The molecular structure was generated by Chem 3D Pro Version (5.0.0 2.15). Minimize Energy and Molecular Dynamics were carried out to try to find the energy-minimized conformation.

Preparation of the achiral macrocyclic ligand L1

The achiral macrocyclic ligand (**L1**) was prepared by a one-pot synthesis method: a solution of *cis*-diaminocyclohexane (15 mmol) in 200 ml of MeOH was added dropwise from a dropping funnel to a stirred solution containing 98% phthalic dicarboxaldehyde (2.15 g, 15 mmol) and $NaBH_4$ (4.0 g, 100 mmol) in 300 ml of MeOH in a 1 L round-bottomed three-necked flask over 12 h at room temperature. The mixture was magnetically stirred for about 2 h at room temperature and then gently heated to 50 °C to ensure the reaction was completed. Then, it was allowed to reach room temperature, at which point 5 ml of H_2O was added to remove unreacted $NaBH_4$. The solvent was treated with 100 ml of H_2O and was then filtered. This solution was extracted with CH_2Cl_2 (300 ml) three times. Evaporation of CH_2Cl_2 under reduced pressure yielded a yellow-colored oil and the pure trimeric ligand was separated by column chromatography (silica gel, CH_2Cl_2–MeOH = 1 : 1). **L1** was then dissolved in 50 ml of EtOH. HBr (10 ml, 48%) in 20 ml of EtOH was added slowly until all the precipitate formed. The mixture was filtered and dried at 60 °C under vacuum for 3 h, giving light yellow microcrystals as the hexahydrobromide salt **L1**·6HBr; (yield, 85%); mp > 298 °C; ESI-MS, *m*/*z*: 649.4632(M + H)$^+$; Calcd for $C_{42}H_{60}N_6$: 648.4879; ^{1}H NMR,($CDCl_3$), (ppm): 1.32(s, 4H, –CH_2–), 1.64(s, 4H, –CH_2–), 1.78(s, 2H, –CH–NH), 2.78(d, *J* = 8.7 Hz, –NH–CH_2–), 3.52(m, *J* = 35.0 Hz, 2H, –CH_2-benzene), 3.68(m, *J* = 21.0 Hz, 2H, –CH_2-benzene), 7.18–7.26(m, 4H, benzene); ^{13}C NMR (in $CDCl_3$), (ppm): 25.24(–CH_2– of cyclohexane), 31.43(–CH_2– of cyclohexane), 60.80(–CH_2–NH_2 of cyclohexane), 50.50(–CH_2-benzene), 128.36(benzene), 139.22(benzene-CH_2); Anal calc. for $C_{42}H_{60}N_6$·6HBr, C, 44.49; H, 5.87; N, 7.41. Found. C, 44.48; H, 5.95; N, 7.46%.

Preparation of the chiral macrocyclic ligand L2

A solution of (1*R*,2*R*)-diaminocyclohexane (15 mmol) in 200 ml of MeOH was added dropwise from a dropping funnel to a

stirred solution containing 98% phthalic dicarboxaldehyde (2.15 g, 15 mmol) and $NaBH_4$ (4.0 g, 100 mmol) in 300 ml of MeOH in a 1 L round-bottomed three-necked flask over 12 h at room temperature. The suspension was magnetically stirred for an additional 2 h at room temperature and then heated to 50 °C. Then, it was allowed to reach room temperature, at which point 5 ml of H_2O was added to remove unreacted $NaBH_4$. The solvent was treated with 100 ml of H_2O and was then filtered. This solution was extracted with CH_2Cl_2 (300 ml) three times. Evaporation of CH_2Cl_2 under reduced pressure yielded a colorless oil, which was then dissolved in 50 ml of EtOH. HBr (10 ml, 48%) in 20 ml of EtOH was added slowly until all the precipitate formed. The mixture was filtered and dried at 60 °C under vacuum for 3 h, giving white microcrystals as the hexahydrobromide salt **L2**·6HBr; (yield, 90%); mp 296–298 °C; $[a]_D^{25}$ = +78.6 (*c* 1, CH_2Cl_2); ESI-MS, *m*/*z*: 649.4859(M + H)$^+$; Calcd for $C_{42}H_{60}N_6$: 648.4879; ^{1}H NMR,($CDCl_3$), (ppm): 1.07(d, *J* = 8.7 Hz, 2H), 1.24(q, *J* = 21.3 Hz, 2H), 1.73(d, *J* = 8.7 Hz, 2H), 2.28(q, *J* = 36.3 Hz, 4H), 2.46(s, 2H), 3.63(d, *J* = 12.9 Hz, 2H), 3.92(d, *J* = 12.9 Hz, 2H), 7.22–7.29(m, 4H); ^{13}C NMR (in $CDCl_3$), (ppm): 25.25(–CH_2– of cyclohexane), 31.42(–CH_2– of cyclohexane), 60.79(–CH_2–NH_2 of cyclohexane), 50.54(–CH_2-benzene), 128.35(benzene), 139.26(benzene-CH_2); Anal calc. for $C_{42}H_{60}N_6$·6HBr, C, 44.49; H, 5.87; N, 7.41. Found. C, 44.51; H, 5.70; N, 7.32%.

Titration procedure

All of the metal stock solutions for potentiometric studies were reagent grade chloride salts prepared with doubly distilled water and standardized by EDTA. CO_2-free Dilute-it ampules of KOH were obtained from J. T. Baker Inc. KOH solutions (about 0.1 M) and were prepared with doubly distilled water and standardized. The extent of carbonate accumulation (<1.8%) was checked periodically by titration with a standard HCl solution. A Corning 250 digital pH meter, fitted with Fisher full-range blue-glass and Fisher calomel reference electrodes were used for potentiometric titrations. A Metrohm of 10 mL capacity piston buret was used for precise delivery of standard KOH. The solution to be studied was contained in a 75 ml jacketed glass cell thermostated at 25.00 ± 0.05 °C by a circulating constant-temperature water bath.

Potentiometric determinations

All pH calibrations were performed with standardized HCl solutions to measure hydrogen ion concentrations directly (pH = −log [H$^+$]). The ionic strength was adjusted to 0.100 M with KCl. Titrations of the ligand in the presence of metal ions in aqueous solution were conducted in the manner described by Martell and Motekaitis.[22] Cell solutions (in general, 50.00 ml) were purged with a purified argon stream. Standard base was introduced into the sample solutions with a Metrohm piston buret. Experimental runs were carried out by adding increments of standard base to a solution containing **L1**·6HBr or **L2**·6HBr plus other components such as KCl solution. The concentration of the sample solution was 1×10^{-3} M for **L1**·6HBr or **L2**·6HBr. The pH range for accurate measurements was considered to be 2–12. The pK_w for the aqueous system, defined as −log([H][OH]) at the ionic strength employed was found to be 13.78. Protonation constants from the direct titrations were calculated from the potentiometric data with the program BEST.

The error in the constants are estimated as ±0.04 log unit on the basis of the σ_{off} value, which measures the deviation of the experimental curve and the curve calculated from the equilibrium constants, being less than 0.01 pH unit in all potentiometric determinations. Species distribution diagrams were computed from the measured equilibrium constants with SPE and plotted with SPEPLOT.[22]

Catalytic experiments

General procedure for the aldol reaction: to a mixture of anhydrous DMSO (8 ml) and ketone (2 ml) was added the macrocyclic ligand (0.05 mmol). The mixture was vigorously stirred for 4 h and was followed by the addition of 4-nitrobenzaldehyde (1 mmol). The resulting mixture was stirred at rt for 8 h and was then treated with an aqueous solution of saturated NH_4Cl. The aqueous layer was separated and extracted with ethyl acetate, dried and evaporated. The pure aldol products, *R*-**1** (Scheme 2) were separated by column chromatography (silica gel, hexane–acetone). Compound ***R*-1:** $[a]_D^{25}$ = + 25.9 (*c* 1, $CHCl_3$), 56% ee; lit.[23] $[a]_D^{25}$ = + 46.2 (*c* 1, CH_2Cl_2); IR_{ν}, 3434 (OH), 1713(C=O), 1600(Ar), 1516, 1376, 1343, 1240, 1164, 1079, 1012, 855, 839, 788, 748, 699, 542 cm^{-1}; ^{1}H NMR ($CDCl_3$), δ_H: 2.22(3H, s, CH_3), 2.85(2H, d, *J* = 6.0 Hz, CH_2), 4.72 (1H, br s, OH), 5.27(1H, dd, *J* = 5.0, 7.0 Hz, CH), 7.54(2H, d, *J*= 9.0 Hz, ArH), 8.21(2H, d, *J* = 8.0 Hz, ArH).

Acknowledgements

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